ROMANIA
Newsletter
Year 16, No. 2 (62), 2nd quarter of 2014

National Agency for Medicines and Medical Devices

- All data herein represent official information and are under direct authority of the National Agency for Medicines and Medical Devices.

- The entire content of the present publication lies under complete legislative protection of the National Agency for Medicines and Medical Devices.

- Any use of present publication content for revenue purposes or its marketing without express consent of the National Agency for Medicines and Medical Devices is forbidden and punishable by law.

- The National Agency for Medicines and Medical Devices reserves exclusive publishing rights.

ISSN 1583-347X

TABLE OF CONTENTS

I

(Legislative acts)

REGULATIONS

REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on the Functioning of the European Union, and in particular Articles 114 and 168(4)(c) thereof,

Having regard to the proposal from the European Commission,

After transmission of the draft legislative act to the national parliaments,

Having regard to the opinion of the European Economic and Social Committee ([1]),

After consulting the Committee of the Regions,

Acting in accordance with the ordinary legislative procedure ([2]),

Whereas:

(1) In a clinical trial the rights, safety, dignity and well-being of subjects should be protected and the data generated should be reliable and robust. The interests of the subjects should always take priority over all other interests.

(2) In order to allow for independent control as to whether these principles are adhered to, a clinical trial should be subject to prior authorisation.

(3) The existing definition of a clinical trial as contained in Directive 2001/20/EC of the European Parliament and of the Council ([3]) should be clarified. For that purpose, the concept of clinical trial should be more precisely defined by introducing the broader concept of 'clinical study' of which the clinical trial is a category. That category should be defined on the basis of specific criteria. This approach takes due account of international guidelines, and is in line with the Union law governing medicinal products, which builds on the dichotomy of 'clinical trial' and 'non-interventional study'.

(4) Directive 2001/20/EC aims to simplify and harmonise the administrative provisions governing clinical trials in the Union. However, experience shows that a harmonised approach to the regulation of clinical trials has only been partly achieved. This makes it in particular difficult to perform a given clinical trial in several Member States. Scientific development, however, suggests that future clinical trials will target more specific patient populations, such as subgroups identified through genomic information. In order to include a sufficient number of patients for such clinical trials it may be necessary to involve many, or all, Member States. The new procedures for the authorisation of clinical trials should stimulate the inclusion of as many Member States as possible. Therefore, in order to simplify the procedures for the submission of an application dossier for the authorisation of a clinical trial, the multiple submission of largely identical information should be avoided and replaced by the submission of one application dossier to all the Member States concerned through a single submission portal. Given that clinical trials carried out in a single Member State are equally important to European clinical research, the application dossier for such clinical trials should also be submitted through that single portal.

(5) As regards Directive 2001/20/EC, experience also indicates that the legal form of a Regulation would present advantages for sponsors and investigators, for example in the context of clinical trials taking place in more than one Member State, since they will be able to rely on its provisions directly, but also in the context of safety reporting and labelling of investigational medicinal products. Divergences of approach among different Member States will be therefore kept to a minimum.

[1] OJ C 44, 15.2.2013, p. 99.
[2] Position of the European Parliament of 3 April 2014 (not yet published in the Official Journal) and decision of the Council of 14 April 2014.
[3] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (OJ L 121, 1.5.2001, p. 34).

(6) The Member States concerned should cooperate in assessing a request for authorisation of a clinical trial. This cooperation should not include aspects of an intrinsically national nature, such as informed consent.

(7) In order to avoid administrative delays for starting a clinical trial, the procedure to be used should be flexible and efficient, without compromising patient safety or public health.

(8) The timelines for assessing an application dossier for clinical trials should be sufficient to assess the file while, at the same time, ensuring quick access to new, innovative treatments and ensuring that the Union remains an attractive place for conducting clinical trials. Against this background, Directive 2001/20/EC introduced the concept of tacit authorisation. This concept should be maintained in order to ensure that timelines are adhered to. In the event of a public health crisis, Member States should have the possibility to assess and authorise a clinical trial application swiftly. No minimal timelines for approval should therefore be established.

(9) Clinical trials for the development of orphan medicinal products as defined in Regulation (EC) No 141/2000 of the European Parliament and of the Council ([4]) and of medicinal products addressed to subjects affected by severe, debilitating and often life-threatening diseases affecting no more than one person in 50 000 in the Union (ultra-rare diseases) should be fostered.

(10) Member States should efficiently assess all clinical trials applications within the given timelines. A rapid yet in- depth assessment is of particular importance for clinical trials concerning medical conditions which are severely debilitating and/or life threatening and for which therapeutic options are limited or non-existent, as in the case of rare and ultra-rare diseases.

(11) The risk to subject safety in a clinical trial mainly stems from two sources: the investigational medicinal product and the intervention. Many clinical trials, however, pose only a minimal additional risk to subject safety compared to normal clinical practice. This is particularly the case where the investigational medicinal product is covered by a marketing authorisation, that is the quality, safety and efficacy has already been assessed in the course of the marketing authorisation procedure" or, if that product is not used in accordance with the terms of the marketing authorisation, that use is evidence- based and supported by published scientific evidence on the safety and efficacy of that product, and the intervention poses only very limited additional risk to the subject compared to normal clinical practice. Those low-intervention clinical trials are often of crucial importance for assessing standard treatments and diagnoses, thereby optimising the use of medicinal products and thus contributing to a high level of public health. Those clinical trials should be subject to less stringent rules, as regards monitoring, requirements for the contents of the master file and traceability of investigational medicinal products. In order to ensure subject safety they should however be subject to the same application procedure as any other clinical trial. The published scientific evidence supporting the safety and efficacy of an investigational medicinal product not used in accordance with the terms of the marketing authorisation could include high quality data published in scientific journal articles, as well as national, regional or institutional treatment protocols, health technology assessment reports or other appropriate evidence.

(12) The Recommendation of the Organisation for Economic Cooperation and Development (OECD) Council on the Governance of Clinical Trials of 10 December 2012 introduced different risk categories for clinical trials. Those categories are compatible with the categories of clinical trials defined in this Regulation as the OECD Categories A and B(1) correspond to the definition of a low-intervention clinical trial as set out in this Regulation, and the OECD Categories B(2) and C correspond to the definition of a clinical trial as set out in this Regulation.

(13) The assessment of the application for a clinical trial should address in particular the anticipated therapeutic and public health benefits (relevance) and the risk and inconvenience for the subject. In respect of the relevance, various aspects should be taken into account, including whether the clinical trial has been recommended or imposed by regulatory authorities in charge of the assessment of medicinal products and the authorisation of their placing on the market and whether surrogate end-points, when they are used, are justified.

(14) Unless otherwise justified in the protocol, the subjects participating in a clinical trial should represent the population groups, for example gender and age groups, that are likely to use the medicinal product investigated in the clinical trial.

(15) In order to improve treatments available for vulnerable groups such as frail or older people, people suffering from multiple chronic conditions, and people affected by mental health disorders, medicinal products which are likely to be of significant clinical value should be fully and appropriately studied for their effects in these specific groups, including as regards requirements related to their specific characteristics and the protection of the health and well-being of subjects belonging to these groups.

(16) The authorisation procedure should provide for the possibility to extend the timelines for the assessment in order to allow the sponsor to address questions or comments raised during the assessment of the application dossier. Moreover, it should be ensured that, within the extension period, there is always sufficient time for assessing the additional information submitted.

[4] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products (OJ L 18, 22.1.2000, p. 1).

(17) The authorisation to conduct a clinical trial should address all aspects of subject protection and data reliability and robustness. That authorisation should therefore be contained in a single administrative decision by the Member State concerned.

(18) It should be left to the Member State concerned to determine the appropriate body or bodies to be involved in the assessment of the application to conduct a clinical trial and to organise the involvement of ethics committees within the timelines for the authorisation of that clinical trial as set out in this Regulation. Such decisions are a matter of internal organisation for each Member State. When determining the appropriate body or bodies, Member States should ensure the involvement of laypersons, in particular patients or patients' organisations. They should also ensure that the necessary expertise is available. In accordance with international guidelines, the assessment should be done jointly by a reasonable number of persons who collectively have the necessary qualifications and experience. The persons assessing the application should be independent of the sponsor, the clinical trial site, and the investigators involved, as well as free from any other undue influence.

(19)The assessment of applications for the authorisation of clinical trials should be conducted on the basis of appropriate expertise. Specific expertise should be considered when assessing clinical trials involving subjects in emergency situations, minors, incapacitated subjects, pregnant and breastfeeding women and, where appropriate, other identified specific population groups, such as elderly people or people suffering from rare and ultra-rare diseases.

(20) In practice, sponsors do not always have all the information needed for submitting a complete application for authorisation of a clinical trial in all of the Member States where a clinical trial is eventually going to be conducted. It should be possible for sponsors to submit an application solely on the basis of documents assessed jointly by those Member States where the clinical trial might be conducted.

(21)The sponsor should be allowed to withdraw the application for authorisation of a clinical trial. To ensure the reliable functioning of the assessment procedure, however, an application for authorisation of a clinical trial should be withdrawn only for the entire clinical trial. It should be possible for the sponsor to submit a new application for authorisation of a clinical trial following the withdrawal of an application.

(22) In practice, in order to reach recruitment targets or for other reasons, sponsors may have an interest in extending the clinical trial to an additional Member States after the initial authorisation of the clinical trial. An authorisation mechanism should be provided to allow for such extension, while avoiding the re-assessment of the application by all the Member States concerned which were involved in the initial authorisation of the clinical trial.

(23) Clinical trials are usually subject to many modifications after they have been authorised. Those modifications may relate to the conduct, the design, the methodology, the investigational or auxiliary medicinal product, or the investigator or clinical trial site involved. Where those modifications have a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the clinical trial, they should be subject to an authorisation procedure similar to the initial authorisation procedure.

(24) The content of the application dossier for authorisation of a clinical trial should be harmonised in order to ensure that all Member States have the same information available and to simplify the application process for clinical trials.

(25) In order to increase transparency in the area of clinical trials, data from a clinical trial should only be submitted in support of a clinical trial application if that clinical trial has been recorded in a publicly accessible and free of charge database which is a primary or partner registry of, or a data provider to, the international clinical trials registry platform of the World Health Organization (WHO ICTRP). Data providers to the WHO ICTRP create and manage clinical trial records in a manner that is consistent with the WHO registry criteria. Specific provision should be made for data from clinical trials started before the date of application of this Regulation.

(26) It should be left to Member States to establish the language requirements for the application dossier. To ensure that the assessment of the application for authorisation of a clinical trial functions smoothly, Member States should consider accepting a commonly understood language in the medical field as the language for the documentation not destined for the subject.

(27) Human dignity and the right to the integrity of the person are recognised in the Charter of Fundamental Rights of the European Union (the ‘Charter’). In particular, the Charter requires that any intervention in the field of biology and medicine cannot be performed without free and informed consent of the person concerned. Directive 2001/20/EC contains an extensive set of rules for the protection of subjects. These rules should be upheld. Regarding the rules concerning the determination of the legally designated representatives of incapacitated persons and minors, those rules diverge in Member States. It should therefore be left to Member States to determine the legally designated representatives of incapacitated persons and minors. Incapacitated subjects, minors, pregnant women and breastfeeding women require specific protection measures.

(28) An appropriately qualified medical doctor or, where appropriate, a qualified dental practitioner should be responsible for all medical care provided to the subject, including the medical care provided by other healthcare professionals.

(29) It is appropriate that universities and other research institutions, under certain circumstances that are in accordance with the applicable law on data protection, be able to collect data from clinical trials to be used for future scientific research, for example for medical, natural or social sciences research purposes. In order to collect data for such purposes it is necessary that the subject gives consent to use his or her data outside the protocol of the clinical trial and has the right to withdraw that consent at any time. It is also necessary that research projects based on such data be made subject to reviews that are appropriate for research on human data, for example on ethical aspects, before being conducted.

(30) In accordance with international guidelines, the informed consent of a subject should be in writing. When the subject is unable to write, it may be recorded through appropriate alternative means, for instance through audio or video recorders. Prior to obtaining informed consent, the potential subject should receive information in a prior interview in a language which is easily understood by him or her. The subject should have the opportunity to ask questions at any moment. Adequate time should be provided for the subject to consider his or her decision. In view of the fact that in certain Member States the only person qualified under national law to perform an interview with a potential subject is a medical doctor while in other Member States this is done by other professionals, it is appropriate to provide that the prior interview with a potential subject should be performed by a member of the investigating team qualified for this task under the national law of the Member State where the recruitment takes place.

(31) In order to certify that informed consent is given freely, the investigator should take into account all relevant circumstances which might influence the decision of a potential subject to participate in a clinical trial, in particular whether the potential subject belongs to an economically or socially disadvantaged group or is in a situation of institutional or hierarchical dependency that could inappropriately influence her or his decision to participate.

(32) This Regulation should be without prejudice to national law requiring that, in addition to the informed consent given by the legally designated representative, a minor who is capable of forming an opinion and assessing the information given to him or her, should himself or herself assent in order to participate in a clinical trial.

(33) It is appropriate to allow that informed consent be obtained by simplified means for certain clinical trials where the methodology of the trial requires that groups of subjects rather than individual subjects are allocated to receive different investigational medicinal products. In those clinical trials the investigational medicinal products are used in accordance with the marketing authorisations, and the individual subject receives a standard treatment regardless of whether he or she accepts or refuses to participate in the clinical trial, or withdraws from it, so that the only consequence of non-participation is that data relating to him or her are not used for the clinical trial. Such clinical trials, which serve to compare established treatments, should always be conducted within a single Member State.

(34) Specific provisions should be defined for the protection of pregnant and breastfeeding women participating in clinical trials and in particular when the clinical trial does not have the potential to produce results of direct benefit to her or to her embryo, foetus or child after birth.

(35) Persons performing mandatory military service, persons deprived of liberty, persons who, due to a judicial decision, cannot take part in clinical trials, and persons, who due to their age, disability or state of health are reliant on care and for that reason accommodated in residential care institutions, that is accommodations providing an uninterrupted assistance for persons who necessitate such assistance, are in a situation of subordination or factual dependency and therefore may require specific protective measures. Member States should be allowed to maintain such additional measures.

(36) This Regulation should provide for clear rules concerning informed consent in emergency situations. Such situations relate to cases where for example a patient has suffered a sudden life-threatening medical condition due to multiple traumas, strokes or heart attacks, necessitating immediate medical intervention. For such cases, intervention within an ongoing clinical trial, which has already been approved, may be pertinent. However, in certain emergency situations, it is not possible to obtain informed consent prior to the intervention. This Regulation should therefore set clear rules whereby such patients may be enrolled in the clinical trial under very strict conditions. In addition, the said clinical trial should relate directly to the medical condition because of which it is not possible within the therapeutic window to obtain prior informed consent from the subject or from his or her legally designated representative. Any previously expressed objection by the patient should be respected, and informed consent from the subject or from his or her legally designated representative should be sought as soon as possible. (37) In order to allow patients to assess possibilities to participate in a clinical trial, and to allow for effective supervision of a clinical trial by the Member State concerned, the start of the clinical trial, the end of the recruitment of subjects for the clinical trial and the end of the clinical trial should be notified. In accordance with international standards, the results of the clinical trial should be reported within one year from the end of the clinical trial.

(38) The date of the first act of recruitment of a potential subject is the date on which the first act of the recruitment strategy described in the protocol was performed, e. g. the date of a contact with a potential subject or the date of the publication of an advertisement for a particular clinical trial.

(39) The sponsor should submit a summary of the results of the clinical trial together with a summary that is understandable to a layperson, and the clinical study report, where applicable, within the defined timelines. Where it is not possible to submit the summary of the results within the defined timelines for scientific

reasons, for example when the clinical trial is still ongoing in third countries and data from that part of the trial are not available, which makes a statistical analysis not relevant, the sponsor should justify this in the protocol and specify when the results are going to be submitted.

(40) In order for the sponsor to assess all potentially relevant safety information, the investigator should, as a rule, report to him all serious adverse events.

(41) The sponsor should assess the information received from the investigator, and report safety information on serious adverse events which are suspected unexpected serious adverse reactions to the European Medicines Agency ('the Agency').

(42) The Agency should forward that information to the Member States for them to assess it.

(43) The members of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) have agreed on a detailed set of guidelines on good clinical practice which is an internationally accepted standard for designing, conducting, recording and reporting clinical trials, consistent with principles that have their origin in the World Medical Association's Declaration of Helsinki. When designing, conducting, recording and reporting clinical trials, detailed questions may arise as to the appropriate quality standard. In such a case, the ICH guidelines on good clinical practice should be taken appropriately into account for the application of the rules set out in this Regulation, provided that there is no other specific guidance issued by the Commission and that those guidelines are compatible with this Regulation.

(44) The conduct of a clinical trial should be adequately monitored by the sponsor in order to ensure the reliability and robustness of the results. Monitoring may also contribute to subject safety, taking into account the characteristics of the clinical trial and respect for fundamental rights of subjects. When establishing the extent of monitoring, the characteristics of the clinical trial should be taken into account.

(45) The individuals involved in conducting a clinical trial, in particular investigators and other healthcare professionals, should be sufficiently qualified to perform their tasks, and the facilities where a clinical trial is to be conducted should be suitable for that clinical trial.

(46) In order to ensure subject safety and the reliability and robustness of data from clinical trials, it is appropriate to provide that there should be arrangements for traceability, storage, return and destruction of investigational medicinal products, depending on the nature of the clinical trial. For the same reasons, there should also be such arrangements for unauthorised auxiliary medicinal products.

(47) During a clinical trial, a sponsor may become aware of serious breaches of the rules for the conduct of that clinical trial. This should be reported to the Member States concerned in order for action to be taken by those Member States, where necessary.

(48) Apart from the reporting of suspected unexpected serious adverse reactions, there may be other events which are relevant in terms of benefit-risk balance and which should be reported in a timely manner to the Member States concerned. It is important for subject safety that, in addition to serious adverse events and reactions, all unexpected events that might materially influence the benefit-risk assessment of the medicinal product or that would lead to changes in the administration of a medicinal product or in overall conduct of a clinical trial are notified to the Member States concerned. Examples of such unexpected events include an increase in the rate of occurrence of expected serious adverse reactions which may be clinically important, a significant hazard to the patient population, such as lack of efficacy of a medicinal product, or a major safety finding from a newly completed animal study (such as carcinogenicity).

(49) Where unexpected events require an urgent modification of a clinical trial, it should be possible for the sponsor and the investigator to take urgent safety measures without awaiting prior authorisation. If such measures constitute a temporary halt of the clinical trial, the sponsor should apply for a substantial modification before restarting the clinical trial.

(50) In order to ensure compliance of the conduct of a clinical trial with the protocol, and in order for investigators to be informed about the investigational medicinal products they administer, the sponsor should supply the investigators with an investigator's brochure.

(51) The information generated in a clinical trial should be recorded, handled and stored adequately for the purpose of ensuring subject rights and safety, the robustness and reliability of the data generated in the clinical trial, accurate reporting and interpretation, effective monitoring by the sponsor and effective inspection by Member States.

(52) In order to be able to demonstrate compliance with the protocol and with this Regulation, a clinical trial master file, containing relevant documentation to allow effective supervision (monitoring by the sponsor and inspection by Member States), should be kept by the sponsor and by the investigator. The clinical trial master file should be archived appropriately to allow for supervision after the clinical trial has ended.

(53) Where there are problems with respect to the availability of authorised auxiliary medicinal products, unauthorised auxiliary medicinal products may be used in a clinical trial in justified cases. The price of the authorised auxiliary medicinal product should not be considered as having an effect on the availability of such medicinal products.

(54) Medicinal products intended for research and development trials fall outside the scope of Directive 2001/83/EC of the European Parliament and of the Council ([5]). Such medicinal products include medicinal products used in the context of a clinical trial. They should be covered by specific rules taking account of their peculiarities. In establishing these rules, a distinction should be made between investigational medicinal products (the tested product and its reference products, including placebos) and auxiliary medicinal products (medicinal products used in the context of a clinical trial but not as investigational medicinal products), such as medicinal products used for background treatment, challenge agents, rescue medication, or used to assess end-points in a clinical trial. Auxiliary medicinal products should not include concomitant medications, that is medications unrelated to the clinical trial and not relevant for the design of the clinical trial.

(55) In order to ensure subject safety and the reliability and robustness of data generated in a clinical trial, and in order to allow for the distribution of investigational and auxiliary medicinal products to clinical trial sites throughout the Union, rules on the manufacturing and import of both investigational and auxiliary medicinal products should be established. As is already the case for Directive 2001/20/EC, those rules should reflect the existing rules of good manufacturing practices for products covered by Directive 2001/83/EC. In some specific cases, it should be possible to allow deviations from those rules in order to facilitate the conduct of a clinical trial. Therefore, the applicable rules should allow for some flexibility, provided that subject safety, as well as reliability and robustness of the data generated in the clinical trial are not compromised.

(56) The requirement to hold an authorisation for manufacture or import of investigational medicinal products should not apply to the preparation of investigational radiopharmaceuticals from radionuclide generators, kits or radionuclide precursors in accordance with the manufacturer's instructions for use in hospitals, health centres or clinics taking part in the same clinical trial in the same Member State.

(57) Investigational and auxiliary medicinal products should be appropriately labelled in order to ensure subject safety and the reliability and robustness of data generated in clinical trials, and in order to allow for the distribution of those products to clinical trial sites throughout the Union. The rules for labelling should be adapted to the risks to subject safety and the reliability and robustness of data generated in clinical trials. Where the investigational or auxiliary medicinal product have already been placed on the market as an authorised medicinal product in accordance with Directive 2001/83/EC and Regulation (EC) No 726/2004 of the European Parliament and of the Council ([6]), as a general rule no additional labelling should be required for clinical trials that do not involve the blinding of the label. Moreover, there are specific products, such as radiopharmaceuticals used as diagnostic investigational medicinal product, where the general rules on labelling are inappropriate in view of the very controlled setting of the use of radiopharmaceuticals in clinical trials.

(58) In order to ensure clear responsibilities, the concept of a ‘sponsor’ of a clinical trial, in line with international guidelines, was introduced by Directive 2001/20/EC. This concept should be upheld.

(59) In practice, there may be loose, informal networks of researchers or research institutions which jointly conduct a clinical trial. Those networks should be able to be co-sponsors of a clinical trial. In order not to weaken the concept of responsibility in a clinical trial, where a clinical trial has several sponsors, they should all be subject to the obligations of a sponsor under this Regulation. However, the co-sponsors should be able to split up the responsibilities of the sponsor by contractual agreement.

(60) In order to ensure that enforcement action may be taken by Member States and that legal proceedings may be brought in appropriate cases, it is appropriate to provide that sponsors that are not established in the Union should be represented by a legal representative in the Union. However in view of the divergent approaches of the Member States as regards civil and criminal liability, it is appropriate to leave to each Member State concerned, as regards its territory, the choice as to whether or not to require such a legal representative, provided that at least a contact person is established in the Union.

(61) Where, in the course of a clinical trial, damage caused to the subject leads to the civil or criminal liability of the investigator or the sponsor, the conditions for liability in such cases, including issues of causality and the level of damages and sanctions, should remain governed by national law.

(62) In clinical trials compensation should be ensured for damages successfully claimed in accordance with the applicable laws. Therefore Member States should ensure that systems for compensation for damages suffered by a subject are in place which are appropriate to the nature and the extent of the risk.

(63) The Member State concerned should be given the power to revoke the authorisation of a clinical trial, suspend a clinical trial or require the sponsor to modify a clinical trial.

(64) In order to ensure compliance with this Regulation, Member States should be able to conduct inspections and should have adequate inspection capacities.

(65) The Commission should be able to control whether Member States correctly supervise compliance with this Regulation. Moreover, the Commission should be able to control whether regulatory systems of third

[5] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67).

[6] Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L 136, 30.4.2004, p. 1.)

countries ensure compliance with the specific provisions of this Regulation and Directive 2001/83/EC concerning clinical trials conducted in third countries.

(66) In order to streamline and facilitate the flow of information between sponsors and Member States as well as between Member States, the Agency should, in collaboration with Member States and the Commission, set up and maintain an EU database, accessed through an EU portal.

(67) In order to ensure a sufficient level of transparency in the clinical trials, the EU database should contain all relevant information as regards the clinical trial submitted through the EU portal. The EU database should be publicly accessible and data should be presented in an easily searchable format, with related data and documents linked together by the EU trial number and with hyperlinks, for example linking together the summary, the layperson's summary, the protocol and the clinical study report of one clinical trial, as well as linking to data from other clinical trials which used the same investigational medicinal product. All clinical trials should be registered in the EU database prior to being started. As a rule, the start and end dates of the recruitment of subjects should also be published in the EU database. No personal data of data subjects participating in a clinical trial should be recorded in the EU database. The information in the EU database should be public, unless specific reasons require that a piece of information should not be published, in order to protect the right of the individual to private life and the right to the protection of personal data, recognised by Articles 7 and 8 of the Charter. Publicly available information contained in the EU database should contribute to protecting public health and fostering the innovation capacity of European medical research, while recognising the legitimate economic interests of sponsors.

(68) For the purposes of this Regulation, in general the data included in a clinical study report should not be considered commercially confidential once a marketing authorisation has been granted, the procedure for granting 27.5.2014 L 158/8 Official Journal of the European Union EN the marketing authorisation has been completed, the application for marketing authorisation has been withdrawn. In addition, the main characteristics of a clinical trial, the conclusion on Part I of the assessment report for the authorisation of a clinical trial, the decision on the authorisation of a clinical trial, the substantial modification of a clinical trial, and the clinical trial results including reasons for temporary halt and early termination, in general, should not be considered confidential.

(69) Within a Member State, there may be several bodies involved in the authorisation of clinical trials. In order to allow for effective and efficient cooperation between Member States, each Member State should designate one contact point.

(70) The authorisation procedure set out in this Regulation is largely controlled by Member States. Nevertheless, the Commission and the Agency should support the good functioning of that procedure, in accordance with this Regulation.

(71) In order to carry out the activities provided for in this Regulation, Member States should be allowed to levy fees. However, Member States should not require multiple payments to different bodies involved in the assessment, in a given Member State, of an application for authorisation of a clinical trial.

(72) In order to ensure uniform conditions for the implementation of this Regulation, implementing powers should be conferred on the Commission in respect of the establishment and modification of rules on cooperation between the Member States when assessing the information provided by the sponsor on the EudraVigilance database and the specification of detailed arrangements for inspection procedures. Those powers should be exercised in accordance with Regulation (EU) No 182/2011 of the European Parliament and of the Council ([7]).

(73) In order to supplement or amend certain non-essential elements of this Regulation, the power to adopt acts in accordance with Article 290 of the Treaty on the Functioning of the European Union (TFEU) should be delegated to the Commission in respect of: the amendment of Annexes I, II, IV and V to this Regulation in order to adapt them to technical progress or to take account of international regulatory developments in which the Union or the Member States are involved, in the field of clinical trials; the amendment of Annex III in order to improve the information on the safety of medicinal products, to adapt technical requirements to technical progress or to take account of international regulatory developments in the field of safety requirements in clinical trials endorsed by bodies in which the Union or the Member States participate; the specification of the principles and guidelines of good manufacturing practice and the detailed arrangements for inspection for ensuring the quality of investigational medicinal products; the amendment of Annex VI in order to ensure subject safety and the reliability and robustness of data generated in a clinical trial or to take account of technical progress. It is of particular importance that the Commission carry out appropriate consultations during its preparatory work, including at expert level. The Commission, when preparing and drawing-up delegated acts, should ensure a simultaneous, timely and appropriate transmission of relevant documents to the European Parliament and to the Council.

(74) Directive 2001/83/EC provides that that Directive does not affect the application of national legislation prohibiting or restricting the sale, supply or use of medicinal products as abortifacients. Directive 2001/83/EC provides that national legislation prohibiting or restricting the use of any specific type of human or animal cells is not, in principle, affected by either that Directive or any of the Regulations referred to therein. Likewise, this Regulation should not affect national law prohibiting or restricting the use of any

[7] Regulation (EU) No 182/2011 of the European Parliament and of the Council of 16 February 2011 laying down the rules and general principles concerning mechanisms for control by Member States of the Commission's exercise of implementing powers (OJ L 55, 28.2.2011, p. 13)

specific type of human or animal cells, or the sale, supply or use of medicinal products used as abortifacients. In addition, this Regulation should not affect national law prohibiting or restricting the sale, supply or use of medicinal products containing narcotic substances within the meaning of the relevant international conventions in force such as the Single Convention on Narcotic Drugs of 1961 of the United Nations. Member States should communicate those national provisions to the Commission.

(75) Directive 2001/20/EC provides that no gene therapy trials may be carried out which result in modifications to the subject's germ line genetic identity. It is appropriate to maintain that provision.

(76) Directive 95/46/EC of the European Parliament and of the Council ([8]) applies to the processing of personal data carried out in the Member States within the framework of this Regulation, under the supervision of the Member States competent authorities, in particular the public independent authorities designated by the Member States and Regulation (EC) No 45/2001 of the European Parliament and of the Council ([9]) applies to the processing of personal data carried out by the Commission and the Agency within the framework of this Regulation, under the supervision of the European Data Protection Supervisor. Those instruments strengthen personal data protection rights, encompassing the right to access, rectification and withdrawal, as well as specify the situations when restriction on those rights may be imposed. With a view to respecting those rights, while safeguarding the robustness and reliability of data from clinical trials used for scientific purposes and the safety of subjects participating in clinical trials, it is appropriate to provide that, without prejudice to Directive 95/46/EC, the withdrawal of informed consent should not affect the results of activities already carried out, such as the storage and use of data obtained on the basis of informed consent before withdrawal.

(77) Subjects should not have to pay for investigational medicinal products, auxiliary medicinal products, medical devices used for their administration and procedures specifically required by the protocol, unless the law of the Member State concerned provides otherwise.

(78) The authorisation procedure set out in this Regulation should apply as soon as possible, in order for sponsors to reap the benefits of a streamlined authorisation procedure. However, in view of the importance of the extensive IT functionalities required for the authorisation procedure, it is appropriate to provide that this Regulation should only become applicable once it has been verified that the EU portal and the EU database are fully functional.

(79) Directive 2001/20/EC should be repealed to ensure that only one set of rules applies to the conduct of clinical trials in the Union. In order to facilitate the transition to the rules set out in this Regulation, sponsors should be allowed to start and conduct a clinical trial in accordance with Directive 2001/20/EC during a transitional period.

(80) This Regulation is in line with the major international guidance documents on clinical trials, such as the 2008 version of the World Medical Association's Declaration of Helsinki and good clinical practice, which has its origins in the Declaration of Helsinki.

(81) As regards Directive 2001/20/EC, experience also shows that a large proportion of clinical trials are conducted by non-commercial sponsors. Non-commercial sponsors frequently rely on funding which comes partly or entirely from public funds or charities. In order to maximise the valuable contribution of such non-commercial sponsors and to further stimulate their research but without compromising the quality of clinical trials, measures should be taken by Member States to encourage clinical trials conducted by those sponsors.

(82) This Regulation is based on the double legal basis of Articles 114 and 168(4)(c) TFEU. It aims at achieving an internal market as regards clinical trials and medicinal products for human use, taking as a base a high level of protection of health. At the same time, this Regulation sets high standards of quality and safety for medicinal products in order to meet common safety concerns as regards these products. Both objectives are being pursued simultaneously. These two objectives are inseparably linked and one is not secondary to another. Regarding Article 114 TFEU, this Regulation harmonises the rules for the conduct of clinical trials in the Union, therefore ensuring the functioning of the internal market in view of the conduct of a clinical trial in several Member States, the acceptability throughout the Union of data generated in a clinical trial and submitted in the application for the authorisation of another clinical trial or of the placing on the market of a medicinal product, and the free movement of medicinal products used in the context of a clinical trial. Regarding Article 168(4)(c) TFEU, this Regulation sets high standards of quality and safety for medicinal products by ensuring that data generated in clinical trials are reliable and robust, thus ensuring that treatments and medicines which are intended to be an improvement of a treatment of patients build on reliable and robust data. Moreover, this Regulation sets high standards of quality and safety of medicinal products used in the context of a clinical trial, thus ensuring the safety of subjects in a clinical trial.

(83) This Regulation respects the fundamental rights and observes the principles recognised in particular by the Charter and notably human dignity, the integrity of the person, the rights of the child, respect for private and family life, the protection of personal data and the freedom of art and science. This Regulation should be applied by the Member States in accordance with those rights and principles.

---

[8] Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data (OJ L 281, 23.11.1995, p. 31).

[9] Regulation (EC) No 45/2001 of the European Parliament and of the Council of 18 December 2000 on the protection of individuals with regard to the processing of personal data by the Community institutions and bodies and on the free movement of such data (OJ L 8, 12.1.2001, p. 1).

(84) The European Data Protection Supervisor has given an opinion ([10]) pursuant to Article 28(2) of Regulation (EC) No 45/2001.

(85) Since the objective of this Regulation, namely to ensure that, throughout the Union, clinical trial data are reliable and robust while ensuring respect for the rights, safety, dignity and well-being of subjects, cannot be sufficiently achieved by the Member States but can rather, by reason of its scale, be better achieved at Union level, the Union may adopt measures, in accordance with the principle of subsidiarity as set out in Article 5 of the Treaty on European Union. In accordance with the principle of proportionality, as set out in that Article, this Regulation does not go beyond what is necessary in order to achieve that objective,

HAVE ADOPTED THIS REGULATION:

CHAPTER I

GENERAL PROVISIONS

Article 1

Scope

This Regulation applies to all clinical trials conducted in the Union.

It does not apply to non-interventional studies.

Article 2

Definitions

1. For the purposes of this Regulation, the definitions of 'medicinal product', 'radiopharmaceutical', 'adverse reaction', 'serious adverse reaction', 'immediate packaging' and 'outer packaging' set out in points (2), (6), (11), (12), (23) and (24), respectively, of Article 1 of Directive 2001/83/EC apply.

2. For the purposes of this Regulation, the following definitions also apply:

(1) 'Clinical study' means any investigation in relation to humans intended:

(a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products;
(b) to identify any adverse reactions to one or more medicinal products; or

(c) to study the absorption, distribution, metabolism and excretion of one or more medicinal products; with the objective of ascertaining the safety and/or efficacy of those medicinal products;

(2) 'Clinical trial' means a clinical study which fulfils any of the following conditions:

(a) the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the Member State concerned;

(b) the decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study; or

(c) diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects.

(3) 'Low-intervention clinical trial' means a clinical trial which fulfils all of the following conditions:

(a) the investigational medicinal products, excluding placebos, are authorised;

(b) according to the protocol of the clinical trial,

(i)the investigational medicinal products are used in accordance with the terms of the marketing authorisation; or

(ii) the use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned; and

(c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned;

(4) 'Non-interventional study' means a clinical study other than a clinical trial;

[10] JO C 253, 3.9.2013, p. 10.

(5) ‘Investigational medicinal product’ means a medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial;

(6) ‘Normal clinical practice’ means the treatment regime typically followed to treat, prevent, or diagnose a disease or a disorder;

(7) ‘Advanced therapy investigational medicinal product’ means an investigational medicinal product which is an advanced therapy medicinal product as defined in point (a) of Article 2(1) of Regulation (EC) No 1394/2007 of the European Parliament and of the Council ([11]);

(8) ‘Auxiliary medicinal product’ means a medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product;

(9) ‘Authorised investigational medicinal product’ means a medicinal product authorised in accordance with Regulation (EC) No 726/2004 or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product, which is used as an investigational medicinal product;

(10) ‘Authorised auxiliary medicinal product’ means a medicinal product authorised in accordance with Regulation (EC) No 726/2004, or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product, which is used as an auxiliary medicinal product;

(11) ‘Ethics committee’ means an independent body established in a Member State in accordance with the law of that Member State and empowered to give opinions for the purposes of this Regulation, taking into account the views of laypersons, in particular patients or patients' organisations;

(12) ‘Member State concerned’ means the Member State where an application for authorisation of a clinical trial or of a substantial modification has been submitted under Chapters II or III of this Regulation respectively;

(13) ‘Substantial modification’ means any change to any aspect of the clinical trial which is made after notification of a decision referred to in Articles 8, 14, 19, 20 or 23 and which is likely to have a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the clinical trial;

(14) ‘Sponsor’ means an individual, company, institution or organisation which takes responsibility for the initiation, for the management and for setting up the financing of the clinical trial;

(15) ‘Investigator’ means an individual responsible for the conduct of a clinical trial at a clinical trial site;

(16) ‘Principal investigator’ means an investigator who is the responsible leader of a team of investigators who conduct a clinical trial at a clinical trial site;

(17) ‘Subject’ means an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control;

(18) ‘Minor’ means a subject who is, according to the law of the Member State concerned, under the age of legal competence to give informed consent;

(19) ‘Incapacitated subject’ means a subject who is, for reasons other than the age of legal competence to give informed consent, incapable of giving informed consent according to the law of the Member State concerned;

(20) ‘Legally designated representative’ means a natural or legal person, authority or body which, according to the law of the Member State concerned, is empowered to give informed consent on behalf of a subject who is an incapacitated subject or a minor;

(21) ‘Informed consent’ means a subject's free and voluntary expression of his or her willingness to participate in a particular clinical trial, after having been informed of all aspects of the clinical trial that are relevant to the subject's decision to participate or, in case of minors and of incapacitated subjects, an authorisation or agreement from their legally designated representative to include them in the clinical trial;

(22) ‘Protocol’ means a document that describes the objectives, design, methodology, statistical considerations and organisation of a clinical trial. The term ‘protocol’ encompasses successive versions of the protocol and protocol modifications;

(23) ‘Investigator's brochure’ means a compilation of the clinical and non-clinical data on the investigational medicinal product or products which are relevant to the study of the product or products in humans;

(24) ‘Manufacturing’ means total and partial manufacture, as well as the various processes of dividing up, packaging and labelling (including blinding);

[11] Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (OJ L 324, 10.12.2007, p. 121).

(25) ‘Start of a clinical trial’ means the first act of recruitment of a potential subject for a specific clinical trial, unless defined differently in the protocol;

(26) ‘End of a clinical trial’ means the last visit of the last subject, or at a later point in time as defined in the protocol;

(27) ‘Early termination of a clinical trial’ means the premature end of a clinical trial due to any reason before the conditions specified in the protocol are complied with;

(28) ‘Temporary halt of a clinical trial’ means an interruption not provided in the protocol of the conduct of a clinical trial by the sponsor with the intention of the sponsor to resume it;

(29) ‘Suspension of a clinical trial’ means interruption of the conduct of a clinical trial by a Member State;

(30) ‘Good clinical practice’ means a set of detailed ethical and scientific quality requirements for designing, conducting, performing, monitoring, auditing, recording, analysing and reporting clinical trials ensuring that the rights, safety and well-being of subjects are protected, and that the data generated in the clinical trial are reliable and robust;

(31) ‘Inspection’ means the act by a competent authority of conducting an official review of documents, facilities, records, quality assurance arrangements, and any other resources that are deemed by the competent authority to be related to the clinical trial and that may be located at the clinical trial site, at the sponsor's and/or contract research organisation's facilities, or at other establishments which the competent authority sees fit to inspect; 27.5.2014 L 158/13 Official Journal of the European Union EN

(32) ‘Adverse event’ means any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment;

(33) ‘Serious adverse event’ means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death;

(34) ‘Unexpected serious adverse reaction’ means a serious adverse reaction, the nature, severity or outcome of which is not consistent with the reference safety information;

(35) ‘Clinical study report’ means a report on the clinical trial presented in an easily searchable format, prepared in accordance with Annex I, Part I, Module 5 of Directive 2001/83/EC and accompanying an application for marketing authorisation.

3. For the purposes of this Regulation, a subject who falls under the definition of both ‘minor’ and ‘incapacitated subject’ shall be deemed to be an incapacitated subject.

Article 3

General principle

A clinical trial may be conducted only if:

(a) the rights, safety, dignity and well-being of subjects are protected and prevail over all other interests; and
(b) it is designed to generate reliable and robust data.

CHAPTER II

AUTHORISATION PROCEDURE FOR A CLINICAL TRIAL

Article 4

Prior authorisation

A clinical trial shall be subject to scientific and ethical review and shall be authorised in accordance with this Regulation.

The ethical review shall be performed by an ethics committee in accordance with the law of the Member State concerned. The review by the ethics committee may encompass aspects addressed in Part I of the assessment report for the authorisation of a clinical trial as referred to in Article 6 and in Part II of that assessment report as referred to in Article 7 as appropriate for each Member State concerned.
Member States shall ensure that the timelines and procedures for the review by the ethics committees are compatible with the timelines and procedures set out in this Regulation for the assessment of the application for authorisation of a clinical trial.

Article 5

Submission of an application

(1) In order to obtain an authorisation, the sponsor shall submit an application dossier to the intended Member States concerned through the portal referred to in Article 80 (the 'EU portal').

The sponsor shall propose one of the Member States concerned as reporting Member State.

If a Member State concerned other than the proposed reporting Member State is willing to be the reporting Member State or where the proposed reporting Member State does not wish to be the reporting Member State, this shall be notified through the EU portal to all Member States concerned not later than three days after the application dossier is submitted.

Member State, that Member State shall be the reporting Member State.

If there is no Member State concerned willing to be the reporting Member State or if there is more than one Member State concerned willing to be the reporting Member State, the reporting Member State shall be selected by agreement among the Member States concerned taking into account the recommendations referred to in point (c) of Article 85(2).
If there is no agreement among the Member States concerned, the proposed reporting Member State shall be the reporting Member State.

The reporting Member State shall notify the sponsor and the other Member States concerned that it is the reporting Member State, through the EU portal, within six days from the submission of the application dossier.

(2) The sponsor shall, when applying for a low-intervention clinical trial, where the investigational medicinal product is not used in accordance with the terms of the marketing authorisation but the use of that product is evidence-based and supported by published scientific evidence on the safety and efficacy of that product, propose one of the Member States concerned where the use is evidence-based, as reporting Member State.

(3) Within 10 days from the submission of the application dossier, the reporting Member State shall validate the application taking into account considerations expressed by the other Member States concerned and notify the sponsor, through the EU portal, of the following:

(a) whether the clinical trial applied for falls within the scope of this Regulation;

(b) whether the application dossier is complete in accordance with Annex I;

Member States concerned may communicate to the reporting Member State any considerations relevant to the validation of the application within seven days from the submission of the application dossier.

(4) Where the reporting Member State has not notified the sponsor within the period referred to in the first subparagraph of paragraph 3, the clinical trial applied for shall be deemed to fall within the scope of this Regulation and the application dossier shall be considered complete.

(5) Where the reporting Member State, taking into account considerations expressed by the other Member States concerned, finds that the application dossier is not complete, or that the clinical trial applied for does not fall within the scope of this Regulation, it shall inform the sponsor thereof through the EU portal and shall set a maximum of 10 days for the sponsor to comment on the application or to complete the application dossier through the EU portal.

Within five days from receipt of the comments or the completed application dossier, the reporting Member State shall notify the sponsor as to whether or not the application complies with the requirements set out in points (a) and (b) of the first subparagraph of paragraph 3.

Where the reporting Member State has not notified the sponsor within the period referred to in the second subparagraph, the clinical trial applied for shall be deemed to fall within the scope of this Regulation and the application dossier shall be considered complete.

Where the sponsor has not provided comments or completed the application dossier within the period referred to in the first subparagraph, the application shall be deemed to have lapsed in all Member States concerned.

(6) For the purposes of this Chapter, the date on which the sponsor is notified in accordance with paragraph 3 or 5 shall be the validation date of the application. Where the sponsor is not notified, the validation date shall be the last day of the respective periods referred to in paragraphs 3 and 5.

Article 6

Assessment report – Aspects covered by Part I

(1) The reporting Member State shall assess the application with regard to the following aspects:

(a) Whether the clinical trial is a low-intervention clinical trial, where claimed by the sponsor;
(b) Compliance with Chapter V with respect to the following:

(i) The anticipated therapeutic and public health benefits taking account of all of the following:

- the characteristics of and knowledge about the investigational medicinal products;
- the relevance of the clinical trial, including whether the groups of subjects participating in the clinical trial represent the population to be treated, or if not, the explanation and justification provided in accordance with point (y) of paragraph 17 of Annex I to this Regulation; the current state of scientific knowledge; whether the clinical trial has been recommended or imposed by regulatory authorities in charge of the assessment and authorisation of the placing on the market of medicinal products; and, where applicable, any opinion formulated by the Paediatric Committee on a paediatric investigation plan in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council ([12]);
- the reliability and robustness of the data generated in the clinical trial, taking account of statistical approaches, design of the clinical trial and methodology, including sample size and randomisation, comparator and endpoints;

(ii) The risks and inconveniences for the subject, taking account of all of the following:

- the characteristics of and knowledge about the investigational medicinal products and the auxiliary medicinal products;
- the characteristics of the intervention compared to normal clinical practice;
- the safety measures, including provisions for risk minimisation measures, monitoring, safety reporting, and the safety plan;
- the risk to subject health posed by the medical condition for which the investigational medicinal product is being investigated;

(c) Compliance with the requirements concerning the manufacturing and import of investigational medicinal products and auxiliary medicinal products set out in Chapter IX;
(d) Compliance with the labelling requirements set out in Chapter X;
(e) The completeness and adequateness of the investigator's brochure.

(2) The reporting Member State shall draw up an assessment report. The assessment of the aspects referred to in paragraph 1 shall constitute Part I of the assessment report.

(3) The assessment report shall contain one of the following conclusions concerning the aspects addressed in Part I of the assessment report:

(a) the conduct of the clinical trial is acceptable in view of the requirements set out in this Regulation;
(b) the conduct of the clinical trial is acceptable in view of the requirements set out in this Regulation, but subject to compliance with specific conditions which shall be specifically listed in that conclusion; or
(c) the conduct of the clinical trial is not acceptable in view of the requirements set out in this Regulation.

(4) The reporting Member State shall submit, through the EU portal, the final Part I of the assessment report, including its conclusion, to the sponsor and to the other Member States concerned within 45 days from the validation date.

(5) For clinical trials involving more than one Member State, the assessment process shall include three phases:

(a) an initial assessment phase performed by the reporting Member State within 26 days from the validation date;
(b) a coordinated review phase performed within 12 days from the end of the initial assessment phase involving all Member States concerned;
(c) a consolidation phase performed by the reporting Member State within seven days from the end of coordinated review phase.

During the initial assessment phase, the reporting Member State shall develop a draft Part I of the assessment report and circulate it to all other Member States concerned.

During the coordinated review phase, all Member States concerned shall jointly review the application based on the draft Part I of the assessment report and shall share any considerations relevant to the application.

During the consolidation phase, the reporting Member State shall take due account of the considerations of the other Member States concerned when finalising Part I of the assessment report and shall record how all such

[12] Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 (OJ L 378, 27.11.2006, p. 1).

considerations have been dealt with. The reporting Member State shall submit the final Part I of the assessment report to the sponsor and all other Member States concerned within the period referred to in paragraph 4.

(6) For the purposes of this Chapter, the date on which the final Part I of the assessment report is submitted by the reporting Member State to the sponsor and to the other Member States concerned shall be the reporting date.

(7) The reporting Member State may also extend the period referred to in paragraph 4 by a further 50 days for clinical trials involving an advanced therapy investigational medicinal products or a medicinal product as defined in point 1 of the Annex to Regulation (EC) No 726/2004, for the purpose of consulting with experts. In such case, the periods referred to in paragraphs 5 and 8 of this Article shall apply *mutatis mutandis*.

(8) Between the validation date and the reporting date, only the reporting Member State may request additional information from the sponsor, taking into account the considerations referred to in paragraph 5.

For the purpose of obtaining and reviewing this additional information from the sponsor in accordance with the third and fourth subparagraph, the reporting Member State may extend the period referred to in paragraph 4 by a maximum of 31 days.

The sponsor shall submit the requested additional information within the period set by the reporting Member State which shall not exceed 12 days from the receipt of the request.

Upon receipt of the additional information, the Member States concerned shall jointly review any additional information provided by the sponsor together with the original application and shall share any considerations relevant to the application. The coordinated review shall be performed within a maximum of 12 days of the receipt of the additional information and the further consolidation shall be performed within a maximum of seven days of the end of coordinated review. When finalising Part I of the assessment report, the reporting Member State shall take due account of the considerations of the Member States concerned and shall record how all such considerations have been dealt with.

Where the sponsor does not provide additional information within the period set by the reporting Member State in accordance with the third subparagraph, the application shall be deemed to have lapsed in all Member States concerned.

The request for additional information and the additional information shall be submitted through the EU portal.

Article 7

Assessment report – Aspects covered by Part II

(1) Each Member State concerned shall assess, for its own territory, the application with respect to the following aspects:

(a) compliance with the requirements for informed consent as set out in Chapter V;
(b) compliance of the arrangements for rewarding or compensating subjects with the requirements set out in Chapter V and investigators;
(c) compliance of the arrangements for recruitment of subjects with the requirements set out in Chapter V;
(d) compliance with Directive 95/46/EC;
(e) compliance with Article 49;
(f) compliance with Article 50;
(g) compliance with Article 76;
(h) compliance with the applicable rules for the collection, storage and future use of biological samples of the subject.

The assessment of the aspects referred to in the first subparagraph shall constitute Part II of the assessment report.

(2) Each Member State concerned shall complete its assessment within 45 days from the validation date and submit, through the EU portal, Part II of the assessment report, including its conclusion, to the sponsor.

Each Member State concerned may request, with justified reasons, additional information from the sponsor regarding the aspects referred to in paragraph 1 only within the period referred to in the first subparagraph.

(3) For the purpose of obtaining and reviewing the additional information referred to in the second subparagraph of paragraph 2 from the sponsor in accordance with the second and third subparagraph, the Member State concerned may extend the period referred to in the first subparagraph of paragraph 2 by a maximum of 31 days.

The sponsor shall submit the requested additional information within the period set by the Member State concerned which shall not exceed 12 days from the receipt of the request.

Upon receipt of the additional information, the Member State concerned shall complete its assessment within a maximum of 19 days.

Where the sponsor does not provide additional information within the period set by the Member State concerned in accordance with the second subparagraph, the application shall be deemed to have lapsed in that Member State concerned.

The request for additional information and the additional information shall be submitted through the EU portal.

Article 8

Decision on the clinical trial

(1) Each Member State concerned shall notify the sponsor through the EU portal as to whether the clinical trial is authorised, whether it is authorised subject to conditions, or whether authorisation is refused.
Notification shall be done by way of one single decision within five days from the reporting date or from the last day of the assessment referred to in Article 7, whichever is later.
An authorisation of a clinical trial subject to conditions is restricted to conditions which by their nature cannot be fulfilled at the time of that authorisation.

(2) Where the conclusion of the reporting Member State as regards Part I of the assessment report is that the conduct of the clinical trial is acceptable or acceptable subject to compliance with specific conditions, that conclusion shall be deemed to be the conclusion of the Member State concerned.

(3) Notwithstanding the first subparagraph, a Member State concerned may disagree with the conclusion of the reporting Member State as regards Part I of the assessment report only on the following grounds:
(a) when it considers that participation in the clinical trial would lead to a subject receiving an inferior treatment than in normal clinical practice in the Member State concerned;
(b) infringement of its national law as referred to in Article 90;
(c) considerations as regards subject safety and data reliability and robustness submitted under paragraph 5 or 8 of Article 6.
Where a Member State concerned disagrees with the conclusion on the basis of the second subparagraph, it shall communicate its disagreement, together with a detailed justification, through the EU portal, to the Commission, to all Member States, and to the sponsor.

(3) Where, regarding the aspects covered by Part I of the assessment report, the clinical trial is acceptable or acceptable subject to compliance with specific conditions, the Member State concerned shall include in its decision its conclusion on Part II of the assessment report.

(4) A Member State concerned shall refuse to authorise a clinical trial if it disagrees with the conclusion of the reporting Member State as regards Part I of the assessment report on any of the grounds referred to in the second subparagraph of paragraph 2, or if it finds, on duly justified grounds, that the aspects addressed in Part II of the assessment report are not complied with, or where an ethics committee has issued a negative opinion which in accordance with the law of the Member State concerned is valid for that entire Member State. That Member State shall provide for an appeal procedure in respect of such refusal.

(5) Where the conclusion of the reporting Member State as regards Part I of the assessment report is that the clinical trial is not acceptable, that conclusion shall be deemed to be the conclusion of all Member States concerned.

(6) Where the Member State concerned has not notified the sponsor of its decision within the relevant periods referred to in paragraph 1, the conclusion on Part I of the assessment report shall be deemed to be the decision of the Member State concerned on the application for authorisation of the clinical trial.

(7) The Member States concerned shall not request additional information regarding the aspects addressed in Part I of the assessment report from the sponsor after the reporting date.

(8) For the purposes of this Chapter, the notification date shall be the date on which the decision referred to in paragraph 1 is notified to the sponsor. Where the sponsor has not been notified in accordance with paragraph 1, the notification date shall be deemed to be the last day of the period provided for in par.1.

(9) If no subject has been included in the clinical trial in a Member State concerned within two years from the notification date of the authorisation, the authorisation shall expire in that Member State concerned unless an extension, on request of the sponsor, has been approved following the procedure set out in Chapter III.

Article 9

Persons assessing the application

(1) Member States shall ensure that the persons validating and assessing the application do not have conflicts of interest, are independent of the sponsor, of the clinical trial site and the investigators involved and of persons financing the clinical trial, as well as free of any other undue influence.

In order to guarantee independence and transparency, the Member States shall ensure that persons admitting and assessing the application as regards the aspects addressed in Parts I and II of the assessment report have no financial or personal interests which could affect their impartiality. These persons shall make an annual declaration of their financial interests.

(2) Member States shall ensure that the assessment is done jointly by a reasonable number of persons who collectively have the necessary qualifications and experience.

(3) At least one layperson shall participate in the assessment.

Article 10

Specific considerations for vulnerable populations

1. Where the subjects are minors, specific consideration shall be given to the assessment of the application for authorisation of a clinical trial on the basis of paediatric expertise or after taking advice on clinical, ethical and psychosocial problems in the field of paediatrics.

2. Where the subjects are incapacitated subjects, specific consideration shall be given to the assessment of the application for authorisation of a clinical trial on the basis of expertise in the relevant disease and the patient population concerned or after taking advice on clinical, ethical and psychosocial questions in the field of the relevant disease and the patient population concerned.

3. Where the subjects are pregnant or breastfeeding women, specific consideration shall be given to the assessment of the application for authorisation of a clinical trial on the basis of expertise in the relevant condition and the population represented by the subject concerned.

4. If according to the protocol a clinical trial provides for the participation of specific groups or subgroups of subjects, where appropriate, specific consideration shall be given to the assessment of the application for authorisation of that clinical trial on the basis of expertise in the population represented by the subjects concerned.

5. In any application for authorisation of a clinical trial referred to in Article 35, specific consideration shall be given to the circumstances of the conduct of the clinical trial.

Article 11

Submission and assessment of applications limited to aspects covered by Part I or Part II of the assessment report

Where the sponsor so requests, the application for authorisation of a clinical trial, its assessment and the conclusion shall be limited to the aspects covered by Part I of the assessment report.

After the notification of the conclusion on the aspects covered by Part I of the assessment report, the sponsor may within two years apply for an authorisation limited to aspects covered by Part II of the assessment report. In that application the sponsor shall declare that he is not aware of any new substantial scientific information that would change the validity of any item submitted in the application on the aspects covered by Part I of the assessment report. In this case, that application shall be assessed in accordance with Article 7 and the Member State concerned shall notify its decision on the clinical trial in accordance with Article 8. In those Member States where the sponsor does not apply for an authorisation limited to aspects covered by Part II of the assessment report within two years, the application on the aspects covered by Part I of the assessment report shall be deemed to have lapsed.

Article 12

Withdrawal

The sponsor may withdraw the application at any time until the reporting date. In such a case, the application may only be withdrawn with respect to all Member States concerned. The reasons for the withdrawal shall be communicated through the EU portal.

Article 13

Resubmission

This Chapter is without prejudice to the possibility for the sponsor to resubmit, following the refusal to grant an authorisation or the withdrawal of an application, an application for authorisation to any intended Member State concerned. That application shall be deemed to be a new application for authorisation of another clinical trial.

Article 14

Subsequent addition of a Member State concerned

(1) Where the sponsor wishes to extend an authorised clinical trial to another Member State ('additional Member State concerned'), the sponsor shall submit an application dossier to that Member State through the EU portal.

The application dossier may be submitted only after the notification date of the initial authorisation decision.

(2) The reporting Member State for the application dossier referred to in paragraph 1 shall be the reporting Member State for the initial authorisation procedure.

(3) The additional Member State concerned shall notify the sponsor through the EU portal, within 52 days from the date of submission of the application dossier referred to in paragraph 1, by way of one single decision as to whether the clinical trial is authorised, whether it is authorised subject to conditions, or whether the authorisation is refused.

An authorisation of a clinical trial subject to conditions is restricted to conditions which by their nature cannot be fulfilled at the time of that authorisation.

(4) Where the conclusion of the reporting Member State as regards Part I of the assessment report is that the conduct of the clinical trial is acceptable or acceptable subject to compliance with specific conditions, that conclusion shall be deemed to be the conclusion of the additional Member State concerned.

Notwithstanding the first subparagraph, an additional Member State concerned may disagree with the conclusion of the reporting Member State as regards Part I of the assessment report only on the following grounds:

(a) when it considers that participation in the clinical trial would lead to a subject receiving an inferior treatment than in normal clinical practice in the Member State concerned;
(b) infringement of its national law as referred to in Article 90;
(c) considerations as regards subject safety and data reliability and robustness submitted under paragraph 5 or 6.

Where an additional Member State concerned disagrees with the conclusion on the basis of the second subparagraph, it shall communicate its disagreement, together with a detailed justification, through the EU portal, to the Commission, to all Member States, and to the sponsor.

(5) Between the date of submission of the application dossier referred to in paragraph 1 and five days before the expiry of the period referred to in paragraph 3, the additional Member State concerned may communicate to the reporting Member State and the other Member States concerned any considerations relevant to the application through the EU portal.

(6) Between the date of submission of the application dossier referred to in paragraph 1 and the expiry of the period referred to in paragraph 3, only the reporting Member State may request additional information from the sponsor concerning the aspects addressed in Part I of the assessment report, taking into account the considerations referred to in paragraph 5.

For the purpose of obtaining and reviewing this additional information from the sponsor in accordance with the third and fourth subparagraphs, the reporting Member State may extend the period referred to in the first subparagraph of paragraph 3 by a maximum of 31 days.
The sponsor shall submit the requested additional information within the period set by the reporting Member State which shall not exceed 12 days from receipt of the request.

Upon receipt of the additional information, the additional Member State concerned together with all other Member States concerned shall jointly review any additional information provided by the sponsor together with the original application and shall share any considerations relevant to the application. The coordinated review shall be performed within a maximum of 12 days from the receipt of the additional information and the further consolidation shall be performed within a maximum of seven days from the end of the coordinated review. The reporting Member State shall take due account of the considerations of the Member States concerned and shall record how all such considerations have been dealt with.

Where the sponsor does not provide additional information within the period set by the reporting Member State in accordance with the third subparagraph, the application shall be deemed to have lapsed in the additional Member State concerned.

The request for additional information and the additional information shall be submitted through the EU portal.

(7) The additional Member State concerned shall assess, for its territory, the aspects addressed in Part II of the assessment report within the period referred to in paragraph 3 and submit, through the EU portal, Part II of the assessment report, including its conclusion, to the sponsor. Within that period it may request, with justified reasons, additional information from the sponsor regarding aspects addressed in Part II of the assessment report as far as its territory is concerned.

(8) For the purpose of obtaining and reviewing the additional information referred to in paragraph 7 from the sponsor in accordance with the second and third subparagraphs, the additional Member State concerned may extend the period referred to in paragraph 7 by a maximum of 31 days.

The sponsor shall submit the requested additional information within the period set by the additional Member State concerned which shall not exceed 12 days from receipt of the request.

Upon receipt of the additional information, the Member State concerned shall complete its assessment within a maximum of 19 days.

Where the sponsor does not provide additional information within the period set by the additional Member State concerned in accordance with the second subparagraph, the application shall be deemed to have lapsed in the additional Member State concerned.

The request for additional information and the additional information shall be submitted through the EU portal.

(9) Where, regarding the aspects covered by Part I of the assessment report, the conduct of the clinical trial is acceptable or acceptable subject to compliance with specific conditions, the additional Member State concerned shall include in its decision its conclusion on Part II of the assessment report.

(10) The additional Member State concerned shall refuse to authorise the clinical trial if it disagrees with the conclusion of the reporting Member State as regards Part I of the assessment report on any of the grounds referred to in second subparagraph of paragraph 4, or if it finds, on duly justified grounds, that the aspects addressed in Part II of the assessment report are not complied with, or where an ethics committee has issued a negative opinion which, in accordance with the law of the additional Member State concerned, is valid for that entire additional Member State. That additional Member State concerned shall provide for an appeal procedure in respect of such refusal.

(11) Where the additional Member State concerned has not notified the sponsor of its decision within the period referred to in paragraph 3, or in case that period has been extended in accordance with paragraph 6 or 8 where that additional Member State concerned has not notified the sponsor of its decision within the extended period, the conclusion on Part I of the assessment report shall be deemed to be the decision of that additional Member State concerned on the application for authorisation of the clinical trial.

(12) A sponsor shall not submit an application dossier in accordance with this Article where a procedure set out in Chapter III is pending as regards that clinical trial.

CHAPTER III

AUTHORISATION PROCEDURE FOR A SUBSTANTIAL MODIFICATION OF A CLINICAL TRIAL

Article15

General principles

A substantial modification, including the addition of a clinical trial site or the change of a principal investigator in the clinical trial site, may only be implemented if it has been approved in accordance with the procedure set out in this Chapter.

Article 16

Submission of application

In order to obtain an authorisation, the sponsor shall submit an application dossier to the Member States concerned through the EU portal.

Article 17

Validation of an application for the authorisation of a substantial modification of an aspect covered by Part I of the assessment report

(1) The reporting Member State for the authorisation of a substantial modification shall be the reporting Member State for the initial authorisation procedure.

Member States concerned may communicate to the reporting Member State any considerations relevant to the validation of the application of a substantial modification within five days from the submission of the application dossier.

(2) Within six days from the submission of the application dossier, the reporting Member State shall validate the application taking into account considerations expressed by the other Member States concerned and notify the sponsor through the EU portal as to whether:

(a) the substantial modification concerns an aspect covered by Part I of the assessment report; and
(b) the application dossier is complete in accordance with Annex II.

(4) Where the reporting Member State has not notified the sponsor within the period referred to in paragraph 2, the substantial modification applied for shall be deemed to concern an aspect covered by Part I of the assessment report and the application dossier shall be deemed to be complete.

(5) Where the reporting Member State, taking into account considerations expressed by the other Member States concerned, finds that the application does not concern an aspect covered by Part I of the assessment report or that the application dossier is not complete, it shall inform the sponsor thereof through the EU portal and shall set a maximum of 10 days for the sponsor to comment on the application or to complete the application dossier through the EU portal.

Within five days from receipt of the comments or the completed application dossier, the reporting Member State shall notify the sponsor as to whether or not the application complies with the requirements set out in points (a) and (b) of paragraph 2.

Where the reporting Member State has not notified the sponsor within the period referred to in the second subparagraph, the substantial modification applied for shall be deemed to concern an aspect covered by Part I of the assessment report and the application dossier shall be deemed to be complete.

Where the sponsor has not provided comments or completed the application dossier within the period referred to in the first subparagraph, the application shall be deemed to have lapsed in all Member States concerned.

(5) For the purposes of Articles 18, 19 and 22, the date on which the sponsor is notified in accordance with paragraph 2 or 4 shall be the validation date of the application. Where the sponsor is not notified, the validation date shall be the last day of the respective periods referred to in paragraphs 2 and 4.

Article 18

Assessment of a substantial modification of an aspect covered by Part I of the assessment report

(1) The reporting Member State shall assess the application with regard to an aspect covered by Part I of the assessment report, including whether the clinical trial will remain a low-intervention clinical trial after its substantial modification, and draw up an assessment report.

(2) The assessment report shall contain one of the following conclusions concerning the aspects addressed in Part I of the assessment report:

(a) the substantial modification is acceptable in view of the requirements set out in this Regulation;
(b) the substantial modification is acceptable in view of the requirements set out in this Regulation, but subject to compliance with specific conditions which shall be specifically listed in that conclusion; or
(c) the substantial modification is not acceptable in view of the requirements set out in this Regulation.

(3) The reporting Member State shall submit, through the EU portal, the final assessment report including its conclusion, to the sponsor and to the other Member States concerned within 38 days from the validation date. For the purposes of this Article and Articles 19 and 23, the reporting date shall be the date on which the final assessment report is submitted to the sponsor and to the other Member States concerned.
(4) For clinical trials involving more than one Member State the assessment process of substantial modification shall include three phases:

(a) an initial assessment phase performed by the reporting Member State within 19 days from the validation date;
(b) a coordinated review phase performed within 12 days from the end of the initial assessment phase involving all Member States concerned; and
(c) a consolidation phase performed by the reporting Member State within seven days from the end of coordinated review phase.

During the initial assessment phase, the reporting Member State shall develop a draft assessment report and circulate it to all Member States concerned.

During the coordinated review phase, all Member States concerned shall jointly review the application based on the draft assessment report and shall share any considerations relevant to the application.

During the consolidation phase, the reporting Member State shall take due account of the considerations of the other Member States concerned when finalising the assessment report and shall record how all such considerations have been dealt with. The reporting Member State shall submit the final assessment report to the sponsor and all other Member States concerned by the reporting date.

(5) The reporting Member State may extend the period referred to in paragraph 3 by a further 50 days for clinical trials involving an advanced therapy investigational medicinal product or a medicinal product as set out in point 1 of the Annex to Regulation (EC) No 726/2004, for the purpose of consulting with experts. In such case, the periods referred to in paragraphs 4 and 6 of this Article shall apply *mutatis mutandis*.

(6) Between the validation date and the reporting date, only the reporting Member State may request additional information from the sponsor, taking into account the considerations referred to in paragraph 4.

For the purpose of obtaining and reviewing this additional information from the sponsor in accordance with the third and fourth subparagraph, the reporting Member State may extend the period referred to in the first subparagraph of paragraph 3 by a maximum of 31 days.

The sponsor shall submit the requested additional information within the period set by the reporting Member State which shall not exceed 12 days from receipt of the request.

Upon receipt of the additional information, the Member States concerned shall jointly review any additional information provided by the sponsor together with the original application and shall share any considerations relevant to the application. The coordinated review shall be performed within a maximum of 12 days from receipt of the additional information and the further consolidation shall be performed within a maximum of seven days from the end of the coordinated review. When finalising the assessment report, the reporting Member State shall take due account of the considerations of the other Member States concerned and shall record how all such considerations have been dealt with.

Where the sponsor does not provide additional information within the period determined by the reporting Member State in accordance with the third subparagraph, the application shall be deemed to have lapsed in all Member States concerned.
The request for additional information and the additional information shall be submitted through the EU portal.

Article 19

Decision on the substantial modification of an aspect covered by Part I of the assessment report

1. Each Member State concerned shall notify the sponsor through the EU portal as to whether the substantial modification is authorised, whether it is authorised subject to conditions, or whether authorisation is refused.

   Notification shall be done by way of a single decision within five days from the reporting date.

   An authorisation of a substantial modification subject to conditions is restricted to conditions which by their nature cannot be fulfilled at the time of that authorisation.

2. Where the conclusion of the reporting Member State is that the substantial modification is acceptable or acceptable subject to compliance with specific conditions, that conclusion shall be deemed to be the conclusion of the Member State concerned.
   Notwithstanding the first subparagraph, a Member State concerned may disagree with that conclusion of the reporting Member State only on the following grounds:

   (a) when it considers that participation in the clinical trial would lead to a subject receiving an inferior treatment than in normal clinical practice in the Member State concerned;
   (b) infringement of its national law as referred to in Article 90;
   (c) considerations as regards subject safety and data reliability and robustness submitted under paragraph 4 or 6 of Article 18.

   Where the Member State concerned disagrees with the conclusion on the basis of the second subparagraph, it shall communicate its disagreement, together with a detailed justification, through the EU portal, to the Commission, to all Member States and to the sponsor.

   A Member State concerned shall refuse to authorise a substantial modification if it disagrees with the conclusion of the reporting Member State as regards Part I of the assessment report on any of the grounds referred to in the second subparagraph, or where an ethics committee has issued a negative opinion which, in accordance with the law of that Member State concerned, is valid for that entire Member State. That Member State shall provide for an appeal procedure in respect of such refusal.

(3) Where the conclusion of the reporting Member State, as regards the substantial modification of aspects covered by Part I of the assessment report, is that the substantial modification is not acceptable, that conclusion shall be deemed to be the conclusion of all Member States concerned.

(4) Where the Member State concerned has not notified the sponsor of its decision within the period referred to in paragraph 1, the conclusion of the assessment report shall be deemed to be the decision of the Member State concerned on the application for authorisation of the substantial modification.

Article 20

Validation, assessment and decision regarding a substantial modification of an aspect covered by Part II of the assessment report

(1) Within six days from the submission of the application dossier, the Member State concerned shall notify the sponsor through the EU portal of the following:

(a) whether the substantial modification concerns an aspect covered by Part II of the assessment report; and
(b) whether the application dossier is complete in accordance with Annex II.

(2) Where the Member State concerned has not notified the sponsor within the period referred to in paragraph 1, the substantial modification applied for shall be deemed to concern an aspect covered by Part II of the assessment report and the application dossier shall be deemed to be complete.

(3) Where the Member State concerned finds that the substantial modification does not concern an aspect covered by Part II of the assessment report or that the application dossier is not complete, it shall inform the sponsor thereof through the EU portal and shall set a maximum of 10 days for the sponsor to comment on the application or to complete the application dossier through the EU portal.

Within five days from receipt of the comments or the completed application dossier, the reporting Member State shall notify the sponsor as to whether or not the application complies with the requirements set out in points (a) and (b) of paragraph 1.

Where the Member State concerned has not notified the sponsor within the period referred to in the second subparagraph, the substantial modification shall be deemed to concern an aspect covered by Part II of the assessment report and the application dossier shall be deemed to be complete.

Where the sponsor has not provided comments nor completed the application dossier within the period referred to in the first subparagraph, the application shall be deemed to have lapsed in the Member State concerned.

(4) For the purpose of this Article, the date on which the sponsor is notified in accordance with paragraph 1 or 3 shall be the validation date of the application. Where the sponsor is not notified, the validation date shall be the last day of the respective periods referred to in paragraphs 1 and 3.

(5) The Member State concerned shall assess the application and shall submit to the sponsor, through the EU portal, Part II of the assessment report, including its conclusion, and the decision as to whether the substantial modification is authorised, whether it is authorised subject to conditions, or whether authorisation is refused.

Notification shall be done by way of a single decision within 38 days from the validation date.

An authorisation of a substantial modification subject to conditions is restricted to conditions which by their nature cannot be fulfilled at the time of that authorisation.

(6) During the period referred to in the second subparagraph of paragraph 5, the Member State concerned may request, with justified reasons, additional information from the sponsor regarding the substantial modification as far as its territory is concerned.

For the purpose of obtaining and reviewing this additional information from the sponsor, the Member State concerned may extend the period referred to in the second subparagraph of paragraph 5 by a maximum of 31 days.

The sponsor shall submit the requested additional information within the period set by the Member State concerned which shall not exceed 12 days from receipt of the request.

Upon receipt of the additional information, the Member State concerned shall complete its assessment within a maximum of 19 days.

Where the sponsor does not provide additional information within the period set by the Member State concerned in accordance with the third subparagraph, the application shall be deemed to have lapsed in that Member State.

The request for additional information and the additional information shall be submitted through the EU portal.

(7) A Member State concerned shall refuse to authorise a substantial modification if it finds, on duly justified grounds, that the aspects covered by Part II of the assessment report are not complied with or where an ethics committee has issued a negative opinion which, in accordance with the law of that Member State concerned, is valid for that entire Member State. That Member State shall provide for an appeal procedure in respect of such refusal.

(8) Where the Member State concerned has not notified the sponsor of its decision within the periods set out in paragraphs 5 and 6, the substantial modification shall be deemed to be authorised in that Member State.

Article 21

Substantial modification of aspects covered by Parts I and II of the assessment report

(1) Where a substantial modification relates to aspects covered by Parts I and II of the assessment report, the application for authorisation of that substantial modification shall be validated in accordance with Article 17.

(2) The aspects covered by Part I of the assessment report shall be assessed in accordance with Article 18 and the aspects covered by Part II of the assessment report shall be assessed in accordance with Article 22.

Article 22

Assessment of a substantial modification of aspects covered by Parts I and II of the assessment report – Assessment of the aspects covered by Part II of the assessment report

(1) Each Member State concerned shall assess, for its own territory, the aspects of the substantial modification which are covered by Part II of the assessment report and submit, through the EU portal, that report, including its conclusion, to the sponsor within 38 days from the validation date.

(2) During the period referred to in paragraph 1, the Member State concerned may request, with justified reasons, additional information from the sponsor regarding this substantial modification as far as its territory is concerned.

(3) For the purpose of obtaining and reviewing the additional information referred to in paragraph 2 from the sponsor in accordance with the third and fourth subparagraph, the Member State concerned may extend the period referred to paragraph 1 by a maximum of 31 days.

The sponsor shall submit the requested additional information within the period set by the Member State concerned which shall not exceed 12 days from the receipt of the request.

Upon receipt of the additional information, the Member State concerned shall complete its assessment within a maximum of 19 days.

Where the sponsor does not provide the requested additional information within the period set by the Member State concerned in accordance with the second subparagraph, the application shall be deemed to have lapsed in that Member State.

The request for additional information and the additional information shall be submitted through the EU portal.

Article 23

Decision on the substantial modification of aspects covered by Parts I and II of the assessment report

(1) Each Member State concerned shall notify the sponsor through the EU portal as to whether the substantial modification is authorised, whether it is authorised subject to conditions, or whether authorisation is refused.

Notification shall be done by way of a single decision within five days from the reporting date or from the last day of the assessment period referred to in Article 22, whichever is later.

An authorisation of a substantial modification subject to conditions is restricted to conditions which by their nature cannot be fulfilled at the time of that authorisation.

(2) Where the conclusion of the reporting Member State is that the substantial modification of aspects covered by Part I of the assessment report is acceptable or acceptable subject to compliance with specific conditions, that conclusion shall be deemed to be the conclusion of the Member State concerned.

Notwithstanding the first subparagraph, a Member State concerned may disagree with the conclusion of the reporting Member State only on the following grounds:

(a) when it considers that participation in the clinical trial would lead to a subject receiving an inferior treatment than in normal clinical practice in the Member State concerned;

(b) infringement of its national law as referred to in Article 90;

(c) considerations as regards subject safety and data reliability and robustness submitted under paragraph 4 or 6 of Article 18. Where the Member State concerned disagrees with the conclusion regarding the substantial modification of aspects covered by Part I of the assessment report on the basis of the second subparagraph, it shall communicate its disagreement, together with a detailed justification through the EU portal to the Commission, to all Member States, and to the sponsor.

(3) Where, regarding the substantial modification of aspects covered by Part I of the assessment report, the substantial modification is acceptable or acceptable subject to compliance with specific conditions, the Member State concerned shall include in its decision its conclusion on the substantial modification of aspects covered by Part II of the assessment report.

(4) A Member State concerned shall refuse to authorise a substantial modification if it disagrees with the conclusion of the reporting Member State as regards the substantial modification of aspects covered by Part I of the assessment report on any of the grounds referred to in second subparagraph of paragraph 2, or if it finds, on duly justified grounds, that the aspects covered by Part II of the assessment report are not complied with, or where an ethics committee has issued a negative opinion which in accordance with the law of the Member State concerned, is valid for that entire Member State. That Member State concerned shall provide for an appeal procedure in respect of such refusal.

(5) Where the conclusion of the reporting Member State as regards the substantial modification of aspects covered by Part I of the assessment report is that the substantial modification is not acceptable, that conclusion shall be deemed to be the conclusion of the Member State concerned.

(6) Where the Member State concerned has not notified the sponsor of its decision within the periods referred to in paragraph 1, the conclusion on the substantial modification of aspects covered by Part I of the assessment report shall be deemed to be the decision of the Member State concerned on the application for authorisation of the substantial modification.

Article 24

Persons assessing the application for a substantial modification

Article 9 applies to assessments made under this Chapter.

CHAPTER IV

APPLICATION DOSSIER

Article 25

Data submitted in the application dossier

(1) The application dossier for the authorisation of a clinical trial shall contain all required documentation and information necessary for the validation and assessment referred to in Chapter II and relating to:

(a) the conduct of the clinical trial, including the scientific context and arrangements taken,
(b) the sponsor, investigators, potential subjects, subjects, and clinical trial sites;
(c) the investigational medicinal products and, where necessary, the auxiliary medicinal products, in particular their properties, labelling, manufacturing and control;
(d) measures to protect subjects;
(e) justification as to why the clinical trial is a low-intervention clinical trial, in cases where this is claimed by the sponsor.

The list of required documentation and information is set out in Annex I.

(2) The application dossier for the authorisation of a substantial modification shall contain all required documentation and information necessary for the validation and assessment referred to in Chapter III:

(a) a reference to the clinical trial or clinical trials which are substantially modified using the EU trial number referred to in the third subparagraph of Article 81(1) (the ‘EU trial number’);

(b) a clear description of the substantial modification, in particular, the nature of and the reasons for substantial modification;
(c) a presentation of data and additional information in support of the substantial modification, where necessary;
(d) a clear description of the consequences of the substantial modification as regards the rights and safety of the subject and the reliability and robustness of the data generated in the clinical trial.

The list of required documentation and information is set out in Annex II.

(3) Non-clinical information submitted in an application dossier shall be based on data derived from studies complying with Union law on the principles of good laboratory practice, as applicable at the time of performance of those studies.

(4) Where reference is made in the application dossier to data generated in a clinical trial, that clinical trial shall have been conducted in accordance with this Regulation or, if conducted prior to the date referred to in the second paragraph of Article 99, in accordance with Directive 2001/20/EC.

(5) Where the clinical trial referred to in paragraph 4 has been conducted outside the Union, it shall have been conducted in accordance with principles equivalent to those of this Regulation as regards the rights and safety of the subject and the reliability and robustness of the data generated in the clinical trial.

(6) Data from a clinical trial started as from the date referred to in the second paragraph of Article 99 shall only be submitted in an application dossier if that clinical trial has been registered prior to its start in a public register which is a primary or partner registry of, or a data provider to, the WHO ICTRP.
Data from a clinical trial started before the date referred to in the second paragraph of Article 99 shall only be submitted in an application dossier if that clinical trial is registered in a public register which is a primary or partner registry of, or a data provider to, the WHO ICTRP or if the results of that clinical trial have been published in an independent peer- reviewed scientific publication.
(7) Data submitted in an application dossier which do not comply with paragraphs 3 to 6 shall not be considered in the assessment of an application for authorisation of a clinical trial or of a substantial modification.

Article 26

Language requirements

The language of the application dossier, or parts thereof, shall be determined by the Member State concerned.

Member States, in applying the first paragraph, shall consider accepting, for the documentation not addressed to the subject, a commonly understood language in the medical field.

Article 27

Update by way of delegated acts

The Commission shall be empowered to adopt delegated acts in accordance with Article 85 in respect of amending Annexes I and II in order to adapt them to technical progress or to take account of international regulatory developments in which the Union or the Member States are involved, in the field of clinical trials.

CHAPTER V

PROTECTION OF SUBJECTS AND INFORMED CONSENT

Article 28

General rules

(1) A clinical trial may be conducted only where all of the following conditions are met:

(a) the anticipated benefits to the subjects or to public health justify the foreseeable risks and inconveniences and compliance with this condition is constantly monitored;
(b) the subjects, or where a subject is not able to give informed consent, his or her legally designated representative, have been informed in accordance with Article 29(2) to (6);
(c) the subjects, or where a subject is not able to give informed consent, his or her legally designated representative, have given informed consent in accordance with Article 29(1), (7) and (8);
(d) the rights of the subjects to physical and mental integrity, to privacy and to the protection of the data concerning them in accordance with Directive 95/46/EC are safeguarded;
(e) the clinical trial has been designed to involve as little pain, discomfort, fear and any other foreseeable risk as possible for the subjects and both the risk threshold and the degree of distress are specifically defined in the protocol and constantly monitored;
(f) the medical care provided to the subjects is the responsibility of an appropriately qualified medical doctor or, where appropriate, a qualified dental practitioner;

(g) the subject or, where the subject is not able to give informed consent, his or her legally designated representative has been provided with the contact details of an entity where further information can be received in case of need;

(h) no undue influence, including that of a financial nature, is exerted on subjects to participate in the clinical trial.

(2) Without prejudice to Directive 95/46/EC, the sponsor may ask the subject or, where the subject is not able to give informed consent, his or her legally designated representative at the time when the subject or the legally designated representative gives his or her informed consent to participate in the clinical trial to consent to the use of his or her data outside the protocol of the clinical trial exclusively for scientific purposes. That consent may be withdrawn at any time by the subject or his or her legally designated representative.

The scientific research making use of the data outside the protocol of the clinical trial shall be conducted in accordance with the applicable law on data protection.

(3) Any subject, or, where the subject is not able to give informed consent, his or her legally designated representative, may, without any resulting detriment and without having to provide any justification, withdraw from the clinical trial at any time by revoking his or her informed consent. Without prejudice to Directive 95/46/EC, the withdrawal of the informed consent shall not affect the activities already carried out and the use of data obtained based on informed consent before its withdrawal.

Article 29

Informed consent

(1) Informed consent shall be written, dated and signed by the person performing the interview referred to in point (c) of paragraph 2, and by the subject or, where the subject is not able to give informed consent, his or her legally designated representative after having been duly informed in accordance with paragraph 2. Where the subject is unable to write, consent may be given and recorded through appropriate alternative means in the presence of at least one impartial witness. In that case, the witness shall sign and date the informed consent document. The subject or, where the subject is not able to give informed consent, his or her legally designated representative shall be provided with a copy of the document (or the record) by which informed consent has been given. The informed consent shall be documented. Adequate time shall be given for the subject or his or her legally designated representative to consider his or her decision to participate in the clinical trial.

(2) Information given to the subject or, where the subject is not able to give informed consent, his or her legally designated representative for the purposes of obtaining his or her informed consent shall:

(a) enable the subject or his or her legally designated representative to understand:

(i) the nature, objectives, benefits, implications, risks and inconveniences of the clinical trial;
(ii) the subject's rights and guarantees regarding his or her protection, in particular his or her right to refuse to participate and the right to withdraw from the clinical trial at any time without any resulting detriment and without having to provide any justification;
(iii) the conditions under which the clinical trial is to be conducted, including the expected duration of the subject's participation in the clinical trial; and
(iv) the possible treatment alternatives, including the follow-up measures if the participation of the subject in the clinical trial is discontinued;

(b) be kept comprehensive, concise, clear, relevant, and understandable to a layperson;
(c) be provided in a prior interview with a member of the investigating team who is appropriately qualified according to the law of the Member State concerned;
(d) include information about the applicable damage compensation system referred to in Article 76(1); and
(e) include the EU trial number and information about the availability of the clinical trial results in accordance with paragraph 6.

(3) The information referred to in paragraph 2 shall be prepared in writing and be available to the subject or, where the subject is not able to give informed consent, his or her legally designated representative.

(4) In the interview referred to in point (c) of paragraph 2, special attention shall be paid to the information needs of specific patient populations and of individual subjects, as well as to the methods used to give the information.

(5) In the interview referred to in point (c) of paragraph 2, it shall be verified that the subject has understood the information.

(6)The subject shall be informed that the summary of the results of the clinical trial and a summary presented in terms understandable to a layperson will be made available in the EU database, referred to in Article 81 (the

'EU database'), pursuant to Article 37(4), irrespective of the outcome of the clinical trial, and, to the extent possible, when the summaries become available.

(7) This Regulation is without prejudice to national law requiring that both the signature of the incapacitated person and the signature of his or her legally designated representative may be required on the informed consent form.

(8) This Regulation is without prejudice to national law requiring that, in addition to the informed consent given by the legally designated representative, a minor who is capable of forming an opinion and assessing the information given to him or her, shall also assent in order to participate in a clinical trial.

Article 30

Informed consent in cluster trials

(1) Where a clinical trial is to be conducted exclusively in one Member State, that Member State may, without prejudice to Article 35, and by way of derogation from points (b), (c), and (g) of Article 28(1), Article 29(1), point (c) of Article 29(2), Article 29(3), (4) and (5), points (a), (b) and (c) of Article 31(1) and points (a), (b) and (c) of Article 32(1), allow the investigator to obtain informed consent by the simplified means set out in paragraph 2 of this Article, provided that all of the conditions set out in paragraph 3 of this Article are fulfilled.

(2) For clinical trials that fulfil the conditions set out in paragraph 3, informed consent shall be deemed to have been obtained if:

(a) the information required under points (a), (b), (d) and (e) of Article 29(2) is given, in accordance with what is laid down in the protocol, prior to the inclusion of the subject in the clinical trial, and this information makes clear, in particular, that the subject can refuse to participate in, or withdraw at any time from, the clinical trial without any resulting detriment; and

(b) the potential subject, after being informed, does not object to participating in the clinical trial.

(3) Informed consent may be obtained by the simplified means set out in paragraph 2, if all the following conditions are fulfilled:

(a) the simplified means for obtaining informed consent do not contradict national law in the Member State concerned;
(b) the methodology of the clinical trial requires that groups of subjects rather than individual subjects are allocated to receive different investigational medicinal products in a clinical trial;
(c) the clinical trial is a low-intervention clinical trial and the investigational medicinal products are used in accordance with the terms of the marketing authorisation;
(d) there are no interventions other than the standard treatment of the subjects concerned;
(e) the protocol justifies the reasons for obtaining informed consent with simplified means and describes the scope of information provided to the subjects, as well as the ways of providing information.

(4) The investigator shall document all refusals and withdrawals and shall ensure that no data for the clinical trial are collected from subjects that refuse to participate in or have withdrawn from the clinical trial.

Article 31

Clinical trials on incapacitated subjects

(1) In the case of incapacitated subjects who have not given, or have not refused to give, informed consent before the onset of their incapacity, a clinical trial may be conducted only where, in addition to the conditions set out in Article 28, all of the following conditions are met:

(a) the informed consent of their legally designated representative has been obtained;
(b) the incapacitated subjects have received the information referred to in Article 29(2) in a way that is adequate in view of their capacity to understand it;
(c) the explicit wish of an incapacitated subject who is capable of forming an opinion and assessing the information referred to in Article 29(2) to refuse participation in, or to withdraw from, the clinical trial at any time, is respected by the investigator;
(d) no incentives or financial inducements are given to the subjects or their legally designated representatives, except for compensation for expenses and loss of earnings directly related to the participation in the clinical trial;
(e) the clinical trial is essential with respect to incapacitated subjects and data of comparable validity cannot be obtained in clinical trials on persons able to give informed consent, or by other research methods;
(f) the clinical trial relates directly to a medical condition from which the subject suffers;
(g) there are scientific grounds for expecting that participation in the clinical trial will produce:

(i) a direct benefit to the incapacitated subject outweighing the risks and burdens involved; or

(ii) some benefit for the population represented by the incapacitated subject concerned when the clinical trial relates directly to the life-threatening or debilitating medical condition from which the subject suffers and such trial will pose only minimal risk to, and will impose minimal burden on, the incapacitated subject concerned in comparison with the standard treatment of the incapacitated subject's condition.

(2) Point (g)(ii) of paragraph 1 shall be without prejudice to more stringent national rules prohibiting the conduct of those clinical trials on incapacitated subjects, where there are no scientific grounds to expect that participation in the clinical trial will produce a direct benefit to the subject outweighing the risks and burdens involved.

(3) The subject shall as far as possible take part in the informed consent procedure.

Article 32

Clinical trials on minors

(1) A clinical trial on minors may be conducted only where, in addition to the conditions set out in Article 28, all of the following conditions are met:

(a) the informed consent of their legally designated representative has been obtained;
(b) the minors have received the information referred to in Article 29(2) in a way adapted to their age and mental maturity and from investigators or members of the investigating team who are trained or experienced in working with children;
(c) the explicit wish of a minor who is capable of forming an opinion and assessing the information referred to in Article 29(2) to refuse participation in, or to withdraw from, the clinical trial at any time, is respected by the investigator;
(d) no incentives or financial inducements are given to the subject or his or her legally designated representative except for compensation for expenses and loss of earnings directly related to the participation in the clinical trial;
(e) the clinical trial is intended to investigate treatments for a medical condition that only occurs in minors or the clinical trial is essential with respect to minors to validate data obtained in clinical trials on persons able to give informed consent or by other research methods;
(f) the clinical trial either relates directly to a medical condition from which the minor concerned suffers or is of such a nature that it can only be carried out on minors;
(g) there are scientific grounds for expecting that participation in the clinical trial will produce: (i) a direct benefit for the minor concerned outweighing the risks and burdens involved; or (ii) some benefit for the population represented by the minor concerned and such a clinical trial will pose only minimal risk to, and will impose minimal burden on, the minor concerned in comparison with the standard treatment of the minor's condition.

(2) The minor shall take part in the informed consent procedure in a way adapted to his or her age and mental maturity.

(3) If during a clinical trial the minor reaches the age of legal competence to give informed consent as defined in the law of the Member State concerned, his or her express informed consent shall be obtained before that subject can continue to participate in the clinical trial.

Article 33

Clinical trials on pregnant or breastfeeding women

A clinical trial on pregnant or breastfeeding women may be conducted only where, in addition to the conditions set out in Article 28, the following conditions are met:

(a) the clinical trial has the potential to produce a direct benefit for the pregnant or breastfeeding woman concerned, or her embryo, foetus or child after birth, outweighing the risks and burdens involved; or
(b) if such clinical trial has no direct benefit for the pregnant or breastfeeding woman concerned, or her embryo, foetus or child after birth, it can be conducted only if:

(i) a clinical trial of comparable effectiveness cannot be carried out on women who are not pregnant or breastfeeding;
(iii) the clinical trial contributes to the attainment of results capable of benefitting pregnant or breastfeeding women or other women in relation to reproduction or other embryos, foetuses or children; and
(iv) the clinical trial poses a minimal risk to, and imposes a minimal burden on, the pregnant or breastfeeding woman concerned, her embryo, foetus or child after birth;

(c) where research is undertaken on breastfeeding women, particular care is taken to avoid any adverse impact on the health of the child; and

(d) no incentives or financial inducements are given to the subject except for compensation for expenses and loss of earnings directly related to the participation in the clinical trial.

Article 34

Additional national measures

Member States may maintain additional measures regarding persons performing mandatory military service, persons deprived of liberty, persons who, due to a judicial decision, cannot take part in clinical trials, or persons in residential care institutions.

Article 35
Clinical trials in emergency situations

(1) By way of derogation from points (b) and (c) of Article 28(1), from points (a) and (b) of Article 31(1) and from points (a) and (b) of Article 32(1), informed consent to participate in a clinical trial may be obtained, and information on the clinical trial may be given, after the decision to include the subject in the clinical trial, provided that this decision is taken at the time of the first intervention on the subject, in accordance with the protocol for that clinical trial" and that all of the following conditions are fulfilled:

(a) due to the urgency of the situation, caused by a sudden life-threatening or other sudden serious medical condition, the subject is unable to provide prior informed consent and to receive prior information on the clinical trial;
(b) there are scientific grounds to expect that participation of the subject in the clinical trial will have the potential to produce a direct clinically relevant benefit for the subject resulting in a measurable health-related improvement alleviating the suffering and/or improving the health of the subject, or in the diagnosis of its condition;
(c) it is not possible within the therapeutic window to supply all prior information to and obtain prior informed consent from his or her legally designated representative;
(d) the investigator certifies that he or she is not aware of any objections to participate in the clinical trial previously expressed by the subject;
(e) the clinical trial relates directly to the subject's medical condition because of which it is not possible within the therapeutic window to obtain prior informed consent from the subject or from his or her legally designated representative and to supply prior information, and the clinical trial is of such a nature that it may be conducted exclusively in emergency situations;
(f) the clinical trial poses a minimal risk to, and imposes a minimal burden on, the subject in comparison with the standard treatment of the subject's condition.

(2) Following an intervention pursuant to paragraph 1, informed consent in accordance with Article 29 shall be sought to continue the participation of the subject in the clinical trial, and information on the clinical trial shall be given, in accordance with the following requirements:

(a) regarding incapacitated subjects and minors, the informed consent shall be sought by the investigator from his or her legally designated representative without undue delay and the information referred to in Article 29(2) shall be given as soon as possible to the subject and to his or her legally designated representative;
(b) regarding other subjects, the informed consent shall be sought by the investigator without undue delay from the subject or his or her legally designated representative, whichever is sooner and the information referred to in Article 29(2) shall be given as soon as possible to the subject or his or her legally designated representative, whichever is sooner.

For the purposes of point (b), where informed consent has been obtained from the legally designated representative, informed consent to continue the participation in the clinical trial shall be obtained from the subject as soon as he or she is capable of giving informed consent.

(3) If the subject or, where applicable, his or her legally designated representative does not give consent, he or she shall be informed of the right to object to the use of data obtained from the clinical trial.

CHAPTER VI

START, END, TEMPORARY HALT AND EARLY TERMINATION OF A CLINICAL TRIAL

Article 36

Notification of the start of a clinical trial and of the end of the recruitment of subjects

1. The sponsor shall notify each Member State concerned of the start of a clinical trial in relation to that Member State through the EU portal.

That notification shall be made within 15 days from the start of the clinical trial in relation to that Member State.

2. The sponsor shall notify each Member State concerned of the first visit of the first subject in relation to that Member State through the EU portal.

   That notification shall be made within 15 days from the first visit of the first subject in relation to that Member State.

3. The sponsor shall notify each Member State concerned of the end of the recruitment of subjects for a clinical trial in that Member State through the EU portal.

   That notification shall be made within 15 days from the end of the recruitment of subjects. In case of re-start of recruitment, paragraph 1 shall apply.

4. Irrespective of the outcome of a clinical trial, within one year from the end of a clinical trial in all Member States concerned, the sponsor shall submit to the EU database a summary of the results of the clinical trial. The content of that summary is set out in Annex IV.

   It shall be accompanied by a summary written in a manner that is understandable to laypersons. The content of that summary is set out in Annex V.

   However, where, for scientific reasons detailed in the protocol, it is not possible to submit a summary of the results within one year, the summary of results shall be submitted as soon as it is available. In this case, the protocol shall specify when the results are going to be submitted, together with a justification.

   In addition to the summary of the results, where the clinical trial was intended to be used for obtaining a marketing authorisation for the investigational medicinal product, the applicant for marketing authorisation shall submit to the EU database the clinical study report within 30 days after the day the marketing authorisation has been granted, the procedure for granting the marketing authorisation has been completed, or the applicant for marketing authorisation has withdrawn the application.

   For cases where the sponsor decides to share raw data on a voluntary basis, the Commission shall produce guidelines for the formatting and sharing of those data.

5. The sponsor shall notify each Member State concerned of a temporary halt of a clinical trial in all Member States concerned for reasons not affecting the benefit-risk balance through the EU portal.

   That notification shall be made within 15 days from the temporary halt of the clinical trial in all Member States concerned and shall include the reasons for such action.

6. When a temporarily halted clinical trial referred to in paragraph 5 is resumed the sponsor shall notify each Member State concerned through the EU portal.

   That notification shall be made within 15 days from the restart of the temporarily halted clinical trial in all Member States concerned.

7. If a temporarily halted clinical trial is not resumed within two years, the expiry date of this period or the date of the decision of the sponsor not to resume the clinical trial, whichever is earlier, shall be deemed to be the date of the end of the clinical trial.

   In the case of early termination of the clinical trial, the date of the early termination shall be deemed to be the date of the end of the clinical trial. In the case of early termination of the clinical trial for reasons not affecting the benefit-risk balance, the sponsor shall notify each Member State concerned through the EU portal of the reasons for such action and, when appropriate, follow-up measures for the subjects.

8. Without prejudice to paragraph 4, where the clinical trial protocol provides for an intermediate data analysis date prior to the end of the clinical trial, and the respective results of the clinical trial are available, a summary of those results shall be submitted to the EU database within one year of the intermediate data analysis date.

Article 37

End of a clinical trial, temporary halt and early termination of a clinical trial and submission of the results

1. The sponsor shall notify each Member State concerned of the end of a clinical trial in relation to that Member State through the EU portal.

   That notification shall be made within 15 days from the end of the clinical trial in relation to that Member State.

2. The sponsor shall notify each Member State concerned of the end of a clinical trial in all Member States concerned through the EU portal.

That notification shall be made within 15 days from the end of the clinical trial in the last Member State concerned.

3. The sponsor shall notify each Member State concerned of the end of a clinical trial in all Member States concerned and in all third countries in which the clinical trial has been conducted through the EU portal.

   That notification shall be made within 15 days from the end of the clinical trial in the last of the Member States concerned and third countries in which the clinical trial has been conducted.

4. Irrespective of the outcome of a clinical trial, within one year from the end of a clinical trial in all Member States concerned, the sponsor shall submit to the EU database a summary of the results of the clinical trial. The content of that summary is set out in Annex IV.

   It shall be accompanied by a summary written in a manner that is understandable to laypersons. The content of that summary is set out in Annex V.

   However, where, for scientific reasons detailed in the protocol, it is not possible to submit a summary of the results within one year, the summary of results shall be submitted as soon as it is available. In this case, the protocol shall specify when the results are going to be submitted, together with a justification.

   In addition to the summary of the results, where the clinical trial was intended to be used for obtaining a marketing authorisation for the investigational medicinal product, the applicant for marketing authorisation shall submit to the EU database the clinical study report within 30 days after the day the marketing authorisation has been granted, the procedure for granting the marketing authorisation has been completed, or the applicant for marketing authorisation has withdrawn the application.

   For cases where the sponsor decides to share raw data on a voluntary basis, the Commission shall produce guidelines for the formatting and sharing of those data.

5. The sponsor shall notify each Member State concerned of a temporary halt of a clinical trial in all Member States concerned for reasons not affecting the benefit-risk balance through the EU portal. That notification shall be made within 15 days from the temporary halt of the clinical trial in all Member States concerned and shall include the reasons for such action.

6. When a temporarily halted clinical trial referred to in paragraph 5 is resumed the sponsor shall notify each Member State concerned through the EU portal. That notification shall be made within 15 days from the restart of the temporarily halted clinical trial in all Member States concerned.

7. If a temporarily halted clinical trial is not resumed within two years, the expiry date of this period or the date of the decision of the sponsor not to resume the clinical trial, whichever is earlier, shall be deemed to be the date of the end of the clinical trial. In the case of early termination of the clinical trial, the date of the early termination shall be deemed to be the date of the end of the clinical trial. In the case of early termination of the clinical trial for reasons not affecting the benefit-risk balance, the sponsor shall notify each Member State concerned through the EU portal of the reasons for such action and, when appropriate, follow-up measures for the subjects.

8. Without prejudice to paragraph 4, where the clinical trial protocol provides for an intermediate data analysis date prior to the end of the clinical trial, and the respective results of the clinical trial are available, a summary of those results shall be submitted to the EU database within one year of the intermediate data analysis date.

Article 38

Temporary halt or early termination by the sponsor for reasons of subject safety

1. For the purposes of this Regulation, the temporary halt or early termination of a clinical trial for reasons of a change of the benefit-risk balance shall be notified to the Member States concerned through the EU portal.

   That notification shall be made without undue delay but not later than in 15 days of the date of the temporary halt or early termination. It shall include the reasons for such action and specify follow-up measures.

2. The restart of the clinical trial following a temporary halt as referred to in paragraph 1 shall be deemed to be a substantial modification subject to the authorisation procedure laid down in Chapter III.

Article 39

Update of the contents of the summary of results and summary for laypersons

The Commission shall be empowered to adopt delegated acts in accordance with Article 89 in order to amend Annexes IV and V, in order to adapt them to technical progress or to take account of international regulatory developments, in which the Union or the Member States are involved, in the field of clinical trials.

CHAPTER VII

SAFETY REPORTING IN THE CONTEXT OF A CLINICAL TRIAL

Article 40

Electronic database for safety reporting

1. The European Medicines Agency established by Regulation (EC) No 726/2004 (the 'Agency') shall set up and maintain an electronic database for the reporting provided for in Articles 42 and 43. That database shall be a module of the database referred to in Article 24 of Regulation (EC) No 726/2004 (the 'EudraVigilance database').

2. The Agency shall, in collaboration with Member States, develop a standard web-based structured form for the reporting by sponsors to the database referred to in paragraph 1 of suspected unexpected serious adverse reactions.

Article 41

Reporting of adverse events and serious adverse events by the investigator to the sponsor

1. The investigator shall record and document adverse events or laboratory abnormalities identified in the protocol as critical to the safety evaluation and report them to the sponsor in accordance with the reporting requirements and within the periods specified in the protocol.

2. The investigator shall record and document all adverse events, unless the protocol provides differently. The investigator shall report to the sponsor all serious adverse events occurring to subjects treated by him or her in the clinical trial, unless the protocol provides differently.

   The investigator shall report serious adverse events to the sponsor without undue delay but not later than within 24 hours of obtaining knowledge of the events, unless, for certain serious adverse events, the protocol provides that no immediate reporting is required. Where relevant, the investigator shall send a follow-up report to the sponsor to allow the sponsor to assess whether the serious adverse event has an impact on the benefit-risk balance of the clinical trial.

3. The sponsor shall keep detailed records of all adverse events reported to it by the investigator.

4. If the investigator becomes aware of a serious adverse event with a suspected causal relationship to the investigational medicinal product that occurs after the end of the clinical trial in a subject treated by him or her, the investigator shall, without undue delay, report the serious adverse event to the sponsor.

Article 42

Reporting of suspected unexpected serious adverse reactions by the sponsor to the Agency

1. The sponsor of a clinical trial performed in at least one Member State shall report electronically and without delay to the database referred to in Article 40(1) all relevant information about the following suspected unexpected serious adverse reactions:

(a) all suspected unexpected serious adverse reactions to investigational medicinal products occurring in that clinical trial, irrespective of whether the suspected unexpected serious adverse reaction has occurred at a clinical trial site in the Union or in a third country;

(b) all suspected unexpected serious adverse reactions related to the same active substance, regardless of pharmaceutical form and strength or indication investigated, in investigational medicinal products used in the clinical trial, occurring in a clinical trial performed exclusively in a third country, if that clinical trial is sponsored:
   (i) by that sponsor, or
   (ii) by another sponsor who is either part of the same parent company as the sponsor of the clinical trial, or who develops a medicinal product jointly, on the basis of a formal agreement, with the sponsor of the clinical trial. For this purpose, provision of the investigational medicinal product or information to a future potential marketing authorisation holder on safety matters shall not be considered a joint development; and

(c) all suspected unexpected serious adverse reactions to investigational medicinal products occurring in any of the subjects of the clinical trial, which are identified by or come to the attention of the sponsor after the end of the clinical trial.

2. The period for the reporting of suspected unexpected serious adverse reactions by the sponsor to the Agency shall take account of the seriousness of the reaction and shall be as follows:

(a) in the case of fatal or life-threatening suspected unexpected serious adverse reactions, as soon as possible and in any event not later than seven days after the sponsor became aware of the reaction;

(b) in the case of non-fatal or non-life-threatening suspected unexpected serious adverse reactions, not later than 15 days after the sponsor became aware of the reaction;

(c) in the case of a suspected unexpected serious adverse reaction which was initially considered to be non-fatal or non- life threatening but which turns out to be fatal or life-threatening, as soon as possible and in any event not later than seven days after the sponsor became aware of the reaction being fatal or life-threatening.

Where necessary to ensure timely reporting, the sponsor may, in accordance with section 2.4 of Annex III, submit an initial incomplete report followed up by a complete report.

3. Where a sponsor, due to a lack of resources, does not have the possibility to report to the database referred to in Article 40(1) and the sponsor has the agreement of the Member State concerned, it may report to the Member State where the suspected unexpected serious adverse reaction occurred. That Member State shall report the suspected unexpected serious adverse reaction in accordance with paragraph 1 of this Article.

Article 43

Annual reporting by the sponsor to the Agency

1. Regarding investigational medicinal products other than placebo, the sponsor shall submit annually through the database referred to in Article 40(1) to the Agency a report on the safety of each investigational medicinal product used in a clinical trial for which it is the sponsor.

2. In the case of a clinical trial involving the use of more than one investigational medicinal product, the sponsor may, if provided for in the protocol, submit a single safety report on all investigational medicinal products used in that clinical trial.

3. The annual report referred to in paragraph 1 shall only contain aggregate and anonymised data.

4. The obligation referred to in paragraph 1 starts with the first authorisation of a clinical trial in accordance with this Regulation. It ends with the end of the last clinical trial conducted by the sponsor with the investigational medicinal product.

Article 44

Assessment by Member States

(1) The Agency shall, by electronic means, forward to the Member States concerned the information reported in accordance with Article 42 and 43.

(2) Member States shall cooperate in assessing the information reported in accordance with Articles 42and 43. The Commission may, by means of implementing acts, set up and modify the rules on such cooperation. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 88(2).

(3) The responsible ethics committee shall be involved in the assessment of the information referred to in paragraphs 1 and 2, if it has been provided for in the law of the Member State concerned.

Article 45

Technical aspects

Technical aspects for safety reporting in accordance with Articles 41 to 44 are contained in Annex III. Where necessary in order to improve the level of protection of subjects, the Commission shall be empowered to adopt delegated acts in accordance with Article 89 in order to amend Annex III for any of the following purposes:

(a) improving the information on the safety of medicinal products;
(b) adapting technical requirements to technical progress;
(c) taking account of international regulatory developments in the field of safety requirements in clinical trials, endorsed by bodies in which the Union or the Member States participate.

Article 46

Reporting with regard to auxiliary medicinal products

Safety reporting with regard to auxiliary medicinal products shall be made in accordance with Chapter 3 of Title IX of Directive 2001/83/EC.

CHAPTER VIII

CONDUCT OF A CLINICAL TRIAL, SUPERVISION BY THE SPONSOR, TRAINING AND EXPERIENCE, AUXILIARY MEDICINAL PRODUCTS

Article 47

Compliance with the protocol and good clinical practice

The sponsor of a clinical trial and the investigator shall ensure that the clinical trial is conducted in accordance with the protocol and with the principles of good clinical practice.

Without prejudice to any other provision of Union law or Commission guidelines, the sponsor and the investigator, when drawing up the protocol and when applying this Regulation and the protocol, shall also take appropriate account of the quality standards and the ICH guidelines on good clinical practice.

The Commission shall make publicly available the detailed ICH guidelines on good clinical practice referred to in the second paragraph.

Article 48

Monitoring

In order to verify that the rights, safety and well-being of subjects are protected, that the reported data are reliable and robust, and that the conduct of the clinical trial is in compliance with the requirements of this Regulation, the sponsor shall adequately monitor the conduct of a clinical trial. The extent and nature of the monitoring shall be determined by the sponsor on the basis of an assessment that takes into consideration all characteristics of the clinical trial, including the following characteristics:

(a) whether the clinical trial is a low-intervention clinical trial;
(b) the objective and methodology of the clinical trial; and
(c) the degree of deviation of the intervention from normal clinical practice.

Article 49

Suitability of individuals involved in conducting the clinical trial

The investigator shall be a medical doctor as defined in national law, or a person following a profession which is recognised in the Member State concerned as qualifying for an investigator because of the necessary scientific knowledge and experience in patient care.
Other individuals involved in conducting a clinical trial shall be suitably qualified by education, training and experience to perform their tasks.

Article 50

Suitability of clinical trial sites

The facilities where the clinical trial is to be conducted shall be suitable for the conduct of the clinical trial in compliance with the requirements of this Regulation.

Article 51

Traceability, storage, return and destruction of investigational medicinal products

1. Investigational medicinal products shall be traceable. They shall be stored, returned and/or destroyed as appropriate and proportionate to ensure the safety of the subject and the reliability and robustness of the data generated in the clinical trial, in particular, taking into account whether the investigational medicinal product is an authorised investigational medicinal product, and whether the clinical trial is a low-intervention clinical trial. The first subparagraph shall also apply to unauthorised auxiliary medicinal products.
2. The relevant information regarding the traceability, storage, return and destruction of medicinal products referred to in paragraph 1 shall be contained in the application dossier.

Article 52

Reporting of serious breaches

1. The sponsor shall notify the Member States concerned about a serious breach of this Regulation or of the version of the protocol applicable at the time of the breach through the EU portal without undue delay but not later than seven days of becoming aware of that breach.

2. For the purposes of this Article, a ‘serious breach’ means a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial.

Article 53

Other reporting obligations relevant for subject safety

(1) The sponsor shall notify the Member States concerned through the EU portal of all unexpected events which affect the benefit-risk balance of the clinical trial, but are not suspected unexpected serious adverse reactions as referred to in Article 42. That notification shall be made without undue delay but no later than 15 days from the date the sponsor became aware of this event.

(2) The sponsor shall submit to the Member States concerned, through the EU portal, all inspection reports of third country authorities concerning the clinical trial. When requested by a Member State concerned, the sponsor shall submit a translation of the report or of its summary in an official language of the Union indicated in the request.

Article 54

Urgent safety measures

1. Where an unexpected event is likely to seriously affect the benefit-risk balance, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects.

2. The sponsor shall notify the Member States concerned, through the EU portal, of the event and the measures taken. That notification shall be made without undue delay but no later than seven days from the date the measures have been taken.

3. This Article is without prejudice to Chapters III and VII.

Article 55

Investigator’s brochure

1. The sponsor shall provide the investigator with the investigator's brochure.

2. The investigator's brochure shall be updated where new and relevant safety information becomes available, and shall be reviewed by the sponsor at least once per year.

Article 56

Recording, processing, handling and storage of information

(1) All clinical trial information shall be recorded, processed, handled, and stored by the sponsor or investigator, as applicable, in such a way that it can be accurately reported, interpreted and verified while the confidentiality of records and the personal data of the subjects remain protected in accordance with the applicable law on personal data protection.

(2) Appropriate technical and organisational measures shall be implemented to protect information and personal data processed against unauthorised or unlawful access, disclosure, dissemination, alteration, or destruction or accidental loss, in particular where the processing involves the transmission over a network.

Article 57

Clinical trial master file

The sponsor and the investigator shall keep a clinical trial master file. The clinical trial master file shall at all times contain the essential documents relating to that clinical trial which allow verification of the conduct of a clinical trial and the quality of the data generated, taking into account all characteristics of the clinical trial, including in particular whether the clinical trial is a low-intervention clinical trial. It shall be readily available, and directly accessible upon request, to the Member States.

The clinical trial master file kept by the investigator and that kept by the sponsor may have a different content if this is justified by the different nature of the responsibilities of the investigator and the sponsor.

Article 58

Archiving of the clinical trial master file

Unless other Union law requires archiving for a longer period, the sponsor and the investigator shall archive the content of the clinical trial master file for at least 25 years after the end of the clinical trial. However, the medical files of subjects shall be archived in accordance with national law.

The content of the clinical trial master file shall be archived in a way that ensures that it is readily available and accessible, upon request, to the competent authorities.

Any transfer of ownership of the content of the clinical trial master file shall be documented. The new owner shall assume the responsibilities set out in this Article.

The sponsor shall appoint individuals within its organisation to be responsible for archives. Access to archives shall be restricted to those individuals.

The media used to archive the content of the clinical trial master file shall be such that the content remains complete and legible throughout the period referred to in the first paragraph.

Any alteration to the content of the clinical trial master file shall be traceable.

Article 59

Auxiliary medicinal products

1. Only authorised auxiliary medicinal products may be used in a clinical trial.

2. Paragraph 1 shall not apply where no authorised auxiliary medicinal product is available in the Union or where the sponsor cannot reasonably be expected to use an authorised auxiliary medicinal product. A justification to this effect shall be included in the protocol.

3. Member States shall ensure that unauthorised auxiliary medicinal products may enter their territories for the purpose of their use in a clinical trial in accordance with paragraph 2.

CHAPTER IX

MANUFACTURING AND IMPORT OF INVESTIGATIONAL MEDICINAL PRODUCTS AND AUXILIARY MEDICINAL PRODUCTS

Article 60

Scope of this chapter

This Chapter shall apply to the manufacture and import of investigational medicinal products and auxiliary medicinal products.

Article 61

Authorisation of manufacturing and import

1. The manufacturing and import of investigational medicinal products in the Union shall be subject to the holding of an authorisation.

2. In order to obtain the authorisation referred to in paragraph 1, the applicant shall meet the following requirements:

(a) it shall have at its disposal, for manufacture or import, suitable and sufficient premises, technical equipment and control facilities complying with the requirements set out in this Regulation;
(b) it shall have permanently and continuously at its disposal the services of at least one qualified person who fulfils the conditions of qualification set out in Article 49(2) and (3) of Directive 2001/83/EC ('qualified person').

3. The applicant shall specify, in the application for authorisation, the types and pharmaceutical forms of the investigational medicinal product manufactured or imported, the manufacturing or import operations, the manufacturing process where relevant, the site where the investigational medicinal products are to be manufactured or the site in the Union to which they are to be imported, and detailed information concerning the qualified person.

4. Articles 42 to 45, and point (e) of Article 46 of Directive 2001/83/EC shall apply *mutatis mutandis* to the authorisation referred to in paragraph 1.
5. Paragraph 1 shall not apply to any of the following processes:

(a) re-labelling or re-packaging, where those processes are carried out in hospitals, health centres or clinics, by pharmacists or other persons legally authorised in the Member State concerned to carry out such processes, and if the investigational medicinal products are intended to be used exclusively in hospitals, health centres or clinics taking part in the same clinical trial in the same Member State;
(b) preparation of radiopharmaceuticals used as diagnostic investigational medicinal products where this process is carried out in hospitals, health centres or clinics, by pharmacists or other persons legally authorised in the Member State concerned to carry out such process, and if the investigational medicinal products are intended to be used exclusively in hospitals, health centres or clinics taking part in the same clinical trial in the same Member State;
(c) the preparation of medicinal products referred to in points (1) and (2) of Article 3 of Directive 2001/83/EC for use as investigational medicinal products, where this process is carried out in hospitals,

health centres or clinics legally authorised in the Member State concerned to carry out such process and if the investigational medicinal products are intended to be used exclusively in hospitals, health centres or clinics taking part in the same clinical trial in the same Member State.

6. Member States shall make the processes set out in paragraph 5 subject to appropriate and proportionate requirements to ensure subject safety and reliability and robustness of the data generated in the clinical trial. They shall subject the processes to regular inspections.

Article 62

Responsibilities of the qualified person

(1) The qualified person shall ensure that each batch of investigational medicinal products manufactured in or imported into the Union complies with the requirements set out in Article 63 and shall certify that those requirements are fulfilled.

(2) The certification referred to in paragraph 1 shall be made available by the sponsor at the request of the Member State concerned.

Article 63

Manufacturing and import

(1) Investigational medicinal products shall be manufactured by applying manufacturing practice which ensures the quality of such medicinal products in order to safeguard the safety of the subject and the reliability and robustness of clinical data generated in the clinical trial ('good manufacturing practice'). The Commission shall be empowered to adopt delegated acts in accordance with Article 89 in order to specify the principles and guidelines of good manufacturing practice and the detailed arrangements for inspection for ensuring the quality of investigational medicinal products, taking account of subject safety or data reliability and robustness, technical progress and global regulatory developments in which the Union or the Member States are involved.
In addition, the Commission shall also adopt and publish detailed guidelines in line with those principles of good manufacturing practice and revise them when necessary in order to take account of technical and scientific progress.

(2) Paragraph 1 shall not apply to the processes referred to in Article 61(5).

(3) Investigational medicinal products imported into the Union shall be manufactured by applying quality standards at least equivalent to those laid down pursuant to paragraph 1.

(4) The Member States shall ensure compliance with the requirements of this Article by means of inspections.

Article 64

Modification of authorised investigational medicinal products

Articles 61, 62 and 63 shall apply to authorised investigational medicinal products only as regards any modification of such products not covered by a marketing authorisation.

Article 65

Manufacturing of auxiliary medicinal products

Where the auxiliary medicinal product is not authorised, or where an authorised auxiliary medicinal product is modified while such modification is not covered by a marketing authorisation, it shall be manufactured according to the good manufacturing practice referred to in Article 63(1) or to at least an equivalent standard, in order to ensure appropriate quality.

CHAPTER X

LABELLING

Article 66

Unauthorised investigational and unauthorized auxiliary medicinal products

(1) The following information shall appear on the outer packaging and on the immediate packaging of unauthorised investigational medicinal products and unauthorised auxiliary medicinal products:

(a) information to identify contact persons or persons involved in the clinical trial;
(b) information to identify the clinical trial;
(c) information to identify the medicinal product;

(d) information related to the use of the medicinal product.

(2) The information which is to appear on the outer packaging and immediate packaging shall ensure subject safety and reliability and robustness of the data generated in the clinical trial, while taking account of the design of the clinical trial, whether the products are investigational or auxiliary medicinal product, and whether they are products with particular characteristics.

The information which is to appear on the outer packaging and immediate packaging shall be clearly legible.

A list of information which is to appear on the outer packaging and immediate packaging is set out in Annex VI.

Article 67

Authorised investigational and authorized auxiliary medicinal products

(1) Authorised investigational medicinal products and authorised auxiliary medicinal products shall be labelled:

(a) in accordance with Article 66(1); or
(b) in accordance with Title V of Directive 2001/83/EC.

(2) Notwithstanding point (b) of paragraph 1, where the specific circumstances, provided for in the protocol, of a clinical trial so require in order to ensure the safety of the subject or the reliability and robustness of data generated in a clinical trial, additional particulars relating to the identification of the clinical trial and of the contact person shall appear on the outer packaging and the immediate packaging of authorised investigational medicinal products. A list of these additional particulars appearing on the outer packaging and immediate packaging is set out in section C of Annex VI.

Article 68

Radiopharmaceuticals used as investigational medicinal products or as auxiliary medicinal products for a medical diagnosis

Articles 66 and 67 shall not apply to radiopharmaceuticals used as diagnostic investigational medicinal products or as diagnostic auxiliary medicinal products.

The products referred to in the first paragraph shall be labelled appropriately in order to ensure the safety of the subject and the reliability and robustness of data generated in the clinical trial.

Article 69

Language

The language of the information on the label shall be determined by the Member State concerned. The medicinal product may be labelled in several languages.

Article 70

Delegated acts

The Commission shall be empowered to adopt delegated acts in accordance with Article 89 in respect of amending Annex VI in order to ensure subject safety and the reliability and robustness of data generated in a clinical trial or to take account of technical progress.

CHAPTER XI

SPONSOR AND INVESTIGATOR

Article 71

Sponsor

A clinical trial may have one or several sponsors.

Any sponsor may delegate, in a written contract, any or all of its tasks to an individual, a company, an institution or an organisation. Such delegation shall be without prejudice to the responsibility of the sponsor, in particular regarding the safety of subjects and the reliability and robustness of the data generated in the clinical trial.

The investigator and the sponsor may be the same person.

Article 72

Co-sponsorship

(1) Without prejudice to Article 74, where a clinical trial has more than one sponsor, all sponsors shall have the responsibilities of a sponsor set out in this Regulation, unless the sponsors decide otherwise in a written contract setting out their respective responsibilities. Where the contract does not specify to which sponsor a given responsibility is attributed, that responsibility shall lie with all sponsors.

(2) By way of derogation from paragraph 1, the sponsors shall be jointly responsible for establishing:

(a) a sponsor responsible for compliance with the obligations of a sponsor in the authorisation procedures set out in Chapters II and III;
(b) a sponsor responsible for being a contact point for receiving all questions from subjects, investigators or any Member State concerned regarding the clinical trial and providing answers to them;
(c) a sponsor responsible for implementing the measures taken in accordance with Article 77.

Article 73

Principal investigator

A principal investigator shall ensure compliance of a clinical trial at a clinical trial site with the requirements of this Regulation.

The principal investigator shall assign tasks among the members of the team of investigators in a way which is not compromising the safety of subjects and the reliability and robustness of the data generated in the clinical trial at that clinical trial site.

Article 74

Legal representative of the sponsor in the Union

(1) Where the sponsor of a clinical trial is not established in the Union, that sponsor shall ensure that a natural or legal person is established in the Union as its legal representative. Such legal representative shall be responsible for ensuring compliance with the sponsor's obligations pursuant to this Regulation, and shall be the addressee for all communications with the sponsor provided for in this Regulation. Any communication to that legal representative shall be deemed to be a communication to the sponsor.

(2) Member States may choose not to apply paragraph 1 as regards clinical trials to be conducted solely on their territory, or on their territory and the territory of a third country, provided that they ensure that the sponsor establishes at least a contact person on their territory in respect of that clinical trial who shall be the addressee for all communications with the sponsor provided for in this Regulation.

(3) As regards clinical trials to be conducted in more than one Member State, all those Member States may choose not to apply paragraph 1 provided that they ensure that the sponsor establishes at least a contact person in the Union in respect of that clinical trial who shall be the addressee for all communications with the sponsor provided for in this Regulation.

Article 75

Liability

This Chapter shall not affect the civil and criminal liability of the sponsor, investigator, or persons to whom the sponsor has delegated tasks.

CHAPTER XII

DAMAGE COMPENSATION

Article 76

Damage compensation

(1) Member States shall ensure that systems for compensation for any damage suffered by a subject resulting from participation in a clinical trial conducted on their territory are in place in the form of insurance, a guarantee, or a similar arrangement that is equivalent as regards its purpose and which is appropriate to the nature and the extent of the risk.

(2) The sponsor and the investigator shall make use of the system referred to in paragraph 1 in the form appropriate for the Member State concerned where the clinical trial is conducted.

(3) Member States shall not require any additional use of the system referred to in paragraph 1 from the sponsor for low-intervention clinical trials, if any possible damage that could be suffered by a subject resulting from the use of the investigational medicinal product in accordance with the protocol of that specific clinical trial on the territory of that Member State is covered by the applicable compensation system already in place.

CHAPTER XIII

SUPERVISION BY MEMBER STATES, UNION INSPECTIONS AND CONTROLS

Article 77

Corrective measures to be taken by Member States

(1) Where a Member State concerned has justified grounds for considering that the requirements set out in this Regulation are no longer met, it may take the following measures on its territory:

(a) revoke the authorisation of a clinical trial;
(b) suspend a clinical trial;
(c) require the sponsor to modify any aspect of the clinical trial.

(2) Before the Member State concerned takes any of the measures referred to in paragraph 1 it shall, except where immediate action is required, ask the sponsor and/or the investigator for their opinion. That opinion shall be delivered within seven days.

(3) The Member State concerned shall immediately after taking a measure referred to in paragraph 1 inform all Member States concerned through the EU portal.

(4) Each Member State concerned may consult the other Member States concerned before taking any of the measures referred to in paragraph 1.

Article 78

Member State inspections

(1) Member States shall appoint inspectors to perform inspections in order to supervise compliance with this Regulation. They shall ensure that those inspectors are adequately qualified and trained.

(2) Inspections shall be conducted under the responsibility of the Member State where the inspection takes place.

(3) Where a Member State concerned intends to carry out an inspection on its territory or in a third country with regard to one or several clinical trials which are conducted in more than one Member State concerned, it shall notify its intention to the other Member States concerned, the Commission and the Agency, through the EU portal, and shall inform them of its findings after the inspection.

(4) Inspections fees, if any, may be waived for non-commercial sponsors.

(5) In order to efficiently use the resources available and to avoid duplications, the Agency shall coordinate the cooperation between Member States concerned on inspections conducted in Member States, in third countries, and inspections conducted in the framework of an application for a marketing authorisation under Regulation (EC) No 726/2004.
(6) Following an inspection, the Member State under whose responsibility the inspection has been conducted shall draw up an inspection report. That Member State shall make the inspection report available to the inspected entity and the sponsor of the relevant clinical trial and shall submit the inspection report through the EU portal.

(7) The Commission shall specify, by means of implementing acts, the detailed arrangements for the inspection procedures including the qualification and training requirements for inspectors. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 88(2).

Article 79

Union controls

(1) The Commission may conduct controls in order to verify:

(a) whether Member States correctly supervise compliance with this Regulation;
(b) whether the regulatory system applicable to clinical trials conducted outside the Union ensures that point 8 of the Introduction and general principles contained in Annex I to Directive 2001/83/EC is complied with;

(c) whether the regulatory system applicable to clinical trials conducted outside the Union ensures that Article 25(5) of this Regulation is complied with.

(2) The Union controls referred to in point (a) of paragraph 1 shall be organised in cooperation with the Member States concerned.

The Commission shall prepare in cooperation with the Member States a programme for the Union controls referred to in points (b) and (c) of paragraph 1.

The Commission shall report on the findings of each Union control carried out. Those reports shall, if appropriate, contain recommendations. The Commission shall submit those reports through the EU portal.

CHAPTER XIV

IT INFRASTRUCTURE

Article 80

EU Portal

The Agency shall, in collaboration with the Member States and the Commission, set up and maintain a portal at Union level as a single entry point for the submission of data and information relating to clinical trials in accordance with this Regulation. The EU portal shall be technically advanced and user-friendly so as to avoid unnecessary work.

Data and information submitted through the EU portal shall be stored in the EU database.

Article 81

EU database

(1) The Agency shall, in collaboration with the Member States and the Commission, set up and maintain a EU database at Union level. The Agency shall be considered to be the controller of the EU database and shall be responsible for avoiding unnecessary duplication between the EU database and the EudraCT and EudraVigilance databases.

The EU database shall contain the data and information submitted in accordance with this Regulation.

The EU database shall identify each clinical trial by a unique EU trial number. The sponsor shall refer to this EU trial number in any subsequent submission relating or referring to that clinical trial.

(2) The EU database shall be established to enable cooperation between the competent authorities of the Member States concerned to the extent that it is necessary for the application of this Regulation and to search for specific clinical trials. It shall also facilitate the communication between sponsors and Member States concerned and enable sponsors to refer to previous submissions of an application for authorisation of a clinical trial or a substantial modification. It shall also enable citizens of the Union to have access to clinical information about medicinal products. To this end all data held in the EU database shall be in an easily searchable format, all related data shall be grouped together by way of the EU trial number, and hyperlinks shall be provided to link together related data and documents held on the EU database and other databases managed by the Agency.

(3) The EU database shall support the recording and submission to the Medicinal Product Dictionary, contained in the EudraVigilance database, of all the data on medicinal products without a marketing authorisation in the Union and substances not authorised as part of a medicinal product in the Union, that are necessary for the maintenance of that dictionary. To this effect and also with the purpose of enabling the sponsor to cross-refer to prior applications, an EU medicinal product number shall be issued for every medicinal product without a marketing authorisation and an EU active substances code shall be issued for each new active substance not previously authorised as part of a medicinal product in the Union. This shall be done before or during the application for authorisation of the first clinical trial with that product or active substance submitted in accordance with this Regulation. Those numbers shall be mentioned in all subsequent applications for clinical trials and for substantial modifications.

The data submitted, in accordance with the first subparagraph, describing medicinal products and substances shall comply with Union and international standards for the identification of medicinal products and active substances. When an investigational medicinal product which already has a marketing authorisation in the Union and/or an active substance which is part of a medicinal product with a marketing authorisation in the Union, is to be used in a clinical trial, the relevant product and active substance numbers shall be referred to in the application for that clinical trial.

(4) The EU database shall be publicly accessible unless, for all or part of the data and information contained therein, confidentiality is justified on any of the following grounds:

(a) protecting personal data in accordance with Regulation (EC) No 45/2001;
(b) protecting commercially confidential information, in particular through taking into account the status of the marketing authorisation for the medicinal product, unless there is an overriding public interest in disclosure;
(c) protecting confidential communication between Member States in relation to the preparation of the assessment report;
(d) ensuring effective supervision of the conduct of a clinical trial by Member States.

(6) Without prejudice to paragraph 4, unless there is an overriding public interest in disclosure, data contained in the application dossier shall not be publicly accessible before the decision on the clinical trial has been made.

(7) The EU database shall contain personal data only insofar as this is necessary for the purposes of paragraph 2.

(8) No personal data of subjects shall be publicly accessible.

(9) The user interface of the EU database shall be available in all official languages of the Union.

(10) The sponsor shall permanently update in the EU database information on any changes to the clinical trials which are not substantial modifications but are relevant for the supervision of the clinical trial by the Member States concerned.

(11) The Agency, the Commission and Member States shall ensure that the data subject may effectively exercise his or her rights to information, to access, to rectify and to object in accordance with Regulation (EC) No 45/2001 and national data protection legislation implementing Directive 95/46/EC, respectively. They shall ensure that the data subject may effectively exercise the right of access to data relating to him or her, and the right to have inaccurate or incomplete data corrected or erased. Within their respective responsibilities, the Agency, the Commission and Member States shall ensure that inaccurate and unlawfully processed data are deleted, in accordance with the applicable law. Corrections and deletions shall be carried out as soon as possible, but no later than 60 days of a request being made by a data subject.

Article 82

Functionality of the EU portal and the EU database

(1) The Agency shall, in collaboration with the Member States and the Commission, draw up the functional specifications for the EU portal and the EU database, together with the time frame for their implementation.

(2) The Management Board of the Agency shall, on the basis of an independent audit report, inform the Commission when it has verified that the EU portal and the EU database have achieved full functionality and the systems meet the functional specifications drawn up pursuant to paragraph 1.

(3) The Commission shall, when it is satisfied that the conditions referred to in paragraph 2 have been fulfilled, publish a notice to that effect in the *Official Journal of the European Union*.

CHAPTER XV

COOPERATION BETWEEN MEMBER STATES

Article 83

National contact points

(1) Each Member State shall designate one national contact point in order to facilitate the functioning of the procedures set out in Chapters II and III.

(2) Each Member State shall communicate the contact point referred to in paragraph 1 to the Commission. The Commission shall publish a list of the national contact points.

Article 84

Support by the Agency and the Commission

The Agency shall support the functioning of the cooperation of the Member States in the framework of the authorisation procedures set out in Chapters II and III of this Regulation by maintaining and updating the EU portal and the EU database in accordance with the experience acquired during the implementation of this Regulation.

The Commission shall support the functioning of the cooperation of the Member States referred to in Article 44(2).

Article 85

Clinical trials coordination and advisory group

(1) A Clinical Trials Coordination and Advisory Group (CTAG), composed of the national contact points referred to in Article 83 is hereby established.

(2) The CTAG shall have the following tasks:

(a) to support the exchange of information between the Member States and the Commission on the experience acquired with regard to the implementation of this Regulation;
(b) to assist the Commission in providing the support referred to in the second paragraph of Article 84;
(c) to prepare recommendations on criteria regarding the selection of a reporting Member State.

(3) The CTAG shall be chaired by a representative of the Commission.

(4) The CTAG shall meet at regular intervals and whenever the situation requires, on a request from the Commission or a Member State. Any item of the agenda of the meeting shall be placed at the request of the Commission or a Member State.

(5) The secretariat shall be provided by the Commission.

(6) The CTAG shall draw up its rules of procedure. The rules of procedure shall be made public.

CHAPTER XVI

FEES

Article 86

General principle

This Regulation shall be without prejudice to the possibility for Member States to levy a fee for the activities set out in this Regulation, provided that the level of the fee is set in a transparent manner and on the basis of cost recovery principles. Member States may establish reduced fees for non-commercial clinical trials.

Article 87

One payment per activity per Member State

A Member State shall not require, for an assessment as referred to in Chapters II and III, multiple payments to different bodies involved in this assessment.

CHAPTER XVII

IMPLEMENTING ACTS AND DELEGATED ACTS

Article 88

Committee procedure

(1) The Commission shall be assisted by the Standing Committee on Medicinal Products for Human Use established by Directive 2001/83/EC. That committee shall be a committee within the meaning of Regulation (EU) No 182/2011.

(2) Where reference is made to this paragraph, Article 5 of Regulation (EU) No 182/2011 shall apply.

Where the committee delivers no opinion, the Commission shall not adopt the draft implementing act and the third subparagraph of Article 5(4) of Regulation (EU) No 182/2011 shall apply.

Article 89

Exercise of the delegation

(1) The power to adopt delegated acts is conferred on the Commission subject to the conditions laid down in this Article.

(2) The power to adopt delegated acts referred to in Articles 27, 39, 45, 63(1) and 70 shall be conferred on the Commission for a period of five years from the date referred to in the second paragraph of Article 99. The Commission shall draw up a report in respect of the delegated powers not later than six months before the end of the five year period. The delegation of powers shall be tacitly extended for periods of an identical

duration, unless the European Parliament or the Council opposes such extension not later than three months before the end of each period.

(3) The delegation of power referred to in Articles 27, 39, 45, 63(1) and 70 may be revoked at any time by the European Parliament or by the Council. A decision of revocation shall put an end to the delegation of the power specified in that decision. It shall take effect the day following the publication of the decision in the *Official Journal of the European Union* or at a later date specified therein. It shall not affect the validity of any delegated acts already in force.

(4) As soon as it adopts a delegated act, the Commission shall notify it simultaneously to the European Parliament and to the Council.

(5) A delegated act adopted pursuant to Articles 27, 39, 45, 63(1) and 70 shall enter into force only if no objection has been expressed either by the European Parliament or the Council within a period of two months from notification of that act to the European Parliament and the Council or if, before the expiry of that period, the European Parliament and the Council have both informed the Commission that they will not object. That period shall be extended by two months at the initiative of the European Parliament or the Council.

CHAPTER XVIII

MISCELLANEOUS PROVISIONS

Article 90

Specific requirements for special groups of medicinal products

This Regulation shall not affect the application of national law prohibiting or restricting the use of any specific type of human or animal cells, or the sale, supply or use of medicinal products containing, consisting of or derived from those cells, or of medicinal products used as abortifacients or of medicinal products containing narcotic substances within the meaning of the relevant international conventions in force such as the Single Convention on Narcotic Drugs of 1961 of the United Nations. The Member States shall communicate that national law to the Commission.

No gene therapy clinical trials may be carried out which result in modifications to the subject's germ line genetic identity.

Article 91

Relation with other Union legislation

This Regulation shall be without prejudice to Council Directive 97/43/Euratom ([13]), Council Directive 96/29/Euratom ([14]), Directive 2001/18/EC of the European Parliament and of the Council ([15]), Directive 2004/23/EC of the European Parliament and of the Council ([16]), Directive 2002/98/EC of the European Parliament and of the Council ([17]), Directive 2010/53/EC of the European Parliament and of the Council ([18]), and Directive 2009/41/EC of the European Parliament and of the Council. ([19])

Article 92

Investigational medicinal products, other products and procedures, free of charge for the subject

Without prejudice to the Member States' competence for the definition of their health policy and for the organisation and delivery of health services and medical care, the costs for investigational medicinal products, auxiliary medicinal products, medical devices used for their administration and procedures specifically required by the protocol shall not be borne by the subject, unless the law of the Member State concerned provides otherwise.

Article 93

[13] Council Directive 97/43/Euratom of 30 June 1997 on health protection of individuals against the dangers of ionizing radiation in relation to medical exposure, and repealing Directive 84/466/Euratom (OJ L 180, 9.7.1997, p. 22).

[14] Council Directive 96/29/Euratom

[15] Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC (OJ L 106, 17.4.2001, p. 1).

[16] Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells (OJ L 102, 7.4.2004, p. 48).

[17] Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC (OJ L 33, 8.2.2003, p. 30).

[18] Directive 2010/53/EU of the European Parliament and of the Council of 7 July 2010 on standards of quality and safety of human organs intended for transplantation (OJ L 207, 6.8.2010, p. 14).

[19] Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms (OJ L 125, 21.5.2009, p. 75).

Data protection

(1) Member States shall apply Directive 95/46/EC to the processing of personal data carried out in the Member States pursuant to this Regulation.

(2) Regulation (EC) No 45/2001 shall apply to the processing of personal data carried out by the Commission and the Agency pursuant to this Regulation.

Article 94

Penalties

(1) Member States shall lay down rules on penalties applicable to infringements of this Regulation and shall take all measures necessary to ensure that they are implemented. The penalties provided for shall be effective, proportionate and dissuasive.

(2) The rules referred to in paragraph 1 shall address, inter alia, the following:

(a) non-compliance with the provisions laid down in this Regulation on submission of information intended to be made publicly available to the EU database;

(b) non-compliance with the provisions laid down in this Regulation on subject safety.

Article 95

Civil and criminal liability

This Regulation is without prejudice to national and Union law on the civil and criminal liability of a sponsor or an investigator.

CHAPTER XIX

FINAL PROVISIONS

Article 96

Repeal

(1) Directive 2001/20/EC is repealed as from the date referred to in the second paragraph of Article 99.

(2) References to Directive 2001/20/EC shall be construed as references to this Regulation and shall be read in accordance with the correlation table laid down in Annex VII.

Article 97

Review

Five years after the date referred to in the second paragraph of Article 99, and every five years thereafter, the Commission shall present a report to the European Parliament and to the Council on the application of this Regulation. That report shall include an assessment of the impact that the Regulation has had on scientific and technological progress, comprehensive information on the different types of clinical trials authorised pursuant to this Regulation, and the measures required in order to maintain the competitiveness of European clinical research. The Commission shall, if appropriate, present a legislative proposal based on that report in order to update the provisions set out in this Regulation.

Article 98

Transitional provisions

(1) By way of derogation from Article 96(1) of this Regulation, where the request for authorisation of a clinical trial has been submitted before the date referred to in the second paragraph of Article 99 of this Regulation pursuant to Directive 2001/20/EC, that clinical trial shall continue to be governed by that Directive until three years from that date.

(2) By way of derogation from Article 96(1) of this Regulation, where the request for authorisation of a clinical trial is submitted between six months after the date of publication of the notice referred to in Article 82(3) of this Regulation and 18 months after the date of publication of that notice, or, if the publication of that notice occurs earlier than 28 November 2015, where that request is submitted between 28 May 2016 and 28 May 2017, that clinical trial may be started in accordance with Articles 6, 7 and 9 of Directive 2001/20/EC. That clinical trial shall continue to be governed by that Directive until 42 months after the date of publication of the notice referred to in Article 82(3) of this Regulation, or, if that publication occurs earlier than 28 November 2015, until 28 May 2019.

Article 99

Entry into force

This Regulation shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Union*.

It shall apply as from six months after the publication of the notice referred to in Article 82(3), but in any event no earlier than 28 May 2016.

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Strasbourg, 16 April 2014.

For the European Parliament	*For the Council*
The President	*The President*
M. SCHULZ	D. KOURKOULAS

ANNEX I

APPLICATION DOSSIER FOR THE INITIAL APPLICATION

A. INTRODUCTION AND GENERAL PRINCIPLES

1. The sponsor shall, where appropriate, refer to any previous applications. If these applications have been submitted by another sponsor, the written agreement from that sponsor shall be submitted.

2. Where a clinical trial has more than one sponsor, detailed information of the responsibilities of each of the sponsors shall be submitted in the application dossier.

3. The application shall be signed by the sponsor or a representative of the sponsor. This signature confirms that the sponsor is satisfied that:

(a) the information provided is complete;

(b) the attached documents contain an accurate account of the information available;

(c) the clinical trial is to be conducted in accordance with the protocol; and

(d) the clinical trial is to be conducted in accordance with this Regulation.

4. The application dossier for an application limited to Part I of the assessment report referred to in Article 11 shall be limited to sections B to J and Q of this Annex.

5. Without prejudice to Article 26, the application dossier for an application limited to Part II of the assessment report referred to in Article 11 and the application dossier for an application referred to in Article 14 shall be limited to sections K to R of this Annex.

B. COVER LETTER

6. The cover letter shall specify the EU trial number and the universal trial number and shall draw attention to any features which are particular to the clinical trial.

7. However, in the cover letter it is not necessary to reproduce information already contained in the EU application form, with the following exceptions:

(a) specific features of the clinical trial population, such as subjects not able to give informed consent, minors and pregnant or breastfeeding women;

(b) whether the clinical trial involves the first administration of a new active substance to humans;

(c) whether scientific advice relating to the clinical trial or the investigational medicinal product has been given by the Agency, a Member State or a third country;

(d) whether the clinical trial is part or is intended to be part of a Paediatric Investigation Plan (PIP) as referred to in Title II, Chapter 3, of Regulation (EC) No 1901/2006 (if the Agency has already issued a decision on the PIP, the cover letter contains the link to the decision of the Agency on its website);

(e) whether investigational medicinal products or auxiliary medicinal products are a narcotic, psychotropic or radiopharmaceutical;

(f) whether the investigational medicinal products consist of or contain a genetically-modified organism or organisms;

(g) whether the sponsor has obtained an orphan designation for the investigational medicinal product for an orphan condition;

(h) a comprehensive list, including the regulatory status, of all investigational medicinal products and a list of all auxiliary medicinal products; and

(i) a list of medical devices which are to be investigated in the clinical trial but which are not part of the investigational medicinal product or products, together with a statement as to whether the medical devices are CE-marked for the intended use.

8. The cover letter shall indicate where the information listed in paragraph 7 is contained in the application dossier.

9. The cover letter shall indicate if the clinical trial is considered by the sponsor to be a low-intervention clinical trial and shall contain a detailed justification thereof.

10. The cover letter shall indicate if the methodology of the clinical trial requires that groups of subjects rather than individual subjects are allocated to receive different investigational medicinal products in a clinical trial, and as a consequence whether informed consent will be obtained by simplified means.

11. The cover letter shall indicate the location in the application dossier of the information necessary for assessing whether an adverse reaction is a suspected unexpected serious adverse reaction, that is the reference safety information.

12. In the case of a resubmission, the cover letter shall specify the EU trial number for the previous clinical trial application, highlight the changes as compared to the previous submission and, if applicable, specify how any unresolved issues in the first submission have been addressed.

C. EU APPLICATION FORM

13. The EU application form, duly completed.

D. PROTOCOL

14. The protocol shall describe the objective, design, methodology, statistical considerations, purpose and organisation of the clinical trial.

15. The protocol shall be identified by:

(a) the title of the clinical trial;

(b) the EU trial number;

(c) the sponsor's protocol code number specific for all versions of it (if relevant);

(d) the date and number of the version, to be updated when it is amended;

(e) a short title or name assigned to the protocol; and

(f) the name and address of the sponsor, as well as the name and function of the representative or representatives of the sponsor authorised to sign the protocol or any substantial modification to the protocol.

16. The protocol shall, when possible, be written in an easily accessible and searchable format, rather than scanned images.

17. The protocol shall at least include:

(a) a statement that the clinical trial is to be conducted in compliance with the protocol, with this Regulation and with the principles of good clinical practice;

(b) a comprehensive list of all investigational medicinal products and of all auxiliary medicinal products;

(c) a summary of findings from non-clinical studies that potentially have clinical significance and from other clinical trials that are relevant to the clinical trial;

(d) a summary of the known and potential risks and benefits including an evaluation of the anticipated benefits and risks to allow assessment in accordance with Article 6; for subjects in a clinical trial in an emergency situation, the scientific grounds for expecting that the participation of the subjects has the potential to produce a direct clinically relevant benefit shall be documented;

(e) where patients were involved in the design of the clinical trial, a description of their involvement;

(f) a description of, and justification for, the dosage, the dosage regime, the route and mode of administration, and the treatment period for all investigational medicinal products and auxiliary medicinal products;

(g) a statement of whether the investigational medicinal products and auxiliary medicinal products used in the clinical trial are authorised; if authorised, whether they are to be used in the clinical trial in accordance with the terms of their marketing authorisations, and, if not authorised, a justification for the use of non-authorised auxiliary medicinal products in the clinical trial;

(h) a description of the groups and subgroups of the subjects participating in the clinical trial, including, where relevant, groups of subjects with specific needs, for example age, gender, participation of healthy volunteers, subjects with rare and ultra-rare diseases;

(i) references to literature and data that are relevant to the clinical trial, and that provide background for the clinical trial;

(j) a discussion of the relevance of the clinical trial in order to allow assessment in accordance with Article 6;

(k) a description of the type of clinical trial to be conducted and a discussion of the trial design (including a schematic diagram of trial design, procedures and stages, if relevant);

(l) a specification of the primary end-points and the secondary end-points, if any, to be measured during the clinical trial;

(m) a description of the measures taken to minimise bias, including, if applicable, randomisation and blinding;

(n)a description of the expected duration of subject participation and a description of the sequence and duration of all clinical trial periods, including follow-up, if relevant;

(o) a clear and unambiguous definition of the end of the clinical trial in question and, if it is not the date of the last visit of the last subject, a specification of the estimated end date and a justification thereof;

(p) a description of the criteria for discontinuing parts of the clinical trial or the entire clinical trial;

(q) arrangements for the maintenance of clinical trial treatment randomisation codes and procedures for breaking codes, if relevant;

(r) a description of procedures for the identification of data to be recorded directly on the Case Report Forms considered as source data;

(s) a description of the arrangements to comply with the applicable rules for the collection, storage and future use of biological samples from clinical trial subjects, where applicable, unless contained in a separate document;

(t) a description of the arrangements for tracing, storing, destroying and returning the investigational medicinal product and unauthorised auxiliary medicinal product in accordance with Article 51;

(u) a description of the statistical methods to be employed, including, if relevant:

- timing of any planned interim analysis and the number of subjects planned to be enrolled;

- reasons for choice of sample size;

- calculations of the power of the clinical trial and clinical relevance;

- the level of significance to be used;

- criteria for the termination of the clinical trial;

- procedures for accounting for missing, unused, and spurious data and for reporting any deviation from the original statistical plan; and

- the selection of subjects to be included in the analyses;

(v) a description of the subject inclusion and exclusion criteria, including criteria for withdrawing individual subjects from treatment or from the clinical trial;

(w) a description of procedures relating to the withdrawal of subjects from treatment or from the clinical trial including procedures for the collection of data regarding withdrawn subjects, procedures for replacement of subjects and the follow-up of subjects that have withdrawn from treatment or from the clinical trial;

(x) a justification for including subjects who are incapable of giving informed consent or other special populations, such as minors;

(y) a justification for the gender and age allocation of subjects and, if a specific gender or age group is excluded from or underrepresented in the clinical trials, an explanation of the reasons and justification for these exclusion criteria;

(z) a detailed description of the recruitment and informed consent procedure, especially when subjects are incapable of giving informed consent;

(aa) a description of the treatments, including medicinal products, which are permitted or not permitted, before or during the clinical trial;

(ab) a description of the accountability procedures for the supply and administration of medicinal products to subjects including the maintenance of blinding, if applicable;

(ac) a description of procedures for monitoring subject compliance, if applicable;

(ad) a description of arrangements for monitoring the conduct of the clinical trial;

(ae) a description of the arrangements for taking care of the subjects after their participation in the clinical trial has ended, where such additional care is necessary because of the subjects' participation in the clinical trial and where it differs from that normally expected for the medical condition in question;

(af) a specification of the efficacy and safety parameters as well as the methods and timing for assessing, recording, and analysing these parameters;

(ag) a description of ethical considerations relating to the clinical trial if those have not been described elsewhere;

(ah) a statement from the sponsor (either in the protocol or in a separate document) confirming that the investigators and institutions involved in the clinical trial are to permit clinical trial-related monitoring, audits and regulatory inspections, including provision of direct access to source data and documents;

(ai) a description of the publication policy;

(aj) duly substantiated reasons for the submission of the summary of the results of the clinical trials after more than one year;

(ak) a description of the arrangements to comply with the applicable rules on the protection of personal data; in particular organisational and technical arrangements that will be implemented to avoid unauthorised access, disclosure, dissemination, alteration or loss of information and personal data processed;

(al) a description of measures that will be implemented to ensure confidentiality of records and personal data of subjects;

(am) a description of measures that will be implemented in case of data security breach in order to mitigate the possible adverse effects.

18. If a clinical trial is conducted with an active substance available in the Union under different trade names in a number of authorised medicinal products, the protocol may define the treatment in terms of the active substance or Anatomical Therapeutic Chemical (ATC) code (level 3-5) only and not specify the trade name of each product.

19. With regard to the notification of adverse events, the protocol shall identify the categories of:

(a) adverse events or laboratory anomalies that are critical to safety evaluations and must be reported by the investigator to the sponsor, and

(b) serious adverse events which do not require immediate reporting by the investigator to the sponsor.

20. The protocol shall describe the procedures for:

(a) eliciting and recording adverse events by the investigator, and the reporting of relevant adverse events by the investigator to the sponsor;

(b) reporting by the investigator to the sponsor of those serious adverse events which have been identified in the protocol as not requiring immediate reporting;

(c) reporting of suspected unexpected serious adverse reactions by the sponsor to the EudraVigilance database; and

(d) follow-up of subjects after adverse reactions including the type and duration of follow-up.

21. In case the sponsor intends to submit a single safety report on all investigational medicinal products used in the clinical trial in accordance with Article 43(2), the protocol shall indicate the reasons thereof.

22. Issues regarding labelling and the unblinding of investigational medicinal products shall be addressed in the protocol, where necessary.

23. The protocol shall be accompanied by the Charter of the Data Safety Monitoring Committee, if applicable.

24. The protocol shall be accompanied by a synopsis of the protocol.

E. INVESTIGATOR'S BROCHURE (IB)

25. An IB, which has been prepared in accordance with the state of scientific knowledge and international guidance, shall be submitted.

26. The purpose of the IB is to provide the investigators and others involved in the clinical trial with information to facilitate their understanding of the rationale for, and their compliance with, key features of the protocol, such as the dose, dose frequency/interval, methods of administration, and safety monitoring procedures.

27. The information in the IB shall be presented in a concise, simple, objective, balanced and non-promotional form that enables a clinician or investigator to understand it and make an unbiased risk-benefit assessment of the appropriateness of the proposed clinical trial. It shall be prepared from all available information and evidence that supports the rationale for the proposed clinical trial and the safe use of the investigational medicinal product in the clinical trial and be presented in the form of summaries.

28. If the investigational medicinal product is authorised, and is used in accordance with the terms of the marketing authorisation, the approved summary of product characteristics (SmPC) shall be the IB. If the conditions of use in the clinical trial differ from those authorised, the SmPC shall be supplemented with a summary of relevant non-clinical and clinical data that support the use of the investigational medicinal product in the clinical trial. Where the investigational medicinal product is identified in the protocol only by its active substance, the sponsor shall select one SmPC as equivalent to the IB for all medicinal products that contain that active substance and are used at any clinical trial site.

29. For a multinational clinical trial where the medicinal product to be used in each Member State concerned is authorised at national level, and the SmPC varies among Member States concerned, the sponsor shall choose one SmPC for the whole clinical trial. This SmPC shall be the one best suited to ensure patient safety.

30. If the IB is not an SmPC, it shall contain a clearly identifiable section called the ‘Reference Safety Information’ (RSI). In accordance with paragraphs 10 and 11 of Annex III, the RSI shall contain product information on the investigational medicinal product and on how to determine what adverse reactions are to be considered as expected adverse reactions, and on the frequency and nature of those adverse reactions.

F. DOCUMENTATION RELATING TO COMPLIANCE WITH GOOD MANUFACTURING PRACTICE (GMP) FOR THE INVESTIGATIONAL MEDICINAL PRODUCT

31. As regards documentation relating to GMP compliance, the following shall apply.

32. No documentation needs to be submitted where the investigational medicinal product is authorised and is not modified, whether or not it is manufactured in the Union.

33. If the investigational medicinal product is not authorised, and does not have a marketing authorisation from a third country that is party to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), and is not manufactured in the Union, the following documentation shall be submitted:

(a) a copy of the authorisation referred to in Article 61; and

(b) certification by the qualified person in the Union that the manufacturing complies with GMP at least equivalent to the GMP in the Union, unless there are specific arrangements provided for in mutual recognition agreements between the Union and third countries.

34. In all other cases, a copy of the authorisation referred to in Article 61 shall be submitted.

35. For processes related to investigational medicinal products set out in Article 61(5), which are not subject to an authorisation in accordance with Article 61, documentation to demonstrate compliance with the requirements referred to in Article 61(6) shall be submitted.

G. INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER (IMPD)

36. The IMPD shall give information on the quality of any investigational medicinal product, the manufacture and control of the investigational medicinal product, and data from non-clinical studies and from its clinical use.

1.1. **Data relating to the investigational medicinal product**

Introduction

37. Regarding data, the IMPD may be replaced by other documentation which may be submitted alone or with a simplified IMPD. The details of this 'simplified IMPD' are set out in section 1.2 'Simplified IMPD by referring to other documentation'.

38. Each section of the IMPD shall be prefaced with a detailed table of contents and a glossary of terms.

39. The information in the IMPD shall be concise. The IMPD must not be unnecessarily voluminous. It is preferable to present data in tabular form accompanied by a brief narrative highlighting the main salient points.

Quality data

40. Quality data shall be submitted in a logical structure such as that of Module 3 of the ICH Common Technical Document format.

Non-clinical pharmacology and toxicology data

41. The IMPD shall also contain summaries of non-clinical pharmacology and toxicology data for any investigational medicinal product used in the clinical trial in accordance with international guidance. It shall contain a reference list of studies conducted and appropriate literature references. Wherever appropriate, it is preferable to present data in tabular form accompanied by a brief narrative highlighting the main salient points. The summaries of the studies conducted shall allow an assessment of the adequacy of the study and whether the study has been conducted according to an acceptable protocol.

42. Non-clinical pharmacology and toxicology data shall be submitted in a logical structure, such as that of Module 4 of the ICH Common Technical Document format.

43. The IMPD shall provide a critical analysis of the data, including justification for omissions of data, and an assessment of the safety of the product in the context of the proposed clinical trial rather than a mere factual summary of the studies conducted.

44. The IMPD shall contain a statement of the good laboratory practice status or equivalent standards, as referred to in Article 25(3).

45. The test material used in toxicity studies shall be representative of that of the clinical trial use in terms of qualitative and quantitative impurity prodossiers. The preparation of the test material shall be subject to the controls necessary to ensure this and thus support the validity of the study.

Data from previous clinical trials and human experience

46. Data from previous clinical trials and human experience shall be submitted in a logical structure, such as that of Module 5 of the ICH Common Technical Document format.

47. This section shall provide summaries of all available data from previous clinical trials and human experience with the investigational medicinal products. It shall also contain a statement of the compliance with good clinical practice of those previous clinical trials, as well as a reference to the public entry referred to in Article 25(6).

Overall risk and benefit assessment

48. This section shall provide a brief integrated summary that critically analyses the non-clinical and clinical data in relation to the potential risks and benefits of the investigational medicinal product in the proposed clinical trial unless this information is already provided in the protocol. In the latter case, it shall cross-refer to the relevant section in the protocol. The text shall identify any studies that were terminated prematurely and discuss the reasons. Any evaluation of foreseeable risks and anticipated benefits for studies on minors or incapacitated adults shall take account of the specific provisions set out in this Regulation.

49. Where appropriate, safety margins shall be discussed in terms of relative systemic exposure to the investigational medicinal product, preferably based on 'area under the curve' (AUC) data, or peak concentration (C_{max}) data, whichever is considered more relevant, rather than in terms of applied dose. The

clinical relevance of any findings in the non-clinical and clinical studies along with any recommendations for further monitoring of effects and safety in the clinical trials shall also be discussed.

1.2. **Simplified IMPD by referring to other documentation**

50. The applicant may refer to other documentation submitted alone or with a simplified IMPD.

Possibility of referring to the IB

51. The applicant may either provide a stand-alone IMPD or cross-refer to the IB for the reference safety information and the summaries of pre-clinical and clinical parts of the IMPD. In the latter case, the summaries of pre- clinical information and clinical information shall include data, preferably in tables, providing sufficient detail to allow assessors to reach a decision on the potential toxicity of the investigational medicinal product and the safety of its use in the proposed clinical trial. If there is some special aspect of the pre-clinical data or clinical data that requires a detailed expert explanation or discussion beyond what would usually be included in the IB, the pre-clinical and clinical information shall be submitted as part of the IMPD.

Possibility of referring to the SmPC

52. The applicant may submit the version of the SmPC valid at the time of application, as the IMPD if the investigational medicinal product is authorised. The exact requirements are detailed in Table 1. Where new data are provided, it should be clearly identified.

Table 1 - Content of the simplified IMPD

Types of previous assessment	Quality data	Non-clinical data	Clinical data
The investigational medicinal product is authorised or has a marketing authorisation in an ICH country and is used in the clinical trial: - in accordance with the conditions specified in the SmPC;			
- within the conditions of the SmPC;	SmPC		
- outside the conditions of the SmPC (for example blinding).	SmPC	If appropriate	If appropriate
	P+A	SmPC	SmPC
Another pharmaceutical form or strength of the investigational medicinal product is authorised or has a marketing authorisation in an ICH country and the investigational medicinal product is supplied by the marketing authorisation holder	SmPC+M+I	Yes	Yes
The investigational medicinal product is not authorised and has no marketing authorisation in an ICH country but the active substance is contained in an authorised medicinal product, and - is supplied by the same manufacturer;			
- is supplied by another manufacturer.	SmPC+P+A	Yes	Yes
	SmPC+S+P+A	Yes	Yes
The investigational medicinal product was subject to a previous clinical trial application and authorised in the Member State concerned and has not been modified, and - no new data are available since last amendment to the clinical trial application,			
- new data are available since last amendment to the clinical trial application,	Reference to previous submission		
- is used under different conditions	New data	New data	New data
	If appropriate	If appropriate	If appropriate

(S: Data relating to the active substance; P: Data relating to the investigational medicinal product; A: Additional information on Facilities and Equipment, Adventitious Agents Safety Evaluation, Novel Excipients, and Solvents for Reconstitution and Diluents)

53. If the investigational medicinal product is defined in the protocol in terms of active substance or ATC code (see above, paragraph 18), the applicant may replace the IMPD by one representative SmPC for each active substance/active substance pertaining to that ATC group. Alternatively, the applicant may provide a collated document containing information equivalent to that in the representative SmPCs for each active substance that could be used as an investigational medicinal product in the clinical trial.

1.3. **IMPD in cases of placebo**

54. If the investigational medicinal product is a placebo, the information requirements shall be limited to quality data. No additional documentation is required if the placebo has the same composition as the tested investigational medicinal product (with the exception of the active substance), is manufactured by the same manufacturer, and is not sterile.

H. AUXILIARY MEDICINAL PRODUCT DOSSIER

55. Without prejudice to Article 65, the documentation requirements set out in sections F and G shall also apply to auxiliary medicinal products. However, where the auxiliary medicinal product is authorised in the Member State concerned, no additional information is required.

I. SCIENTIFIC ADVICE AND PAEDIATRIC INVESTIGATION PLAN (PIP)

56. If available, a copy of the summary of scientific advice of the Agency, or of any Member State or third country, with regard to the clinical trial shall be submitted.

57. If the clinical trial is part of an agreed PIP, a copy of the Agency's decision on the agreement on the PIP, and the opinion of the Paediatric Committee, unless these documents are fully accessible via the internet shall be submitted. In the latter case, a link to this documentation in the cover letter is sufficient (see section B).

J. CONTENT OF THE LABELLING OF THE INVESTIGATIONAL MEDICINAL PRODUCTS

58. A description of the content of the labelling of the investigational medicinal product in accordance with Annex VI shall be provided.

K. RECRUITMENT ARRANGEMENTS (INFORMATION PER MEMBER STATE CONCERNED)

59. Unless described in the protocol, a separate document shall describe in detail the procedures for inclusion of subjects and shall provide a clear indication of what the first act of recruitment is.

60. Where the recruitment of subjects is done through advertisement, copies of the advertising material shall be submitted, including any printed materials, and audio or visual recordings. The procedures proposed for handling responses to the advertisement shall be outlined. This includes copies of communications used to invite subjects to participate in the clinical trial and arrangements for information or advice to the respondents found not to be suitable for inclusion in the clinical trial.

L. SUBJECT INFORMATION, INFORMED CONSENT FORM AND INFORMED CONSENT PROCEDURE (INFORMATION PER MEMBER STATE CONCERNED)

61. All information given to the subjects (or, where applicable, to their legally designated representatives) before their decision to participate or abstain from participation shall be submitted together with the form for written informed consent, or other alternative means according to Article 29(1) for recording informed consent.

62. A description of procedures relating to informed consent for all subjects, and in particular:

(a) in clinical trials with minors or incapacitated subjects, the procedures to obtain informed consent from the legally designated representatives, and the involvement of the minor or incapacitated subject shall be described;

(b) if a procedure with consent witnessed by an impartial witness is to be used, relevant information on the reason for using an impartial witness, on the selection of the impartial witness and on the procedure for obtaining informed consent shall be provided;

(c) in the case of clinical trials in emergency situations as referred to in Article 35, the procedure for obtaining the informed consent of the subject or the legally designated representative to continue the clinical trial shall be described;

(d) in the case of clinical trials in emergency situations as referred to in Article 35, the description of the procedures followed to identify the urgency of the situation and to document it;

(e) in the case of clinical trials where their methodology requires that groups of subjects rather than individual subjects are allocated to receive different investigational medicinal products, as referred to in Article 30, and where, as a consequence, simplified means for obtaining informed consent will be used, the simplified means shall be described.

63. In the cases set out in paragraph 62, the information given to the subject and to his or her legally designated representative shall be submitted.

M. SUITABILITY OF THE INVESTIGATOR (INFORMATION PER MEMBER STATE CONCERNED)

64. A list of the planned clinical trial sites, the name and position of the principal investigators and the planned number of subjects at the sites shall be submitted.

65. Description of the qualification of the investigators in a current curriculum vitae and other relevant documents shall be submitted. Any previous training in the principles of good clinical practice or experience obtained from work with clinical trials and patient care shall be described.

66. Any conditions, such as economic interests and institutional affiliations that might influence the impartiality of the investigators shall be presented.

N. SUITABILITY OF THE FACILITIES (INFORMATION PER MEMBER STATE CONCERNED)

67. A duly justified written statement on the suitability of the clinical trial sites adapted to the nature and use of the investigational medicinal product and including a description of the suitability of facilities, equipment, human resources and description of expertise, issued by the head of the clinic/institution at the clinical trial site or by some other responsible person, according to the system in the Member State concerned, shall be submitted.

O. PROOF OF INSURANCE COVER OR INDEMNIFICATION (INFORMATION PER MEMBER STATE CONCERNED)

68. Proof of insurance, a guarantee, or a similar arrangement shall be submitted, if applicable.

P. FINANCIAL AND OTHER ARRANGEMENTS (INFORMATION PER MEMBER STATE CONCERNED)

69. A brief description of the financing of the clinical trial.

70. Information on financial transactions and compensation paid to subjects and investigator/site for participating in the clinical trial shall be submitted.

71. Description of any other agreement between the sponsor and the site shall be submitted.

Q. PROOF OF PAYMENT OF FEE (INFORMATION PER MEMBER STATE CONCERNED)

72. Proof of payment shall be submitted, if applicable.

R. PROOF THAT DATA WILL BE PROCESSED IN COMPLIANCE WITH UNION LAW ON DATA PROTECTION

73. A statement by the sponsor or his or her representative that data will be collected and processed in accordance with Directive 95/46/EEC shall be provided.

ANNEX II

APPLICATION DOSSIER FOR SUBSTANTIAL MODIFICATION

A. INTRODUCTION AND GENERAL PRINCIPLES

1. Where a substantial modification concerns more than one clinical trial of the same sponsor and the same investigational medicinal product, the sponsor may make a single request for authorisation of the substantial modification. The cover letter shall contain a list of all clinical trials to which the application for substantial modification relates, with the EU trial numbers and respective modification code numbers of each of those clinical trials.

2. The application shall be signed by the sponsor or a representative of the sponsor. This signature shall confirm that the sponsor is satisfied that:

(a) the information provided is complete;

(b) the attached documents contain an accurate account of the information available; and

(c) the clinical trial will be conducted in accordance with the amended documentation.

B. COVER LETTER

3. A cover letter with the following information:

(a) in its subject line, the EU trial number with the title of the clinical trial and the substantial modification code number which allows unique identification of the substantial modification, and which shall be used consistently throughout the application dossier;

(b) identification of the applicant;

(c) identification of the substantial modification (the sponsor's substantial modification code number and date), whereby the modification may refer to several changes in the protocol or scientific supporting documents;

(d) a highlighted indication of any special issues relating to the modification and an indication as to where the relevant information or text is located in the original application dossier;

(e) identification of any information not contained in the modification application form that might impact on the risk to subjects; and

(f) where applicable, a list of all clinical trials which are substantially modified, with EU trial numbers and respective modification code numbers.

C. MODIFICATION APPLICATION FORM

4. The modification application form, duly completed.

D. DESCRIPTION OF THE MODIFICATION

5. The modification shall be presented and described as follows:

(a) an extract from the documents to be amended showing previous and new wording in track changes, as well as an extract showing only the new wording, and an explanation of the changes; and

(b) notwithstanding point (a), if the changes are so widespread or far-reaching that they justify an entirely new version of the document, a new version of the entire document (in such cases, an additional table lists the amendments to the documents, whereby identical changes can be grouped).

6. The new version of the document shall be identified by the date and an updated version number.

E. SUPPORTING INFORMATION

7. Where applicable, additional supporting information shall at least include:

(a) summaries of data;

(b) an updated overall risk/benefit assessment

(c) possible consequences for subjects already included in the clinical trial;

(d) possible consequences for the evaluation of the results;

(e) documents which relate to any changes to the information provided to subjects or their legally designated representatives, the informed consent procedure, informed consent forms, information sheets, or to letters of invitation; and

(f) a justification for the changes sought in the application for a substantial modification.

F. UPDATE OF EU APPLICATION FORM

8. If a substantial modification involves changes to entries on the EU application form referred to in Annex I, a revised version of that form shall be submitted. The fields affected by the substantial modification shall be highlighted in the revised form.

G. PROOF OF PAYMENT OF FEE (INFORMATION PER MEMBER STATE CONCERNED)

9. Proof of payment shall be submitted, if applicable.

ANNEX III

SAFETY REPORTING

1. REPORTING OF SERIOUS ADVERSE EVENTS BY THE INVESTIGATOR TO THE SPONSOR

1. The investigator does not need to actively monitor subjects for adverse events once the clinical trial has ended with regard to the subjects treated by him, unless otherwise provided for in the protocol.

2. REPORTING OF SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS (SUSARS) BY THE SPONSOR TO THE AGENCY IN ACCORDANCE WITH ARTICLE 42

2.1. **Adverse events and causality**

2. Medication errors, pregnancies and uses outside what is foreseen in the protocol, including misuse and abuse of the product, shall be subject to the same obligation to report as adverse reactions.

3. In determining whether an adverse event is an adverse reaction, consideration shall be given to whether there is a reasonable possibility of establishing a causal relationship between the event and the investigational medicinal product based on an analysis of available evidence.

4. In the absence of information on causality provided by the reporting investigator, the sponsor shall consult the reporting investigator and encourage him to express an opinion on this issue. The causality assessment given by the investigator shall not be downgraded by the sponsor. If the sponsor disagrees with the investigator's causality assessment, the opinion of both the investigator and the sponsor shall be provided with the report.

2.2. **Expectedness, unexpectedness and the RSI**

5. In determining whether an adverse event is unexpected, consideration shall be given to whether the event adds significant information on the specificity, increase of occurrence, or severity of a known, already documented serious adverse reaction.

6. The expectedness of an adverse reaction shall be set out by the sponsor in the RSI. Expectedness shall be determined on the basis of events previously observed with the active substance and not on the basis of the anticipated pharmacological properties of a medicinal product or events related to the subject's disease.

7. The RSI shall be contained in the SmPC or the IB. The covering letter shall refer to the location of the RSI in the application dossier. If the investigational medicinal product is authorised in several Member States concerned with different SmPCs, the sponsor shall select the most appropriate SmPC, with reference to subject safety, as the RSI.

8. The RSI may change during the conduct of a clinical trial. For the purpose of reporting SUSARs the version of the RSI at the moment of occurrence of the SUSAR shall apply. Thus, a change of the RSI impacts on the number of adverse reactions to be reported as SUSARs. Regarding the applicable RSI for the purpose of the annual safety report, see section 3 of this Annex.

9. If information on expectedness has been provided by the reporting investigator, this shall be taken into consideration by the sponsor.

2.3. **Information for the reporting of SUSARs**

10. The information shall at least include:

(a) a valid EU trial number;
(b) a sponsor study number;
(c) an identifiable coded subject;
(d) an identifiable reporter;
(e) a SUSAR;
(f) a suspect investigational medicinal product (including active substance name-code);
(g) a causality assessment.

11. In addition, in order to properly process the report electronically, the following administrative information shall be provided:

(a) the sender's (case) safety report unique identifier;

(b) the receive date of the initial information from the primary source;

(c) the receipt date of the most recent information;

(d) the worldwide unique case identification number; (e) the sender identifier.

2.4. **Follow-up reports of SUSARs**

12. If the initial report of a SUSAR referred to in point (a) of Article 42(2) (fatal or life-threatening) is incomplete, for example if the sponsor has not provided all the information within seven days, the sponsor shall submit a completed report based on the initial information within an additional eight days.

13. The clock for initial reporting (day 0 = Di 0) starts as soon as the information containing the minimum reporting criteria has been received by the sponsor.

14. If significant new information on an already reported case is received by the sponsor, the clock starts again at day zero, that is the date of receipt of the new information. This information shall be reported as a follow-up report within 15 days.

15. If the initial report of a SUSAR referred to in Article 42(2)(c) (initially considered to be non-fatal or non-life- threatening but which turns out to be fatal or life-threatening) is incomplete, a follow-up report shall be made as soon as possible, but within a maximum of seven days of first knowledge of the reaction being fatal or life- threatening. The sponsor shall submit a completed report within an additional eight days.

16. In cases where a SUSAR turns out to be fatal or life-threatening, whereas initially it was considered as non-fatal or not life-threatening, if the initial report has not yet been submitted, a combined report shall be created.

2.5. **Unblinding treatment allocation**

17. The investigator shall only unblind the treatment allocation of a subject in the course of a clinical trial if unblinding is relevant to the safety of the subject.

18. When reporting a SUSAR to the Agency, the sponsor shall only unblind the treatment allocation of the affected subject to whom the SUSAR relates.

19. If an event is potentially a SUSAR the blind shall be broken for that subject only by the sponsor. The blind shall be maintained for other persons responsible for the ongoing conduct of the clinical trial (such as the management, monitors, investigators) and those persons responsible for data analysis and interpretation of results at the conclusion of the clinical trial, such as biometrics personnel.

20. Unblinded information shall be accessible only to persons who need to be involved in the safety reporting to the Agency, to Data Safety Monitoring Boards ('DSMB'), or to persons performing ongoing safety evaluations during the clinical trial.

21. However, for clinical trials carried out in high morbidity or high mortality disease, where efficacy end-points could also be SUSARs or when mortality or another 'serious' outcome, that may potentially be reported as a SUSAR, is the efficacy end-point in a clinical trial, the integrity of the clinical trial may be compromised if the blind is systematically broken. Under these and similar circumstances, the sponsor shall highlight in the protocol which serious events are to be treated as disease-related and are not subject to systematic unblinding and expedited reporting.

22. If following unblinding, an event turns out to be a SUSAR the reporting rules for SUSARs set out in Article 42 and in Section 2 of this Annex shall apply.

3. ANNUAL SAFETY REPORTING BY THE SPONSOR

23. The report shall contain, in an appendix, the RSI in effect at the start of the reporting period.

24. The RSI in effect at the start of the reporting period shall serve as RSI during the reporting period.

25. If there are significant changes to the RSI during the reporting period they shall be listed in the annual safety report. Moreover, in this case the revised RSI shall be submitted as an appendix to the report, in addition to the RSI in effect at the start of the reporting period. Despite the change to the RSI, the RSI in effect at the start of the reporting period serves as RSI during the reporting period.

ANNEX IV

CONTENT OF THE SUMMARY OF THE RESULTS OF THE CLINICAL TRIAL

The summary of the results of the clinical trial shall contain information on the following elements:

A. CLINICAL TRIAL INFORMATION:

1. Clinical trial identification (including title of the trial and protocol number);

2. Identifiers (including EU trial number, other identifiers);

3. Sponsor details (including scientific and public contact points);

4. Paediatric regulatory details (including information whether the clinical trial is a part of a Paediatric Investigation Plan);

5. Result analysis stage (including information about intermediate data analysis date, interim or final analysis stage, date of global end of the clinical trial). For clinical trials replicating studies on already authorised investigational medicinal products and used in accordance with the terms of the marketing authorisation, the summary of the results should also indicate identified concerns in the overall results of the clinical trial relating to relevant aspects of the efficacy of the related medicinal product;

6. General information about the clinical trial (including information about main objectives of the trial, trial design, scientific background and explanation of rationale for the trial; date of the start of the trial, measures of protection of subjects taken, background therapy; and statistical methods used);

7. Population of subjects (including information with actual number of subjects included in the clinical trial in the Member State concerned, in the Union and in third countries; age group breakdown, gender breakdown).

B. SUBJECT DISPOSITION:

1. Recruitment (including information on the number of subjects screened, recruited and withdrawn; inclusion and exclusion criteria; randomisation and blinding details; investigational medicinal products used);

2. Pre-assignment Period;

3. Post Assignment Periods.

C. BASELINE CHARACTERISTICS:

1. Baseline Characteristics (Required) Age;

2. Baseline Characteristics (Required) Gender;

3. Baseline Characteristics (Optional) Study Specific Characteristic.

D. END POINTS:

1. End point definitions ([*])

2. End point #1

Statistical analyses

3. End point #2

Statistical analyses

E. ADVERSE EVENTS:

1. Adverse events information;

2. Adverse event reporting group;

3. Serious adverse event;

4. Non-serious adverse event.

[*] Information shall be provided for as many end points as defined in the protocol.

F. ADDITIONAL INFORMATION:

1. Global Substantial Modifications;

2. Global Interruptions and re-starts;

3. Limitations, addressing sources of potential bias and imprecisions and Caveats;

4. A declaration by the submitting party on the accuracy of the submitted information.

ANNEX V

CONTENT OF THE SUMMARY OF THE RESULTS OF THE CLINICAL TRIAL FOR LAYPERSONS

The summary of the results of the clinical trial for laypersons shall contain information on the following elements:

1. Clinical trial identification (including title of the trial, protocol number, EU trial number and other identifiers);

2. Name and contact details of the sponsor;

3. General information about the clinical trial (including where and when the trial was conducted, the main objectives of the trial and an explanation of the reasons for conducting it);

4. Population of subjects (including information on the number of subjects included in the trial in the Member State concerned, in the Union and in third countries; age group breakdown and gender breakdown; inclusion and exclusion criteria);

5. Investigational medicinal products used;

6. Description of adverse reactions and their frequency;

7. Overall results of the clinical trial;

8. Comments on the outcome of the clinical trial;

9. Indication if follow up clinical trials are foreseen; 10. Indication where additional information could be found.

ANNEX VI

LABELLING OF INVESTIGATIONAL MEDICINAL PRODUCTS AND AUXILIARY MEDICINAL PRODUCTS

A. UNAUTHORISED INVESTIGATIONAL MEDICINAL PRODUCTS

A.1. **General rules**

1. The following particulars shall appear on the immediate and the outer packaging:

(a) name, address and telephone number of the main contact for information on the product, clinical trial and emergency unblinding; this may be the sponsor, contract research organisation or investigator (for the purpose of this Annex this is referred to as the 'main contact');

(b) the name of the substance and its strength or potency, and in the case of blind clinical trials the name of the substance is to appear with the name of the comparator or placebo on the packaging of both the unauthorised investigational medicinal product and the comparator or placebo;

(c) pharmaceutical form, route of administration, quantity of dosage units;

(d) the batch or code number identifying the contents and packaging operation;

(e) a clinical trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;

(f) the subject identification number and/or the treatment number and, where relevant, the visit number;

(g) the name of the investigator (if not included in (a) or (e));

(h) directions for use (reference may be made to a leaflet or other explanatory document intended for the subject or person administering the product);

(i) 'For clinical trial use only' or similar wording;

(j) the storage conditions;

(k) period of use (expiry date or re-test date as applicable), in month and year format and in a manner that avoids any ambiguity; and

(l) 'Keep out of reach of children', except when the product is for use in trials where the product is not taken home by subjects.

2. Symbols or pictograms may be included to clarify certain information mentioned above. Additional information, warnings or handling instructions may be displayed.

3. The address and telephone number of the main contact shall not be required to appear on the label if subjects have been given a leaflet or card which provides these details and have been instructed to keep this in their possession at all times.

A.2. **Limited labelling of immediate packaging**

A.2.1. *Immediate and outer packaging provided together*

4. When the product is provided to the subject or the person administering the medicinal product in an immediate packaging and outer packaging intended to remain together, and the outer packaging carries the particulars listed in section A.1., the following particulars shall appear on the immediate packaging (or any sealed dosing device that contains the immediate package):

(a) name of the main contact;

(b) pharmaceutical form, route of administration (may be excluded for oral solid dose forms), quantity of dosage units and, in the case of clinical trials which do not involve the blinding of the label, the name/ identifier and strength/potency;

(c) batch and/or code number identifying the contents and packaging operation;

(d) a clinical trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;

(e) the subject identification number and/or the treatment number and, where relevant, the visit number; and

(f) period of use (expiry date or re-test date as applicable), in month and year format and in a manner that avoids any ambiguity.

A.2.2. *Small immediate packaging*

5. If the immediate packaging takes the form of blister packs or small units such as ampoules on which the particulars required in section A.1. cannot be displayed, the outer packaging provided shall bear a label with those particulars. The immediate packaging shall contain the following:

(a) name of the main contact;

(b) route of administration (may be excluded for oral solid dose forms) and, in the case of clinical trials which do not involve the blinding of the label, the name/identifier and strength/potency;

(c) batch or code number identifying the contents and packaging operation;

(d) a clinical trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;

(e) the subject identification number/treatment number and, where relevant, the visit number; and

(f) period of use (expiry date or re-test date as applicable), in month and year format and in a manner that avoids any ambiguity.

B. UNAUTHORISED AUXILIARY MEDICINAL PRODUCTS

6. The following particulars shall appear on the immediate and the outer packaging:

(a) name of the main contact;

(b) name of the medicinal product, followed by its strength and pharmaceutical form;

(c) statement of the active substances expressed qualitatively and quantitatively per dosage unit;

(d) batch or code number identifying the contents and packaging operation;

(e) clinical trial reference code allowing identification of the clinical trial site, investigator and subject;

(f) directions for use (reference may be made to a leaflet or other explanatory document intended for the subject or person administering the product);

(g) 'For clinical trial use only' or similar wording;

(h) the storage conditions; and

(i) period of use (expiry date or retest date as applicable).

C. ADDITIONAL LABELLING FOR AUTHORISED INVESTIGATIONAL MEDICINAL PRODUCTS

7. In accordance with Article 67(2), the following particulars shall appear on the immediate and the outer packaging:

(a) name of the main contact;

(b) clinical trial reference code allowing identification of the clinical trial site, investigator, sponsor and subject;

(c) 'For clinical trial use only' or similar wording.

D. REPLACING OF INFORMATION

8. The particulars listed in sections A, B and C, other than those particulars listed in paragraph 9, may be omitted from the label of a product and made available by other means, for example by use of a centralised electronic randomisation system, use of a centralised information system, provided that the safety of the subject and the reliability and robustness of data are not compromised. This shall be justified in the protocol. 27.5.2014 L 158/73 Official Journal of the European Union EN

9. The particulars referred to in the following points shall not be omitted from the label of a product: (a) paragraph 1, points (b), (c), (d), (f), (j) and (k); (b) paragraph 4, points (b), (c), (e), and (f); (c) paragraph 5, points (b), (c), (e), and (f); (d) paragraph 6, points (b), (d), (e), (h), and (i).

ANNEX VII

CORRELATION TABLE

Directive 2001/20/EC	This Regulation
Article 1 (1)	Article 1, Article 2 (1) and (2) points 1, 2 and 4 Article 2 (2) point 30
Article 1 (2)	-
Article 1 (3), first subparagraph	Article 47, third subparagraph
Article 1 (3), second subparagraph	Article , second subparagraph
Article 1 (4)	Article 2
Article 2	-
Article 3 (1)	Articles 4, 28, 29 and 76
Article 3 (2)	Article 28 (1) (f)
Article 3 (3)	Article 28 (1) (g)
Article 3 (4)	Article 10 (1), 28, 29 and 32
Article 4	Article 10 (2), 28, 29 and 31
Article 5	Articles 4-14
Article 6	Articles 4-14
Article 7	-
Article 8	Articles 4-14
Article 9	Articles 15-24
Article 10 (a)	Article 54
Article 10 (b)	Articles 37 and 38
Article 10 (c)	Article 81
Article 11	Article 77
Article 12	Article 61 (1)-(4)
Article 13 (1)	Article 61 (2) Article 62 (1) and Article 63 (1) and (3) Article 63 (1)
Article 13 (2)	-
Article 13 (3), first subparagraph	Article 62
Article 13 (3), second subparagraph	-
Article 13 (3), third subparagraph	Articles 66-70
Article 13 (4)	Article 78 (1), (2) and (5)
Article 13 (5)	Article 78 (6)
Article 14	-
Article 15 (1)	-
Article 15 (2)	Articles 57, 58 and 78 (7)
Article 15 (3)	

Article 15 (4) Article 15 (5) Article 16 Article 17 (1) (a) to (c) Article 17 (1) (d) Article 17 (2) Article 17 (3) (a) Article 17 (3) (b) Article 18 Article 19, first paragraph, first sentence Article 19, first paragraph, second sentence Article 19, second paragraph Article 19, third paragraph Article 20 Article 21 Article 22 Article 23 Article 24	Article 41 Article 42 - Article 43 - Article 44 (1) - Article 75 Article 74 Article 92 - - Article 88 - - -

EMERGENCY ORDINANCE no. 23 of 13 May 2014 for amendment of Law 95/2006 on healthcare reform and amendment of certain legislation

ISSUED BY: THE ROMANIAN GOVERNMENT
PUBLISHED IN: THE OFFICIAL GAZETTE OF ROMANIA, no. 359 of 15 May 2014

Considering Romania's duty as a full EU Member State to transpose and implement Directives adopted by the European Union, and taking into account negative consequences of failure to urgently promote this legislation ensuring the primary framework for transposition of Directive 89/105/EEC of the Council of 21 December 1988 relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of the public health insurance system,

taking into consideration the need to avoid opening the infringement procedure and enforcement of monetary sanctions against Romania, in accordance with provisions of Article 260 (3) of the Treaty on the Functioning of the European Union, accelerating the mechanism for imposition of financial penalties on notification of the Court of Justice by the European Commission, on non-compliance with a Member State's responsibilities concerning notification of measures for transposition of a directive approved in accordance with a legislative procedure,

to avoid opening of action against Romania's failure to comply with its duties as an EU member state, in light of the European Commission request leading to commitment of Romanian authorities to compliance with national provisions concerning transparency of measures regulating inclusion of medicinal products into the scope of national health insurance systems, with provisions of Directive 89/105/EEC,

considering that, after notification by the European Commission, Romania has undertaken to propose, before the end of April 2014, legislation for resolution of the issue of transparency of measures concerning compensation of medicinal products prices, to its avoid progress to infringement level,

considering the Minister's of Foreign Affairs request to the Minister of Health, on taking notice of the non-compliance with European Commission requirements, for accelerated adoption of regulations for transposition of European legislation in that respect,

having in mind that Romania's obligation as a Member State to ensure full transposition of provisions of this Directive can only be considered fulfilled on notification of all measures for transposition of this Directive, thus avoiding opening of the infringement procedure,

considering the Zero Tolerance Policy adopted by the Commission for cases of non-transposition, according to COM (2012) 259 (Communication on Better Governance for the Single Market), requiring Member States to undertake a zero-tolerance objective concerning respecting a transposition deficit target and a conformity deficit target of 0%.

,taking into account that absence of these regulations precludes Romanian patients' access to novel treatments, vital for their life and health, urgent measures are mandatory for elimination of irregularities potentially arising from non-implementation of this directive,

to prevent deterioration or even irrecoverable damage to the health condition, particularly of patients depending on access to new medicinal products, it is necessary to limit detrimental effects upon the population's overall health condition,

considering the need for emergency adoption of the organisational framework of the healthcare system, so as not to affect the quality of medical assistance and public health,

considering the need for regulation of the framework for implementation of systems included in the healthcare insurance information platform – the patient electronic healthcare dossier and the national system of the social health insurance card, as well as for observance of their deadlines for implementation agreed upon with international financial bodies,

considering that introduction of a new electronic system for collection of personal and medical data, namely the patient electronic healthcare dossier, the role of the social health insurance card is considered a single document attesting the status as "insured person" of citizens, ensuring access of authorised persons to data available on the patient electronic healthcare dossier, taking into account that introduction of this electronic device leads to increased quality of medical services granted to patients, by decreasing time allocated to bureaucratic activities, thus increasing time available for actual patient care,

considering that providing for the operational character of the social health insurance card leads to provision of medical services to insured persons, depending on their health condition and medical history as recorded on the patient electronic health dossier, fully available to the respective medical service provider not requiring supply by the insured person of current medical records provided by other medical service providers,

taking into consideration that the two electronic devices (the patient electronic health dossier and the social health insurance card) improve access to medical services for insured persons, eliminating bureaucratic activities in that respect, whereas providing for a mechanism for elimination of services not performed but reported for reimbursement,

considering that, as of May 2014, the National Health Insurance House commences distribution of cards for a determined patient sample group, namely persons diagnosed with acute renal impairment on dialysis,

considering the need for harmonisation of data available on the social health insurance card with that provided in the patient electronic health dossier,

taking into account that failure to adopt these immediate measures and ther implementation rules, through Emergency Ordinance, would generate major irregularities with negative impact upon the population's health condition as well as on efficient use of human and financial resources of the healthcare system, and that any delay by Romanian authorities may result in action against failure to fulfil its obligations as a Member State, in accordance with Article 258 of the Treaty on the Functioning of the European Union,

considering the impending need of removal of legislative barriers, namely elimination of discrimination concerning the possibility provided to general medical assistants/nurses, midwives and medical assistants to retire upon request, in line with Law 263/2010 regarding the integrated public pension system, as amended,

taking into account that the issue of under-financing of the Romanian medical system and thereby of healthcare professionals requires identification of

immediate alternative solutions to ensure sufficient and fully trained working force nationally,

having in mind one of the Ministry of Health general targets to permanently improve population's health condition and provide indiscriminating access to health services of all population categories (rural population included),

considering the increased tendency of healthcare professionals' migration to other Member States, as shown by the release, as of 2007, of over 20,000 documents required for recognition in the EU of nurse and midwife Romanian diplomas and another 4,000 such documents before the end of 2014,

considering the increased rate of this staff migration to private healthcare facilities providing more attractive working and wage conditions,

given the risk in this context of decrease of the retirement age concerning dramatic decrease of the number of nurses and midwives employed in public healthcare units already having to cope with a major shortage of specialised staff,

taking into account regulations in force on contest procedure on the filling of vacancies resulted from retirement to be performed in minimum 45 days,

considering the major imbalance resulting in this context from the provision regarding retirement of medical assistants/nurses and midwives at ages stipulated by Law 263/2010 regarding the integrated public pension system, as amended and the risk of blockage of public healthcare units and, consequently, prevention of the equal access to health services for all categories of population, particularly those in poor/rural areas,

having in mind the major impact of such issues upon public health, which involves overall public interest and represents extraordinary and emergency situations whose regulation cannot be postponed,

the Government of Romania hereby adopts this Emergency Ordinance.

ARTICLE I

Law 95/2006 on healthcare reform, published in the Official Gazette of Romania, Part I, No. 372 of 28 April 2006, as amended, is hereby amended as follows:

1. Under Article 29 (2), a new paragraph, (3), is introduced, which reads as follows:

"(3) The manner of use and setup of the patient electronic health dossier is established through implementation rules related to the patient electronic health dossier, approved through Government Decision."

2. Under Article 54, a new paragraph, (8), is introduced after paragraph (7), which reads as follows:

"(8) The manner of inclusion, extension of indications, non-inclusion or exclusion of medicinal products on/from the list mentioned under paragraph (7) is shown under Article 232^1."

3. A new Article, 232^1, is introduced after Article 232, which reads as follows:

"ARTICLE 232^1

(1) The criteria for assessment of medical technologies, the dossier to be submitted by applicants, methodological devices used in the assessment process concerning inclusion, extension of indications, non-inclusion or exclusion of medicinal products in/from the List of International Non-proprietary Names of

medicinal products for insured persons, with or without personal contribution, based on medical prescription, in the social health insurance system, as well as the International Non-proprietary Names of medicinal products granted within national health programs are approved through Order of the Minister of Health, as proposed by the National Agency for Medicines and Medical Devices.
(2) The assessment technology for inclusion, extension of indications, exclusion of indications, non-inclusion or exclusion of medicinal products in/from the List of International Non-proprietary Names of medicinal products for insured persons, with or without personal contribution, based on medical prescription, in the social health insurance system, as well as International Non-proprietary Names corresponding to medicinal products granted within national health programs, as well as the means for appeal are approved through Order of the Minister of Health, as proposed by the National Agency for Medicines and Medical Devices."

4. Under Article 331, paragraphs (2) - (5) are repealed.

ARTICLE II

In 2014, reassessment of medicinal products in the List of International Non-proprietary Names containing medicinal products for insured persons, with or without personal contribution, based on medical prescription and within the social health insurance system, as well as the International Non-proprietary Names of medicinal products granted in the context of national health programs, under the conditions stipulated in Article I point 3, are performed until 30 October 2014.

ARTICLE III

Emergency Government Ordinance no. 144/2008 on profession of the positions of general physician, midwife and medical assistant/nurse, as well as the organisation and operation of the Romanian Order of Nurses, Midwives and Medical Assistants published in the Official Gazette of Romania, Part I, no. 785 of 24 November 2008, approved as amended through Law 53/2014, is amended as follows:

1. Under Article 22, paragraph (2) is amended as follows:

"(4) General medical assistants/nurses, midwives and medical assistants irrespective of gender retire at 65 years old."

2. Under Article 22, two new paragraphs, (5^1) and (5^2), are introduced after paragraph (5), which read as follows:

"(5^1) Upon request, general medical assistants/nurses, midwives may retire, under the conditions stipulated by Law 263/2010 regarding the integrated public pension system, as amended.
(5^2) By waiver from provisions of Article 56 (1) c) of Law 53/2003 – Labour code, republished, as amended, the working contract of nurses, midwives and medical assistants legally ceases on cumulative fulfilment of the conditions regarding the 65 years age limit and the minimum subscription period to the public pensions system on the date of communication of the decision for retirement for age limit, disability pension, anticipated old-age pension, anticipated pension, pension for age limit with decreased standard retirement age, as per provisions of paragraph (5^1)."

PRIME-MINISTER
VICTOR-VIOREL PONTA

Countersigned:
Minister of health,
Nicolae Bănicioiu

Deputy Prime Minister,
Minister of Internal Affairs,
Gabriel Oprea

Minister for Public Finance,
Ioana-Maria Petrescu
Minister Delegate for Budget,
Liviu Voinea

Deputy Minister for Foreign Affairs,
Bogdan Lucian Aurescu,
Secretary of State

Bucharest, 13 May 2014
No. 23.

DECISION
No. 2/22.04.2014

on approval of Regulations for authorisation of sites for conduct of clinical trials on medicinal products for human use

The Scientific Council of the National Agency for Medicines and Medical Devices (NAMMD), established based on Order of the Minister of Health no. 374/02.04.2014, in accordance with the Regulation for the organisation and operation of the NAMMD Scientific Council, Article 8 (1), hereby adopts through written procedure the following

DECISION

Single article - Regulations for authorisation of sites for conduct of clinical trials on medicinal products for human use are approved, in accordance with the Annex which is integral part of this Decision.

PRESIDENT
of the Scientific Council
of the National Agency for Medicines and Medical Devices,
Acad. Prof. Dr. Leonida Gherasim

ANNEX
to SCD no. 2/22.04.2014

Regulations for authorisation of sites for conduct of clinical trials on medicinal products for human use

CHAPTER I
Introduction

Article 1. – These regulations enable application of provisions of Article 4 (2) d) of Government Decision no. 734/2010 on organisation and operation of the National Agency for Medicines and Medical Devices, of Government Decision no. 63/2002 on approval of Good Laboratory Practice principles, their inspection and assessment of compliance with these principles as well as inspection and assessment of their compliance concerning tests performed upon chemical substances, as amended, of Order of the Minister of Public Health no. 904/2006 on harmonisation of member states legislation, regulations and administrative measures on approval of rules relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, of Order of the Minister of Public Health no. 903/2006 on approval of the Principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products.

CHAPTER II
General provisions

Article 2. - (1) Evaluation of medicinal products for human use by means of clinical trials, with or without therapeutic benefit, can only be conducted at sites authorised by the National Agency for Medicines and Medical Devices.

(2) Issuance of the Authorisation for conduct of *clinical trials with therapeutic benefit/phase I clinical trials or bioequivalence clinical trials* (in accordance with the draft provided in Annex 1) is proof of fulfilment of conditions for authorisation.

(3) Sites holding Authorisation for conduct of Phase I clinical trials are also allowed to perform bioequivalence clinical trials.

Article 3 - (1) The manager of the site submits the application for authorisation to the National Agency for Medicines and Medical Devices, specifying the name of the healthcare facility/legal person, clinic(s), department(s), clinical/paraclinical laboratories etc. within the healthcare facility involved in the application.

(2) The application for authorisation is accompanied by the documents attesting fulfilment of conditions for grant of a certain type of Authorisation for conduct of clinical trials, as shown under Articles 5 (2), 9 and 18.

Article 4 - (1) The authorisation issued by the National Agency for Medicines and Medical Devices is valid available for two years and may be extended upon request by the respective site.

(2) – The National Agency for Medicines and Medical Devices is notified on any amendment during the authorisation validity period, likely to change the data underlying grant of authorisation.

(3) – In such circumstances, the site applies for update of the authorisation granted by the National Agency for Medicines and Medical Devices so as to reflect implementation of intervening changes, without change of the validity period.

CHAPTER III

Special provisions

SECTION 1

Authorisation of clinical trials with therapeutic benefit

Article 5. - (1) Assessment of medicinal products through clinical trials with therapeutic benefits can only be performed at specialised healthcare sites performing an activity compliant with CAEN codes 8610 – Hospital activities and 7219 – Other research and experimental development on natural sciences and engineering or 8622 – Specialist medical practice activities.

(2) The National Agency for Medicines and Medical Devices grants the Authorisation for conduct of clinical trials with therapeutic benefit, after assessment of the following documents:

a) the healthcare authorisation for operation of a medical facility;

b) a document attesting registration of the healthcare facility as provider of activities under CAEN code 7219 – Other research and experimental development on natural sciences and engineering.

c) a membership certificate granted by a professional organisation for healthcare professionals involved in clinical trials;

d) the List of Standard Operating Procedures (see Annex 2 for the minimal list of Standard Operating Procedures) or certification of implementation of a quality management system in accordance with ISO standards in force for clinical trials; certification becomes mandatory one year following entry into force of these regulations;

e) the documents describing the secured IT infrastructure for data management and archiving of the clinical trial dossier;

f) the list of staff qualified to act as main investigator, together with the attached proof of confirmation of respective titles (senior physician or specialist physician with a minimum 3-year experience) and curriculum vitae;

g) proof of existence of an emergency service within the respective site or of a contract for emergency medical services signed with specialised sites.

Article 6. – Qualified staff needs to be hired at the proposed site for conduct of clinical trials with therapeutic benefit (e.g. general physicians, healthcare specialists trained in the area targeted by the clinical trials, physicians in training in clinical/surgery fields, clinical pharmacologists, appropriate auxiliary staff).

Article 7. – (1) The proposed site for conduct of clinical trials with therapeutic benefit must meet the requirements for areas, utilities, facilities and devices, mentioned in legislation in force, namely Order of the Minister of Health no. 914/2006 on approval of the Norms regarding the conditions to be fulfilled by a hospital in order to receive the sanitary authorisation for operation, Order of the Minister of Health and Family no. 1338/2007 on approval of the Norms on the functional structure of medical and dental offices.

(2) The proposed site for conduct of clinical trials with therapeutic benefit must own licensed and secured IT systems.

(3) The proposed site for conduct of clinical trials with therapeutic benefit must comply with requirements on archiving areas for clinical trial dossiers compliant with provisions of Order of the Minister of Health no. 903/2006 on approval of the Principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as requirements for authorisation of manufacturing or importation of such products as well as Scientific Council Decision no. 51/2006 on approval of Guidance on the content of the trials master file and archiving.

Article 8. – In case the proposed site does not allow for conduct of assays, tests, clinical and paraclinical investigations, these can be performed as per agreement with other sites authorised/accredited by authorised bodies.

SECTION 2
Authorisation for conduct of Phase I clinical trials

Article 9. – Clinical assessment of medicinal products through Phase I clinical trials can only be performed at sites specially authorised for this purpose, performing activities in accordance with CAEN code 7219 – Other research and experimental development on natural sciences and engineering.

Article 10. – The following sites may apply for Authorisation for conduct of Phase I clinical trials:

a) medical sites provided with their own bioanalytical laboratory, specialised in pharmacokinetic determinations;

b) medical sites signatory of a collaboration agreement with bioanalytical laboratories specialised in pharmacokinetic determinations, covering at least the validity period of the authorisation;

c) bioanalytical laboratories specialised in pharmacokinetic determinations, signatory of a collaboration agreement with a medical site, covering at least the validity period of the authorisation;

d) bioanalytical laboratories specialised in pharmacokinetic determinations, provided with a clinical site in line with provisions of this Decision;

e) legal entities signatory of collaboration agreements with a bioanalytical laboratory specialised in pharmacokinetic determinations and with a medical site, covering at least the validity period of the authorisation;

f) legal entities signatory of collaboration agreements with a medical site, providing proof of contract at the time of submission of an application for authorisation of a clinical trial with a bioanalytical laboratory specialised in pharmacokinetic determinations, covering at least the validity period of the authorisation, when a conditional authorisation shall be granted.

Article 11. – The National Agency for Medicines and Medical Devices grants an Authorisation for conduct of Phase I clinical trials, after verification of the following documents:

a) the healthcare authorisation for operation of a medical facility;

b) a document attesting registration of the applicant as service provider under CAEN code 7219 – Other research and experimental development on natural sciences and engineering.

c) a membership certificate granted by a professional organisation for healthcare professionals involved in clinical trials;

d) list of its Standard Operating Procedures (see Annex 2 for the minimal list of Standard Operating Procedures) or certification of implementation of a quality management system in accordance with ISO standards in force for clinical trials; certification becomes mandatory one year following entry into force of these regulations;

e) the documents describing the secured IT infrastructure for data management and archiving of the clinical trial dossier;

f) the list of staff qualified to act as main investigator, together with the attached proof of confirmation of respective titles (senior physician or specialist physician with a minimum 3-year experience) and curriculum vitae;

g) proof of an emergency service within the respective site, in accordance with Annex 3;

h) proof of a bioanalytical laboratory, certified for Good Laboratory Practice (GLP) by the Romanian competent authority, or of a contract with a certified/accredited laboratory;

i) employment/collaboration agreement with a clinical pharmacologist with at least 3 years experience in this field;

Article 12. – Qualified staff should be hired at sites proposed for conduct of Phase I clinical trials (general physicians, medical specialists trained in the area targeted by clinical trials, physicians in training in clinical or surgery areas, clinical pharmacologists, appropriate auxiliary staff).

Article 13. – (1) The sites proposed for conduct of Phase I clinical trials must meet the requirements for areas, utilities, facilities and devices, mentioned in legislation in force, namely in Order of the Minister of Health no. 914/2006 on approval of the Norms regarding conditions to be met by a hospital for functioning authorisation.

(2) The proposed site for conduct of clinical trials with therapeutic benefit must own licensed and secured IT systems.

(3) The sites proposed for conduct of Phase I clinical trials must comply with requirements on archiving areas for clinical trial dossiers compliant with provisions of Order of the Minister of Health no. 903/2006 on approval of the Principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products as well as Scientific Council Decision no. 51/2006 on approval of Guidance on the content of the trials master file and archiving.

Article 14. - (1) In case the proposed site does not allow for conduct of assays, tests, clinical and paraclinical investigations, these can be performed as per agreement with other sites authorised/accredited by authorised bodies.

(2) The applicant must certify existence of an on-site emergency service.

Article 15. – The applicant healthcare facility must be provided with the following:

a) a dedicated section allowing for simultaneous care of at least 8 healthy volunteers/patients;

b) conditions proper for medical examination and surveillance for collection and storage of samples;

c) staff qualified for provision of emergency medical care.

Article 16. - Bioanalytical laboratories specialised in pharmacokinetic determinations must be certified/accredited. For trials performed in Romania only, bioanalytical laboratories specialised in pharmacokinetic determinations

must hold an authorisation for Good Laboratory Practice (GLP), granted by the National Agency for Medicines and Medical Devices, in accordance with Government Decision no. 63/2002, as amended.

Article 17. - Phase I clinical trials shall be coordinated by a clinical pharmacologist employed as per Article 11 i).

SECTION 3

Authorisation for conduct of bioequivalence clinical trials

Article 18. - (1) Clinical evaluation of medicinal products through bioequivalence clinical trials can only be performed at sites specially authorised for this purpose in accordance with CAEN 7219 code – Other research and experimental development on natural sciences and engineering.

2) Holding an Authorisation for conduct of bioequivalence clinical trials does not entitle the holder to conduct Phase I clinical trials as well.

Article 19. – The following sites may apply for an authorisation for conduct of bioequivalence clinical trials:

a) medical sites provided with their own bioanalytical laboratory, specialised in pharmacokinetic determinations;

b) medical sites signatory of a collaboration agreement with a bioanalytical laboratory specialised in pharmacokinetic determinations, covering at least the validity period of the authorisation;

c) bioanalytical laboratories specialised in pharmacokinetic determinations, signatory of a collaboration agreement with medical site, covering at least the validity period of the authorisation;

d) bioanalytical laboratories specialised in pharmacokinetic determinations, provided with a clinical site in accordance with the provisions of this Order;

e) legal entities signatory of collaboration agreements with a bioanalytical laboratory specialised in pharmacokinetic determinations and with a medical site, covering at least the validity period of the authorisation.

Article 20. – The National Agency for Medicines and Medical Devices grants an Authorisation for conduct of bioequivalence clinical trials, after assessment of the following documents:

a) the healthcare authorisation for operation of a medical facility;

b) a document attesting registration of the applicant as service provider under CAEN code 7219 – Other research and experimental development on natural sciences and engineering

. c) free practice license of healthcare professionals involved in clinical trials;

d) list of its Standard Operating Procedures (see Annex 2 for the minimal list of Standard Operating Procedures) or certification of implementation of a quality management system in accordance with ISO standards in force for clinical trials; certification becomes mandatory one year following entry into force of these regulations;

e) the documents describing the secured IT infrastructure for data management and archiving of the clinical trial dossier;

f) the list of staff qualified to act as main investigator, together with the attached proof of confirmation of respective titles (senior physician, clinical pharmacologist or specialist physician, with a minimum 3-year experience) and curriculum vitae;

g) proof of existence of an emergency site in accordance with Annex 3;

h) proof of a bioanalytical laboratory, authorised for Good Laboratory Practice (GLP) by the National Agency for Medicines and Medical Devices, or of a contract signed with such laboratory;

i) employment/collaboration agreement with a clinical pharmacologist with at least 3 years experience in this field;

Article 21. – (1) The sites proposed for conduct of bioequivalence clinical trials must comply with requirements concerning areas, utilities, facilities and devices, stipulated by regulations in force, namely Order of the Minister of Health no. 914/2006 and Scientific Council Decision no. 15/07.06.2010 on approval of the Guideline on the investigation of bioequivalence.

(2) Sites proposed for conduct of bioequivalence clinical trials must hold authorisations and secured IT systems.

(3) The sites proposed for conduct of bioequivalence clinical trials must comply with requirements on archiving spaces for clinical trial dossiers compliant with provisions of Order of the Minister of Health no. 903/2006 on approval of the Principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products and Scientific Council Decision no. 51/2006 on approval of Guidance on the content of the trials master file and archiving.

Article 22. - (1) In case the proposed site does not allow for conduct of assays, tests, clinical and paraclinical investigations, these can be performed as per agreement with other sites authorised/accredited by authorised bodies

(2) The applicant must certify the existence of an on-site emergency service.

Article 23. - The applicant healthcare facility must be provided with the following:

a) a dedicated section allowing for simultaneous care of at least 12 healthy volunteers;

b) conditions proper for medical examination and surveillance for collection and storage of samples;

c) staff qualified for provision of emergency medical care.

Article 24. - Bioanalytical laboratories specialised in pharmacokinetic determinations must hold a GLP certificate issued by the National Agency for Medicines and Medical Devices, in accordance with Government Decision no. 63/2002, as amended, and with Scientific Council Decision no. 15/07.06.2010 on approval of the Guideline on the investigation of bioequivalence.

ANNEX 1
to SCD no. 2/ 22.04.2014

NAMMD HEADER

AUTHORISATION
for conduct of clinical trials
on medicinal product for human use

The National Agency for Medicines and Medical Devices, set up based on Emergency Government Ordinance no. 72/2010 on reorganisation of healthcare facilities and amendment of public health legislation based on Article 4 (2) d) of Government Decision no. 734/2010 on the organisation and operation of the National Agency for Medicines and Medical Devices, Scientific Council Decision no. 2/22.04.2014 on approval of Regulations for authorisation of sites for conduct of clinical trials on medicinal products for human use and according to documentation submitted, hereby grants Authorisation for conduct ***of clinical trials with therapeutic benefit/Phase I/bioequivalence clinical trials*** **to:**

Holder of authorisation:

Headquarters:

Areas of expertise:

Manager:

Number of authorisation:

Notifications:

In accordance with the legislation in force, the National Agency for Medicines and Medical Devices must be notified with regard to any amendment of data included in the Authorisation for conduct of clinical trials on medicinal products for human use or the authorisation dossier

This authorisation of valid 2 years after grant.

PRESIDENT

ANNEX 2
to SCD no. 2/22.04.2014

Minimal list of Standard Operating Procedures

- Procedure for the stages of clinical trials
- Procedure for subject recruitment and identification
- Procedure for subjects informed consent
- Procedure for establishment of source documents and minimal information
- Procedure for assessment and report of serious adverse events
- Procedure for draft of procedures
- Procedure for organisation of the investigator team and delegation of responsibilities within a clinical trial
- Procedure for trial medication – reception, storage and handling
- Procedure for document archiving

ANNEX 3
to SCD no. 2/22.04.2014

MINIMUM EMERGENCY EQUIPMENT
for emergency services of sites conducting Phase I and bioequivalence clinical trials

1. Monitor of vital functions (TA, EKG, pulse oximeter)
2. Defibrillator (with battery)
3. Injectomate/pump for infusion
4. External heart stimulator
5. Source of medicinal oxygen
6. Cardiopulmonary resuscitation kit
7. PEEP ventilator
8. Surgical vacuum
9. Stethoscope and tensiometer
10. Glucose meter and glucose test strips
11. Ophthalmoscope
12. Reflex hammer
13. Expendables required for treatment of medical emergencies (syringes, sterile and non-sterile surgical gloves, peripheral catheters, intubation probes, laryngeal mask, aspiration probes, duodenal/gastric probes, Foley probes, tracheostomy cannulae, scalpel, infusors etc.)
14. Adjustable beds
15. Alarm system (for calling qualified care)
16. Direct telephone line
17. Medicinal products and solutions for infusion or parenteral use, unless otherwise specified, required for treatment of medical emergencies (physiological serum, Ringer's solution, 5%, 10%, 33% glucose, colloidal solutions, mannitol, analgesics, bronchodilators for inhalation, adrenalin, atropine, diazepam, ketamine, succinylcholine, muscular paralysis inducing drugs for long-term use, hydrocortisone hemisuccinate, dexametazone, nitroglycerin, dobutamine, metoprolol, amiodarone, xylin, heparine, antiemetics, furosemidum, B1 and B6 vitamins, sodium bicarbonate, insulin, aminophyllinum, antihypertensives, clonidine, antispastics).

DECISION

No. 5/05.06.2014

on adoption of the Guideline on Good Pharmacovigilance Practices – Annex I – Definitions (Rev. 2)

The Scientific Council of the National Agency for Medicines and Medical Devices (NAMMD), established based on Order of the Minister of Health no. 374/02.04.2014, in accordance with the Regulation on the organisation and operation of the NAMMD Scientific Council, Article 8 (1), hereby adopts through written procedure the following

DECISION

Article 1. - The Guideline on Good Pharmacovigilance Practices – Annex I – Definitions (Rev. 2) is adopted, in accordance with the Annex, which is integral part of this Decision.

Article 2. – On this Decision coming into force, SCD no. 14/22.04.2013 on approval of the Guideline on Good Pharmacovigilance Practices – Annex I – Definitions, Rev. 1, is repealed.

PRESIDENT
of the Scientific Council
of the National Agency for Medicines and Medical Devices,

Acad. Prof. Dr. Leonida Gherasim

ANNEX
to SCD no. 5/05.06.2014

GUIDELINE ON GOOD PHARMACOVIGILANCE PRACTICES
(Good Pharmacovigilance Practices - GVP) Rev.2
ANNEX I - DEFINITIONS
Updated version

Date of entry into force: 8 January 2014

Table of contents

- **Labelling**
- **Medicinal product**
- **Medicinal product derived from human blood or human plasma**
- **Minimum criteria for reporting**
- **Missing information**
- **Misuse of a medicinal product**
- **Misuse of a medicinal product for illegal purposes**
- **Name of the medicinal product**
- **Newly identified signal**
- **Non-interventional trial; synonym: Non-interventional study**
- **Occupational exposure to a medicinal product**
- **Off-label use**
- **Ongoing clinical trial**
- **Ongoing signal**
- **Overdose**
- **Package leaflet**
- **Periodic safety update report (PSUR)**
- **Pharmacovigilance**
- **Pharmacovigilance system**
- **Pharmacovigilance system master file (PSMF)**
- **Post-authorisation safety study (PASS)**
- **Potential risk**
- **Quality adherence**
- **Quality assurance**
- **Quality control and assurance**
- **Quality improvements**
- **Quality of a pharmacovigilance system**
- **Quality objectives**
- **Quality planning**
- **Quality requirements**
- **Quality system of a pharmacovigilance system**
- **Reference safety information**
- **Registry**
- **Risk-benefit balance**
- **Risk management plan (RMP)**
- **Risk management system**
- **Risk minimisation activity; synonym: Risk minimisation measure**
- **Risks related to use of a medicinal product**
- **Safety concern**
- **Serious adverse reaction**
- **Signal**
- **Signal management process**
- **Signal validation**
- **Solicited sources of individual case safety reports**
- **Spontaneous report, synonym: Spontaneous notification**
- **Stimulated reporting**
- **Substance**
- **Summary of product characteristics (SmPC)**
- **Target population (treatment); synonym: Treatment target population**
- **Target population (vaccine); synonym: Vaccine target population**
- **Traditional herbal medicinal product**
- **Unexpected adverse reaction**
- **Upper management**
- **Vaccination**
- **Vaccination failure**

- **Vaccine**
- **Vaccine failure**
- **Vaccine pharmacovigilance**
- **Vaccine product-related reaction**
- **Vaccine quality defect-related reaction**
- **Valid individual case safety report**
- **Validated signal**

Note: This version has been updated in accordance with the following issues:

- Addition of definitions consulted with the public and finalised for Module XV (Direct healthcare professional communication);
- Addition of definitions consulted with the public and finalised for Considerations P.I (Immunisation, Immunisation anxiety-related reaction, Immunisation error-related reaction, Target population (vaccine), Vaccination, Vaccination failure, Vaccine failure, Vaccine pharmacovigilance, Vaccine product-related reaction, Vaccine quality defect-related reaction);
- Addition of definitions from the European Union Regulatory Network Incident Management Plan for Medicines for Human Use (Crisis, Incident);
- Amendments to the definitions of Missing information and Safety concern in order to meet EU legal requirements;
- Move of definition of Important missing information to explanatory note to definition of Missing information;
- Addition of explanatory notes for the definition of Off-label use in accordance with Module V;
- Addition of an explanatory note on abbreviations used in the definition for Immunological medicinal product.

Abuse of a medicinal product
Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects [Law 95/2006[20], Article 695 (15)].

Advanced therapy medicinal product (ATMP)
A medicinal product for human use that is either a gene therapy medicinal product, a somatic cell therapy product or a tissue engineered products as defined in provisions of Article 2 (1) a) of (EC) Regulation 1394/2007.

Adverse event (AE); synonym: Adverse experience
Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product, and which does not necessarily have a causal relationship with this treatment [Article 21(m) of Order of the Minister of Health no. 904/2006 on approval of Rules relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use].
An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse event following immunisation (AEFI)
See ***Vaccine pharmacovigilance, Vaccine product-related reaction, Vaccine quality defect-related reaction, Immunisation error-related reaction, Immunisation anxiety-related reaction***

Adverse reaction; synonyms: Adverse drug reaction (ADR), Suspected adverse (drug) reaction, Adverse effect, Undesirable effect
A response to a medicinal product which is noxious and unintended [Article 695 (10) of Law 95/2006].[21].

[20] Law 95/2006 on healthcare reform, Title XVII – The medicinal product, as amended, hereinafter "Law 95/2006"
107/213
[21] In the context of clinical trials, an adverse reaction is defined as all untoward and unintended responses to an investigational medicinal product related to any dose administered [Art. 2(n) of Directive 2001/20/EC].

Audit
A systematic, disciplined, independent and documented process for obtaining audit evidence and evaluating it objectively to determine the extent to which the audit criteria are fulfilled (see ISO 19011 (3.1) [22]].

Audit finding(s)
Results of the evaluation of the collected audit evidence against audit criteria (see ISO 19011 (3.4)[23]].

The results of the audit performed by the auditor must be supported by proof, consisting of the opinion and report of the auditor; these have a cumulative character and are mainly obtained through audit procedures implemented during the audit process.
*See **Audit***

Audit plan
Description of activities and arrangement for an individual audit (see ISO19011 (3.12)[24]]
*See also **Audit***

Audit programme
Set of one or more audits planned for a specific timeframe and directed towards a specific purpose (see ISO 19011 (3.11)[25])
*See also **Audit***

Audit recommendation
Describes the course of action management might consider to rectify conditions that have gone awry, and to mitigate weaknesses in systems of management control (see Sawyer LB et al, 2003[26]).
Audit recommendations should be positive and as specific as possible. They should also identify who is to act on them (Sawyer LB et al, 2003).
*See also **Audit***

Clinical trial
Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the objective of ascertaining its (their) safety and/or efficacy. This includes clinical trials carried out in either one site or multiple sites, whether in one or more Member State [Article 21 a) of Order of the Minister of Public Health no. 904/2006].
*See also **Ongoing clinical trial, Completed clinical trial, Investigational medicinal product***

Closed signal
In periodic benefit-risk evaluation reports, a signal for which an evaluation was completed during the reporting interval (see Annex IV, ICH- E2C(R2) Guideline).
This definition is also applicable to Periodic safety update reports.
*See also **Signal***

Company core data sheet (CCDS)
For medicinal products, a document prepared by the marketing authorisation holder (MAH) containing, in addition to safety information, material related to indications, dosing, pharmacology and other information concerning the product (see Annex IV, ICH-E2C(R2) Guideline).

[22] International Organisation for Standardisation (ISO); www.iso.org
[23] International Organisation for Standardisation (ISO); www.iso.org
[24] International Organisation for Standardisation (ISO); www.iso.org
[25] International Organisation for Standardisation (ISO); www.iso.org
[26] Sawyer LB, Dittenhofer MA. Sawyer's Internal Auditing. Ed. a 5a, Altamonte Springs, FL: The IIA Research Foundation; 2003. 120/213

*See **Company core safety information***

Company core safety information (CCSI)
For medicinal products, all relevant safety information contained in the company core data sheet prepared by the marketing authorisation holder and which the marketing authorisation holder requires to be listed in all countries where the company markets the product, except when the local regulatory authority specifically requires a modification (see Annex IV, ICH-E2C(R2) Guideline).
It is the reference information by which listed and unlisted are determined for the purposes of periodic reporting for marketed products, but not by which expected and unexpected are determined for expedited reporting (see Annex IV, ICH-E2C(R2) Guideline).
*See also **Company core data sheet***

Compassionate use of a medicinal product
Making a medicinal product available for compassionate reasons to a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by an authorised medicinal product (the medicinal product concerned must either be subject of an application for a central marketing authorisation or must be undergoing clinical trials) [Article 83 (2) of Regulation (EC) 726/2004].

Completed clinical trial
Study for which a final clinical study report is available (see ICH-E2F Guideline, Volume 10 of the Rules Governing Medicinal Products in the EU).
*See also **Clinical trial***

Consumer
For the purpose of reporting cases of suspected adverse reactions, a person who is not a healthcare professional such as a patient, lawyer, friend or relative/parent/child of a patient (see Annex IV, ICH-E2D Guideline).

Crisis
In the context of the European Union Regulatory Network Incident Management Plan for Medicines for Human Use, a crisis is defined as a situation where, after assessment of the associated risks, urgent and coordinated action within the EU regulatory network is required to manage and control the situation (see European Union Regulatory Network Incident Management Plan for Medicines for Human Use[4]).
*See also **Incident***

Data lock point
For a periodic safety update report (PSUR), the date designated as the cut-off date for data to be included in a PSUR.
For a periodic benefit-risk evaluation report (PBRER), the date designated as the cut-off date for data to be included in a PBRER, based on the international birth date (see Annex IV, ICH-E2C(R2) Guideline).
For a development safety update report (DSUR), the date designated as the cut-off date for data to be included in a DSUR, based on the development international birth date (see ICH-E2F Guideline, Volume 10 of the Rules Governing Medicinal Products in the EU).
Date includes day and month (see ICH-E2F Guideline, Volume 10 of the Rules Governing Medicinal Products in the EU).
*See also **Periodic safety update report, Development safety update report, International birth date, Development international birth date***

Development international birth date (DIBD)
Date of first approval (or authorisation) for conducting an interventional clinical trial in any country (see ICH-E2F Guideline, Volume 10 of the Rules Governing Medicinal Products in the EU).

Development safety update report (DSUR)
Format and content for periodic reporting on drugs under development (see ICH-E2F Guideline, Volume 10 of the Rules Governing Medicinal Products in the EU).

Direct healthcare professional communication (DHPC)
A communication intervention by which important information is delivered directly to individual healthcare professionals by a marketing authorisation holder or by a competent authority, to inform them of the need to take certain actions or adapt their practices in relation to a medicinal product.
DHPCs are not replies to enquiries from healthcare professionals.

EU reference date; synonym: Union reference date
For medicinal products containing the same active substance or the same combination of active substances, the date of the first marketing authorisation in the EU of a medicinal product containing that active substance or that combination of active substances; or if this date cannot be ascertained, the earliest of the known dates of the marketing authorisations for a medicinal product containing that active substance or that combination of active substances [Article 819^{3}(5) of Law 95/2006, as amended].

Failure to vaccinate
An indicated vaccine was not administered appropriately for any reason (see CIOMS-WHO). For interpreting what is appropriate, consider the explanatory note for ***Immunisation error-related reaction.***
See also Vaccination failure

Generic medicinal product
A medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies (Article 704 (2) b) of Law 95/2006).

Good pharmacovigilance practices (GVP) for the European Union (EU)
A set of guidelines for the conduct of pharmacovigilance in the EU, drawn up by the European Medicines Agency (EMA) in cooperation with competent authorities in Member States and interested parties, based on Article 820^{1} of Law 95/2006, as amended, and applying to marketing authorisation holders in the EU, the Agency and competent authorities in Member States.

Healthcare professional
For the purposes of reporting suspected adverse reactions, healthcare professionals are defined as medically qualified persons, such as physicians, dentists, pharmacists, nurses and coroners (see Annex IV, ICH-E2D Guideline).

Herbal medicinal product
Any medicinal product, exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations [Article 695 (31) of Law 95/2006, as amended].

Herbal substances are all mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried, form, but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances. Herbal substances are precisely defined by the plant part used and the botanical name according to the binominal system [Article 695 (32) of Law 95/2006].
Herbal preparations are preparations obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates [Article 695 (33) of Law 95/2006].

Homeopathic medicinal product
Any medicinal product prepared from substances called homeopathic stocks in accordance with a homeopathic manufacturing procedure described by the European Pharmacopoeia or, in the absence thereof, by the pharmacopoeias currently used officially in EU Member States. A homeopathic medicinal product may contain a number of active principles (Article 695 (4) of Law 95/2006).

Identified risk
An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest (see ICH-E2F Guideline, Volume 10 of the Rules Governing Medicinal Products in the EU).
Examples include:
• adverse reactions adequately demonstrated in non-clinical studies and confirmed by clinical data;
• adverse reactions observed in well-designed clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparator group on a parameter of interest suggests a causal relationship;
• adverse reactions suggested by a number of well-documented spontaneous reports where causality is strongly supported by temporal relationship and biological plausibility, such as anaphylactic reactions or application site reactions (see ICH-E2F Guideline, Volume 10 of the Rules Governing Medicinal Products in the EU).
In a clinical trial, the comparator may be placebo, an active substance or non-exposure.
Adverse reactions included in section 4.8 of the summary of product characteristics (SmPC) are also considered identified risks, unless they are class-related reactions which are mentioned in the SmPC but which are not specifically described as occurring with this product (these would normally be considered as a potential risk)).
See also ***Risks related to use of a medicinal product, Important identified risk and Important potential risk, Important missing information, Unexpected adverse reaction***

Illegal purposes
See ***Misuse for illegal purposes***.

Immunological medicinal product
Any medicinal product consisting of vaccines, toxins, serums or allergen products:
Vaccines, toxins and serums shall cover in particular agents used to produce active immunity (such as cholera vaccine, BCG[27], polio vaccine, smallpox vaccine), agents used to diagnose the state of immunity (including in particular tuberculin and tuberculin PPD[28], toxins for the Schick and Dick Tests for diphtheria and scarlet fever, brucellin) and agents used to produce passive immunity (such as diphtheria antitoxin, anti-smallpox globulin, antilymphocytic globulin).
Allergen products shall mean any medicinal product which is intended to identify or induce a specific acquired alteration in the immunological response to an allergizing agent [Article 695 (3) of Law 95/2006, as amended].

Immunisation
The process of making a person immune.
For the context of Considerations P.I, immunisation refers to the process of making a person immune to an infection.
See also ***Vaccination***

Immunisation anxiety-related reaction
An adverse event following immunisation arising from anxiety about the immunisation (see CIOMS-WHO[13]).

Immunisation error-related reaction

[27] vaccin Bacillus Calmette - Guérin
[28] purified protein derivative

An adverse event following immunisation that is caused by inappropriate vaccine handling, prescribing or administration and thus by its nature is preventable.
In this definition *immunisation* means the usage (handling, prescribing and administration) of a vaccine for the purpose of immunising individuals (see CIOMS-WHO[14]) , which in the EU is preferably referred to as *vaccination* (in the report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance the terms *immunisation* and *vaccination* are used interchangeably[29])
Inappropriate refers to usage (handling, prescribing and administration) other than what is licensed and recommended in a given jurisdiction based on scientific evidence or expert recommendations (see CIOMS-WHO[14]).
See also ***Adverse reaction, Vaccine pharmacovigilance, Vaccination***

In this definition immunisation means the usage (handling, prescribing and administration) of a vaccine for the purpose of immunising individuals (see CIOMS-WHO[4]), which in the EU is preferably referred to as *vaccination* (in the report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance the terms *immunisation* and *vaccination* are used interchangeably[13]).
See also ***Adverse reaction, Vaccine pharmacovigilance, Vaccination***

Important identified risk and Important potential risk
An identified risk or potential risk that could have an impact on the risk-benefit balance of the product or have implications for public health (see ICH-E2F Guideline, Volume 10 of the Rules Governing Medicinal Products in the EU).
What constitutes an important risk will depend upon several factors, including the impact on the individual, the seriousness of the risk and the impact on public health. Normally, any risk that is likely to be included in the contraindications or warnings and precautions section of the product information should be considered important (see Annex IV, ICH-E2C(R2) Guideline).
See also ***Risk-benefit balance, Identified risk, Potential risk, Safety concern***

Important potential risk
See ***Important identified risk and Important potential risk***

Incident
A situation where an event occurs or new information arises, irrespective whether this is in the public domain or not, in relation to (an) authorised medicinal product(s) which could have a serious impact on public health.
The incident may be related to quality, efficacy or safety concerns, but most likely to safety and/or quality (and possibly subsequent supply shortages). In addition, situations that do not seem at a first glance to have a serious impact on public health, but are in the public domain - subject of media attention or not - and may lead to serious public concerns about the product, may also need to be considered as incidents. Likewise, other situations which might have a negative impact on the appropriate use of a medicinal products (e.g. resulting in patients stop taking their medicine) may fall within the definition of an incident.
In the context of this the European Union Regulatory Network Incident Management Plan for Medicines for Human Use Incident Management Plan, an incident relates to (a) medicinal product(s) authorised in the EU, irrespective of their route of authorisation.

Individual case safety report (ICSR); synonym: Adverse (drug) reaction report
Format and content for the reporting of one or several suspected adverse reactions to a medicinal product that occur in a single patient at a specific point of time.[30].
See also ***Minimum criteria for reporting***

[29] Council for International Organizations of Medical Sciences (CIOMS). Definition and application of terms of vaccine pharmacovigilance (report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance). Genève: CIOMS; 2012.
[30] In the context of a clinical trial, an individual case is the information provided by a primary source to describe suspected unexpected serious adverse reactions related to the administration of one or more investigational medicinal products to an individual patient at a particular point of time.

International birth date (IBD)
The date of the first marketing authorisation for any product containing the active substance granted to any company in any country in the world (see Annex IV, ICH-E2C(R2) Guideline).

Investigational drug
Experimental product under study or development. This term is more specific than investigational medicinal product, which includes comparators and placebos (see ICH-E2F Guideline, Volume 10 of the Rules Governing Medicinal Products in the EU).
See also ***Investigational medicinal product***

Investigational medicinal product
An investigational medicinal product is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form [Article 21 d) of Order of the Minister of Health no. 904/2006].
See also ***Clinical trial***

Labelling
Information on the immediate or outer packaging [Article 695 (25) of Law 95/2006, as amended].

Medicinal product
Any substance or combination of substances:
a) presented as having properties for treating or preventing disease in human beings; or
b) which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis [Article 695 (1) of Law 95/2006].

Medicinal product derived from human blood or human plasma
Any medicinal product based on blood constituents which is prepared industrially by a public or private establishment, such as a medicinal product including, in particular, albumin, coagulating factor(s) and immunoglobulin(s) of human origin [Article 695 (9) of Law 95/2006, as amended].

Minimum criteria for reporting
For the purpose of reporting cases of suspected adverse reactions, the minimum data elements for a case are: an identifiable reporter, an identifiable patient, an adverse reaction and a suspect medicinal product (see Annex IV, ICH-E2D Guideline).
For the purpose of validation of individual case safety reports as qualifying for reporting in the EU, see Module VI.
*See also I****ndividual case safety report***

Missing information
Gaps in knowledge, related to safety or particular patient populations, which could be clinically significant.
It is noted that there is an ICH definition for important missing information, which is: critical gaps in knowledge for specific safety issues or populations that use the marketed product (see Annex IV, ICH-E2C(R2) Guideline).

Misuse of a medicinal product
Situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorised product information.
See also ***Misuse of a medicinal product for illegal purposes***

Misuse of a medicinal product for illegal purposes

Misuse of a medicinal product for illegal purposes is misuse with the additional connotation of an intention of misusing the medicinal product to cause an effect in another person. This includes, amongst others: the sale, to other people, of medicines for recreational purposes and use of a medicinal product to facilitate assault.
See also ***Misuse of a medicinal product***

Name of the medicinal product
The name which may be either an invented name not liable to confusion with the common name, or a common or scientific name accompanied by a trade mark or the name of the marketing authorisation holder [Article 695 (20) of Law no. 95/2006, as amended].
The common name is the international non-proprietary name (INN) recommended by the World Health Organization (WHO), or, if one does not exist, the usual common name [Article 695 (21) of Law no. 95/2006, as amended].
The complete name of the medicinal product is the name of the medicinal product followed by the strength and pharmaceutical form.

Newly identified signal
In periodic benefit-risk evaluation reports, a signal first identified during the reporting interval, prompting further actions or evaluation (see Annex IV, ICH-E2C(R2) Guideline).
This definition could also apply to a previously closed signal for which new information becomes available in the reporting interval prompting further action or evaluation (see Annex IV, ICH-E2C(R2) Guideline).
This definition is also applicable to periodic safety update reports.
See also ***Signal, Closed signal***

Non-interventional trial; synonym: Non-interventional study
A study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures is applied to the patients and epidemiological methods is used for the analysis of collected data [Article 21 (c) of Order of the Minister of Public Health no. 904/2006].
Thus, a trial is non-interventional if the following requirements are cumulatively fulfilled:
- the medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorisation;
- the assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study; and
- no additional diagnostic or monitoring procedures are applied to the patients and epidemiological methods are used for the analysis of collected data (see Volume 10 of the Rules Governing Medicinal Products in the EU, Questions & Answers, Version 10.0).

Non-interventional studies are defined by the methodological approach used and not by the scientific objectives. Non-interventional studies may include database research or review of records where all the events of interest have already happened (this may include case-control, cross-sectional, cohort and other study designs making secondary use of data). Non-interventional studies also include those involving primary data collection (e.g. prospective observational studies and registries in which the data collected derive from routine clinical care), provided that the conditions set out above are met. In these studies, interviews, questionnaires and blood samples may be performed as normal clinical practice.
Non-interventional trials do not fall in the scope of Order of the Minister of Public Health no. 904/2006.

Occupational exposure to a medicinal product
For the purpose of reporting cases of suspected adverse reactions, an exposure to a medicinal product as a result of one’s professional or non-professional occupation.

Off-label use
Situations where a medicinal product is intentionally used for a medical purpose not in accordance with the authorised product information.
Off-label use includes use in non-authorised paediatric age categories. Unless specifically requested, it does not include use outside the EU in an indication authorised in that territory which is not authorised in the EU.

Ongoing clinical trial
Trial where enrolment has begun, whether a hold is in place or analysis is complete, but for which a final clinical study report is not available (see ICH-E2F Guideline, Volume 10 of the Rules Governing Medicinal Products in the EU).
See also ***Clinical trial, Completed clinical trial***

Ongoing signal
In periodic benefit-risk evaluation reports, a signal that remains under evaluation at the data lock point (see Annex IV, ICH-E2C(R2) Guideline).
This definition is also applicable to periodic safety update reports.
See also ***Signal, Data lock point***

Overdose
Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorised product information. Clinical judgement should always be applied.

Package leaflet
A leaflet containing information for the user which accompanies the medicinal product [Article 695 (26) of Law 95/2006].

Periodic safety update report (PSUR)
Format and content for providing an evaluation of the risk-benefit balance of a medicinal product for submission by the marketing authorisation holder at defined time points during the post-authorisation phase.
In the EU, periodic safety update reports should follow the format described in Module VII.

Pharmacovigilance
Science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem (see WHO [31]).
In line with this general definition, underlying objectives of pharmacovigilance in accordance with the applicable EU legislation for are:

- preventing harm from adverse reactions in humans arising from the use of authorised medicinal products within or outside the terms of marketing authorisation or from occupational exposure; and
- promoting the safe and effective use of medicinal products, in particular through providing timely information about the safety of medicinal products to patients, healthcare professionals and the public.

Pharmacovigilance is therefore an activity contributing to the protection of patients' and public health.

Pharmacovigilance system
A system used by the marketing authorisation holder and by Member States to fulfil the tasks and responsibilities listed in Section X of Law 95/2006, Title XVII – The medicinal product, and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance [Article 695 (28^1) c) of Law 95/2006].
In general, a pharmacovigilance system is a system used by an organisation to fulfil its legal tasks and responsibilities in relation to pharmacovigilance and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance.

[31] World Health Organisation (WHO) "The importance of pharmacovigilance: safety monitoring of medicinal products", Geneva, WHO; 2002.

Pharmacovigilance system master file (PSMF)
A detailed description of the pharmacovigilance system used by the marketing authorisation holder with respect to one or more authorised medicinal products [Article 695 point 28[1] d) of Law 95/2006, as amended].
See also ***Pharmacovigilance system***

Post-authorisation safety study (PASS)
Any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures [Article 695 (14) of Law 95/2006].
A post-authorisation safety study may be an interventional clinical trial or may follow an observational, non-interventional study design.
See also ***Clinical trial, Non-interventional trial***

Potential risk
An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed (see ICH-E2F Guideline, Volume 10 of the Rules Governing Medicinal Products in the EU).
Examples include:

- non-clinical toxicological findings that have not been observed or resolved in clinical studies;
- adverse events observed in clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparator group (placebo or active substance, or unexposed group), on the parameter of interest raises a suspicion of, but is not large enough to suggest, a causal relationship;
- a signal arising from a spontaneous adverse reaction reporting system;
- an event known to be associated with other active substances within the same class or which could be expected to occur based on the properties of the medicinal product (see ICH-E2F Guideline, Volume 10 of the Rules Governing Medicinal Products in the EU).

See also ***Adverse event, Signal***

Quality adherence
Carrying out tasks and responsibilities in accordance with quality requirements [IR Article 8(3)]
See also ***Quality requirements***

Quality assurance
See ***Quality control and assurance***

Quality control and assurance
Monitoring and evaluating how effectively the structures and processes have been established and how effectively the processes are being carried out [IR 520/2012 Art 8(3)].
This applies for the purpose of fulfilling quality requirements.

See ***Quality requirements***

Quality improvements
Correcting and improving the structures and processes where necessary [IR 520/2012 - Art 8(3)].
This applies for the purpose of fulfilling quality requirements.
See also ***Quality requirements***

Quality of a pharmacovigilance system
All characteristics of the pharmacovigilance system which are considered to produce, according to estimated likelihoods, outcomes relevant to the objectives of pharmacovigilance.
See also ***Pharmacovigilance system, Quality system of a pharmacovigilance system***

Quality objectives

*See **Quality requirements***

Quality planning
Establishing structures and planning integrated and consistent processes [Article 8(3) of IR 520/2012].
This applies for the purpose of fulfilling quality requirements.
*See also **Quality requirements***

Quality requirements
Those characteristics of a system which are likely to produce the desired outcome, or quality objectives.
*See also **Pharmacovigilance system, Quality system of a pharmacovigilance system***

Quality system of a pharmacovigilance system
The organisational structure, responsibilities, procedures, processes and resources of the pharmacovigilance system as well as appropriate resource management, compliance management and record management [IR 520/2012 Article 10 (2)].
The quality system is part of the pharmacovigilance system.
*See also **Pharmacovigilance system and Quality of a pharmacovigilance system***

Reference safety information
In periodic benefit-risk evaluation reports for medicinal products, all relevant safety information contained in the reference product information (e.g. the company core data sheet) prepared by the marketing authorisation holder and which the marketing authorisation holder requires to be listed in all countries where it markets the product, except when the local regulatory authority specifically requires a modification (see Annex IV, ICH-E2C(R2) Guideline).
It is a subset of information contained within the marketing authorisation holder's reference product information for the periodic benefit-risk evaluation report. Where the reference product information is the company core data sheet, the reference safety information is the company core safety information (see Annex IV, ICH-E2C(R2) Guideline).
*See also **Company core data sheet, Company core safety information***

Registry
An organised system that uses observational methods to collect uniform data on specified outcomes in a population defined by a particular disease, condition or exposure.

Risk-benefit balance
An evaluation of the positive therapeutic effects of the medicinal product in relation to the risks (Article 695 (29) of Law 95/2006), i.e. any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health [Article 695 (28), first point of Law 95/2006]).
*See also **Risks related to use of a medicinal product***

Risk management plan (RMP)
A detailed description of the risk management system [see Article 695 (28)[1] b) of Law 95/2006].
To this end, it must identify or characterise the safety profile of the medicinal product(s) concerned, indicate how to characterise further the safety profile of the medicinal product(s) concerned, document measures to prevent or minimise the risks associated with the medicinal product, including an assessment of the effectiveness of those interventions and document post-authorisation obligations that have been imposed as a condition of the marketing authorisation [Article 30 of IR 520/2012].
*See also **Risk management system, Risk minimisation activity***

Risk management system
A set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to a medicinal product, including the assessment of the effectiveness of those activities and interventions [Article 695 (28[1)] a) of Law 95/2006].

Risk minimisation activity; synonym: Risk minimisation measure
A public health intervention intended to prevent or reduce the probability of the occurrence of an adverse reaction associated with the exposure to a medicine, or to reduce its severity should it occur [See Annex IV, Guideline ICH-E2C(R2)].
These activities may consist of routine risk minimisation (e.g. product information) or additional risk minimisation activities (e.g. healthcare professional or patient communications/educational materials).

Risks related to use of a medicinal product
Any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health and any risk of undesirable effects on the environment [Article 695 (28) of Law 95/2006].

Safety concern
An important identified risk, important potential risk or missing information.
It is noted that the ICH definition of safety concern is: an important identified risk, important potential risk or important missing information, i.e. includes the qualifier "important" in relation to missing information (see Annex IV, ICH-E2C(R2) Guideline). The ICH-E2E Guideline (see Annex IV) uses the terms safety issue and safety concern interchangeably with the same definition for safety concern as defined in the ICH-E2C(R2) Guideline.
See also ***Important identified risk and Important potential risk, Missing information***

Serious adverse reaction
An adverse reaction which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect [Article 695 (11) of Law 95/2006].

"Life-threatening" in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe (see Annex IV, ICH-E2D Guideline).
Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse (see Annex IV, ICH-E2D Guideline).
Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.
See also ***Adverse reaction***

Signal
Information arising from one or multiple sources, including remarks and experiments, which suggests a new potentially causal association, or a new aspect of a known association between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action [IR Art 19(1)].
For the purpose of monitoring data in the EudraVigilance database, only signals related to an adverse reaction is considered [IR Art 19(1)].
For the purpose of Section 16.2 of the periodic benefit-risk evaluation report, signals relate to adverse effects (see Annex IV, ICH-E2C(R2) Guideline).
See also ***Validated signal, Newly identified signal, Closed signal, Ongoing signal, Signal management process, Adverse reaction***

Signal management process
Includes the following activities: signal detection, signal validation, signal confirmation, signal analysis and prioritisation, signal assessment and recommendation for action [IR 520/2012 Art 21(1)].

It therefore is a set of activities performed to determine whether, based on an examination of individual case safety reports (ICSRs), aggregated data from active surveillance systems or studies, literature information or other data sources, there are new risks causally associated with an active substance or a medicinal product or whether known risks have changed.
See also ***Signal validation***

Signal validation
Process of evaluating the data supporting a detected signal in order to verify that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, therefore justifying further analysis of the signal [see Commission Implementing Regulation no. 520/2012, Article 21(1)].
See also ***Validated signal***

Solicited sources of individual case safety reports
Organised data collection systems, which include clinical trials, registries, post-authorisation named - patients use programmes, other patient support and disease management programmes, surveys of patients or healthcare providers or information gathering on efficacy or patient compliance. For the purpose of safety reporting, solicited reports should not be considered spontaneous but classified as individual case safety reports from studies and therefore should have an appropriate causality assessment by a healthcare professional or the marketing authorisation holder (see Annex IV, ICH-E2D).
See also ***Clinical trial, Post-authorisation safety study, Non-interventional trial***

Spontaneous report, synonym: Spontaneous notification
An unsolicited communication by a healthcare professional or consumer to a company, regulatory authority or other organisation (e.g. the World Health Organization, a regional centre, a poison control centre) that describes one or more adverse reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organised data collection scheme (see Annex IV, ICH-E2D).
In this context, an adverse reaction refers to a suspected adverse reaction.
Stimulated reporting can occur in certain situations, such as after a direct healthcare professional communication (DHPC), a publication in the press or questioning of healthcare professionals by company representatives, and adverse reaction reports arising from these situations are considered spontaneous reports (see Annex IV, ICH-E2D), provided the report meets the definition above. Reporting can also be stimulated by invitation from patients' or consumers' organisations to their members. Reporting made in the context of early post-marketing phase vigilance (EPPV), e.g. in Japan, is also considered stimulated reporting.
See also ***Adverse reaction***

Stimulated reporting
See ***Spontaneous report***

Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility (see Annex IV, ICH-E2A Guideline).
Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure [Article 812 (1) of Law 95/2006]. Conditions of use outside the marketing authorisation include off-label use, overdose, misuse, abuse and medication errors.
See also ***Adverse event, Serious adverse reaction, Unexpected adverse reaction, Off-label use, Overdose, Misuse of a medicinal product, Abuse of a medicinal product, Occupational exposure to a medicinal product***

Substance
Any matter irrespective of origin which may be human (e.g. human blood and human blood products), animal (e.g. micro-organisms, whole animals, parts of organs, animal secretions, toxins, extracts, blood products), vegetable (e.g. micro-organisms, plants, part of plants, vegetable secretions, extracts) or chemical (e.g. elements, naturally occurring chemical materials and chemical products obtained by chemical change or synthesis) [Article 695 (2) of Law 95/2006].

Summary of product characteristics (SmPC)
Part of the marketing authorisation of a medicinal product setting out the agreed position of the product as distilled during the course of the assessment process which includes the information described in Article 708 of Law 95/2006. It is the basis of information for healthcare professionals on how to use the product safely and effectively. The package leaflet is drawn in accordance with the summary of product characteristics (based on A Guideline on Summary of Product Characteristics, Volume 2C of the Rules Governing Medicinal Products in the EU).

Target population (treatment); synonym: Treatment target population
The patients who might be treated with the medicinal product in accordance with the indication(s) and contraindications in the authorised Product information.

Target population (vaccine); synonym: Vaccine target population
Persons who might be vaccinated in accordance with the indication(s) and contraindications in the authorised product information and official recommendations for vaccinations.

Traditional herbal medicinal product
A herbal medicinal product that fulfils the conditions laid down in Article 714 (1) and 659 (3) of Law 95/2006, as amended, i.e.

a) it has (an) indication(s) exclusively appropriate to traditional herbal medicinal products which, by virtue of their composition and purpose, are intended and designed for use without the supervision of a medical practitioner for diagnostic purposes or for prescription or monitoring of treatment;

b) it is exclusively for administration in accordance with a specified strength and posology;
c) it is an oral, external and/or inhalation preparation;
d) the period of traditional use as laid down in Article 716 (1)(c) of Law 95/2006, as amended, has elapsed;
e) the data on the traditional use of the medicinal product are sufficient; in particular the product proves not to be harmful in the specified conditions of use and the pharmacological effects or efficacy of the medicinal product are plausible on the basis of long-standing use and experience [Article 714 of Law 95/2006].
Regarding d), the product must have been in medicinal use throughout a period of at least 30 years, including at least 15 years within the EU (see Article 716 (1) c) of Law 95/2006, as amended, and European Commission Questions & Answers Document on Registration of Traditional Herbal Medicinal Products, 2011).
See also ***Herbal medicinal product***

Unexpected adverse reaction
An adverse reaction, the nature, severity or outcome of which is not consistent with the summary of product characteristics [Article 695 (12) of Law 95/2006][32].
This includes class-related reactions which are mentioned in the summary of product characteristics (SmPC) but which are not specifically described as occurring with this product. For products authorised nationally, the relevant SmPC is that authorised by the competent authority in the Member State to whom the reaction is being reported. For centrally authorised products, the relevant SmPC is the SmPC authorised by the European Commission. During the time period between a CHMP opinion in favour of granting a marketing authorisation and the Commission decision granting the marketing authorisation, the relevant SmPC is the SmPC annexed to the CHMP opinion.
See also ***Summary of product characteristics***

Upper management
Group of persons in charge of the highest executive management of an organisation.
Membership of this group is determined by the governance structure of the organisation.

[32] For investigational medicinal products, an unexpected adverse reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. the investigator's brochure for an unauthorised investigational product or the summary of product characteristics for an authorised product) [Order of the Minister of Health No. 904/2006, Art 2(p)]

While it is envisaged that the upper management usually is a group, the head of the organisation is the one person at the top of the organisation with ultimate responsibility for ensuring that the organisation complies with relevant legislation.

Vaccination
The administration of a vaccine with the aim to produce immune response.
See also ***Immunisation***

Vaccination failure
Vaccination failure due to actual vaccine failure or failure to vaccinate (see CIOMS-WHO[5]).
Vaccination failure may be defined based on clinical endpoints or immunological criteria, where correlates or surrogate markers for disease protection exist. Primary failure (e.g. lack of seroconversion or seroprotection) needs to be distinguished from secondary failure (waning immunity).
See also ***Vaccine failure, Failure to vaccinate***

Vaccine
See ***Immunological medicinal product***

Vaccine failure
Confirmed or suspected vaccine failure.

Confirmed clinical vaccine failure
Occurrence of the specific vaccine-preventable disease in a person who is appropriately and fully vaccinated taking into account the incubation period and the normal delay for the protection to be acquired as a result of immunisation (see CIOMS-WHO[5]).

Suspected clinical vaccine failure
Occurrence of disease in an appropriately and fully vaccinated person, but the disease is not confirmed to be the specific vaccine-preventable disease, e.g. disease of unknown serotype in a fully vaccinated person (based on CIOMS-WHO[5]).

Confirmed immunological vaccine failure
Failure of the vaccinated person to develop the accepted marker of protective immune response after being fully and appropriately vaccinated, as demonstrated by having tested or examined the vaccinated person at an appropriate time interval after completion of immunisation (based on CIOMS-WHO[5]).

Suspected immunological vaccine failure
Failure of the vaccinated person to develop the accepted marker of protective immune response after being fully and appropriately vaccinated, but with the testing or examination of the vaccinated person done at an inappropriate time interval after completion of immunisation (based on CIOMS-WHO[5]).
For interpreting what means appropriately vaccinated, consider the explanatory note for ***Immunisation error-related reaction.***
See also ***Vaccination failure***

Vaccine pharmacovigilance
The science and activities relating to the detection, assessment, understanding and communication of adverse events following immunisation and other vaccine- or immunisation-related issues, and to the prevention of untoward effects of the vaccine or immunisation (see CIOMS-WHO[5]).
In this definition, immunisation means the usage of a vaccine for the purpose of immunising individuals (see CIOMS-WHO[5]), which in the EU is preferably referred to as *vaccination* (in the report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance the terms *immunisation* and *vaccination* are used interchangeably[5]). Usage includes all processes that occur after a vaccine product has left the manufacturing/packaging site, i.e. handling, prescribing and administration of the vaccine (see CIOMS-WHO[5]).

An adverse event following immunisation (AEFI) is any untoward medical occurrence which follows immunisation and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease. While this AEFI definition is compatible with the definition of adverse event applied in the EU, the AEFI definition is not needed to describe pharmacovigilance for vaccines in the EU.
However, EU guidance on pharmacovigilance for vaccines makes use of the terminology suggested by CIOMS-WHO[5] regarding possible causes of adverse events, turning them into suspected adverse reactions. A coincidental event is an AEFI that is caused by something other than the vaccine product, immunisation error or immunisation anxiety (see CIOMS-WHO[5]).
See also ***Adverse event, Immunisation anxiety-related reaction, Immunisation error-related reaction, Vaccine product-related reaction, Vaccine quality defect-related reaction, Vaccination***

Vaccine product-related reaction
An adverse event following immunisation that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product (see CIOMS-WHO[14]).
In this definition immunisation means the usage (handling, prescribing and administration) of a vaccine for the purpose of immunising individuals (see CIOMS-WHO[14]), which in the EU is preferably referred to as vaccination (in the report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance the terms immunisation and vaccination are used interchangeably[14]).
See also ***Adverse reaction, Vaccine pharmacovigilance***

Vaccine quality defect-related reaction
An adverse event following immunisation that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product including its administration device as provided by the manufacturer (see CIOMS-WHO[13]).
In this definition immunisation means the usage (handling, prescribing and administration) of a vaccine for the purpose of immunising individuals (see CIOMS-WHO [13]), , which in the EU is preferably referred to as vaccination (in the report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance the terms *immunisation* and *vaccination* are used interchangeably[13]).
For the purpose of this definition, a vaccine quality defect is defined as any deviation of the vaccine product as manufactured from its set quality specifications.
See also ***Adverse reaction, Vaccine pharmacovigilance***

Valid individual case safety report
See ***Individual case safety report***

Validated signal
A signal where the signal validation process of evaluating the data supporting the detected signal has verified that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and therefore justifies further analysis of the signal [based on IR Art 25 (1)].
See also **Signal**

DECISION

No. 6/05.06.2014

on approval of Regulations for authorisation by the National Agency for Medicines and Medical Devices of clinical trials/notification to the National Agency for Medicines and Medical Devices of non-interventional studies on medicinal products for human use in Romania

The Scientific Council of the National Agency for Medicines and Medical Devices (NAMMD), established based on Order of the Minister of Health No. 374/02.04.2014, in accordance with the Regulation on organisation and operation of the NAMMD Scientific Council, Article 8 (1), adopts through written procedure the following

DECISION

Article 1. - The Regulations for authorisation by the National Agency for Medicines and Medical Devices of clinical trials/notification to the National Agency for Medicines and Medical Devices of non-interventional studies on medicinal products for human use in Romania are approved, in accordance with the Annexes which are integral parts of this Decision.

Article 2. – On this Decision coming into force, the following are repealed:

- SCD no. 29/16.12.2010 on approval of regulations on authorisation by the National Agency for Medicines and Medical Devices of clinical trials/notification to the National Agency for Medicines and Medical Devices of non-interventional studies conducted on medicinal products for human use in Romania;
- SCD no. 26/13.12.2011 on approval of amendment of Scientific Council Decision no. 29/16.12.2010 on approval of regulations on authorisation by the National Agency for Medicines and Medical Devices of clinical trials/notification to the National Agency for Medicines and Medical Devices of non-interventional studies conducted on medicinal products for human use in Romania
- SCD no. 8/17.04.2012 on approval of amendment of the Annex to Scientific Council Decision no. 29/16.12.2010 on approval of the Regulations on the authorisation by the National Agency for Medicines and Medical Devices of clinical trials/notification to the National Agency for Medicines and Medical Devices of non-interventional studies on medicinal products for human use in Romania.

PRESIDENT
of the Scientific Council
of the National Agency for Medicines and Medical Devices,
Acad. Prof. Dr. Leonida Gherasim

ANNEX to SCD no. 6/05.06.2014

REGULATIONS
for authorisation by the National Agency for Medicines and Medical Devices of clinical trials/notification to the National Agency for Medicines and Medical Devices of non-interventional studies on medicinal products for human use in Romania

CHAPTER I
General principles

Article 1. - (1) Clinical trials undertaken in Romania are authorised by the National Agency for Medicines and Medical Devices (NAMMD) in accordance with Law 95/2006 on healthcare reform, Title XVII – The medicinal product, as amended, Government Decision no. 734/21.07.2010 on the organisation and operation of the National Agency for Medicines and Medical Devices, as amended, and Order of the Minister of Public Health no. 904/2006 on the approval of the Norms on the implementation of GMP rules in clinical trials carried out on medicinal products for human use.

(2) Non-interventional studies are an exception to provisions of paragraph (1), as defined in Order of the Minister of Health no. 904/2006, which shall be notified to the NAMMD.

Article 2. - Clinical trials must be conducted in accordance with all clinical trial regulations in force.

CHAPTER II
Clinical trial authorisation procedure

Article 3. - (1) For initiation of a clinical trial authorisation procedure, the applicant shall pay the clinical trial authorisation fee, established through Order of the Minister of Health in force concerning NAMMD fees.

(2) To perform the payment, at least 2 weeks in advance of submission of the application for clinical trial authorisation, the applicant shall submit to the NAMMD a cover letter related to the payment of the clinical trial fee, accompanied by the filled-in clinical trial fee payment form.

(3) The fee is to be paid to the accounts published on the NAMMD website.

(4) The NAMMD confirms the respective payment by e-mail.

Article 4. - (1) Following fee payment confirmation, the applicant may submit to the NAMMD an application for authorisation, using the format shown in SCD No. 22/2010 on approval of the Guidance for the request for authorisation of a clinical trial on a medicinal product for human use, addressed to the competent authority, notification of substantial amendments and declaration of the end of the trial in Romania.

(2) At the same time with submission of the application, the applicant shall also forward a signed cover letter, on paper, as shown in SCD no. 22/2010.

(3) On request, the documents mentioned in Annex 1, which is integral part of these regulations, shall be attached and forwarded in electronic format (on CD/DVD), structured in accordance with Annex 2.

Article 5. – The assessment period starts on submission of the documentation (day 0).

Article 6. - (1) The NAMMD reviews the validity of all documents required under Annex 1 (validation stage) and in 10 days forwards to the applicant a letter of information on validation of the application.

(2) If the documentation submitted by the applicant is complete, the application is considered valid and the assessment period is continued.

(3) If the documentation submitted by the applicant contains the essential documents related to the trial and supplementations are however necessary, requests for supplementation of the documentation are made; the assessment period is stopped until the date of submission of the required supplementations.

(4) If the documentation does not comprise the essential trial documents, the application for authorisation is rejected.

Article 7. - Documents under Article 4 (3) must be drawn up in accordance with provisions of SCD No. 22/2010.

Article 8. - The documentation is submitted in either English or Romanian.

Article 9. – (1) Labelling of medicinal products used in clinical trials is either Romanian or English (only for NAMMD use, for translation checking purposes);

(2) If the sponsor is Romanian, the label is submitted in Romanian only.

(3) Labelling is submitted in Romanian only for clinical trials performed in Romania.

Article 10. Applicants are advised to submit substantial amendments to the main trial documentation within 50 days as of payment confirmation; otherwise, the time for assessment of documentation is extended accordingly.

Article 11. - NAMMD examination of an accurate and properly formatted application for authorisation is to be completed as soon as possible, in line with the deadline set in Order of the Minister of Public Health no. 904/2006.

Article 12. - In case of documentation set up compliant with regulations in force and sufficiently substantiated, the NAMMD grants the authorisation for the performance of the clinical trial in the format mentioned in Annex 3, which is integral part of these regulations.

Article 13. - (1) If, following assessment of documentation, additional information or key clarifications to trial documentation is found necessary, the NAMMD notifies the applicant thereof.

(2) The deadline for assessment for clinical trial authorisation/refusal as specified in Order of the Minister of Public Health no. 904/2006 is extended with the time from applicant receipt of the NAMMD notification to receipt by NAMMD of the information required.

Article 14. - If, following assessment, documentation is found noncompliant with regulations in force and insufficiently substantiated, within the deadline provided in Order of the Minister of Public Health no. 904/2006, the NAMMD notifies the applicant on rejection of authorisation, accompanied by an explanatory report.

Article 15. - (1) The applicant may require revision of the refusal decision within 30 days as of issuance of the NAMMD decision; the application for revision must be accompanied by supporting documentation.

(2) The NAMMD examines the application and formulates an opinion within 30 days as of admission of the application for revision.

Article 16. - (1) The authorisation covers the entire conduct of a clinical trial, approved by the NAMMD; the trial starts within 1 year after the date of approval, otherwise the authorisation is no longer valid and the application must be resubmitted.

(2) The applicant informs the NAMMD about start of the trial in Romania (date of inclusion of the first patient/subject).

(3) In the end of the trial, the applicant informs the NAMMD about start of the trial, as shown in SCD no. 22/2010 and informs the NAMMD about the number of subjects enrolled in Romania.

Article 17. – The applicant submits to the NAMMD a copy of the National Ethics Commission/Institutional Ethics Commission opinion as soon as it becomes available.

Article 18. - A clinical trial may only start on condition the NAMMD has granted the authorisation for clinical trial conduct and after grant of the favourable opinion of the National Ethics Commission, for multicentre trials, or the Institutional Ethics Commission, for single-centre trials.

CHAPTER III
Procedure for notification of amendments

Article 19. – In accordance with Order of the Minister of Health no. 904/2006, after start of the trial, the sponsor may amend the clinical trial documentation.

Article 20. - (1) The notification is mandatory only in case of substantial amendments (in accordance with SCD No. 22/2010).

(1) Immediate notification/submission of non-substantial amendments is not necessary (as under Minister of Public Health Order No. 904/2006).

Article 21. - (1) To start an authorisation procedure for a substantial amendment, the applicant must pay the fee for assessment of amendments, as established through the Minister of Health Order in force concerning NAMMD fees.

(2) To pay the fee, the applicant submits a cover letter to the NAMMD, accompanied by a filled-in form for payment of amendment fee, at least 2 weeks prior to the submission of the application for clinical trial authorisation.

(3) The NAMMD confirms the respective payment by e-mail.

Article 22. - (1) After confirmation of the payment, the applicant submits to the NAMMD a notification in the format provided in SCD No. 22/2010.

(2) At the same time with the application, the applicant also submits a signed cover letter.

(3) On request, the documents mentioned in SCD No. 22/2010, section III.7, Form and content of the notification, are attached.

Article 23. - (1) The period for assessment of amendments starts with submission of documentation (day 0).

(2) The NAMMD responds to the notification of an amendment within 35 calendar days as of receipt of a valid notification.

Article 24. - (1) The NAMMD assesses the validity of the notification.

(2) When the submission of the amendment is not considered valid (e.g. the dossier does not contain the necessary as per SCD No. 22/2010), the NAMMD informs the applicant within 10 calendar days of the aforementioned 35-day period, while stating the grounds for this decision.

Article 25. - If documentation is set up in accordance with legal provisions in force and sufficiently substantiated, the NAMMD notifies approval of the amendment.

Article 26. - (1) If, following assessment of the documentation, the NAMMD ascertains that additional information or essential clarifications to the documentation submitted are required, the NAMMD notifies the applicant in writing.

(2) The assessment period until approval/refusal of the amendment is extended with the time from applicant receipt of the request notification to NAMMD receipt of the information required.

Article 27. – If, following assessment of documentation, this is found not to be compliant with regulations in force and not satisfactorily substantiated, this leads to rejection of the proposed amendment.

Article 28. - (1) The applicant may require revision of the rejection decision within 30 days as of issuance of the NAMMD decision; the application for revision must be accompanied by supporting documentation.

(2) The NAMMD examines the application and formulates an opinion within 30 days as of receipt of the application for revision.

Article 29. – An amendment may only be implemented if:

- The NAMMD has notified its approval of the amendment and the CNBMDM has expressed its favourable opinion (if the amendment requires both NAMMD approval and CNBMDM opinion);
- The NAMMD has forwarded the approval of the amendment (if the amendment only requires NAMMD approval);
- The CNBMDM has expressed a favourable opinion (if the amendment only requires CNBMDM opinion).

CHAPTER IV
Importation of investigational medicinal products

Article 30. - The notification of investigational medicinal products (IMPs) importation is performed in compliance with legislation in force.

CHAPTER V
Analysis of biological samples

Article 31. - Analysis of biological samples collected during clinical trials are carried out in certified or accredited laboratories in Romania or other countries.

Article 32. - In case the analysis of biological samples is not performed in Romania, these shall be sent to other member states/exportation in third countries shall be done in compliance with legal provisions in force.

CHAPTER VI
Good Clinical Practice (GCP) inspection

Article 33. - GCP inspection is conducted in accordance with legal provisions in force.

CHAPTER VII
Requests concerning manner of trial subjects recruitment

Article 34. – (1) Recruitment of subjects for clinical trials conducted in Romania may only be done through healthcare professionals (physicians and pharmacists), except for healthy volunteers, who may also be recruited by other means.

(2) The media may not be used for recruitment.

CHAPTER VIII
Reporting of adverse reactions occurring in clinical trials

Article 35. - It is the sponsor's obligation to report to the NAMMD adverse reactions and other information according to provisions of SCD No. 27/2011 on approval of the Guidance on the collection, verification and presentation of adverse reaction/event reports arising from clinical trials on medicinal products for human use.

CHAPTER IX
Requirements regarding investigator's qualification

Article 36. – In order to fulfil provisions of Article 13 of Order of the Minister of Public Health no. 904/2006 and Articles 37 and 39 of SCD no. 39/2006 on qualification and training of investigators and knowledge of and compliance with Good Clinical Practice (GCP) Regulations and other legal regulations in the field, the application for authorisation of a clinical trial is accompanied by the documents specified in Annex 1, which are integral part of these Regulations.

CHAPTER X
Authorisation of sites for conduct of clinical trials

Article 37. – Clinical trials may only be conducted on sites authorised by the Ministry of Public Health, in accordance with provisions of SCD no. 2/22.04.2014 on approval of Regulations for authorisation of sites for conduct of clinical trials on medicinal products for human use.

Article 38. – The authorisation is granted by the NAMMD on request by the interested site, in accordance with legal regulations in force.

Article 39. – (1) The amendments concerning investigation centres refer to the initial documents submitted for support of the application for authorisation for conduct of a clinical trial, as described under Section III.4.4 of SCD no. 22/2010.

(2) Non-exhaustive list of amendments typically considered important:

- addition of new centres;
- change of the new investigator from an already authorised site;
- change of the investigation site from an already authorised site (clinic/medical unit).

CHAPTER XI
Notification procedure for non-interventional studies

Article 40. - Notification of non-interventional studies consists of submission to the NAMMD by an applicant of a notification address, set up according to provisions of Annex 6, which is integral part of these Regulations, accompanied by the following documents:

- copy of the trial design;
- list of the sites where the trial will be conducted;
- information on the duration of the trial and the number of patients to be enrolled;
- list of the investigators containing their names, surnames and workplaces;
- trial endpoints:

a) The scientific endpoints of the trial must be clearly stated, as well as the relevance for the medical practice of the data obtained during the trial conduct;

b) The indicators for assessment of trial endpoints must be specified.

Article 41. - The clinical trial applicant is responsible for transmitting to the NAMMD the results of the non-interventional study, as well as for interpretation and statistical significance of results in one year as of trial ending.

Article 42. - In case of non-interventional studies, the NAMMD does not request fees for activities undertaken.

Article 43. - The NAMMD maintains a separate database of non-interventional studies, also including the results of non-interventional studies carried out in Romania.

Article 44. – The NAMMD notifies the applicant about the approval, rejection or need for completion of the documentation in 60 days as of submission of the notification.

ANNEX 1
to Regulations

DOCUMENTS
Accompanying the application to the NAMMD for authorisation of a clinical trial

KEY DOCUMENTATION
1. General information
1.1. Cover letter
1.2. Application form
1.3. Confirmation of EudraCT number receipt
1.4. If the applicant is different from the sponsor, a legal authorisation letter from the sponsor, empowering the applicant to act on behalf of the sponsor

2. Information on the protocol
2.1. Protocol containing all amendments
2.2. Summary of the protocol in Romanian
2.3. Opinion of the main investigator/coordinator on the ethical aspects of the trial

3. Investigator's Brochure (IB) or Document replacing the IB, in accordance with the content established in subsection II.6 of SCD no. 22/2010.

4. Investigational Medicinal Product Dossier (IMPD)/simplified IMPD
In accordance with the content established in subsections II.7 and II.7.3 of SCD no. 22/2010
The Investigational Medicinal Product Dossier (IMPD) includes:
- Evidence of GMP compliance
- Examples of labels in Romanian and English

5. The NIMPD dossier, in accordance with the content established in subsection II.8 of SCD no. 22/2010

6. Information on the staff and facilities
- Facilities made available for the trial:
  - Authorisation of the healthcare unit for the conduct of clinical trials,
  - Consent of the healthcare unit's director on conduct of the clinical trial
- CVs of the main investigator and subinvestigators;
- CV of the coordinator-investigator in Romania (for multicentre trials), if appointed;
- Copy of the confirmation order in the specialised field for the main investigator;
- Form attesting the qualification of the main investigator, containing the List of subinvestigators, of whom at least one is a physician;
- Proof of graduation from a course referring to Good Clinical Trial Practice for all investigators and subinvestigators;
- Any other documents attesting the qualification and training of investigators in accordance with the area of the study.

7. Confirmation of payment

ADDITIONAL DOCUMENTATION
1. Copy of the National Bioethics Committee of Medicines and Medical Devices, if available;
2. Copy/Summary of any scientific counselling, if any;
3. Copy of the EMA decision concerning agreement expressed concerning the PIP, as well as the opinion of the Paediatric Committee, if any;
4. List of competent authorities (CAs) in the EU to whom the application and decision details have been submitted;
5. Information about all active clinical trials on the same PIP.

ANNEX 2
to Regulations

- **1. General information**
- **2. Protocol-related information**
- **3. Investigator's brochure or document replacing the IB**
- **4. Investigational Medicinal Product Dossier (IMPD) /simplified IMPD**
- **5. NIMPD dossier**
- **6. Information on the staff and facilities**
- **7. Additional documents**

ANNEX 3
to Regulations

THE MINISTRY OF HERALTH
THE NATIONAL AGENCY FOR MEDICINES AND MEDICAL DEVICES
48 Av. Sănătescu street, sector 1
011478 Bucharest
Tel.: +40-21.317.11.02
Fax:+40-21.316.34.97

AUTHORISATION
for conduct of a clinical trial

The National Agency for Medicines and Medical Devices, based on Article 4 (2) d) of Government Decision no. 734/21.07.2010, as amended, and on Article 37 of Order of the Minister of Public Health no. 904/2006, hereby authorises conduct of the clinical trial according to Protocol No.:

EudraCT No.:

Title:

Sponsor:

Investigators:

Institution (trial site):

Remarks:

PRESIDENT,
.....

ANNEX 4
To Regulations

FORM
for reporting serious unexpected suspected adverse reactions

Suspected adverse reaction Protocol no. Notification no.

Investigational medicinal product Patient no.

I. Information on the adverse reaction

1.Patient's initials	1.Country	2. Birthdate			2.a. Age	3.Gender	4-6 Manifestation of the adverse reaction			8-12 Fill in accordingly
		Day	Month	Year			Day	Month	Year	[ ] Death [ ] Life-threatening [ ] Hospitalisation/Prolonging hospitalisation [ ] Major or chronic handicap/disability [ ] Congenital disorder/disease
7.Reaction's description (including relevant outcomes/laboratory testings)										

II. Information about the suspected investigational medicinal product

14. Name of the investigational medicinal product		20. The adverse reaction has subsided after the discontinuation of the trial [ ] Yes [ ] No
15. Daily dose	16. Route of administration	21. The adverse reaction has reoccurred after the second administration of the investigational medicinal product [ ] Yes [ ] No
17. Administration indication(s)		
18. Period of administration (from/until)	19. Duration of administration	

III. Concomitant indication and history

22. Concomitant medication and administration dates (excluding that meant for treatment of the reaction)
23. Other relevant medical history data (such as diagnosis, allergic reactions, pregnancies etc.)

IV. Information about the sponsor and the investigator

24.a. Name and address of the sponsor		24.b. Name of the investigator
24.c. Date of receipt by the sponsor	25.a. Type of information [ ] Initial [ ] Sequential	25.b. Manner of informing the sponsor
Date of notification	Date of receipt	[ ] Additional information is to be attached

Sponsor's signature

ANNEX 5
to Regulations

FORM
for main investigator/coordinator qualification and arrangements made for participation in the clinical trial

Investigational medicinal product …….... Protocol No. .....….
Name of the main investigator/coordinator .....….....
Investigator's address ……...….....……
Curriculum Vitae/summary: ..... Attached YES [ ]
Qualification (profession) ……..…….....
Experience in clinical trials: .....
Experience with other medicinal products relevant to the proposed trial
…….....
Regular duties:
Involvement in other clinical trials:
Time necessary for this protocol:
Availability of subjects suitable for the clinical trial:
I hereby accept to participate as main investigator/coordinator in the clinical trial mentioned:
I hereby agree to allow control of all documents:
I hereby agree to allow access to basic documentation:
I hereby agree to sign the commitment form and conduct the trial according to the approved protocol, in compliance with the revised Helsinki Declaration of Human Rights and Good Clinical Practice in Romania.
During the trial, the following will participate as sub-investigators:

Signature

Date.....
(day/month/year)
Title

Monitor

(Name)

ANNEX 6
to Regulations

NOTIFICATION
on conduct of a non-interventional study in Romania

To

THE NATIONAL AGENCY FOR MEDICINES AND MEDICAL DEVICES

APPLICANT SPONSOR ☐ INVESTIGATOR ☐ CRO* ☐

Name and surname

Profession

Institution

Address

Telephone/fax number

*) Contract research organisation

We are hereby notifying conduct of a non-interventional study on a medicinal product authorised for marketing in Romania:

- Title of the clinical trial: .....

Information about the investigational medicinal product
- Trade name/code
- Active substance
- ATC code
- Pharmaceutical form
- Doses
- Route of administration
- Marketing Authorisation Holder
- Country

This notification is accompanied by:

- ❑ Copy of the study design
- ❑ Study endpoints
- ❑ List of the sites where the study is conducted;
- ❑ Information about trial duration and number of patients to be enrolled.
- ❑ List of investigators containing the names and surnames of the investigators and their workplaces

THE MINISTRY OF HERALTH
THE NATIONAL AGENCY FOR MEDICINES AND MEDICAL DEVICES
48 Av. Sănătescu street, sector 1
011478 Bucharest
Tel.: +40-21.317.11.02
Fax:+40-21.316.34.97

DECISION
no. 1/25.06.2014
on approval of the 2012 annual report of the National Agency for Medicines and Medical Devices

The Administration Council of the National Agency for Medicines and Medical Devices, summoned through Order of the Minister of Health no. 652/04.06.2014, convened in the meeting of 25 June 2014;

On seeing the need for approval of the 2012 Activity Report of the National Agency for Medicines and Medical Devices;

Based on Article 10 f) of Government Decision No. 734/2010 related to the organisation and operation of the National Agency for Medicines and Medical Devices, as amended, hereby adopts the following

DECISION

Article 1 – Approves the 2012 annual report of the National Agency for Medicines and Medical Devices, as shown in the Annex, which is integral part of this Decision, which is to be published in the Official Gazette of Romania, Part III.

Article 2 – The Minister of Health is notified of this Decision.

PRESIDENT
of the Administration Council
of the National Agency for Medicines and Medical Devices,
Dr. Marius SAVU

2012 ANNUAL REPORT
THE NATIONAL AGENCY FOR MEDICINES AND MEDICAL DEVICES

INTRODUCTION

In 2012, the National Agency for Medicines and Medical Devices (NAMMD) carried out the same concentrated work to reach the goals imposed by the Agency's foremost mission, namely assessment of the authorisation dossier for marketing of quality, safe and effective medicinal products and surveillance of the safety of medicinal products for human use in the therapeutic circuit, via inspection and pharmacovigilance activities.

As customary in recent years, the NAMMD's accomplishments in the medicinal product field for human use have been based upon the efforts undertaken by Agency experts in its scientific departments (The National Procedure Department - NPD, the European Procedures Department - EPD, the Pharmaceutical Inspection Department - PID, the Medicinal Products Quality Control Department - MPQCD, the Biological Products Evaluation and Control Department - BPECD, the Policies and Strategies Department - PSD), continuously supported by support departments (The Information Logistics and Electronic Management of Data Department – ILEMDD), the Human Resources and Payroll Department - HRPD, the Economic Department - ED, the General Administration Department - GAD). By means of an adequate communication strategy, the NAMMD has permanently aimed at strengthening its credibility to its partners as an authentic guardian and initiator of public health in Romania.

In the same way as for all competent authorities in the field of medicinal products for human use throughout the entire European Union, for the NAMMD too one of the main targets is to create an efficient liaison with all stakeholders e.g. healthcare, research and industry professionals, patients, the public and the media. All NAMMD specialists, pharmacists, physicians, biologists, involved in either assessment for authorisation, or control, inspection and/or pharmacovigilance, implicitly also contribute to implementation of the NAMMD communication strategy by actual involvement in the set-up of responses to media and/or any stakeholder queries, in identification of new requirements of the Agency's partners, in organising and participating to meetings. Increased openness towards streamlining of the communication with all partners in the field has resulted in to meetings with Marketing Authorisation Holders, associations of international and Romanian medicinal product manufacturers, patients, associations of companies coordinating conduct of clinical trials, associations of medicinal product suppliers etc.

Assessment of the 2012 outcomes proves full accomplishment by the NAMMD of tasks and duties as a national competent authority in the medicinal product field for human use; efforts undertaken by Agency employees have been more intense, in direct proportion with this year's severe deficit of specialised staff. In spite of such adverse circumstances, the has Agency managed to reach its targets and has continued, in the sixth year of Romania's membership to the European Union (EU), to perform key activities in addition to its current activity of marketing authorisation, inspection, quality control and pharmacovigilance, among which:

- **Active participations in bimonthly/monthly/quarterly meetings of scientific committees and coordinating European working groups in the field of the medicinal product for human use (European Medicines Agency-EMA, Heads of Medicines Agencies-HMA, European Directorate for the Quality of Medicines-EDQM, European Commission).**

All NAMMD scientific departments have ensured the participation, via assigned representatives, to meetings of scientific committees and European working groups, related to various issues such as regulation and European procedures on medicinal products, particularly an active participation in:

- EMA's CHMP (The Committee for Medicinal Products for Human Use), as corapporteurs in re-examination procedures;
- EMA's PDCO (Paediatric Committee) - PIP (Paediatric Investigation Plan) assessment, participation in set-up of the 2012 Romanian Annual Paediatric Report forwarded to the EMA/PDCO for the European Commission and participation to teleconferences and monthly/bimonthly meetings of working subgroups (Extrapolation of safety and efficacy in the context of the development of paediatric medicinal product and Pharmaceutical Formulation– active participation and set up of assessment reports);
- the Committee for coordination of MRP and DCP-CMDh procedures and meetings of Working Groups on variations and active substance master file. Currently, Romania acts as Reference Member State in 16 decentralised procedures;
- the Committee on Herbal Medicinal Products, with RO as rapporteur/assessor of certain community monographs;
- the Pharmacovigilance Working Group and, as of July 2012, the newly set-up Pharmacovigilance Risk-Assessment Committee (PRAC);
- the EU Council Working Group for Medicines and Medical Devices, including participation to debates for set-up and harmonisation, in all Member States, of clinical trial legislation. A new regulatory proposal for introduction of the Regulation on clinical trials was made in July 2012, aiming to repeal Directive 2001/20/EC on regulation of clinical trials; the NAMMD has been assigned by the Ministry of Health for participation in debates over the new Regulation on clinical trials. Thus, the NAMMD has successfully proved its status as active participant to debates, by expressing opinions about:

- NAMMD agreement with the need for support to the European Commission proposal concerning amendment of the previous clinical trial regulatory framework;
- NAMMD disagreement concerning:
  - Election of the Rapporteur Member State by the sponsor, on account of the fact that the decision must lie with participating member states, which must consider the number of applications for authorisation of clinical trials;
  - Tacit authorisation of clinical trials, considering the obligation of the competent authority to protect the subjects enrolled in trials, which can only be accomplished by thorough assessment of documentation by the respective member state.
- NAMMD comments concerning:
  - approach of ethical issues, requiring explicit specification of preservation/setup of an Ethics Committee (EC) as a body involved in assessment, as well provision for EC favourable opinion as a condition for start of the trial onset (i.e., compliance with the Declaration of Helsinki is required);
  - deadlines proposed for assessment of documentation, considered too short considering the need for expert opinion (e.g. in case of clinical trials on advanced therapy medicinal products) as well as the risk of insufficient time for the Reference Member State to manage Interested Member States' comments/requests for clarification or supplementation.
- the need to also provide for the option for withdrawal ("opt-out"), on scientific grounds, considering that the sole purpose of clinical trials is assessment of efficacy and safety of the investigational medicinal products, not comparative assessment of clinical practices in various Member States;
- ensurance of operation of the EU platform, as mandatory condition for conduct of the procedure for clinical trial authorisation.

- **Transposition into national legislation of provisions of Directive 2010/84/EU on the new manner of approach of pharmacovigilance and of Directive 2011/62/EU as regards the prevention of the entry into the legal supply chain of falsified medicinal products**

The steadfast efforts of two working groups assigned by the NAMMD President for transposition into national legislation of provisions of Directive 2010/84/EU and Directive 2011/62/EU, have resulted in draft and issuance of two Emergency Ordinances of the Romanian Government (Emergency Government Ordinance 35/July 2012 amending certain healthcare regulations and Emergency Government Ordinance 91/December 2012, amending

Law 95/2006 on healthcare reform, as amended, as regards pharmacovigilance and the prevention of the entry into the legal supply chain of falsified medicinal products).

- **Regulatory work and technical support to the Ministry of Health, upon request.**

In July 2012, the NAMMD Scientific Council agreed on Scientific Council Decision (SCD) on approval of mandatory monthly reporting of placement on the market in Romania, respectively of sales of medicinal products for human use by authorised wholesale distributors/importers/manufacturers. Approval of this regulatory Scientific Council Decision through Order of the Minister of Health is pending.

The NAMMD provides technical support to the Ministry of Health in:

- set up of the lists for national tenders for supply of medicinal products in hospital sections and national programs (draft of the Annexes to Order of the Minister of Health on medicinal products included in national health programs);
- ensuring technical support for quarterly appearance of the CANAMED (the national price catalogue), based on update of the Index of medicinal products.

- **Participation in reunions/workshops/informal meetings with stakeholders concerning legislation and procedure issues.**

- active participation in the "Pharmacovigilance Workshop" organised by the Romanian College of Pharmacists, in collaboration with ARPIM and APMGR, Bucharest, 31 August 2012.
- participation in informal reunions with the Romanian Association of International Medicines Manufacturers (ARPIM), the Generic Drug Manufacturers Association in Romania (APMGR) and independent Marketing Authorisation Holders (MAHs) in view of debating over legal issues such as:
  - implementation of new pharmacovigilance legislation,
  - the list of medicinal products exempt from safety elements imprinted on the packaging,
  - other regulations in the field of the medicinal product (approval of variations to MAs, approval of clinical trials etc.).
- meetings with the management of the Cantacuzino Institute to find solutions for the current situation.

- **Audit by representatives of the World Health Organisation (WHO)**

During 9-12 October 2012, the NAMMD hosted the WHO audit "Strengthening of the National Competent Authority", for assessment of the status of the national regulatory system (NRS) in the field of vaccines, in 6 areas:

- marketing authorisation,
- pharmacovigilance,
- official batch release,
- laboratory access,
- pharmaceutical inspection,
- clinical trials.

Implementation in the various audited areas was rated between 94% - 100%.

The audit team's report highlighted the following strengths:

- thoroughly documented and established system of legal provisions,
- batch release granted for locally manufactured vaccines (document testing and analysis) and imported vaccines (Mutual Recognition Procedure),
- thoroughly established quality management system, providing effective document control,
- involvement of the same staff in assessment, control and inspection activities, thus allowing for comprehensive outlook upon vaccine quality.

The following strengths have been listed as regards control laboratories:

- Staff aware of its responsibilities;

- High level of technical expertise;
- Thoroughly established quality management system;

The following strengths have been highlighted in marketing authorisation work:

- Legal provisions in place;
- Implementation of a European legislation;
- Similarity with competent regulatory bodies (EMA/European national competent authorities);
- Existence of a large scale of experience levels;
- Detailed requirements and directions, made public on the NAMMD website, available to all applicants.

- **Participation with specialised papers in various scientific events:**

- Farmacist.ro Forum, Bucharest, April 2012

- Forum of the pharmaceutical industry, Bucharest, June 2012

- Romania and Bulgaria HealthCare&Medical Investments Conference, Bucharest, July 2012

- National Conference of Pharmacy, Bucharest, November 2012

In the frame of NAMMD current activities, a few figures may be of significance for the scope of assessment and authorisation. In 2012, the three commissions for marketing authorisation/marketing authorisation renewal (the Marketing Authorisation Commission for National Procedure, the Marketing Authorisation Commission for European Procedures, the Marketing Authorisation Commission for Marketing Authorisation Renewal) reunited in 24 individual working meetings for discussion of assessment reports for decision on marketing authorisation of various medicinal products for which applications had been submitted. The Commissions have decided upon grant of 1125 Marketing Authorisations (MAs), of which 914 through European procedures (decentralised, mutual recognition, mutual recognition-repeat-use) and 211 through national procedure.

The database provided by the Index of medicinal products for human use has been supplemented with MA-related information: trade name, Marketing Authorisation Holder (MAH), batch release responsible person, packaging, Summary of Product Characteristics, leaflet.

Information regarding medicinal products included in the Index on the NAMMD website has been updated for availability to external users.

Among other activities, the Pharmaceutical Inspection Department (PID) conducted 24 inspections for assessment of compliance with Good Manufacturing Practice (GMP) rules in manufacturing/import/GMP certification authorisation, 6 inspections on Good Laboratory Practice (GLP) in laboratories performing bioequivalence studies, 4 inspections on Good Analytical Laboratory Practice (GALP) for authorisation of independent sites for control of medicinal product quality, 3 inspections for authorisation at the sites of medicinal product importers, 6 inspections for assessment of compliance with Good Clinical Practice (GCP), 2 pharmacovigilance inspections at the sites of Romanian MAHs and MAH representatives in Romania, 110 inspections for authorisation. In other respects, 3 follow-up inspections have been carried out for assessment of the manufacturing process and implementation of corrective measures proposed as included in measure plans submitted to the NAMMD for authorisation; 13 follow-up inspections have been carried out for assessment of the distribution process and implementation of corrective measures proposed as included in measure plans submitted to the NAMMD for authorisation; export declarations have been approved for 1855 medicinal products manufactured/marketed in Romania.

As of April 2012, the PID has undertaken assessment of documentation submitted for approval of medicinal product donations, in accordance with legislation in force; 81 approvals for donations were released by the end of 2012.

As regards “parallel import” activities, 52 parallel import authorisations (PIAs) have been released for the Romanian pharmaceutical market.

”Parallel export” consisted in 560 responses to requests for information from 19 EU competent authorities (in addition to about 120 responses for clarification and supplementation of initially provided information), for grant of parallel import authorisation for the respective member states. Therefore, there is an obvious disparity between “parallel import” and „parallel export”, as shown by large number of requests from the 19 fellow EU competent agencies

regarding provision of information about MAs issued in Romania, required for grant of parallel import authorisation by a national agency in the respective country. „Parallel export" is known to actually represent intracommunity trade performed within the EU. In its respect, although national competent authorities have little room for intervention, they should nevertheless be aware of the true scope of the phenomenon. This underlies adoption by the NAMMD Scientific Council of Decision (SCD) no. 9/10 July 2012 on Approval of mandatory monthly reporting of placement on the Romanian market and of sales of medicinal products for human use by authorised wholesale distributors/importers/manufacturers; the decision has been submitted for approval through Order of the Minister of Health. The decision comes in response to findings by NAMMD inspectors of non-compliances in wholesale distribution, i.e. failure of all parties concerned to meet their obligation regarding compulsory monthly reporting of placement on the Romanian market and sales of medicinal products for human use, in accordance with SCD no. 5/2011 and SCD no. 17/2011 on extension of term provided in Article 4 of NAMMD Scientific Council Decision No.5/22.02.2011, set for 01.11.2011.

Clinical trials, performed in accordance with European regulations in force, attest the clinical efficacy and safety of medicinal products proposed for authorisation. Authorisation of medicinal products requires conduct of many clinical trials, their number varying depending on the individual product and its stage of development. As a rule, all four clinical trial stages should be accomplished in relation to one medicinal product. In 2012, the number of applications for authorisation for conduct of clinical trials is practically constant in comparison to 2011, showing a slight decrease from previous years, as results from comparison between the yearly numbers of applications (248 in 2012, 246 in 2011, as opposed to 266 in 2010, 253 in 2009 or 275 in 2008).

This year as well, therapeutic areas for which authorisation of clinical trials has been required have been as follows: psychiatry, neurology, oncology, diabetology, rheumatology, gastroenterology, pneumology, infectious diseases, hematology, cardiology, endocrinology.

Throughout 2012, the NAMMD granted 221 authorisations for conduct of clinical trials, mostly for Phase III (146) and Phase II (60) clinical trials.

Moreover, following assessment in the National Procedure Assessment Service of protocols of bioequivalence clinical trials, 73 authorisations were granted in this respect.

It is worth mentioning that year 2012 involved participation of the NAMMD through its representatives to meetings of working groups of European bodies in the medicinal product field, for debate on proposed amendment of EU legislation for clinical trials.

As regards pharmacovigilance, the scope of work carried out in the Pharmacovigilance and Risk Management Service as part of the European Procedures Department, year 2012 proved increased responsibility of Romanian physicians in what concerns adverse reaction (AR) reporting. If, for instance, in 2008, there were 280 spontaneous reports submitted, their number increased to 525 in 2009 and 939 (serious and non-serious) in 2010. In 2011, the NAMMD received 1011 adverse reactions reports (448 non-serious and 563 serious), directly by physicians (105 non-serious and 83 serious) and by MAHs, from physicians in respective areas (343 non-serious and 480 serious). Apart from submission of serious adverse reactions to the Agency, MAHs also have to submit them directly into the European database for adverse reactions to medicinal products (EudraVigilance). In 2012, 1272 ARs were reported to the NAMMD (719 serious and 553 non-serious adverse reactions).

The increasing numbers of reports speak for the growing importance physicians assign to their patients' safety; however, intensified involvement on behalf of healthcare professionals is expected in this respect.

The new European legislation (transposed into Romanian legislation through Emergency Government Ordinance 35/2012 amending certain healthcare regulations), has meant amendment, under the chapter *Pharmacovigilance* of Law 95/2006 on healthcare reform, as amended, also empowering other professional categories, apart from physicians, and even patients, to report adverse reactions to medicinal products to the competent authority/MAH. Each AR occurrence submitted to the European database (EudraVigilance) or the database of the World Health Organisation (WHO) means a step forward as regards better knowledge of medicinal products.

Even the possibility of AR reporting by a category called "*consumer*/consummator" has even been introduced through law (including, apart from patients, jurists, patient's next of kin, neighbours). In accordance with the recommendations of the European Good

Pharmacovigilance Practice Guideline, for confirmation of adverse events/reactions reported by persons included in this category, the NAMMD Pharmacovigilance Service intends to require reporter consent to contact the prescribing physician.

More accurate determination of the safety profile of the medicinal product is thus expected through joint physician-pharmacist-assistant-consumer effort.

It is thus worth mentioning that the first steps for implementation of the new pharmacovigilance approach have already been taken in 2012. Of the 1272 ARs reported, 1003 were submitted by physicians, 12 by pharmacists, 60 by assistants and 32 by consumers.

In the context of completion of transposition into national legislation of Directive 2011/62/EU as regards the prevention of the entry into the legal supply chain of falsified medicinal products and setup of the new frame for implementation of the new provisions, the establishment of a general framework for bilateral cooperation and exchange of information in the field of medicinal products counterfeiting has been one of the main objectives, in cooperation with the General Inspectorate of Romanian Police.

The main lines for NAMMD - General Inspectorate of Romanian Police collaboration have been:

- Compliance with the legislation for medicinal products for human use;
- Exchange of information to meet legal assignments of both institutions;
- Supervision of operation of markets for identification of cases of non-compliance with national and/or community legislation in terms of falsification of medicinal products and legal provisions on medicinal products for human use, enabling the two authorities to take the required measures, in accordance with the abilities of each of them and their correlation;
- Media coverage and notification of the general public and businesses in medicinal products for human use, concerning measures taken in cases of violation of national and/or community legislation on medicinal product counterfeiting;
- Mutual support to ensure effective operation and security of the medicinal product for human use, also as regards regulatory amendments required.

Since its set-up in 2010, through merger of the NMA with the Technical Office for Medical Devices, the NAMMD has been the sole institution authorised and able to assess performance and safety of medical devices in use.

In 2012, a control activity has been carried out. It consisted of periodic check-up of medical devices and concerned all medical devices assembled and commissioned, with a high risk degree, at the sites of all users of medical devices, in both public and private sector, and consists of assessment of performances and safety of medical devices in use; the bulletin for periodic check-up is one of the documents required in view of signing the medical service contract between health insurance houses and cabinets/hospitals/medical centres.

In March 2012, RENAR conducted the surveillance of laboratories for testing and assay of medical devices within the Laboratories Technical Department (LTD) and the Nuclear Unit (NU), which analysed the manner of performance of field testing. Results have been found appropriate.

In 2012, due to tremendous efforts, the List of medical devices undergoing control through periodic check-up was reviewed, so as to contain only medical devices with the highest risk for patients and users. Thus, the replacement of Order of the Minister of Health no.1662/2007 on periodic check-up control of medical devices is envisaged, as amended.

Having few employees, the Technical-Medical Units Assessment Department must ensure activity of approval of medical technique units (medical optics, medical devices and auditive/orthopaedic/other types of prosthesis) throughout the country, by performing the initial evaluation of organisations in view of granting an operation approval, surveillance evaluations every two years, as well as observation and sanctioning of contraventions in accordance with Law 176/2000 on medical devices, as amended.

NAMMD ACTIVITIES IN 2012

1. Activity of the Scientific Council (SC) of the National Agency for Medicines/National Agency for Medicines and Medical Devices

In 2012, the Scientific Council adopted 9 Scientific Council Decisions; out of these, 4 regulatory decisions are pending approval through Order of the Minister of Health (OMH) and

are to be published in the Official Gazette of Romania, Part I; the remainder of 5 SCDs are posted on the NAMMD website and published in the bilingual NAMMD Newsletter of 2012.

For implementation of provisions of Title XVII - The medicinal product of Law 95/2006 on healthcare reform, published in the Official Gazette of Romania, Part I, no. 372/28.04.2006, and in accordance with provisions of Government Decision 734/2010 on organisation and operation of the NAMMD, the Agency establishes rules, directions and other mandatory regulations, concerning its specific activity in the field of the medicinal product for human use, submitted for approval to the Ministry of Health as regulatory SCDs. Approval is expressed through Order of the Minister of Health, subsequently published in the Official Gazette of Romania, Part I.

As regards regulatory SCDs (as shown in the details provided under section 3 of this Report. "Regulatory activity", it should be noted that regulatory provisions of SCD no. 9/10 July 2012, setting up mandatory monthly reporting of marketing in Romania, namely of sales of medicinal products for human use by authorised wholesale distributors/importers/ manufacturers aim at provision of traceability of medicinal products throughout the entire chain, from manufacturing and/or distribution to community pharmacy, hospital pharmacy, drugstore.

Non-regulatory SCDs referred to:

- approval of the Guideline on NAMMD use of the EU Administration Procedure on official release of biological product batches;
- approval of the Regulations on the manner of handling of proposals for "umbrella" trade names and other trade names for medicinal products for human use in relation to food supplements, cosmetics and medical devices;
- approval of the Guideline on Good Manufacturing Practice for medicinal products for human use;
- approval of amendment of the Annex to SCD no. 29/16.12.2010 on approval of Regulations on authorisation by the National Agency for Medicines and Medical Devices of clinical trials/notification to the National Agency for Medicines and Medical Devices of non-interventional studies on medicinal products for human use in Romania.

2. Activity of the NAMMD Administration Council (AC)

In 2012, the Administrative Council (AC) adopted 5 Administration Council Decisions (ACDs).

Thematically speaking, ACDs have covered various aspects of current activities, such as amendment of the Regulation on the organisation and operation of the AC, draft of amendment of Order of the Minister of Health no. 1369/2009 on approval of fees required by the (former) Technical Office for Medical Devices, as amended, approval of investments and others.

3. Regulatory activity

The Legal Department and other NAMMD professional departments have set up documentation (drafts of regulatory documents, substantiation notes) for promotion via the chief credit accountant, namely the Ministry of Health, of the following regulatory documents:

- Emergency Ordinance on amendment and supplementation of Law 95/2006 on healthcare reform concerning transposition of Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use, published in the Official Journal of the European Union no. L384/74 of 31 December 2010;
- Emergency Ordinance on amendment and supplementation of Law no. 95/2006 on healthcare reform for transposition of Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products, published in the Official Journal of the European Union no. L174/86 of 01.07.2011;
- Order of the Minister of Health for amendment of Order of the Minister of Health no.716/2009 on approval of tariffs and marketing authorisation maintenance fee required by the National Medicines Agency;

- Order of the Minister of Health for amendment of Order of the Minister of Health no. 1369/2009 on approval of fees required by the Technical Office for Medical Devices for activities performed, published in the Official Gazette of Romania, Part I, no. 752/04.11.2009.

Given growth in complexity of NAMMD activity as a national authority within the network of EU competent authorities in the medicinal product field for human use, work of the NAMMD Scientific Council for approval of certain regulatory SCDs was continued in 2012 as well.

Of the 9 Scientific Council Decisions approved, 4 have been submitted for Ministry of Health approval through Order of the Minister of Health. These SCDs refer to:

- approval of NAMMD procedure for cancellation of applications for marketing autorisation/ marketing autorisation renewal for medicinal products for human use;
- approval of the procedure and rules for accreditation by the NAMMD of national Good Clinical Practice training providers;
- amendment of SCD no. 19/07.11.2008 on approval of Regulations for manufacturing/importation authorisation of manufacturers and importers of medicinal products for human use, including investigational medicinal products and grant of the Good Manufacturing Practice certificate to manufacturers of medicinal products for human use and/or active substances;
- Approval of the mandatory monthly reporting of placement on the Romanian market and of sales of medicinal products for human use by authorised wholesale distributors/importers/manufacturers.

Compliance with the mandatory monthly reporting of inputs/outputs by all manufacturers/importers/wholesale distributors means provision of traceability of medicinal products throughout the entire chain, from manufacturing and/or distribution to the level of community pharmacy, hospital pharmacy, drugstore, enabling the NAMMD to:

- assess the justness of release of medicinal products with or without medical prescription,
- track falsified medicinal products and
- prevent their entry into the authorised distribution network,
- fight the existence of illegal parallel circuits for medicinal product sales, namely
- grant fast recall of non-compliant medicinal product batches or in case of health emergencies.

4. Activity of NAMMD commissions

4.1. NAMMD Marketing authorisation commissions (CAPP)

As in previous years, in 2012, as a consequence of the setup of 3 commissions for marketing authorisation/marketing authorisation renewal approved through NAMMD Administration Council Decision (CAPP-National Procedure, CAPP-European Procedures, CAPP-Renewals), whose structure has been established through Decision of the NAMMD President), assessment reports have been discussed, in order to provide an opinion concerning marketing authorisation of various medicinal products for human use for which an application has been submitted in this respect, as well as other aspects related to the marketing authorisation of medicinal products for human use.

In 2012, 24 working sessions took place with the participation of various commissions.

The Commissions approved the issuance of 1125 marketing authorisations, of which 914 through European procedures (decentralised, mutual recognition, mutual recognition-repeat-use) and 211 through national procedure.

4.2. Commission for the Inspection of Good Manufacturing Practices (GMP), Good Distribution Practice (GDP), Good Laboratory Practices (GLP), Good Analytic Laboratory Practices (GALP), Good Clinical Practices (GCL) and Pharmacovigilance

In accordance with its own regulation for organisation and operation, approved through a NAMMD Administration Council Decision and in a structure approved through President Decision, the Commission continued its activity in 2012 as well. The Commission reviews inspection reports issued by Agency inspectors, concerning the manner of compliance by inspected units with Good Manufacturing Practice, Good Distribution Practice, Good

Laboratory Practice, Good Analytical Laboratory Practice, Good Clinical Practice rules and/or with other issues concerning work of the Pharmaceutical Inspection Department.

The Commission acts as mediator in cases of inspection decisions disputed by the inspected site.

In 2012, the Commission for GMP, GDP, GLP, GALP, GCL and Pharmacovigilance inspection conducted 181 inspection reports, of which:

- 34 inspection reports on compliance with Good Manufacturing Practice rules;
- 123 inspection reports on compliance with Good Distribution Practice rules;
- 6 unexpected inspection reports on compliance with Good Distribution Practice rules;
- 4 inspection reports on compliance with Good Analytical Laboratory Practice rules;
- 2 pharmacovigilance inspection reports.

4.3. Commission for verification of compliance of NAMMD inspection staff with the professional ethic and deontology code

The Commission operates in accordance with Decision no. 651/2009 of the NAMMD President and with its own organisational and operation rules, as approved by Administration Council decision.

The goal of the Commission is verification of compliance by Agency inspecting staff with the Code of Ethics, as approved through Order of the Minister of Health no. 160/2004.

In 2012, there were no requests for summons of the Commission.

4.4 Commission for management of crisis situations caused by concerns arising in relation with medicinal product quality, safety and/or efficacy

The Commission for management of crisis situations operates in accordance with Decision of the NAMMD President and with its own organisational and operation rules, as approved through Administration Council Decision.

In 2012, there were no requests for summons of the Commission.

5. Marketing authorisation and related activities

In direct relation to the increasingly stricter regulation of activities specific to a competent authority in the EU medicinal product field, year 2012 was as complex as the previous year with regard to assessment of documentation submitted to the NAMMD for marketing authorisation (MA), renewal of marketing authorisation and post-authorisation surveillance of medicinal products.

Performed in accordance with specific provisions related to national and European procedures (mutual recognition, decentralised, repeated mutual recognition procedures), in 2012, marketing authorisation and related activities were conducted in line with the organisational structure of 2011, established in 2010 and approved through Order of the Minister of Health on the organisation and setup of the National Procedure Department and the European Procedures Department.

5.1. Marketing authorisation through national and European procedures

In 2012, a number of 1400 applications for marketing authorisation/marketing authorisation renewal were received, 402 through national procedure and 998 through European procedures (Decentralised Procedure-DCP, Mutual Recognition Procedure-MRP and "*repeat use*" procedure).

Assessment work performed within the European Procedures Department resulted in grant of 914 marketing authorisations and Annexes 1-5, which represents an increase compared to last year (883).

As regards assessment through national procedure, this resulted in grant of 211 marketing authorisations, confirming the decreasing tendency for the number of applications for marketing authorisations granted through national procedure, in favour of authorisations granted through European Procedures (EPs).

Overall, it is evident that, in the context of the past few years, the number of MAs granted by the Agency in 2012 was larger, namely: MAs through NP and EPs: 2009=927, 2010=813, 2011 = 1030 and 2012 = 1125.

A comparative perspective shows an almost unchanged number of decisions for discontinuation of authorisation/renewal procedure, on MAH request for trade reasons, in 2009 and 2011, namely: number of MA applications discontinued: 2009=134 and 2011=131, compared to 2010=202 and 2012=247.

5.2. Assessment of variations to Marketing Authorisation (MA) terms

In 2012, a number of 6429 applications for variation to MA terms were submitted concerning medicinal products authorised through national and European procedures, of which 3102 applications for type IA, IB and II variations to MA terms, MA notifications for nationally authorised products and 3327 for type IA, IB and II variations to MA terms, MA notifications through European procedures.

The above numbers do not include either applications for discontinuation of applications for variation (for medicinal products whose marketing authorisation has expired and in relation to which no application has been submitted for renewal as well as medicinal products for which decisions were issued for discontinuation of marketing authorisation or variation procedures on company request), or applications for variation in accordance with SCD 30/2010 on approval of the manner of handling of Type IA and IB variations not amending marketing authorisation terms for nationally authorised medicinal products.

5.2.1. As concerns **post-authorisation assessment of variations to terms of marketing authorisation (MA) granted through national procedure**, the Agency received assessed and approved:

- 3151 applications for type I variations;
- 596 applications for type II variations;
- 87 applications for MA transfer;
- 226 changes of packaging design and printing;
- 969 safety and efficacy variations.

5.2.2. In 2012, as regards **post-authorisation assessment of variation to terms of marketing authorisation (MA) granted through European procedures**, for medicinal products for human use authorised through decentralised/mutual recognition/repeated mutual recognition procedure, the Agency approved:

- 1994 applications for type IA variations with Romania as a concerned member state; 7 applications for type IA variations for Romania as a reference member state;
- 2116 applications for type IB variations with Romania as a concerned member state; 19 applications for type IB variations with Romania as a reference member state;
- 535 applications for type II variations with Romania as a concerned member state;
- 80 applications for MA transfer with Romania as a reference member state;
- 42 notifications in accordance with Article 61 (3) of Directive 2001/83/EC;
- 5 safety and efficacy variations.

5.3. Assessment of applications and documentation for approval of clinical trials on medicinal products for human use

In 2012, the number of applications for authorisation of clinical trials has remained constant and following slight decrease in 2011, as evident from comparing the yearly number of applications submitted (248 in 2012 vs. 246 in 2011, 266 in 2010, 253 in 2009 or 275 in 2008).

Most of these are Phase III clinical trial applications (158 applications in 2012), meaning that the respective medicinal products undergo advanced research and are therefore nearing authorisation. Phase II clinical trials are the second most frequent type of clinical trial applications (75 applications in 2012); these are exploratory studies concerning the most effective dose for medicinal products whose safety and tolerability have been proven.

In Romania, there are few applications for performance of Phase I clinical trials (4 applications in 2012), which requires special conditions.

Therapeutic areas for which clinical trial authorisation was required in 2012 have been the following: psychiatry, neurology, oncology, diabetology, rheumatology, gastroenterology, pneumology, infectious diseases, haematology, cardiology, endocrinology.

In 2012, the NAMMD granted 221 authorisations for performance of clinical trials, mostly for Phase III (146) and II (60) clinical trials.

Moreover, 50 applications for observational clinical trials were received; acknowledgement letters have been issued on 25 observational studies.

In 2012, the Clinical Trial Service of the National Procedure Department approved 615 substantial amendments and 222 amendments for new investigational sites; moreover, 73 authorisations for conduct of bioequivalence clinical trials were granted after assessment by the National Procedure Assessment Service of the protocol of bioequivalence clinical trials.

5.4. Monitoring and control of advertising material for medicinal products for human use

In 2012, the National Medicines Agency and Medical Devices assessed for approval 495 advertising materials to the general public concerning OTC medicinal products; 465 advertising materials for OTCs have also been assessed for re-approval.

Of these, 16 applications for advertising material were not approved and respective applicants have received notifications of rejection of advertising.

As regards advertising materials to be used in educational programmes, 139 educational items were assessed and approved.

In the same way as during the previous two years, in 2012 as well the same special emphasis was placed upon surveillance and control of advertising of medicinal products for human use. Thus, under the special heading on the Agency's website, "Advertising", various notifications to healthcare professionals have been posted, dealing with certain medicinal products for which withdrawal from the press has been required, following non-compliance with advertising regulations provided for in the Guideline on evaluation of advertising in medicinal products for human use, approved through SCD no. 21/2011.

5.5. Pharmacovigilance

Issues related to safety of medicinal products currently authorised in Romania are managed through the NAMMD's Pharmacovigilance and risk management service, part of the Agency's European Procedures Department, whose activity is entirely compliant with Law no. 95/2006 and specific European Guidelines.

As confirmed by recent increasingly manifest concern with regulation, pharmacovigilance represents an extremely dynamic and interactive field of activity, developed in time as a requisite for patient safety. According to public documents of the European Commission, pharmacovigilance is "the science relating to the detection, assessment and prevention of adverse effects and all related activities".

As key part of authorisation of medicinal products for human use, pharmacovigilance work already has considerable history in Romania, as detailed in the NAMMD Activity report, 2011 .

In Romania, pharmacovigilance is conducted based on European legislation, transposed into national law. In addition to other pursuits, pharmacovigilance includes assessment and submission of adverse reactions through the EudraVigilance system (the European network for pharmacovigilance data-processing and management), assessment of Periodic Safety Update Reports (PSURs) as forwarded by pharmacovigilance systems of authorisation holding companies, assessment of Risk Management Plans, harmonisation of Summaries of Product Characteristics (SmPCs), by implementation of European Commission Decisions based on the recommendations of the Committee for Human Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA).

Pharmacovigilance also involves approval of direct healthcare professional communications concerning special warnings on medicinal product safety, as well as translation of EMA press releases and Q&A documents, actually notifications from the monthly CHMP meetings, for posting on the NAMMD website. An additional NAMMD

pharmacovigilance task is response to requests for non-urgent information from the European and international rapid alert system.

For protection of public health, in line with European regulations in force, all types of information available related to medicinal product safety are currently posted on the NAMMD website.

To increase their awareness concerning the importance of spontaneous suspected adverse reactions reporting, an appeal to reporting is addressed to physicians both directly, during scientific symposia, national conferences and congresses as well as through direct healthcare professional communications.

In this context, the incentive designed by the Agency for AR reporting, in cooperation with the Romanian College of Physicians, after entry into force of Emergency Government Ordinance no. 35/July 2012, consists of granting Continuing Medical Education (CME) and Continuing Pharmaceutical Education (CPE) Credits to reporters (physicians and pharmacists), in accordance with the procedure agreed by the two institutions.

Romanian physicians have proven increased interest in AR reporting for patient safety throughout the past years.

Therefore, for instance, 280 spontaneous reports were submitted in 2004, 525 were reported in 2009, 938 in 2010 and 1011 (serious and non-serious adverse reactions) in 2011.

In 2012, pharmacovigilance activities mainly materialised in the following:

a) management of safety data issued from spontaneous reporting:

- validations/confirmations of adverse reaction (AR) reporting to the European database for adverse reactions, EudraVigilance (ICSR and SUSAR) - 1750
- spontaneous adverse reactions
  - non-serious: 554 (of which 95 to physicians)
  - serious: 978 forwarde3d to the EudraVigilance (of which 109 to physicians)
  - 345 follow-up reports.
- 323 electronic transmissions of adverse reactions to the WHO database (the Uppsala Monitoring Centre) via the VigiFlow electronic channel;
- 198 confirmations of submission of spontaneous reporting of adverse reactions from physicians in the network;
- 388 information points for physicians on grant of Continuing Medical Education (CME) credits for adverse reaction reporting;
- 252 responses to MAH requests concerning adverse reactions reported to the NAMMD involving medicinal products authorised in Romania;
- 158 response letters on MAH requests concerning pharmacovigilance-related aspects.

b) Collection, validation and archiving of 2218 Periodic Safety Update Reports (PSURs) for medicinal products authorised through national or European procedures (decentralised, mutual recognition, mutual recognition – repeat use procedures).

- 1 PSUR assessment report was issued for medicinal products undergoing MA renewal through national procedure.

c) Pharmacovigilance activities within the European national authority system coordinated by the EMA:

- Handling of EMA press releases and “Questions and Answers” documents – documents for request of information, handling and proofreading of translations, sent for publication on the NAMMD website: 74;

- “Lines to take” documents approved by the EMA;

- management of documents (record, archiving, notification of the press officer), notification of the Pharmacovigilance and Risk Management Service on provision of responses to potential requests of information: 52;

- approval and management of 50 Direct Healthcare Professional Communications (DHPCs) related to safety concerns raised in relation with medicinal products;

- transmission of 152 medicinal product safety information letters to the Ministry of Health, the National Health Insurance House (NHIH), the College of Physicians, the College of Pharmacists;

- activities concerning MAH notification for SmPC and leaflet harmonisation following referral procedure, upon request of the PhWWP/CHMP/CMDh for individual medicinal products or groups of medicinal products: 13;

d) pharmacovigilance activities in the context of rapid alert/non-urgent information (AR/INU) action:

- replies (INU) upon request for information by certain EU national authorities concerning information about individual medicinal products or medicinal products categories, other information concerning measures for enforcement of pharmacovigilance legislation: 23

e) assessment of MA applicant compliance with requirements for detailed description of the pharmacovigilance system:

- assessment reports of the summary of the MA applicant's pharmacovigilance system concerning requirements for detailed description of the pharmacovigilance system (DDPS) for authorisation through decentralised/mutual recognition/mutual recognition – repeat use procedure:
  - Romania as a concerned member state: 1612 reports
  - Romania as a reference member state: 5 reports
- assessment reports of the MA applicant's pharmacovigilance system concerning requirements for Detailed Description of the Pharmacovigilance System (DDPS) for authorisation through national procedure: for 174 medicinal products from 65 MAHs/applicants.
- assessment reports of applications for variation to MA applicant's summary of the pharmacovigilance system concerning requirements for detailed description of the pharmacovigilance system (DDPS) for authorisation:
  - ✓ Applications for national procedure approved:30
  - ✓ Applications for national procedure assessed:63
  - ✓ Applications assessed for DCP/MRP/MRP-RU procedures:73
  - ✓ Applications for parallel import procedure: 80

f) assessment and approval of educational materials included in the Risk Management Plan (RMP) for centrally authorised medicinal products based on European Commission Decision in accordance with Article 127a of Directive (EC) 2001/83

- 51 completed dossiers containing 92 educational materials;
- 14 dossiers in progress (17 educational materials).

5.6. Other activities

- Management of the database for the Index of medicinal products for human use consisted of introduction of new medicinal products authorised through national, European and centralised procedures, implementation of MA changes for already authorised medicinal products, introduction of approved variations to approved MA terms, keeping track of medicinal products undergoing MA renewal and of MA withdrawal/discontinuation decisions. Thus, the National Procedure Department (with support from IT experts in the Information Logistics and Electronic Management of Data Department) managed to ensure:

a) Maintenance of the database of authorised medicinal products:

- Addition of 945 medicinal products (authorised through national/European/ centralised procedure) – introduction of information concerning MA granted: trade name, MAH, batch release responsible person, packagings and set-up of *links* for SmPC, packagings, leaflets and MAs;
- Addition of 4950 variations to MAs granted through national/European/centralised procedure (introduction of information concerning amendments to MA terms): Trade name, MAH, batch release responsible person, packagings etc.);
- Set-up of links for SmPCs, packagings, leaflets and labelling – containing updated information, enabling easy access of external users to Annexes 1, 2, 3 of the Index of Medicinal Products posted on the NAMMD website;
- Issuance of 247 decisions for MA withdrawal/discontinuation (withdrawal of national MA when the same product is granted marketing authorisation through European procedure; discontinuation of a valid MA on request by the company);
- Management of data concerning MA maintenance fee: 4230 medicinal products;
- Assessment of the National Brochure of the prices of medicinal products authorised for marketing in Romania (quarterly and whenever required by the Ministry of Health) in terms of CIM codes and technical identification data;

- Transmission of the Index of Medicinal Products to the NHIH in the format agreed for reception of SIIS (single integrated information system) data (quarterly and whenever required by the NHIH);
- 24425 PDF files, as current versions of Annexes I, II and III, have been published on the NAMMD website, via the Index of medicinal products in web format, for the aforementioned products.

b) Various responses to requests of the Ministry of Health, NHIH, other institutions, legal and natural entities): 97.

As regards ”parallel import” activities, 52 parallel import authorisations (PIAs) have been granted.

In this respect, 74 requests for information (plus 30 requests for disambiguation and completion of information received) delivered to 9 EU competent authorities required for PIA release and amendment of PIAs granted (13 variations to PIAs were sent);

”Parallel export” activities consisted of:

- issuance of 560 responses to requests for information received from 19 EU competent authorities (plus another about 120 responses for disambiguation and completion of initially forwarded information), for grant of a parallel import authorisation for the respective member states;

The following activities have also been continued:

- management of responses received under application of provisions of Article 729 and 730 of Law no. 95/2006, i.e. notification of temporary or permanent discontinuation of manufacturing and notification of actual medicinal product marketing (“*sunset clause*“);

As regards *“sunset clause”* implementation, assessment of the database set up according to documents submitted by the MAH is worth mentioning. About **115** reports have been submitted from companies/representations (dossiers and electronic formats), on behalf of 194 MAHs**.** Work related with application of the clause is expected to be completed by the first quarter of 2013.

- Management of the database related to EMA authorised medicinal products based on provisions of Article 127a of Directive 2001/83/EC and monitoring of implementation of conditions and restrictions placed on the MAH by the European Commission;
- Management of European Commission (EC) decisions related to referrals, draft of the letters to MAHs involved for request of submission of variation applications for implementation of the EC Decision.

6. Inspection of Good Manufacturing Practice (GMP), Good Distribution Practice (GDP), Good Laboratory Practice (GLP), Good Analytical Laboratory Practice (GALP), Good Clinical Practice (GCP), Good Pharmacovigilance practice and market surveillance

In the course of 2012, the Pharmaceutical Inspection Department (PID) continued to perform activities mentioned in specific legislation (Law no. 95/2006, Title XVII – The medicinal product and secondary legislation thereof), in accordance with the department’s *Standard Operating Procedures (SOPs)*, endeavouring to effectively accomplish its tasks by the deadlines stipulated by law.

The following have been prepared and issued in the PID Processes Administration Service:

- 30 Good Manufacturing Practice (GMP) certificates (for Romanian and foreign manufacturers);
- 54 manufacturing authorisations, annexes included;
- 49 import authorisations, annexes included;
- 7 Good Laboratory Practice (GLP) certificates;
- 18 certificates for Qualified Persons;
- 1 authorisation for independent control units;
- 150 dossiers for the inspected units, and for units requesting update of annexes to manufacturing/import authorisations have been issued and handled;
- 147 applications for waiver from legal provisions concerning medicinal product packaging/labelling have been solved;
- management of databases of inspection encoding, the list of authorised/certified manufacturing units, authorised importers, medicinal products for which the export declaration has been approved, and Qualified Persons.

Inspection work in the fields of Good Manufacturing Practice (GMP), Good Laboratory Practice (GLP), Good Analytical Laboratory Practice (GALP), Good Clinical Practice (GCP), and Good Pharmacovigilance in 2012 consisted of:

- 24 GMP inspections in Romania, for manufacturing authorisation;
- 3 follow-up inspections, for assessment of manufacturing work and the manner of implementation of corrective measures proposed in measure plans forwarded to the NAMMD in view of authorisation;
- 3 inspections to medicinal prodcut importers, for authorisation purposes;
- 1 certification inspection for GMP compliance of pharmaceutical companies from third countries;
- 6 GLP inspections in laboratories performing bioequivalence studies;
- 4 GALP inspections in independent sites for medicinal product quality control;
- 6 inspection assessing compliance with GCP rules;
- 2 pharmacovigilance inspections at Romanian MAH sites, and Romanian MAH representatives sites, according to the yearly inspection plan of the Pharmaceutical Inspection Department.

In February and March 2012, a NAMMD-PID inspector, an inspector from the Agence Française de Sécurité Sanitaire des Produits de Santé and other inspectors from the Czech State Institute for Drug Control participated in two inspections requested by the European Medicines Agency (EMA), enforcing the reconfirmation of GMP compliance by two US manufacturers for centrally authorised medicinal products.

In June 2012, a NAMMD PID inspector acted as lead in the inspection at the site of a manufacturer in Romania, organised in the context of the PIC/S programme (Pharmaceutical Inspection Co-operation Scheme) for joint visit; 2 GMP inspectors (France and Poland) also took part in this inspection.

As regards inspection of Good Distribution Practice (GDP), inspections conducted in 2012 were as follows:

- 110 inspections for authorisation;
- grant of 243 wholesale distribution authorisations and their annexes;
- 13 follow-up inspections to assess distribution and the manner of corrective actions implementation as submitted to the NAMMD for authorisation purposes;
- together with representatives of the Ministry of Health (the Supervisory Body of the Ministry of Health), the Fraud Squad and local police inspectorates, 6 unexpected inspections were conducted at several sites of a wholesale distribution unit authorised by the NAMMD; no critical deficiencies concerning the performed activity have been found.
- 4 inspections for supervision of the quality of distributed medicinal products, consisting of check of traceability of medicinal products purchased/traded by wholesale distributors. This resulted in enforcement of penalties and suspension of the wholesale distribution authorisation for 3 inspected units;
- 149 dossiers for the inspected sites, namely applicants for update of Annexes to wholesale distribution authorisations, were set up and handled;
- the dossier for 372 applications for approval of export declaration was approved, leading to approval of export declarations for 1855 medicinal products manufactured/sold in Romania.

As regards certification of Qualified Persons, the dossier for grant of the Certificate attesting the Qualified Person status was checked and assessed; 18 such certificates were granted.

As of April 2012, the PID has undertaken assessment of documentation submitted for approval of donations of medicinal products, in accordance with legislation in force; 81 approvals for donation and the associated annexes were released before the end of 2012.

In 2012 as well, the PID collaborated with the department responsible for approval of advertising material on medicinal products for human use (The Information Logistics and Electronic Management of Data Department), assessing issues related with MAH non-compliance with legislation concerning advertising of medicinal products for human use.

This year, in accordance with provisions of SCD no. 4/22.02.2011 on approval of basic criteria for NAMMD inspectors' acceptance of free sample provision and approval of the Annex to Scientific Council Decision No. 3/23.03.2010 on approval of Implementation rules on provision of free samples of medicinal products for human use, 75 applications for provision of samples were received and assessed for 80 authorised products; the PID has

authorised provision of samples for 64 medicinal products; moreover, reports on the situation of samples offered to healthcare professionals have been received and assessed, of which 19, submitted by 16 MAHs or their representatives, have been accepted. A database has been set up on MAH management of medical samples provision.

Surveillance of medicinal product quality and management of rapid alerts consisted of:

a) Execution of the sampling scheme for medicinal product quality monitoring:

- Of the 32 products proposed, 27 were sampled and 5 were not found in the distribution network;

- 26 samples have been declared compliant, following laboratory testing; 1 has been declared non-compliant (the product has been recalled and destroyed).

In addition to the sampling plan, the following have been sampled in 2012:

- 3 medicinal products sampled on request of the Quality Control Department, for participation in market surveillance studies proposed by the OMCL network (Official Medicines Control Laboratories); all samples of medicinal products have been declared appropriate;

- 12 medicinal products sampled for resolution of medicinal product quality complaints; all medicinal products sampled have been found compliant;

- 5 medicinal products sampled from distribution units within the EMA/EDQM coordinated scheme for surveillance of centrally authorised medicinal products; the testing of these products has been performed by laboratories in other EU competent authorities, and the results were found compliant.

b) follow-up inspections of the quality of medicinal products in the distribution network (warehouse, pharmacies):

- 330 thematic inspections in 2025 wholesale and retail distribution units.

c) inspections of the quality of oxygen used in hospitals:

- 200 were carried out in hospitals across the country to stop use of unauthorised oxygen (liquid oxygen is provided by GMP certified producers, whereas compressed oxygen for 13 hospitals (6.5 %), less than the previous year, is still provided by unauthorised manufacturers). The Ministry of Health has been informed on the situation.

d) Cooperation with other bodies for resolution of issues related to legislation on medicinal products and/or the quality of certain products sold in Romania:

- 8 joint actions with specialised local bodies, carried out by field inspectors (1 Cluj, 2 Târgu Mureş, 3 Galaţi, 2 Bacău).

e) Resolution of 28 complaints relating to possible quality noncompliances of medicinal products for human use:

- all complaints received have been resolved as follows: 20 have been filed without additional measures, 6 have been found justified, resulting in recall of the respective medicinal products from the market (4), request for submission of application for variation (1) or imposition of penalty on wholesaler (1). Two complaints have been redirected as outside the NAMMD scope. Most complaints were submitted (20) by NAMMD field inspectors and referred to inappropriate imprinting of primary/secondary packaging or set up of Leaflets of certain medicinal products. Remaining complaints have been filed by patients or healthcare professionals.

f) Recall from the market of quality noncompliant medicinal products: in 2012, the NAMMD requested recall of 60 medicinal products (more than during the previous year), of which:

- 34 medicinal products were identified with intrinsic quality nonconformities and have therefore been proposed for destruction (4 following complaints, 23 due to rapid alert/nonconformities with GMP rules), 7 voluntary recalls performed by manufacturers);

- 3 medicinal products had packaging/leaflet inscription nonconformities and have been proposed for remedy/destruction;

- 19 medicinal products recalled in accordance with Order of the Minister of Health no. 279/30.03.2005.

- 4 medicinal products recalled following withdrawal of marketing authorisations.

g) Rapid alert system:

- in 2012, 112 rapid alerts were received and resolved, within the EMA Rapid Alert System, the Pharmaceutical Inspection Cooperation Scheme (PIC/S). Of these, 8 have

envisaged products authorised and imported/distributed in Romania; in 2012, the NAMMD issued no Rapid Alert.

h) Cooperation with the EMA, the EDQM, European competent authorities, concerning surveillance of the quality of raw materials/finished products manufactured in third countries:

- measures decided in accordance with joint authorities' decisions related to 14 cases reported of non-compliance with GMP rules by active substances or medicinal products manufacturers from third countries;

- steps taken to change active substance suppliers related suspension/withdrawal by the EDQM of 12 certificates of conformity with the European Pharmacopoeia.

i) Creating and updating the databases for all PID services, updating information on the NAMMD website and introducing in the EudraGMP database of information concerning NAMMD activities related to manufacturing authorisation/import/GMP certification.

j) Coordination of activities of the Territorial Inspection Units (TIU) related to surveillance of medicinal product quality.

In October 2012, the PID was audited by representatives of the World Health Organisation, as part of the audit mission to Romania for assessment of NAMMD regulatory activities concerning vaccines for human use. The audit ended with favourable conclusions regarding PID activity and recommendation for improvement.

In December 2012, a NAMMD-PID inspector took part as facilitator, in conjunction with PIC/S inspectors from Belgium and Singapore, in the workshop organised by the World Health Organisation for training of GMP inspectors, conducted in China.

In 2012, PID activity related to harmonisation with EU legislation of inspection legislation consisted of participation to transposition of Directive 2011/62, amending Directive 2001/83. The new regulations have been approved through Emergency Government Ordinance no. 91/2012.

7. Quality control of medicinal products for human use

Quality control of medicinal products for human use is part of the NAMMD general policy for accomplishment of its mission to ensure medicinal product quality, safety and efficacy by laboratory tests.

This activity is performed by two NAMMD departments: the Medicine Quality Control Department (MQCD) and the Biological Product Evaluation and Control Department (BPCD).

Process-based approach is used for activities in both control departments, in line with requirements of standards SR EN ISO 9001/2008 and SR EN ISO 17025/2005.

Both NAMMD control departments are part of the European network of Official Medicines Control Laboratories (OMCL), coordinated by the European Directorate for the Quality of Medicines (EDQM), and participate in all related activities.

7.1. The main types of tests performed by the Medicines Quality Control Department (MQCD) are as follows: physico-chemical tests, pharmacotoxicological tests, micro-biological tests and radio-pharmaceutics tests.

The main activities performed in 2012 envisaged:

a) Quality control of non-biological (chemical) and biological medicinal products.

In 2012, 58 medicinal products were submitted for MPQCD testing (27 – as part of the Annual Plan for Sampling and Testing, 15 – products subject of complaints, 16 – international collaborations), of which 47 have been concluded and 10 are currently undergoing various stages of testing. For medicinal products still under testing, microbiological and pharmacotoxicological tests have been performed. These have not been concluded in 2012, because of objective grounds (supplementation of the analytical documentation concerning the product's purity has not yet been submitted by the manufacturer, deadline: April 2013, in accordance with the deadline required through MRP etc.)

According to procedures, a set of specific tests (individual parameters) was performed for each medicinal product tested, according to characteristics.

For the 47 medicinal products tested within the MPQCD in 2012, 410 individual parameters were analysed, according to the techniques described in the European Pharmacopoeia or the manufacturer's pharmaceutical files.

Among frequent and complex analytical techniques used in 2012, in the context of medicinal product quality control, the following are worth mentioning: HPLC, pH-metry, Karl Ficher, spectrophotometry (IR, UV-Vis), pharmacotechnical testing (dissolution, mechanical resistance), volumetric dosing, determination of substance melting points, determination of liquid densities, determination of refractive indices, antibiotic microbiological dosage, sterilities (parenterals) and microbiological contaminations (ophthalmic solutions, syrups and paediatric solutions, certain film-coated tablets and capsules), endotoxin determinations (LAL test).

Products sampled by the Pharmaceutical Inspection Department (PID) as included in the Sampling and Testing Plan have been assessed on a case-by-case basis, from a physico-chemical, pharmacological, microbiological or radiopharmaceutical viewpoint.

Laboratory investigations of medicinal products included in this category have not revealed quality deficiencies, except for one product, for which a non-compliant certificate of analysis has been issued and has subsequently been recalled from the market.

For certain medicinal products, although compliant from in terms of quality, MAHs have been asked to update respective specifications and methods of analysis in accordance with PhEur monographs, by submission of applications for approval of variations to MA terms.

As regards medicinal products subject to complaints from patients or healthcare units, the PID has required laboratory testing (physico-chemical, pharmacological or microbiological, as required), for 15 medicinal products received/sampled locally, suspected of quality deficiencies. Among these, only one complaint was just, the other 14 being compliant with approved quality provisions.

In 2012 as well, the MPQCD has continued its collaboration with European institutions on medicinal product quality control, by participation to studies initiated by the EDQM and the International Pharmaceutical Federation (IPF).

- Studies initiated and coordinated by the European Directorate for the Quality of Medicines and HealthCare (EDQM):

- PTS (Proficiency Testing Scheme) studies – Inter-laboratory studies for measurement of professional performance, based on analytical protocols forwarded by the EDQM.

In 2012, 3 inter-laboratory studies have been conducted within the MPQCD.

The evaluation of performances and testing capability in resolution of difficult issues related to medicinal product control relies on interpretation of outcomes obtained by each laboratory, depending on several statistical operators (average of determinations, standard deviation, relative standard deviation).

An integrated value, ”the Z-score”, is obtained by processing the above operators, expressing professional capacity and ability for each laboratory and considered a performance indicator when ≤ 2.

As shown by data from the 3 studies as communicated by the EDQM, as far as the 6 samples analysed by the MPQCD are concerned, values obtained comply with the specified performance criterion, since ,,the Z-score” scored lower than 2.

- CRS studies - Chemical reference substances - 1 sample, tested for assessment of the laboratory technique, described in the PhEur monograph, concerning assay of antifungal activity by microbiological dosage in the tested substance. The outcomes, found compliant by the EDQM, are to be used in the next review of the monograph of the respective substance.
    - MRP studies for surveillance of the quality of medicinal products authorised through European procedures - 1 sample.

These are inter-laboratory tests performed on medicinal products authorised through European procedures, in accordance with PA/PH/OMCL(06)116 7R – “Co-operation in Post-marketing Surveillance of Mutual Recognition / Decentralised Procedure Products”.

Laboratory testing performed within the MPQCD for the respective sample, has ascertained reproducibility of the control methodology underlying the approved documentation, whereas the medicinal product was found appropriate in terms of quality. According to procedure, results obtained have been forwarded to the EDQM and entered into the EDQM-MRP electronic database.

- Inter-laboratory studies initiated by the International Pharmaceutical Federation (IPF);

Inter-laboratory PTS studies were performed (a HPLC dosage, pH determination through potentiometry, of two unknown samples, assessment of purity through determination of the melting point for a sample).

All such tests have been compliant with the analytical requirements of IPF laboratories, according to evaluation documents forwarded.

b) Assessment of chemo-pharmaceutical documentation (DSSA, finished products, clinical trials);

The MPQCD has conducted work in that respect since 2005, interconnected with control activities.

In 2012, the following were performed within the MPQCD:

- Assessment of Active Substance Master Files (DSSAs) through European procedures;
- Assessment of quality – through European procedures;
- Assessment of ASMFs through national procedure;
- Assessment of quality – through national procedure;
- Assessment of clinical trial documentation.

In 2012, of 711 assessments for medicinal products undergoing authorisation procedure, 642 ASMFs were assessed (90.3%).

As regards assessment of clinical trial documentation, 26 complete quality studies were assessed (active substances, Investigational Medicinal Products - IMPs), all for the Voluntary Harmonisation Procedure (VHP) (voluntary harmonisation procedure for assessment of multinational clinical trials in the EU), as well as 8 amendments to IMP documentation.

7.2. Activity of the **Biological Product Evaluation and Control Department** (BPECD) covers the following aspects:

a) Current laboratory control activity of quality parameters of national and imported biological products for human use.

In 2012, no applications for testing of biological product batches have been submitted, mainly in result of suspension of the manufacturing activity of the internal manufacturer, INCDMI "Cantacuzino" (whose products undergo "batch to batch testing" for batch release procedure within the BPECD).

In accordance with quality assurance requirements and recommendations of external audits, for maintenance of operators' skills under circumstances of no requests for testing, specific exercises have been planned and performed.

Thus, conduct of a skill practice exercise by staff of the Laboratory for Determination through Serology Tests (LDST) was deemed necessary, as regards vaccine control (and particularly influenza vaccine control). Skill practice exercises have been performed for **2** testing methods (double diffusion, single radial immunodiffusion) according to SOPs of the LDST.

Results obtained have been analysed and compared with previous ones.

The Laboratory for Physical-Chemical Determinations and Immunochemistry (LPCDI) has performed the following activities:

- method validation: *pH potentiometric determination;* preparation of validation report;
- performance of calibrations and determinations for assessment of correct operation of the newly acquired Karl-Fischer volumetric titrator;
- performance of determinations for maintenance of testing skills and assessment of understanding of working methods.

b) Laboratory control of quality parameters for biological products for human use for grant of marketing authorisation/marketing authorisation renewal.

Applications lacking in 2012, no testing was conducted on biological product samples submitted within the marketing authorisation/marketing authorisation renewal procedure.

c) Postmarketing surveillance via registration of all imported biological products;

In the context of the postmarketing surveillance, MAHs submitted data relative to 185 biological product batches, which have been assessed by the specialist assigned and stored in electronic format.

d) Assessment of dossiers submitted for grant of MA/MA renewal of national/imported products or for approval of Type I/II variations or approval of applications for MA transfer/changes of design or approval of applications for performance of clinical trials,

activities followed by issuance of reports for assessment of biological product quality, reports for support of variations or other amendments.

Starting with January 2012, the BPECD has also performed validation of applications for variations to MAs (type IB and II) for biological products (responsible person: biol. Adina Chende-Roman).

During 2012, this activity consisted of:

- 138 validations of applications for Type IB and II variations
- 6 invalidations of applications for Type IB and II variations.

In 2012, the BPECD assessed 2 products submitted for authorisation through national procedure for which 1 report requiring supplementation has been issued and 62 products submitted for MA renewal through national procedure (58 foreign and 4 national), for which 86 reports have been issued:

- 46 reports with request for supplementation, 33 with proposal for MA approval; 7 assessment reports of postauthorisation supplementations.

The BPECD has also assessed dossiers for variations / changes of design / MA transfer, submitted through national procedure, for which 486 reports have been issued, as follows:

- 122 applications for type IA variations;
- 99 applications for type IB variations;
- 236 applications for type II variations;
- 24 applications for modification of design;
- 5 applications for MA transfer.

In 2012 as well, quality documentation has been assessed as related to products submitted through the mutual recognition and decentralised procedures, concluding in submission of assessment reports according to deadline, as follows:

Mutual recognition procedure

33 reports have been issued for 23 products:

- 4 reports with proposal for authorisation;
- 8 reports – conditions for authorisation;
- 6 reports proposing MA renewal;
- 15 reports containing MA conditions for renewal.

The BPECD also assessed support dossiers for variations submitted through Mutual Recognition Procedure, for which 95 reports have been issued, of which: 29 assessment reports for Type IB variations and 66 assessment reports for Type II variations).

Decentralised procedure

12 reports have been issued for 9 products pending authorisation:

- 1 final report;
- 4 assessment reports for authorisation, with request for supplementation;
- 7 reports containing the conditions for authorisation.

In 2012, the BPECD also assessed quality documentation submitted for approval of applications for performance of clinical trials for 19 biological products; 25 assessment reports have been issued, of which:

- 17 reports containing requests for supplementation of quality documentation;
- 8 final (positive) reports for assessment of quality documentation

As regards amendment of marketing authorisation terms for biological medicinal products for human use, following approval of Type I or II variations or following proofreading, the BPECD has performed 47 changes to MAs in 2012.

8. Ensuring communication and transparency

The NAMMD pays special attention to ensuring good information transfer and communication with stakeholders and the media, in accordance with Law no. 544/2001 on free access to information of public interest and of Law no. 95/2006, Title XVII – The medicinal product, on transparency in EU competent authorities work.

8.1. External communication

In 2012, in line with *its communication strategy for 2011-2015*, the Agency ensured:

- internal and external communications, opinions, communication with the written press and the media (by telephone, e-mail, TV interviews), relationship with other Romanian and foreign specialised institutions in this field;
- free access to public information in accordance with provisions of Law 544/2001, readily or upon request, for media representatives and any stakeholder, providing information about NAMMD work or the safety of medicinal products for human use;
- Cooperation of all departments for transparency purposes in Agency work, to ensure public accessibility/availability and passive transparency by providing for reactive information following application;
- The pooling of data from scientific departments and structuring of information requested for preparation of responses required by stakeholders;
- notification of the mass-media and/or other applicants within deadlines stipulated by regulations in force, on publication of information as stipulated under Article 5 of Law 544/2001, also specifying site of publication;
- notification of the applicant, within deadlines stipulated by regulations in force, on waivers from free access of the requested information;
- distribution to the media of NAMMD official releases and opinions.

The Agency provides correct information to its partners concerning work performed in all fields within its scope.

On its website, the NAMMD publishes quarterly bilingual Newsletters, reflecting its regulatory work in the area of medicinal products in line with European legislation and other Agency priority activities. The content of the NAMMD Newsletter includes:

- Laws, ordinances, Government decisions on medicinal products for human use or other areas of NAMMD interest;
- Orders of the Minister of Health for approval of NAMMD Scientific Council decisions and Orders of the Minister of Health in other areas of NAMMD interest;
- Decisions of the NAMMD Scientific Council;
- Decisions of the NAMMD Administration Council;
- Quarterly list of applications for marketing authorisation/marketing authorisation renewal submitted to the NAMMD;
- Quarterly List of EMA newly centrally authorised medicinal products, for which the European Commission has issued the decision on translation into Romanian of medicinal product information;
- Quarterly list of medicinal products authorised for marketing by the NAMMD;
- A quarterly list of medicinal product batches recalled by the NAMMD for quality defects.

The NAMMD develops the Index of medicinal products for human use, including all medicines authorised for circulation on the pharmaceutical market in Romania, with data on trade name, International Non-proprietary Name (INN), marketing authorisation holder, pharmaceutical form, strength, route of administration, type of packaging, manner of release etc. and posts it on its website. In 2012, implementation was continued, for each medicine, of electronic versions of the Summary of Product Characteristics (SmPC), leaflet and information on labelling and inscription.

The NAMMD develops and keeps updated information available on the Agency's bilingual website. Hence, the NAMMD website has published and continually updated the following information and documents:

- Press releases relating to safety of medicinal products;
- Direct healthcare professional communications;
- Notifications to Marketing Authorisation Holders (MAH) or other interested parties on issues of interest;
- Information related to medicinal products authorised through centralised procedure
- SmPCs for medicinal products authorised in Romania through mutual recognition procedure and decentralised procedure;
- SmPCs for medicinal products authorised in Romania through national procedure;

- List of NAMMD employees assigned as full members/alternates in the Management Board, scientific committees and working groups of the European Medicines Agency (EMA);
- List of EMA experts appointed by the NAMMD.

The following information is permanently posted and updated under “Pharmaceutical inspection”:

- List of Romanian manufacturers of medicinal products and active pharmaceutical substances;
- List of third country manufacturers, certified by the NAMMD;
- List of Romanian importers of medicinal products;
- List of Romanian distributors of medicinal products;
- List of laboratories of control of medicinal products;
- List of recalled batches;
- List of Qualified Persons approved by the NAMMD,

as well as other contact data for submission of medicinal product quality complaints.

For support of external partners involved in European procedures for the marketing authorisation of medicinal products for human use, the NAMMD website contains two sections dedicated to the procedures in question, also been posted on the new website:

- <CP> (centralised procedure)
- <MRP and DCP> (mutual recognition procedure and decentralised procedure), containing data on contact persons and useful information for authorisation through these procedures.

The following headings were considered of particular utility by external NAMMD website users:

a) Medicinal product legislation, structured according to type:

- Laws, Ordinances, Government Decisions;
- Orders of the Minister of Health;
- NAMMD Scientific Council Decisions;
- NAMMD Administration Council Decisions.

b) The Index of medicinal products for human use authorised for marketing on the Romanian pharmaceutical market.

c) Important notifications and EMA and NAMMD Press releases.

The large number of visitors of the NAMMD website, over 100 000 visitors/year, is proof of increased stakeholder interest in information posted.

Moreover, in 2012, the NAMMD continued to inform stakeholders about its activity, otherwise than by means of NAMMD Newsletters. Thus, several articles have been published in Romanian professional magazines (“Farmacist.ro“, “Medical Business“, “Medica Academia, “Pharma Business“) referring to various issues related to Agency work.

NAMMD representatives have participated with professional presentations in numerous scientific/professional manifestations held in Romania and abroad.

8.2. Internal communication

In 2012, the Agency continued supplementation and update of information (available to NAMMD staff on the Intranet), for optimal and efficient professional/organisational information.

NAMMD staff has access to the following information available on the “Intranet“:

- Instructions of the NAMMD President;
- NAMMD quality-related policies;
- NAMMD regulations;
- Glossary of quality assurance;
- Activity plans of each department;
- Useful forms;
- Information provided by the Pharmacopoeia service;
- Information about training courses organised by the NAMMD or by professional companies;
- Reports issued by the employees receiving training in Romania and abroad;
- Situation of staff training;
- Outcomes of the “staff motivation“ poll;

- Useful information;
- Useful addresses etc.

9. Quality management activity

Activities performed by the QAB aim to establish, document, implement, maintain and permanently improve the efficacy of NAMMD Quality Management System (QMS).

Considering the Policy on quality and quality objectives, established by the top management, as well as processes identified and implemented, the size and structure of the NAMMD and *SR EN ISO 9001* and *9004* principles in force, in 2012, the QAB, together with the other organisational structures, has participated to implementation, development and improvement of the NAMMD Quality Management System.

Activities have been performed as follows:

- The internal quality audit process was carried out in accordance with the Internal Quality Audit Program in 2012, approved by the President of the organisation.

Findings and conclusions of internal quality audits, whose objectives consisted of ensuring compliance with *Standard Operating Procedures (SOPs)* applying to audited processes, are established in accordance with SOP ANMDMAC/G/00 in force.

Other processes performed by the Quality Assurance Bureau:

- Counselling in quality management system (QMS) issues provided to various NAMMD organisational structures, for set up of objective proof, related to the External audit conducted by the WHO team, October 2012.

Note: the following copies have been requested by the WHO audit team: *NAMMD Quality Manual (MC-ANMDM), SOPs*, codes: ANMDMAC/G/ 003 and 005, in force, as well as tables of contents of the other *general PSOs* (001…015), applicable at organisational level (NAMMD).

External auditors of the WHO team have not found/communicated any non-compliances in that respect.

- Set-up of the documents requested by the Ministry of Health, related to the stage of implementation of internal/management control system on: 25.01, 23.07.2012 [in collaboration with the Internal (public) Audit Bureau].
- New update of declarations of interests/confidentiality undertakings/individual and non-individual job descriptions.
- Set-up/update of QAB databases (in electronic format).
- Monitoring/Improvement of staff health.

QAB schedule for 2012 as approved by the President of the institution, has been observed.

The NAMMD has a robust Quality Management System (QMS), based on *international standards 9001, 9004, 17025, 19011* etc. in force.

PSO status at organisational/departmental level is as follows:

General PSOs: 15
Specific PSOs: 290
Interdepartmental PSOs: 16
All PSOs/NAMMD departments: 321

NAMMD top management is involved in QMS-related activities, showing its preoccupation with implementation of a process-based approach.

10. Medical devices

10.1 Control activity through regular check of medical devices

As of 2010, after merger with the Technical Office for Medical Devices, the NAMMD has become the single institution assigned for assessment of performance and safety of medical devices in use.

In 2012, control activities consisting of regular check-up of medical devices were carried out for all higher risk medical devices installed and operating at the sites of all medical device users, both private and public. Checks have consisted of assessment of performance and safety of medical devices in use, regular check-up bulletins being documents required for set

up of medical care agreements between health insurance houses and medical practices/hospitals/medical centres.

In 2012, work of the Laboratories Technical Departments and the Nuclear Unit was as follows:

- Total number of applications registered: 1037
- Total number of periodic check-up bulletins issued: 1938
- Total number of approvals for use issued: 231
- Total number of medical devices assessed: 6430
- Total number of trial reports issued: 6079
- Total number of negative trials (rejected medical devices): 92

In March 2012, the RENAR conducted an activity for surveillance and monitoring of laboratories for testing and assay of medical devices within the Technical Department - Laboratories (TD-L) and the Nuclear Unit (NU), examining the manner of field testing performance. Results have been found appropriate.

In 2012, intense efforts have been made to ensure review of the List of medical devices submitted for control through regular check-ups, so as to ensure inclusion into the List of medical devices only of highest risk to patients and users, required for future replacement of Order of the Minister of Health no. 1662/2007 on control through regular check-up of medical devices, as amended.

In spite of several barriers encountered (insufficient staff, financial difficulties), the TD-L and the Nuclear Unit have made special efforts to ensure steadfast activity in the context of mandatory preservation of acceptable safety and performance level of medical devices in use.

10.2 Inspection and assessment of technical-medical units

The Technical-Medical Units Assessment Service works under Law No. 176/2000 on medical devices, as amended, and Order No. 1636/2004 on approval of Methodological rules for implementation of Law No. 176/2000, as amended, on licensing of medical technical units, involving assessment of organisations' ability to perform services requiring Ministry of Health approval.

In spite of its small number of employees, the department is assigned for work over the entire country, performing not only initial unit assessment for approval and surveillance as well as biennial assessments, but also detection and application of penalties for breach of legal provisions as per Law No. 176/2000, as amended.

Staff in this Department has accomplished the following results:

- Number of registered applications for assessment: 156;
- Number of assessment performed and reports issued: 79;
- Number of ongoing works: 30;
- Number of activities cancelled (for reason of unsubmitted assessment dossier): 16;
- number of ongoing assessment activities:12
- number of assessment-surveillance activities: 376
- number of assessment-surveillance activities, completed, with finalised reports: 183
- number of assessment-surveillance activities, undergoing assessment: 92
- number of assessment-surveillance activities, in process of completion: 55
- number of assessment-surveillance activities, for confirmation of termination or approval for performance: 46
- missions for assessment and surveillance activities: 83

Six control activities were performed, resulting in application of 3 penalties for breach of legal provisions.

11. International relations

In 2012, NAMMD specialists continued to take part in activities of various collaborator European institutions and organisations:

11.1. Participation in activities of the European Medicines Agency (EMA)

Since 2003, at the initiative of the European Medicines Agency, NAMMD representatives have actively participated as active observers to EMA working groups, scientific committees and groups for implementation of medicinal product related information technology.

This involvement has always been the optimal means of keeping the Agency connected to European activities related to medicinal products for human use.

As full members since 2007, participating in EMA scientific committees and working parties, NAMMD experts have participated in over 100 meetings in 2011. EMA Scientific Committees and Working Groups are:

- The Committee for Medicinal Products for Human Use - CHMP;
- The Committee for Orphan Medicinal Products - COMP;
- The Committee for Herbal Medicinal Products - HMPC;
- The Paediatric Committee - PDCO;
- The Committee for Advanced Therapies - CAT;
- The CHMP Safety Working Party;
- The CHMP Pharmacovigilance Working Party – PhWP, whose activity will be discontinued on replacement with the Pharmacovigilance Risk Assessment Committee – PRAC, expected on entry into force by the beginning of July 2012 of the Directive for amendment and supplementation, as regards pharmacovigilance, of Directive 2001/83/EC;
- The CHMP Blood Products Working Party;
- The CHMP Biologics Working Party;
- The CHMP Vaccines Working Party;
- The CHMP/CVMP Quality Working Party;
- The GMP/GDP Inspectors Working Group;
- The EudraGMP database sub-working group;
- The GCP Inspectors Working Group;
- The GLP Inspectors Working Group;
- The Pharmacovigilance Inspectors Working Group;
- The Working Group on the database of medicinal products authorised in the EU (EudraPharm TIG);
- The Working Group on the database of adverse reactions (EudraVigilance TIG);
- The Working Group on the European database for clinical trials (EudraCT Clinical trials TIG);
- The Working Group on the European network (EudraNet TIG);
- The Working Group on the electronic transmission of data (e - Submission);
- The Working Group on European Union Telematics Controlled Terms (EUTCT);
- The Working Group on Product Information Management (PIM);
- The Working Group of the Quality Review of Documents;
- The Invented Name Review Group.

11.2. Participation in activities of the “Heads of Medicines Agencies” body

NAMMD representatives are actively involved in meetings of the “Heads of Medicines Agencies” (HMA) European body as well as meetings of its working group, namely:

- The Co-ordination Group for Mutual Recognition and Decentralised Procedures (CMD-h);
- The HMA Working Group of Quality Managers;
- The EMACOLEX - European Medicines Agencies Cooperation on Legal Issues;
- The Working Group of Communication Professionals (WGCP);
- The Working Group of Enforcement Officers (WGEO);
- The Clinical Trials Facilitation Group (CTFG);
- The Homeopathic Medicinal Products Working Group (HMPWG).

11.3. Participation in activities of the European Union Council and of the European Commission (EC)

In 2012, NAMMD experts participated in meetings of the Council of the European Union and of the European Commission (EC), i.e. the Working group on medicinal products

and medical devices of the EU Council, preparing proposals for amendment of Directive 84/2010/EU and proposals for a new Regulation on clinical trials for repeal of Directive 20/2001/EC on clinical trials in the EU, the Standing Committee, the Pharmaceutical Committee, Notice to Applicants, the United Nations Interregional Crime and Justice Research Institute for the „SAVEmed Microstructure secured and self-verifying medicines" project.

11.4. Participation in World Health Organisation (WHO) activities

The NAMMD is a member of the WHO Scheme on certification of the quality of medicinal products circulating on the international market.

In 2012, the Agency released the Certificate of the product in WHO format for 529 medicinal products of Romanian manufacturers seeking authorisation for these products in other states.

11.5. Participation in European Council activities

In 2012, NAMMD representatives participated in the two meetings of the **Working Group** on the classification for release of medicinal products for human use.

11.6. Participation in European Pharmacopoeia Commission activities

As member of the European Pharmacopoeia Commission, the NAMMD representative has been actively involved in specific working sessions in 2012, as well as in the yearly meeting of the secretaries of national Pharmacopoeias in Convention on the Elaboration of a European Pharmacopoeia member countries.

Cooperation with the European Directorate for the Quality of Medicines (EDQM) was continued, for issuance and update of "Romanian Standard Terms", in accordance with terms adopted by the European Pharmacopoeia Commission.

11.7. Participation in activities of the Pharmaceutical Inspection Cooperation Scheme (PIC/S)

NAMMD activity as a PIC/S member consisted of participation through its representatives in the two yearly meetings of the PIC/S Committee of Officials, participation in the joint visit organised by the Polish inspectorate, as well as in the annual PIC/S organised training seminar for inspectors on "Good Inspection Practice".

11.8. Participation in the activities of the Official Medicines Control Laboratories (OMCL)

For description of these activities, please see points 7.1 c) and 7.2 d).

12. Information, Logistics and Electronic Management of Data

In 2012 as well, the Logistics and Information Service managed preservation of optimum parameters of communication channels with the EMA and provision of real-time information exchange between the Agency and external collaborators (MAHs, distributors, healthcare professionals, patients, organisations and associations).

In 2012, maintenance, amendment and update was continued of the Product Index of medicinal products for human use database. Moreover, statistical data reports were extracted periodically on request by the Minister of Health, the National Health Insurance House, the NAMMD President and various Agency departments.

As regards cooperation with other institutions, upon EMA request, responses to various forms on information technology were prepared; the database concerning NAMMD experts was administered and related information was updated via the application made available by the EMA, necessary steps have been taken to ensure access to the "External experts" database under EMA administration, participation in EudraPharm, EudraNet and EUTCT working groups has been ensured in accordance with nominations made in 2012 (participation in 8 events).

Throughout the year, maintenance of connections to the European EudraNet network (EudraCT, EudraLink, EudraMail, EudraPharm, EudraVigilance, PIM, CTS, EPITT) was monitored in the context of the activity of administration, configuration and repair of local equipment.

Maintenance of the NAMMD website (*www.anm.ro*) and other software applications has been ensured throughout the year (search engines – Index, search after key words, management of recalled medicinal products, management of GMP units - all pending); a new section, "Suggestions", and a new website, "Counterfeiting" (ongoing project – *www.crimemedicine.ro)*; at the same time, many activities concerning updating of the website various sections (Newsletters, Orders of the Minister of Health, press releases, Q&A documents, Important notifications, Direct Healthcare Professional Communications etc.) have been ensured; the Agency's intranet website has been maintained, amended and updated.

Maintenance and administration of NAMMD servers (folder servers, web-intranet servers, internet servers for several services, accounting servers) have been ensured.

Moreover, an EMAIL server has been set up and configured on the Linux platform for the new domain, anmdm.ro, containing future users' accounts.

Also, maintenance and troubleshooting of software and hardware of existing computers was performed and installation and configuration of new computers were ensured. Maintenance and troubleshooting of the NOD32 antivirus programme and other safety programmes on NAMMD servers have also been provided.

The Data and Document Management Service ensures receipt of documents at Agency level and their distribution to concerned offices, release of all documents in the Agency to external collaborators to facilitate prompt movement of documents among Agency departments.

A number of 1125 marketing authorisations and their annexes have been issued in 2012, namely 914 through European procedures and 211 through national procedure.

Also, typing/drafting has been insured for:

- 529 product certificates in WHO format for Romanian medicinal products;
- 182 letters for 666 medicinal products, confirming status of the medicinal product undergoing renewal of marketing authorisation, bearing the "suitable for marketing" specification";
- 596 notification letters sent to manufacturers on MA release in accordance with President directions and maintenance of a copy in the product dossier.

Receipt, administrative assessment and registration in the entry/exit Register and introduction into "Registry A" and the "Ongoing work" databases of:

- 420 applications for marketing authorisation/marketing authorisation renewal through national procedure;
- 998 applications for marketing authorisation/marketing authorisation renewal through DCP/MRP;
- 3102 applications for Type IA, IB, II variations, MA notifications through national procedure;
- 3327 applications for Type IA, IB, II variations, MA notifications through decentralised/mutual recognition procedure;
- 7718 drafts and payment forms for issue of invoice for marketing authorisation/marketing authorisation renewal and variations through decentralised/mutual recognition procedure;
- 27473 documents (responses to NAMMD requests for MA authorisation/renewal documentation, variations, clinical trials, advertising, adverse reaction reporting etc.).

24 meetings of the Marketing Authorisation Commission(s) have been organised and 1003 product dossiers have been assessed.

The NAMMD server has been updated with its 1125 marketing authorisations issued in 2012 and the 5 corresponding Annexes, concerning the leaflet, Summary of Product Characteristics, packaging, data on the qualitative and quantitative composition of the medicinal product, data on the product manufacturing.

13. Ensurance of set-up and implementation of NAMMD policies and strategies

In 2012, in collaboration with other departments, the Policies and Strategies Department (PSD) contributed to fulfilment of the NAMMD mission, by setting up the 2011-2015 NAMMD organisational strategy, namely by:

- strengthening NAMMD status as expert and reliable source of accurate medicinal product related information, provided to stakeholders in due time;
- active and priority participation to implementation of the Agency's *Communication Strategy* 2011-2015, internally and externally, permanently aiming at identification of areas and manners of improvement, as well as adaptation to new requirements and the dynamics of legal and socio-economic amendments.
- - *The organisational strategy,* establishing strategic objectives and Guidelines of the Agency's activity, in accordance with the legal framework in force, and the relationship between the NAMMD and the Ministry of Health and between the NAMMD and stakeholders;
- - *The communication strategy*, establishing objectives of internal and external Agency communication activity and strengthening its status as expert and reliable source of accurate information in the medicinal product field, provided in due time to stakeholders: healthcare, research and industry professionals, patients, general public and the media.

In 2012, constant efforts have been made towards transposition into Romanian legislation of two new European Directives concerning a new pharmacovigilance approach (Directive 2010/84/EU) as well as prevention of entry of falsified medicinal products into the legal supply chain (Directive 2011/62/EU), which have both amended Directive 2001/83/EC on the Community code relating to medicinal products for human use.

The transposition, examination of transpositions and preparation of emergency ordinance drafts have been performed within two working groups, assigned through Decisions of the NAMMD President, as well as through collaboration with the Ministry of Health and the Ministry of Justice.

In spite of its main involvement in transposition of the directive on pharmacovigilance (Directive 2010/84/EU), the PSD however took part in two working groups, as well as in talks with the Ministry of Health and the Ministry of Justice for completion of transposition legislation.

These activities resulted in draft of 2 emergency ordinances (Emergency Ordinance no. 35 of July 2012 Emergency Ordinance no. 91 of December 2012), amending Law 95/2006 on healthcare reform, as regards pharmacovigilance and prevention of the entry of falsified medicinal products into the legal supply chain.

Together with the other professional departments, the PSD participated in proper NAMMD operation in the European network of competent authorities in the medicinal product field, acting as interface between the Agency and the European and international authorities in this field through:

- Management and monitoring of participation of NAMMD staff assigned as full members or alternates to scientific committees and working groups of the EMA, HMA, EDQM, European Council, EU Council, European Commission, the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S);

- Periodic update of the List of NAMMD employees assigned as full members or alternates to scientific committees and working groups, in accordance with President decisions and their posting on the NAMMD website;

- Insuring communication with the EMA for assignment of NAMMD experts as full members/alternates;

- Check-up/Summarization of the forms prepared by NAMMD experts;

- Communication with the secretariats of working groups/scientific committees of the cited bodies for transmission of forms;

- electronic evidence of documents received on paper from the WHO, EDQM, OMCL etc. and their distribution for information or grant of opinion; the Policy and Strategy Department has prepared the NAMMD Annual Activity Report for 2011 by corroboration of data from NAMMD departments activity reports.

Similarly to 2012, the Policies and Strategies Department managed to provide secretarial and organisation work for the NAMMD Scientific Council (SC) (in accordance with the *interdepartmental SOP*) through:

- handling and centralisation of 9 Scientific Council Decisions (SCDs), 4 of which regulatory, from draft to publication, in accordance with the *interdepartmental SOP*;
- set-up of the SC meeting agenda, submission of documents to Scientific Council members review, on paper/in electronic format;
- ensurance of scientific secretarial work for 1 Scientific Council meeting in 2012 and for approval of 2 SCD drafts through written procedure;
- set-up of the documentation of drafts of Minister of Health Orders on approval of regulatory SCDs;
- Drafting of the minutes of SC meetings;
- Handling of the electronic versions of SCDs from draft to publication (both in the Official Gazette of Romania, Part I, for SCDs approved through Order of the Minister Health, as well as on the NAMMD website, under the headings "Legislation" and "Newsletters") in the directories for Scientific Council meetings;
- updating the record of contact coordinates of SC members;
- set-up of the integrated evidence of Decisions approved by the SC in 2012, while mentioning, as required, the stage of approval of the Order of the Minister of Health/ Order of the Minister of Health on approval of a SCD, date of publication in the Official Gazette of Romania, Part I and the publishing Newsletter.

Set-up of NAMMD Newsletters has been continued, which have been posted on the NAMMD website, namely:

- 4 newsletters in Romanian (no. 4/2011; no. 1/2012; no. 2/2012; no. 3/2012)
- 7 newsletters in English (no. 4/2010; no. 1/2011; no. 2/2011; no. 3/2011; no. 4/2011; no. 1/2012; no. 2/2012).

The PSD participated as interface between the NAMMD and stakeholders for update and improvement of information available on the NAMMD website, in collaboration with the other departments, by posting:

- 65 regulatory documents, in Romanian and English version;
- 24 supplementations, amendments, recalls, proofreading;
- NAMMD Newsletters into Romanian and English;
- updated information about SC members' declarations of interest;
- Updated list of NAMMD employees assigned as full members or alternates to scientific committees and working groups of the European Medicines Agency (EMA) and updated List of EMA experts appointed by the NAMMD.

The PSH has also ensured:

- translation into English of **7** quarterly Informative Bulletins of 2010 and 2011 (no. 4/2010; no. 1/2011; no. 2/2011; no. 3/2011; no. 4/2011; no. 1/2012; no. 2/2012);
- Checking translation of 159 EMA press releases, EMA Q & A documents, Direct Communications to Healthcare Professionals, action lines proposed by the EMA ("Lines to take"), educational materials etc.;
- Follow-up of various sites in view of ensuring compliance of the terminology with European terminology (particularly EMA and EUDRA);
- accessing other sites for documentation in view of identifying information for various presentations;
- translation/ensurance of consultancy for translation of 11 SCDs;
- Provision of advice for check of translation of 13 SmPCs and leaflets, message exchanges and communication in English with European bodies;
- Checking translation of **4** assessment reports and documents in English, in the context of the Mutual Recognition Procedure;
- Ensurance of linguistic consultation for issuance of about **514** articles for correspondence and communication with various international bodies and representatives of companies or the pharmaceutical industry, on behalf of the Economic Department and of the Information Logistics and Electronic Management of Data Department;
- update of the English version of the NAMMD website via translation of legislation, notifications and press releases:

- translation and/or provision of consultation for translation of **2** papers in English, presented abroad by NAMMD specialists;

- translation of 25 documents and presentation materials for the WHO audit of December 2012 and of all materials connected to this visit;

- translation of the quality manuals of the NAMMD, BPECD and the Pharmacovigilance Service;

- translation of 7 CVs requested by NAMMD representatives to EMA working groups;

- translation, upon request of various departments, of 95 addresses and specific communications.

In line with the *2011-2015 NAMMD Communication Strategy*, in 2012, the PSD ensured:

- The internal and external communication, namely formulation of views, communication with the written media and the television (by telephone, e-mail, broadcast interviews), relationships with other Romanian and foreign institutions specialised in this field;

- Free access was ensured to public information in accordance with Law 544/2001, *ex officio* and/or upon request, for both the media, and the general public, providing information on NAMMD activities or information on the safety of medicinal products for human use;

- Cooperation with all NAMMD departments for ensured transparency of the Agency's activity by ensuring public accessibility/availability, namely passive transparency by ensuring reactive information following request;

- pooling from scientific departments and adjustment of required information in view of set-up and issuance of the reply required by stakeholders;

- Notification of media representatives and/or other applicants within deadlines imposed by rules in force, if the information required is already communicated *ex officio* by means of specified under Article 5 of Law No. 544/2001, also stating where the required information can be found;

- Notification of the applicant, according to deadlines imposed by rules in force, if the required information has been identified as waved from free access;

- Set-up/Verification and distribution of official communications and NAMMD position to the media;

- Participation to draft and transmission of mail exchanges with internal and external partners, related to issues specific to NAMMD activity;

- Daily monitoring of the mass-media (TV press and written press) in the healthcare field.

Communication with Romania's permanent representation at EU/Brussels was performed through:

- More than 500 e-mails received from the permanent representative of Romania to the EU and / or the Ministry of Health were monitored / entered into electronic records, regarding participation of NAMMD experts assigned to working groups of the European Council, to the Pharmaceutical Committee and the Standing Committee of the European Commission and redirecting them to NAMMD appointed experts.

- coordination and monitoring of participation of NAMMD experts appointed to meetings of previously mentioned working groups/committees and provision of mail with the Representation on this issue, as required;

- coordination and participation to the monitoring/handling in electronic databases of 49 European Commission Decisions referring to: conditionally authorised medicinal products (based on Article 127a of Directive 2001/83/EC), MA suspension/withdrawal/amendment (based on Article 107, 29, 31 of Directive 2001/83/EC) and forwarding these documents to NAMMD specialists appointed for implementation.

The PSD has also ensured conduct of Pharmacopoeia related activities by coordination of technical-scientific work resulted after Romania's accession to the "Convention on the Elaboration of the European Pharmacopoeia" within the European Council, namely by:

- participation, by an assigned representative, to the yearly sessions of the European Pharmacopoeia Commission, as its member;

- centralisation and analysis of the dossier forwarded in electronic version by the European Pharmacopoeia Commission/EDQM.

14. NAMMD legal work

Professional activities of the Legal Department (LD) have mainly envisaged accomplishment of tasks specified in the NAMMD Regulation on the Organisation and Operation (ROO), approved through Order of the Minister of Health no. 1031/2011, as well as other activities.

For accurate description of activities performed in 2012 from a statistical viewpoint, the following activities were performed:

- grant of approval on legality of measures to be taken and of any other documents which could determine the institution's patrimonial liability;
- grant of approval concerning the correct interpretation of legislation related to NAMMD's field of activity;
- Preparation of minutes and Decisions of the NAMMD Administration Council;
- Participation via representatives assigned by NAMMD management to meetings of the scientific councils and EMA working groups, to other working groups of competent authorities in the field of the medicinal product, e.g. the participation of 2 experts of the Legal Department to the Legislation working group (EMACOLEX - European Medicines Agencies Cooperation on Legal and Legislative Issues) reunited in Copenhagen, Denmark, March 2012;
- Management of activities related to exchanges for petition resolution in accordance with Ordinance no. 27/30.01.2002 regulating the resolution of petitions.
- draft and approval of 196 Decisions of the NAMMD President.
- other activities:
  - management of the NAMMD security structure activities;
  - participation, as members, to work of commissions for assessment of procedures for purchase of equipment and services;
  - participation to work of commissions for yearly inventory of assets;
  - participation to counselling upon request by departments;
  - provision of visa for preventive financial control of the institution's financial-accounting documents;
  - preparation of documents required for external travels of NAMMD staff to meetings of scientific councils working groups of the EMA or other European or international medicinal product related bodies.

Moreover, in collaboration with other departments, the Legal Department contributed to control of falsified medicinal products, which determined continuation in 2012 as well of the existing cooperation with the General Inspectorate of the Romanian Police, based on the cooperation protocol signed in March 2010, aiming at establishing a framework for bilateral cooperation and exchange of information on falsification of medicinal products for human use, in accordance with specific attributions and competences stipulated by the legislation in force.

A noteworthy initiative in 2012 has been start of the "SAVEmed Microstructure secured and self-verifying medicines" project for action against counterfeiting of medicinal products, initiated by the United Nations Interregional Crime and Justice Research Institute (UNICRI). In that respect, the NAMMD Legal Department representative took part in two of the meetings occasioned by the respective project (March and November 2012). As regards Romania, the project in question envisages achievement of two targets:

- implementation of a single point of control (SPOC) in Romania, with the Romanian General Prosecutor's Office as a national contact point;
- preparation,, in cooperation with 15 participant countries, of a good practice guideline on communication between the public and private sector for facilitating exchange of information on prevention of entry of falsified medicinal products into the legal supply chain.

It should be noted that the duty concerning implementation of a SPOC system is expressly provided for by Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products, transposed into national legislation through Government Emergency Ordinance no. 91/2012.

Following assessment of the Romanian regulatory field, it has been concluded that a system is applicable in Romania, as in other EU member states, implying:

- as primary stage – signing of collaboration protocols/memoranda between national institutions involved, namely: the General Prosecutor's Office, the General Inspectorate of

Police, the Border Police, the Customs 'Authority, the Ministry of Health, the National Agency for Medicines and Medical Devices;

● second stage – set up of a data system with single point of contact with Romania's General Prosecutor's Office.

Such approaches are instrumental for set up the framework for implementation of provisions of Directive 2011/62/EU, transposed into national legislation through Government Emergency Ordinance no.91/December 2012.

15. Management of human resources

15.1. Human resources policy

Obviously, similar to previous years, objectives of the Human Resources and Payroll Department have been preserved, as follows:

- Provision of human resources for NAMMD structures, especially in sectors where department and top management reviews highlighted lack of qualified university graduates (particularly medico-pharmaceutical) among staff, for proper covering of jobs in specialised departments, whose work practically ensures accomplishment of the Agency's scope.

- Improvement of human resources through employee training and continued professional improvement by:

- Training and professional improvement of existing specialised personnel, for training of highly qualified specialists, able to deal with the entire range of assignments and tasks involved in the NAMMD object of activity;

- Training and professional improvement of existing specialised personnel, for training of highly qualified specialists, able to deal with the entire range of assignments and tasks involved in the NAMMD object of activity;

- Training, improvement and evaluation of NAMMD staff; it is worth mentioning that such training is carried out according to yearly plans at department level, according to each employee's specific activity and training. Training has been delivered on both hiring and afterwards, organised regularly as ongoing training provided both internally and, depending on the Agency's financing possibilities, externally, provided by institutions specialised in various areas such as quality assurance management (ISO 9001 and 9004), training specific to pharmaceutical inspection, pharmacovigilance, assessment and authorisation of clinical trials, financial-accounting legislation etc.

Moreover, the following have to be noted:

- active participation with presentations at various congresses in the medicinal product field, as well as constant and remarkable participation of NAMMD experts in working groups of European and international bodies in the medicinal product field;

- Identification of means for staff motivation given the lack of any possibilities in 2012 for wage-related compensations (bonuses, pay rises etc.) for special professional merits. Potential solutions:

- assignment to management positions of staff selected for abilities demonstrated in accomplishment of tasks and responsibilities pertaining to the respective position;

- strengthening of an adequate system for assessment of performance.

15.2. Ensuring human resources within NAMMD structures

In 2012, personnel-related activities were performed within the Human Resources and Payroll Department (HRPD). As regards accomplishment of the main departmental goal, namely provision of qualified personnel, this has been gravely impeded by the applicable legal framework set up through Government Emergency Ordinance No. 34/2009 on budget rectification for 2009 and regulation of certain financial-fiscal measures ("Measures on public expenditure" providing for "freeze of examination/contest based hiring proceedings in relation to vacancies in public institutions").

As a consequence, acute understaffing emerging as of 2009 has been preserved, since the only jobs available for temporary use, on Ministry of Health permission, have been labour contracts suspended for strictly determined periods.

15.3. Development of human resources through employee training and professional improvement

Continual Agency involvement in the decision making process at European level by active participation in European scientific committees and working groups, with proposals for viable solutions able to contribute to amendment of current legislation in the area of medicinal products for human use, requires high level of competence among NAMMD specialists. This target can only be reached by means of a programme for ongoing training, specific to professional development, on Agency site, and by participation to training organised nationally and internationally by various authorities and bodies in the field.

According to possibilities of funding by European bodies and the Agency's limited available budget, part of NAMMD specialists were able to benefit from training. In 2012, significant participation can be noted, occasionally with presentation of specialist papers, to the following professional training sessions provided in Romania:

- "The Pharmacovigilance Workshop" - Management and reporting of adverse reactions to medicinal products – Handling and reporting of adverse reactions to medicinal products", organised by the Romanian College of Pharmacists, Bucharest, 31 August 2012;
- Informal meetings with the ARPIM, APMGR and independent MAHs dealing with legal issues related to implementation of new pharmacovigilance legislation;
- The "Mass spectrometry and Atomic emission spectometry" seminar, organised by Viola – Shimadzu Romania, 27 March 2012, Bucharest;
- The national seminar on "Ionic chromatography", organised by Metrohm, Romania, 29 March 2012, Bucharest;
- The seminar "Bucharest User Forum - United States Pharmacopeia", organised by Chromaktiv SRL, 19 April 2012, Bucharest;
- The symposium "Fascinating by Analytics - reliable and reproducible HPLC analysis with Merck-Millipore", organised by Merck-Millipore, 26 April 2012, Bucharest;
- The conference of nuclear medicine "Actualities and perspectives in nuclear medicine" organised in the context of Expomedica 2012, 8 June 2012, The Parliament House - Bucharest;
- The course "Sartorius Single Use Systems School", organised by the Sartorius Company, 5 September 2012, Bucharest;
- The seminar "Steritest School", organised by Merk Millipore Romania, 24 October 2012, Bucharest;
- "PHARMA – Standards, reference materials and impurities", seminar organised by LGC Standards, 22 November 2012, Bucharest;
- The course "Estimate of measurement uncertainty and validation of testing methods in accordance with SR ISO 15189:2007", organised by the Association for Quality in Laboratories (CALILAB) at the Faculty of Biology, 19-20 October 2012, Bucharest;
- The 8th National Conference of the Order of Biologists, Biochemists and Chemists in the Health System in Romania (OBBCSSR), the Faculty of Biology, 21 October 2012, Bucharest;
- The National Conference of Pharmacy, interdisciplinary pharmacist-physician conference organised by the Romanian College of Pharmacists, 15-17 November 2012;
- The "Public relations and communications assistant" course, provided by SC Tak Education Group SRL, 11-13 May 2012, Sinaia.

The following training sessions have been provided abroad:

- the course addressing clinical assessors on efficacy of orphan medicinal products, „Workshop on significant benefit of orphan drugs", organised by the European Medicines Agency (EMA), London, 12.01.2012;
- Course for clinical assessors on assessment of paediatric data, EMA headquarters, London, 22-23 October 2012;
- Training course "HMPC Assessors Training on non-European Traditional Medicines", London, 25 September 2012;
- Course for clinical assessors on the quality of the opinion of Scientific Committees, organised by the EMA through Adobe Connect Teleconference;
- Conference: "Formulation strategies for pharmaceutical products", Berlin, 21-22 March 2012;

- EudraVigilance Data Analysis System (EVDAS) Training for National Competent Autorities – training course, London, 13 April 2012;

- Yearly meeting related to centrally authorised medicinal products and mutual/decentralised procedure, organised and sponsored by the EDQM, 15-16 November 2012, Sofia;

- The ”Quality control of the influenza vaccine” (“Control of bacterial endotoxins” test - LAL), organised by the World Health Organisation and the NIBSC, 14-18 May 2012, South Mimms, Hertfordshire;

- The training symposium “Batch release for medicinal products derived from human blood and plasma: principles, procedures and tools”, organised by the EDQM, Strasbourg, 10-11 May 2012;

- “The 5th meeting of international partners on the possible transfer of flu vaccine technology to vaccine manufacturers in developing countries” - 27-29 March 2012, Belgrade,

- Annual meeting of the Official Medicines Control Laboratories (OMCL), organised by the EDQM, Copenhagen, Denmark, 11-15 June 2012;

- successful examination for the degree of Microbiology specialist – May 2012 – by Daniela Motounu, Biologist;

- European Pharmacopoeia related course, organised by the EDQM in the context of the meeting of the EMA Biological Working Group, 12 September 2012, London;

- Course on assessment of similar biological medicinal products containing monoclonal antibodies, organised by the EMA, 23 October 2012, London.

16. Economic activity

In 2012, the Economic Department developed and managed a balanced budget of revenues and expenses from the state budget, amounting to 17,736,000 lei; expenses amounted to 17,205,505 lei.

These expenses consisted of: staff expenses (12,731,418 lei), expenses on goods and services (3,389,004 lei) and capital expenses (1,085,083 lei).

All expenses did not exceed the approved 2012 budget in accordance with legal provisions on economic and financial discipline.

All financial activities were performed by the Economic Department (ED).

It should be emphasised that the Budget approved and allocated in 2012 has been lower than required by the NAMMD, thus leading to insufficient means as compared to real Agency needs.

17. General administration activity

In the same way as during previous years, the General Administration Department (GAD) has been able to fulfil its objectives as well as provide prompt and efficient response to requests from other NAMMD structures.

Thus, the GAD most substantial achievements consisted in conduct and completion of activities related to equipment and refurbishment of NAMMD buildings *(NAMMD main headquarters located on 58 Titulescu Av. and the headquarters located on 20 Demostene Str.),* aiming to reduce the costs of utilities and furnishing of an optimal and operational area of work to improve the work setting.

Moreover, the Public Purchases Service organised and accomplished the entire purchase process needed for proper NAMMD operation, consistent with its objective needs and the approved budget, thus preparing documentation needed for 420 applications (purchase requisitions).

18. Internal audit

The internal audit structure set up at NAMMD level is subordinated to the NAMMD president, thus providing independence required for performance of internal audit activities for objective assessment of deficiencies detected in audited Agency departments and provision of adequate recommendations.

In 2012, the activity of the Internal Audit Bureau consisted of 4 audit missions:

- Assessment of activities of the Human Resources Department;

- Assessment of activities of the Policies and Strategies Department;
- Assessment of activities of the National Procedure Department;
- Assessment of activities of the Technical-Laboratory Department, the Technical-Medical Units Assessment Department and the Nuclear unit.

The objectives established in the context of missions performed at the sites of audited structures have been as follows:

- Organisation and operation of activities performed by audited structures;
- Manner of performance of activities undertaken by audited structures;
- Compliance with Revenues and Expenses Budget established values and terms; Working programs at the level of audited structures.

Risks potentially affecting NAMMD activity during the period assessed are of organisational, operational, legislative and financial nature.

The main recommendations provided consist of continued compliance with legislation in force and with NAMMD Regulation for Organisation and Operation.

As regards monitoring of implementation of recommendations, it should be noted that all recommendations of the Internal Audit Bureau to audited structures are provided in line with notifications made on preparation of the public internal audit report.

For strengthened and improved internal audit activity, Ministry of Health specialists have proposed development and publication of procedural guidelines on public internal audit of healthcare activities.

19. Difficulties encountered

In performance of its activities, the NAMMD has encountered several difficulties, the primary of which has been recruitment and maintenance of specialised staff, coping with the lack of financial means to ensure continual training of staff and access to the latest scientific progress in general and particularly in their own professional field, limited character of data bases.

20. Priorities for 2013

As in past years, at the end of 2012, the NAMMD outlined its priorities for 2013 as follows:

- Strengthening of Agency scientific staff following cessation of hiring freeze in the healthcare field;
- Strengthening of Agency's role in terms of medicinal product policy – amendment of legislation for establishment of the manufacturer and supplier public responsibility and the Agency's capacity for application of penalties, in case of non-compliance;
- Implementation of legislation on traceability and Agency control of medicinal products throughout the entire chain, for actual avoidance of the entry of falsified medicinal products into the authorised supply chain;
- Preparation and submission to the Ministry of Health of proposals for amendment of clinical trial legislation, for clarification of the definition of *Contract Research Organisations (CRO)* as well as of rules to be followed by clinical monitors, investigators and structures performing clinical trials, namely their responsibilities towards the hospital, investigators etc.,
- Agency increasing involvement in decisions made at European level, by active participation in European working groups, proposal of workable solutions amending current legislation in the medicinal product field, by increasing NAMMD degree of integration into the issue of medicinal products at European level by means of rapporteurship, pharmacovigilance assessment, assessment of authorisation dossier at high level of scientific competence as Reference Member State in the context of the decentralised procedure for marketing authorisation.
- Agency involvement in completion of the "SAVEmed Microstructure secured and self-verifying medicines" project (initiated by the UNICRI - United Nations Interregional) by accomplishment of the two targets established for Romania:

● implementation of a single point of control (SPOC) in Romania, with the Romanian General Prosecutor's Office as a national contact point;

● preparation,, in cooperation with 15 participant countries, of a good practice guideline on communication between the public and private sector for facilitating exchange of information on prevention of entry of falsified medicinal products into the legal supply chain.

- continued participation of certain representatives of NAMMD management to working meetings with representatives of all stakeholders and parties involved in the pharmaceutical market (manufacturers, suppliers) for regulatory endeavour to implement a medicinal product traceability system in Romania and identify all issues possibly instrumental as starting points for viable solutions in this respect;

- participation to meetings of various patient associations with speeches on various issues of interest e.g. generic vs. innovative medicinal product, clarification of the term ”falsified medicinal product”, the meaning of clinical trials and their significance to patients enrolled as clinical trial subjects, use of *off-label* medicinal products according to NAMMD perspective, importance of suspected adverse reaction reporting by both healthcare professionals and patients, in the light of the new community approach of pharmacovigilance transposed into national legislation in July 2012 and others.

- Revision of Order of the Minister of Health no. 1369/2009 on approval of tariffs imposed by the (former) Technical Office for Medical Devices, as amended, for clarification of certain issues related to travelling expenses and undertaking of measures enabling main credit officer understanding of the need for hiring, thus leading to better control at national level of application of Law 176/2000 on medical devices, as amended.

CONCLUSIONS

Throughout its self-assessment process, the NAMMD has been fully aware of the importance of establishing its targets and as well as of an adequate number of options appropriately prepared; the NAMMD equally acknowledges the importance of monitoring and assessment of its policy for protection and promotion of public health.

To ensure adequate compliance with stakeholders‘ needs (healthcare professionals, pharmaceutical industry, patients, the general public, the media), as well as its capacity for performance of effective regulatory policy, meant to help it reach its main target, namely to safeguard public health, the NAMMD is constantly involved in self-assessment.

From NAMMD perspective, year 2012 has involved:

- Active participation in debates, bimonthly/monthly/biannual meetings of scientific committees and working groups of coordinating European bodies in the field of medicinal products for human use (the European Medicines Agency - EMA, ‘the Heads of Medicines Agencies - HMA, the European Directorate for the Quality of Medicines and Healthcare - EDQM, the European Commission);
- Transposition into national legislation of provisions of Directive EU 2010/84 on new pharmacovigilance approach and Directive EU 2011/62 as regards prevention of the entry into the legal EU supply chain of falsified medicinal products;
- Regulatory work resulting in adoption of NAMMD Scientific Council Decisions and grant of technical support on request by the Ministry of Health;
- Continued implementation of NAMMD strategies: organisational and communication strategies (2011-2015);
- Continued participation to reunions/workshops/conferences/informal meetings with stakeholders, debates on various issues arising in the area of medicinal products for human use;
- Conduct of NAMMD audit by the WHO team on “Strengthening of the national competent authority”, for assessment of the status of the national regulatory system (NRS) in the vaccine field;
- Participation of NAMMD representatives, with specialist papers, to various scientific events, displaying openness towards communication and transparency in the respective area of activity.

The NAMMD has a thoroughly established Quality Management System based on international *standards 9001, 9004, 17025, 19011* etc. in force.

NAMMD top management is involved into Quality Management System activities, at the same time being concerned with implementation of a process-based approach.

The following difficulties have been encountered in conduct of the Agency's activity: under-financing, insufficient human resources, insufficient staff training, communication barriers, low motivation of staff.

To ensure QMS improvement, in October 2012, the WHO external audit team recommended appropriate financing to provide for human resources required for conduct of specific processes, dedicated and specialised human resources, which can only be ensured by means of ongoing training and motivation.

Projects:

- Strengthening of Agency role as regards medicinal product policy – amendment of legislation for establishment of manufacturer and supplier public responsibility and ensurance of Agency capability to enforce penalties in case of non-compliance;
- Ensuring a better understanding of the clinical trial issue;
- Continued participation of NAMMD management representatives to working meetings with representatives of all stakeholders involved in the pharmaceutical market (manufacturers, suppliers, patients);
- Review of Order of the Minister of Health no. 1369/2009 on approval of fees required by the Technical Office for Medical Devices, as amended, for clarification of issues related to travelling expenses;
- Taking the necessary steps to ensure main credit officer understanding of the need for hiring for better control of implementation, at national level, of Law 176/2000 on medical devices, as amended.
- Increased Agency involvement in decision making at European level, by active participation in European working groups, proposal of workable solutions for amendment of current legislation in the medicinal product area, by increased NAMMD integration in medicinal product related issues at European level, rapporteurship, pharmacovigilance assessment, assessment of authorisation documentation at high level of scientific competence as Reference Member State in the context of the decentralised procedure for marketing authorisation.
- Agency involvement in completion of the "SAVEmed Microstructure secured and self-verifying medicines" project, initiated in 2012 by the United Nations Interregional Crime and Justice Research Institute (UNICJRI), through contribution for accomplishment of the two main objectives for our country:
  - Implementation of a SPOC (single point of control) system in Romania, with the General Prosecutor's Office as a national contact point;
  - preparation,, in cooperation with 15 participant countries, of a good practice guideline on communication between the public and private sector for facilitating exchange of information on prevention of entry of falsified medicinal products into the legal supply chain.

The above represent projects requiring more staff specialised in medicinal products for human use and medical devices, as well as more flexibility in the hiring process and last but not least (perhaps by return to self-financing status), a budget allowing direct competition with the other EU competent authorities in medicinal products for human use.

Medicinal product batches recalled during the 2nd quarter of 2014

No.	Product recalled	Pharmaceutical form	Strength	INN	Manufacturer/MAH	Batch	Grounds for recall	Proposed action	Date of recall
1	PANADOL EXTRA	film-coated tablets		COMBINATIONS	SmithKline Dungavan Ltd, Ireland /GSK Consumer Healthcare, GREAT BRITAIN	110471, 110952, 120054, 120283, 120447, 120550, 120867	Expiry of the 2-year deadline (in accordance with Order of the Minister of Health no. 279/2005) following approval by the NAMMD of the variation to MA no. 5550/ 2005/01-07 of 01.03.2012 (trade name printing in Braille)	Voluntary withdrawal and destruction	03.04.2014
2	COLDREX MAXGRIP LEMON	powder for oral suspension (box x 10 sachets)		COMBINATIONS	SmithKline Beecham/GSK Consumer Healthcare S.R.L.	1030, 1031, 1036, 1037, 1047, 1048, 1049, 1050, 1051, 1063, 1064, 1065, 1068, 1069, 1071, 2001, 2010, 2011, 2017, 2018, 2019, 2020, 2021, 2029, 2030, 2031, 2032, 2045, 2046, 2047, 2048, 2049, 2050	Expiry of the 2-year deadline (in accordance with Order of the Minister of Health no. 279/2005) following approval by the NAMMD of the variation to MA no. 3868/2003/02 of 06.03.2012 (trade name printing in Braille)	Voluntary withdrawal and destruction	03.04.2014
3	COLDREX MAXGRIP LEMON	powder for oral suspension (box x 5 sachets)		COMBINATIONS	SmithKline Beecham, SPAIN/ SmithKline Beecham, GREAT BRITAIN	1018, 1043, 2009, 2028	Expiry of the 2-year deadline (in accordance with Order of the Minister of Health no. 279/2005) following approval by the NAMMD of the variation to MA no. 3868/2003/02 of 06.03.2012 (trade name printing in Braille)	Voluntary withdrawal and destruction	03.04.2014

No.	Product recalled	Pharmaceutical form	Strength	INN	Manufacturer/MAH	Batch	Grounds for recall	Proposed action	Date of recall
4	COLDREX LEMON	powder for oral suspension		COMBINATIONS	SmithKline Beecham, SPAIN/ SmithKline Beecham, Great Britain	1069, 1070, 1071, 1072, 1089, 1090, 2006, 1050, 1051, 1063, 1064, 1065, 1068, 1069, 1071, 2001, 2010, 2011, 2017, 2007, 2015, 2016, 2017, 2018, 2022, 2023, 2024, 2025, 2026, 2027, 2034, 2035, 2036, 2042, 2043, 2044	Expiry of the 2-year deadline (in accordance with Order of the Minister of Health no. 279/2005) following approval by the NAMMD of the variation to MA no. 7276/2006/01-02 of 06.03.2012 (trade name printing in Braille)	Voluntary withdrawal and destruction	03.04.2014
5	COLDREX JUNIOR HOTREM	powder for oral suspension		COMBINATIONS	SmithKline Beecham, SPAIN/GSK Consumer Healthcare S.R.L.	1020, 1032, 1052, 2002, 2007, 2017	Expiry of the 2-year deadline (in accordance with Order of the Minister of Health no. 279/2005) following approval by the NAMMD of the variation to MA no. 8193/2006/01-02 of 01.03.2012 (trade name printing in Braille)	Voluntary withdrawal and destruction	03.04.2014
6	PANADOL RAPIDE	film-coated tablets	500 mg	paraceta-molum	GSK Dungavan Ltd, Ireland/GSK Consumer Healthcare, Great Britain	110316, 110364, 110938, 120351	Expiry of the 2-year deadline (in accordance with Order of the Minister of Health no. 279/2005) following approval by the NAMMD of the variation to MA no. 3843/2003/01 of 01.03.2012 (trade name printing in Braille)	Voluntary withdrawal and destruction	03.04.2014
7	GONAL-F 900 IU/1.5 ml	Solution for injection in injection pen	66 µg/ 1.5 ml	follitropinum alfa	Merck Serono, Italy/Merck Serono Europe Ltd	BA016315	Potential microbial contamination	Withdrawal and destruction	14.04.2014
8	SOLPADEINE	effervescent tablets		COMBINATI	GSK Dungarvan Ltd,	105096,	Expiry of the 1-year deadline	Voluntary	22.04.2014

No.	Product recalled	Pharmaceutical form	Strength	INN	Manufacturer/MAH	Batch	Grounds for recall	Proposed action	Date of recall
				ONS	Ireland/Hipocrate Romania	105118, 115080, 125016, 125072	following MA transfer from GSK Consumer Healthcare, GREAT BRITAIN to S.C. Hipocrate 2000 S.R.L.	withdrawal and destruction	
9	TOPAMAX	tablets	25 mg	topiramatum	Janssen-Cilag SPA, Italy/Johnson & Johnson	BKS2N00, BIS3Q00	Expiry of the 2-year deadline (in accordance with Order of the Minister of Health no. 279/2005) following renewal	Voluntary withdrawal and destruction	24.04.2014
10	TOPAMAX	tablets	50 mg	topiramatum	Janssen-Cilag SPA, Italy/Johnson & Johnson	BJS0700	Expiry of the 2-year deadline (in accordance with Order of the Minister of Health no. 279/2005) following renewal	Voluntary withdrawal and destruction	24.04.2014
11	TOPAMAX	tablets	100 mg	topiramatum	Janssen-Cilag SPA, Italy/Johnson & Johnson	BKS3000, BHS4G00	Expiry of the 2-year deadline (in accordance with Order of the Minister of Health no. 279/2005) following renewal	Voluntary withdrawal and destruction	24.04.2014
12	SEROXAT	tablets	20 mg	paroxetinum	SmithKline Beecham Consumer Healthcare, GREAT BRITAIN/GSK Consumer Healthcare S.R.L.	603, 604, 605,	Contamination during the process of obtaining the active substance	Voluntary withdrawal and destruction	25.04.2014
13	VIMPOCETIN	capsules	5 mg	vimpocetinum	S.C. Vimspectrum S.R.L.	09 017	Product for which the 2-year shelf life has expired (in accordance with Order of the Minister of Health no. 279/2005) following renewal on 27.04.2012 (New MA: no. 2012/01-02)	Voluntary withdrawal and destruction	25.04.2014
14	THIOGAMMA 600 INJEKT	concentrate for solution for infusion	600 mg	acidum thiocticum	Solupharm Pharmatzeutische GmbH, GERMANY/ Worwag Pharma GmbH, Germany	All batches	Presence of particles in the solution (found during stability studies)	Withdrawal and destruction	07.05.2014
15	MST CONTINUS	modified-release tablets	10 mg	morphynum	Mundipharma GmbH, GERMANY/Mundipharma GES.M.B.H, Austria	162720, 167035, 168039	Expiry of the 2-year deadline (in accordance with Order of the Minister of Health no. 279/2005) following approval by the	Voluntary withdrawal and destruction	27.05.2014

No.	Product recalled	Pharmaceutical form	Strength	INN	Manufacturer/MAH	Batch	Grounds for recall	Proposed action	Date of recall
							NAMMD of the variation concerning change of the manufacturing site (as of 08.05.2012)		
16	MST CONTINUS	modified-release tablets	30 mg	morphynum	Mundipharma GmbH, GERMANY/Mundipharma GES.M.B.H, Austria	167090, 168040, 169892	Expiry of the 2-year deadline (in accordance with Order of the Minister of Health no. 279/2005) following approval by the NAMMD of the variation concerning change of the manufacturing site (as of 08.05.2012)	Voluntary withdrawal and destruction	27.05.2014
17	MST CONTINUS	modified-release tablets	60 mg	morphynum	Mundipharma GmbH, GERMANY/Mundipharma GES.M.B.H, Austria	167039, 168041, 169461	Expiry of the 2-year deadline (in accordance with Order of the Minister of Health no. 279/2005) following approval by the NAMMD of the variation concerning change of the manufacturing site (as of 08.05.2012)	Voluntary withdrawal and destruction	27.05.2014
18	MST CONTINUS	modified-release tablets	100 mg	morphynum	Mundipharma GmbH, GERMANY/Mundipharma GES.M.B.H, Austria	166509, 167433, 168397	Expiry of the 2-year deadline (in accordance with Order of the Minister of Health no. 279/2005) following approval by the NAMMD of the variation concerning change of the manufacturing site (as of 08.05.2012)	Voluntary withdrawal and destruction	27.05.2014
19	MST CONTINUS	modified-release tablets	200 mg	morphynum	Mundipharma GmbH, GERMANY/Mundipharma GES.M.B.H, Austria	163155, 167096	Expiry of the 2-year deadline (in accordance with Order of the Minister of Health no. 279/2005) following approval by the NAMMD of the variation concerning change of the manufacturing site (as of 08.05.2012)	Voluntary withdrawal and destruction	27.05.2014
20	SEVREDOL	film-coated tablets	10 mg	morphynum	Bard Pharmaceuticals	166911,	Expiry of the 2-year deadline (in	Voluntary	27.05.2014

No.	Product recalled	Pharmaceutical form	Strength	INN	Manufacturer/MAH	Batch	Grounds for recall	Proposed action	Date of recall
					Ltd., GREAT BRITAIN/ Mundipharma GES.M.B.H, Austria	168401, 169884	accordance with Order of the Minister of Health no. 279/2005) following approval by the NAMMD of the variation concerning change of the manufacturing site (as of 08.05.2012)	withdrawal and destruction	
21	SEVREDOL	film-coated tablets	20 mg	morphynum	Bard Pharmaceuticals Ltd., GREAT BRITAIN/ Mundipharma GES.M.B.H, Austria	166858, 167262, 168404, 169003	Expiry of the 2-year deadline (in accordance with Order of the Minister of Health no. 279/2005) following approval by the NAMMD of the variation concerning change of the manufacturing site (as of 08.05.2012)	Voluntary withdrawal and destruction	27.05.2014
22	OXYCONTIN	modified-release tablets	10 mg	morphynum	Bard Pharmaceuticals Ltd., GREAT BRITAIN/ Mundipharma GES.M.B.H, Austria	167495, 166400, 168422, 168753, 169847	Expiry of the 2-year deadline (in accordance with Order of the Minister of Health no. 279/2005) following approval by the NAMMD of the variation concerning change of the manufacturing site (as of 08.05.2012)	Voluntary withdrawal and destruction	27.05.2014
23	OXYCONTIN	modified-release tablets	20 mg	morphynum	Bard Pharmaceuticals Ltd., GREAT BRITAIN/ Mundipharma GES.M.B.H, Austria	165286, 166519, 168746, 170244	Expiry of the 2-year deadline (in accordance with Order of the Minister of Health no. 279/2005) following approval by the NAMMD of the variation concerning change of the manufacturing site (as of 08.05.2012)	Voluntary withdrawal and destruction	27.05.2014
24	OXYCONTIN	modified-release tablets	40 mg	morphynum	Bard Pharmaceuticals Ltd., GREAT BRITAIN/ Mundipharma GES.M.B.H, Austria	163425, 170122	Expiry of the 2-year deadline (in accordance with Order of the Minister of Health no. 279/2005) following approval by the NAMMD of the variation concerning change of the	Voluntary withdrawal and destruction	27.05.2014

No.	Product recalled	Pharmaceutical form	Strength	INN	Manufacturer/MAH	Batch	Grounds for recall	Proposed action	Date of recall
							manufacturing site (08.05.2012)		
25	OXYCONTIN	modified-release tablets	80 mg	morphynum	Bard Pharmaceuticals Ltd., GREAT BRITAIN/ Mundipharma GES.M.B.H, Austria	163925, 168112, 170126	Expiry of the 2-year deadline (in accordance with Order of the Minister of Health no. 279/2005) following approval by the NAMMD of the variation concerning change of the manufacturing site (08.05.2012)	Voluntary withdrawal and destruction	27.05.2014
26	CLARITINE	tablets	10 mg	loratadinum	Schering Plough Labo NV, BELGIUM/Merck Sharp & Dohme Romania SRL	2RXFA07002, 2RXFA09006, 2RXFA10006, 2RXFA18004, 2RXFA20001, 3RXFA20003, 3RXFA28001, 3RXFA33003	Product distributed with previous shelf-life imprinted after expiry of the 6-month period for implementation of the variation on the secondary packaging, approved by the NAMMD on amendment of the shelf life	Voluntary withdrawal and destruction	12.06.2014
27	DIPROSALIC	ointment		COMBINATIONS	Schering Plough Labo NV, Belgium/Merck Sharp & Dohme Romania SRL	1EKDA23003, 2EKDA04002, 2EKDA08002, 2EKDA17001, 2EKDA32004, 3EKDA03001	Product distributed with previous shelf-life imprinted after expiry of the 6-month period for implementation of the variation on the secondary packaging, approved by the NAMMD on amendment of the shelf life	Voluntary withdrawal and destruction	12.06.2014
28	VANCOMICINA ACTAVIS	powder for concentrate for solution for infusion	1000 mg	vancomicinum	Actavis Nordic A/S, DENMARK/Actavis Group PTC ehf, Iceland	5001070, 5001136, 5001210	Potential foreign particles inside the containers	Withdrawal and destruction	23.06.2014
29	PANADOL BABY	oral suspension	120 mg/ 5 ml	COMBINATIONS	Farmaclair FRANCE/ GSK Consumer Healthcare, Great Britain	J183, J184 J185, J202 J221, J223 J205, J207 J220, K014 K015, K016 K033,K034K048 K049 K050 K072 K073,K074K0	Expiry of the 2-year deadline (in accordance with Order of the Minister of Health no. 279/2005) following approval by the NAMMD of the variation to MA no. 8154/2006/01-02 of 07.06.2012 (trade name printing in Braille)	Voluntary withdrawal and destruction	23.06.2014

No.	Product recalled	Pharmaceutical form	Strength	INN	Manufacturer/MAH	Batch	Grounds for recall	Proposed action	Date of recall
						75, K076 K101,K102K100,K124 K125, K126 K158, K159 K160, K162 K164, K191 K192,K204K205,K206K207			
30	COLDREX JUNIOR	tablets		COMBINATIONS	Famar FRANCE/GSK Consumer Healthcare, Great Britain	1034, 1071 2038, 2016	Expiry of the 2-year deadline (in accordance with Order of the Minister of Health no. 279/2005) following approval by the NAMMD of the variation to MA no. 5687/2005/01-02 of 30.05.2012, on update of leaflet information on product labelling	Voluntary withdrawal and destruction	23.06.2014

Applications for marketing authorisation/marketing authorisation renewal submitted to the NAMMD during the 1st quarter of 2014

During the 1st quarter of 2014, 233 applications have been submitted for marketing authorisation/marketing authorisation renewal related to medicinal products, corresponding to the following therapeutic groups:

A02 - Drugs for acid related disorders
A04 – Antiemetics
A07 – Antidiarrheals, intestinal anti-inflammatory/anti-infective agents
A09 – Digestives, including enzymes
A10 – Drugs used in diabetes
A12 – Mineral supplements
B01 – Antithrombotic agents
B02 – Antihemorrhagics
B03 – Antianemic preparations
B05 – Blood substitutes and perfusion solutions
C01 – Cardiac therapy
C03 – Diuretics
C08 – Calcium channel blockers
C09 – Agents acting on the renin-angiotensin system
C10 – Lipid modifying agents
D01 – Antifungals for dermatological use
D06 – Antibiotics and chemotherapeutics for dermatological use
G01 – Gynaecological antiinfectives and antiseptics
G03 – Sex hormones and modulators of the genital system
G04 - Urologicals
H05 – Calcium homeostasis
J01 – Antibacterials for systemic use
J02 – Antimycotics for systemic use
J05 – Antivirals for systemic use
L01 – Antineoplastic agents
L02 – Endocrine therapy
M01 – Anti-inflammatory and antirheumatic products
M02 – Topical products for joint and muscular pain
M05 – Drugs for treatment of bone diseases
N01 – Anesthetics
N02 - Analgezics
N03 - Antiepileptics
N04 – Anti-parkinson drugs
N05 - Psycholeptics
N06 - Psychoanaleptics
N07 – Other nervous system drugs
P02 – Anthelmintics

R01 – Nasal preparations
R03 – Drugs for obstructive airway diseases
R05 – Cough and cold preparations
S01 - Ophthalmologicals
V03 – All other therapeutic products

Medicinal products authorised for marketing by the NAMMD during the 1st quarter of 2014

INN	Invented name	Pharmaceutical form	Strength	Manufacturer	Country	MA number		
ACECLOFENACUM	AFLAMIL 100mg	film-coated tablets	100mg	GEDEON RICHTER ROMANIA S.A.	ROMANIA	6250	2014	02
ACETYLCYSTEINUM	ACC 600 mg FILM-COATED TABLETS EFERVESCENTE	effervescent tablets	600mg	HEXAL AG	GERMANY	6175	2014	01
ACETYLCYSTEINUM	ACC JUNIOR 20 mg/ml	syrup	20mg/ml	HEXAL AG	GERMANY	6174	2014	02
ACICLOVIRUM	ACICLOVIR-RICHTER 200 mg	tablets	200mg	GEDEON RICHTER ROMANIA SA	ROMANIA	6158	2014	01
ACICLOVIRUM	ACICLOVIR-RICHTER 50mg/g	cream	50mg/g	GEDEON RICHTER ROMANIA S.A.	ROMANIA	6168	2014	02
ACIDUM ACETYLSALICYLICUM	ROMPIRIN E 100 mg	gastroresistant tablets	100mg	ANTIBIOTICE SA	ROMANIA	6267	2014	03
ACIDUM ACETYLSALICYLICUM	MIO-ASS 75 mg	gastroresistant tablets	75mg	POLIPHARMA INDUSTRIES S.R.L.	ROMANIA	6107	2014	02
ACIDUM IBANDRONICUM	ACID IBANDRONIC AUROBINDO 150 mg	film-coated tablets	150mg	AUROBINDO PHARMA (MALTA) LIMITED	MALTA	6313	2014	02
ACIDUM RISEDRONICUM	RISEDRONAT SODIC SANDOZ 35 mg	film-coated tablets	35mg	SANDOZ S.R.L.	ROMANIA	6129	2014	16
ACIDUM TIOCTICUM (ALFA-LIPOICUM)	THIOSSEN 600 mg (see A16AX01)	film-coated tablets	600mg	AAA - PHARMA GmbH	GERMANY	6103	2014	03
ACIDUM TIOCTICUM (ALFA-LIPOICUM)	THIOSSEN 600 mg (see N07XN03)	film-coated tablets	600mg	AAA - PHARMA GmbH	GERMANY	6103	2014	03
ACIDUM URSODEOXYCHOLICUM	ACID URSODEOXICOLIC STRIDES 250 mg	capsules	250mg	STRIDES ARCOLAB INTERNATIONAL LIMITED	GREAT BRITAIN	6191	2014	08
ACIDUM ZOLEDRONICUM	FAYTON 4 mg/100 ml	solution for infusion	4mg/100ml	GLENMARK PHARMACEUTICALS S.R.O	THE CZECH REPUBLIC	6130	2014	04
ACIDUM ZOLEDRONICUM	ZERLINDA 4 mg/100 ml	solution for infusion	4mg/100ml	ACTAVIS GROUP PTC EHF.	ICELAND	6135	2014	02

ALANIL-GLUTAMINA	DIPEPTIVEN 200mg/ml	concentrate for solution for infusion	200mg/ml	FRESENIUS KABI AB	SWEDEN	6104	2014	02
ALBUMINUM HUMANUM	ALBIOMIN 50g/l	solution for infusion	50g/l	BIOTEST PHARMA GMBH	GERMANY	6150	2014	01
ALBUMINUM HUMANUM	ALBIOMIN 200g/l	solution for infusion	200g/l	BIOTEST PHARMA GMBH	GERMANY	6151	2014	02
ALBUMINUM HUMANUM	ALBUNORM 50g/l	solution for infusion	50g/l	OCTAPHARMA (IP) LTD.	GREAT BRITAIN	6085	2014	05
ALBUMINUM HUMANUM	ALBUNORM 200g/l	solution for infusion	200g/l	OCTAPHARMA (IP) LTD.	GREAT BRITAIN	6086	2014	04
ALBUMINUM HUMANUM	ALBUNORM 250 g/l	solution for infusion	250g/l	OCTAPHARMA (IP) LTD.	GREAT BRITAIN	6087	2014	02
ALFUZOSINUM	ALFURAN MR 10 mg	prolonged-release tablets	10mg	TERAPIA SA	ROMANIA	6310	2014	01
ALPRAZOLAMUM	ALPRAZOLAM LPH 0.25 mg	tablets	0.25 mg	LABORMED PHARMA S.A.	ROMANIA	6154	2014	03
ALPRAZOLAMUM	ALPRAZOLAM LPH 0.5 mg	tablets	0.5 mg	LABORMED PHARMA S.A.	ROMANIA	6155	2014	03
ALPRAZOLAMUM	ALPRAZOLAM LPH 1 mg	tablets	1mg	LABORMED PHARMA S.A.	ROMANIA	6156	2014	03
ALPRAZOLAMUM	XANAX XR 0.5 mg	prolonged-release tablets	0.5 mg	PFIZER EUROPE MA EEIG	GREAT BRITAIN	6253	2014	02
ANASTROZOLUM	ANASTROZOL TERAPIA 1 mg	film-coated tablets	1mg	TERAPIA S.A.	ROMANIA	6222	2014	08
ANASTROZOLUM	ANASTROZOL MEDISON PHARMA 1 mg	film-coated tablets	1mg	MEDISON PHARMA SRL	ROMANIA	6160	2014	03
ATORVASTATINUM	ATORVASTATIN BEXIMCO PHARMA 10 mg	film-coated tablets	10mg	BEXIMCO PHARMA UK LTD.	GREAT BRITAIN	6296	2014	04
ATORVASTATINUM	ATORVASTATIN BEXIMCO PHARMA 20 mg	film-coated tablets	20mg	BEXIMCO PHARMA UK LTD.	GREAT BRITAIN	6297	2014	04
ATORVASTATINUM	ATORVASTATIN BEXIMCO PHARMA 40 mg	film-coated tablets	40mg	BEXIMCO PHARMA UK LTD.	GREAT BRITAIN	6298	2014	04
ATORVASTATINUM	ATORVASTATINA TORRENT 10 mg	film-coated tablets	10mg	TORRENT PHARMA S.R.L.	GERMANY	6289	2014	017
ATORVASTATINUM	ATORVASTATINA TORRENT 20 mg	film-coated tablets	20mg	TORRENT PHARMA S.R.L.	GERMANY	6290	2014	017

ATORVASTATINUM	ATORVASTATINA TORRENT 40 mg	film-coated tablets	40mg	TORRENT PHARMA S.R.L.	GERMANY	6291	2014	017
ATORVASTATINUM	ATORVASTATINA TORRENT 80 mg	film-coated tablets	80mg	TORRENT PHARMA S.R.L.	GERMANY	6292	2014	07
BENDAMUSTINUM	BENDINFUS 2.5 mg/ml	powder for suspension for infusion	2.5 mg/ml	HELM AG	GERMANY	6223	2014	06
BENDAMUSTINUM	RHOMUSTIN 2.5 mg/ml	powder for suspension for infusion	2.5 mg/ml	HELM AG	GERMANY	6225	2014	06
BENDAMUSTINUM	BENDAMUSTINA HELM 2.5 mg/ml	powder for suspension for infusion	2.5 mg/ml	HELM AG	GERMANY	6224	2014	06
BETAHISTINUM	VERTISAN 24 mg	tablets	24 mg	HENNIG ARZNEIMITTEL GMBH & CO.KG	GERMANY	6133	2014	08
BISOPROLOLUM	BISOBLOCK 5 mg	tablets	5mg	ACTAVIS GROUP PTC ehf	ICELAND	6073	2014	02
BISOPROLOLUM	BISOBLOCK 10 mg	tablets	10mg	ACTAVIS GROUP PTC ehf	ICELAND	6074	2014	02
BISOPROLOLUM	CONCOR 5 mg	film-coated tablets	5mg	MERCK KGAA	GERMANY	6251	2014	01
BISOPROLOLUM	CONCOR 10 mg	film-coated tablets	10mg	MERCK KGAA	GERMANY	6252	2014	01
BISOPROLOLUM	CONCOR COR 5 mg	film-coated tablets	5mg	MERCK KGAA	GERMANY	6095	2014	04
BISOPROLOLUM	CONCOR COR 2.5 mg	film-coated tablets	2.5 mg	MERCK KGAA	GERMANY	6094	2014	04
BISOPROLOLUM	CONCOR COR 10 mg	film-coated tablets	10mg	MERCK KGAA	GERMANY	6096	2014	04
BISOPROLOLUM	SOBYC 2.5 mg	film-coated tablets	2.5 mg	KRKA, D.D., NOVO MESTO	SLOVENIA	6210	2014	10
BISOPROLOLUM	SOBYC 5 mg	film-coated tablets	5mg	KRKA, D.D., NOVO MESTO	SLOVENIA	6211	2014	10
BISOPROLOLUM	SOBYC 10 mg	film-coated tablets	10mg	KRKA, D.D., NOVO MESTO	SLOVENIA	6212	2014	10
CANDESARTANUM CILEXETIL	ATACAND 8 mg	tablets	8mg	ASTRAZENECA AB	SWEDEN	6232	2014	017

CANDESARTANUM CILEXETIL	ATACAND 16 mg	tablets	16mg	ASTRAZENECA AB	SWEDEN	6233	2014	017
CANDESARTANUM CILEXETIL	ATACAND 32 mg	tablets	32mg	ASTRAZENECA AB	SWEDEN	6234	2014	017
CARVEDILOLUM	TALLITON 6.25 mg	tablets	6.25mg	EGIS PHARMACEUTICALS PLC	HUNGARY	6237	2014	01
CARVEDILOLUM	TALLITON 25 mg	tablets	25mg	EGIS PHARMACEUTICALS PLC	HUNGARY	6239	2014	01
CARVEDILOLUM	TALLITON 12.5 mg	tablets	12.5 mg	EGIS PHARMACEUTICALS PLC	HUNGARY	6238	2014	01
CARVEDILOLUM	CARVEDIGAMMA 3,125 mg	film-coated tablets	3,125mg	WORWAG PHARMA GMBH & CO. KG	GERMANY	6204	2014	03
CARVEDILOLUM	CARVEDIGAMMA 6.25 mg	film-coated tablets	6.25mg	WORWAG PHARMA GMBH & CO. KG	GERMANY	6205	2014	03
CARVEDILOLUM	CARVEDIGAMMA 12.5 mg	film-coated tablets	12.5 mg	WORWAG PHARMA GMBH & CO. KG	GERMANY	6206	2014	03
CARVEDILOLUM	CARVEDIGAMMA 25 mg	film-coated tablets	25mg	WORWAG PHARMA GMBH & CO. KG	GERMANY	6207	2014	03
CARVEDILOLUM	GLADYCOR 6.25 mg	tablets	6.25mg	ANTIBIOTICE S.A.	ROMANIA	6181	2014	01
CARVEDILOLUM	GLADYCOR 12.5 mg	tablets	12.5 mg	ANTIBIOTICE S.A.	ROMANIA	6182	2014	01
CARVEDILOLUM	GLADYCOR 25 mg	tablets	25mg	ANTIBIOTICE S.A.	ROMANIA	6183	2014	01
CEFAZOLINUM	CEFAZOLIN IPP 2 g	powder for solution for injection/infusion	2g	IPP INTERNATIONAL PHARMA PARTNERS GMBH	GERMANY	6314	2014	06
CEFTAZIDIMUM	CEFTAMIL 1 g	powder for solution for injection/infusion	1g	ANTIBIOTICE S.A.	ROMANIA	6072	2014	03
CEFTRIAXONUM	CEFORT 500 mg	powder for solution for injection/infusion	500mg	ANTIBIOTICE SA	ROMANIA	6269	2014	08
CEFTRIAXONUM	CEFORT 2 g	powder for solution for injection/infusion	2g	ANTIBIOTICE SA	ROMANIA	6271	2014	08
CEFTRIAXONUM	CEFORT 250 mg	powder for	250mg	ANTIBIOTICE SA	ROMANIA	6268	2014	08

		solution for injection/infusion						
CEFTRIAXONUM	CEFORT 1 g	powder for solution for injection/infusion	1g	ANTIBIOTICE SA	ROMANIA	6270	2014	012
CEFUROXIMUM	CEFUROXIMA ATB 250 mg	tablets	250mg	ANTIBIOTICE S.A.	ROMANIA	6287	2014	02
CEFUROXIMUM	CEFUROXIMA ATB 500 mg	tablets	500mg	ANTIBIOTICE S.A.	ROMANIA	6288	2014	02
CELECOXIBUM	ACLEXA 100 mg	capsules	100mg	KRKA, D.D., NOVO MESTO	SLOVENIA	6148	2014	08
CELECOXIBUM	ACLEXA 200 mg	capsules	200mg	KRKA, D.D., NOVO MESTO	SLOVENIA	6149	2014	08
CELECOXIBUM	CALIDEM 100 mg	capsules	100mg	EGIS PHARMACEUTICALS PLC	HUNGARY	6197	2014	08
CELECOXIBUM	CALIDEM 200 mg	capsules	200mg	EGIS PHARMACEUTICALS PLC	HUNGARY	6198	2014	08
CELECOXIBUM	CELETOR 100 mg	capsules	100mg	TORRENT PHARMA SRL	ROMANIA	6218	2014	013
CELECOXIBUM	CELETOR 200 mg	capsules	200mg	TORRENT PHARMA SRL	ROMANIA	6219	2014	013
CILOSTAZOLUM	PLADIZOL 100 mg	tablets	100mg	GLENMARK PHARMACEUTICALS S.R.O.	THE CZECH REPUBLIC	6134	2014	01
CILOSTAZOLUM	CILOSTAZOL TEVA 100 mg	tablets	100mg	TEVA PHARMACEUTICALS S.R.L.	ROMANIA	6192	2014	012
CILOSTAZOLUM	VELYN 50 mg	tablets	50mg	TERAPIA SA	ROMANIA	6275	2014	010
CILOSTAZOLUM	VELYN 100 mg	tablets	100mg	TERAPIA SA	ROMANIA	6276	2014	010
CINOLAZEPAMUM	GERODORM 40 mg	tablets	40mg	GEROT PHARMAZEUTIKA G.M.B.H	AUSTRIA	6228	2014	012
CLONAZEPAMUM	RIVOTRIL 0.5 mg	tablets	0.5 mg	ROCHE ROMANIA S.R.L.	ROMANIA	6229	2014	01
COMBINATIONS	NEODOLPASSE 0.30 mg+0.12 mg/ml	solution for infusion	0.30mg+ 0.12mg/ml	FRESENIUS KABI AUSTRIA GMBH	AUSTRIA	6185	2014	03
COMBINATIONS	MILGAMMA 100+100 mg	lozenges	100+100 mg	WORWAG PHARMA GMBH & CO. KG	GERMANY	6226	2014	03

COMBINATIONS	CALCIU D3 FORTE 1000 mg/800 IU	chewable tablets	1000mg/ 800UI	TAKEDA NYCOMED AS	NORWAY	6110	2014	014
COMBINATIONS	SOLUTIE CONTRA AFTELOR BUCALE 2.425 mg/21.34 mg/ml	oromucosal drops, solution	2.425mg/ 21.34mg/ml	MEDUMAN S.A.	ROMANIA	6209	2014	01
COMBINATIONS	STREPSILS MENTA	candies		RECKITT BENCKISER HEALTHCARE INTERNATIONAL LTD.	GREAT BRITAIN	6311	2014	02
COMBINATIONS (BECLOMETASONUM+ FORMOTEROLUM)	FOSTER NEXTHALER 100/6 micrograms per dose	inhalation powder	100/6micrograms per dose	CHIESI PHARMACEUTICALS GMBH	AUSTRIA	6161	2014	03
COMBINATIONS (CANDESARTANUM CILEXETIL+HCT)	CANDISIL 8 mg/12.5 mg	tablets	8mg/12.5 mg	LABORATORIOS LICONSA, S.A.	SPAIN	6115	2014	014
COMBINATIONS (CANDESARTANUM CILEXETIL+HCT)	CANDISIL 16 mg/12.5 mg	tablets	16mg/12.5 mg	LABORATORIOS LICONSA, S.A.	SPAIN	6116	2014	014
COMBINATIONS (CANDESARTANUM CILEXETIL+HCT)	CANDISIL 32 mg/12.5 mg	tablets	32mg/12.5 mg	LABORATORIOS LICONSA, S.A.	SPAIN	6117	2014	014
COMBINATIONS (CANDESARTANUM CILEXETIL+HCT)	CANDISIL 32 mg/25 mg	tablets	32mg/25mg	LABORATORIOS LICONSA, S.A.	SPAIN	6118	2014	014
COMBINATIONS (DIENOGESTUM+ ETINILESTRADIOLUM)	SIBILLA ZILNIC 2 mg/0.03 mg (see G03HB)	film-coated tablets	2mg/0.03 mg	GEDEON RICHTER ROMANIA S.A.	ROMANIA	6202	2014	03
COMBINATIONS (DIENOGESTUM+ ETINILESTRADIOLUM)	SIBILLA ZILNIC 2 mg/0.03 mg (see G03AA)	film-coated tablets	2mg/0.03 mg	GEDEON RICHTER ROMANIA S.A.	ROMANIA	6202	2014	03
COMBINATIONS (GESTODENUM+ ETINILESTRADIOLUM)	MINELLA 60 micrograms/15 micrograms	film-coated tablets	60micrograms/ 15micrograms	TEVA PHARMACEUTICALS S.R.L.	ROMANIA	6266	2014	03
COMBINATIONS (IBUPROFENUM+ CODEINUM)	IBUPROFEN/CODEINA FOSFAT ROCKSPRING 400 mg/30 mg	film-coated tablets	400mg/30mg	ROCKSPRING HEALTHCARE LIMITED	GREAT BRITAIN	6147	2014	01
COMBINATIONS (INDAPAMIDUM+ AMLODIPINUM)	NATRIXAM 1.5 mg/5 mg	modified-release tablets	1.5 mg/5mg	LES LABORATOIRES SERVIER	FRANCE	6125	2014	06

COMBINATIONS (INDAPAMIDUM+ AMLODIPINUM)	NATRIXAM 1.5 mg/10 mg	modified-release tablets	1.5 mg/10mg	LES LABORATOIRES SERVIER	FRANCE	6126	2014	06
COMBINATIONS (INDAPAMIDUM+ AMLODIPINUM)	FLUDEXAM 1.5 mg/5 mg	modified-release tablets	1.5 mg/5mg	LES LABORATOIRES SERVIER	FRANCE	6127	2014	06
COMBINATIONS (INDAPAMIDUM+ AMLODIPINUM)	FLUDEXAM 1.5 mg/10 mg	modified-release tablets	1.5 mg/10mg	LES LABORATOIRES SERVIER	FRANCE	6128	2014	06
COMBINATIONS (LIPIDS)	SMOFlipid 200 g/1000 ml	emulsion for infusion	200g/1000ml	FRESENIUS KABI AB	SWEDEN	6105	2014	06
COMBINATIONS (PERINDOPRILUM+ AMLODIPINUM+ INDAPAMIDUM)	CO-AMLESSA 2 mg/5 mg/0.625 mg	tablets	2mg/5mg/ 0.625mg	KRKA, D.D., NOVO MESTO	SLOVENIA	6141	2014	09
COMBINATIONS (PERINDOPRILUM+ AMLODIPINUM+ INDAPAMIDUM)	CO-AMLESSA 4 mg/10 mg/1.25 mg	tablets	4mg/10mg/ 1.25 mg	KRKA, D.D., NOVO MESTO	SLOVENIA	6142	2014	09
COMBINATIONS (PERINDOPRILUM+ AMLODIPINUM+ INDAPAMIDUM)	CO-AMLESSA 4 mg/1.25 mg/10 mg	tablets	4mg/1.25 mg/ 10mg	KRKA, D.D., NOVO MESTO	SLOVENIA	6143	2014	09
COMBINATIONS (PERINDOPRILUM+ AMLODIPINUM+ INDAPAMIDUM)	CO-AMLESSA 8 mg/5 mg/2.5 mg	tablets	8mg/5mg/2.5 mg	KRKA, D.D., NOVO MESTO	SLOVENIA	6144	2014	09
COMBINATIONS (PERINDOPRILUM+ AMLODIPINUM+ INDAPAMIDUM)	CO-AMLESSA 8 mg/10 mg/2.5 mg	tablets	8mg/10mg/ 2.5 mg	KRKA, D.D., NOVO MESTO	SLOVENIA	6145	2014	09
COMBINATIONS (SPIRONOLACTONUM+ FUROSEMIDUM)	DIOCOR 50 mg/20 mg	capsules	50mg/20mg	SANIENCE S.R.L.	ROMANIA	6255	2014	03
COMBINATIONS (TELMISARTANUM+ HYDROCHLOROTHIAZIDUM)	TELMISARTAN/HIDROCLOROTIAZIDA TERAPIA 80 mg/12.5 mg	tablets	80mg/12.5 mg	TERAPIA S.A.	ROMANIA	6067	2014	021

COMBINATIONS (TELMISARTANUM+ HYDROCHLOROTHIAZIDUM)	TELMISARTAN/HIDROCLOROTIAZIDA TERAPIA 80 mg/25 mg	tablets	80mg/25mg	TERAPIA S.A.	ROMANIA	6068	2014	021
COMBINATIONS (TELMISARTANUM+ HYDROCHLOROTHIAZIDUM)	TELMISARTAN/HIDROCLOROTIAZIDA TERAPIA 40 mg/12.5 mg	tablets	40mg/12.5 mg	TERAPIA S.A.	ROMANIA	6066	2014	021
COMBINATIONS (TRAMADOLUM+ PARACETAMOLUM)	TRAUMOBOL 37.5mg/325mg	capsules	37.5mg/325mg	ROMPHARM COMPANY S.R.L.	ROMANIA	6078	2014	02
IRON (III) COMPLEX - ISOMALTOSE	DIAFER 50 mg/ml	solution for injection	50 mg/ml	PHARMACOSMOS A/S	DENMARK	6263	2014	04
DEXLANSOPRAZOLUM	DEXILANT 30 mg	modified-release capsules	30mg	TAKEDA PHARMA A/S	DENMARK	6090	2014	02
DEXLANSOPRAZOLUM	DEXILANT 60 mg	modified-release capsules	60mg	TAKEDA PHARMA A/S	DENMARK	6091	2014	02
DEXLANSOPRAZOLUM	DEXLANSOPRAZOL TAKEDA 30 mg	modified-release capsules	30mg	TAKEDA PHARMA A/S	DENMARK	6092	2014	02
DEXLANSOPRAZOLUM	DEXLANSOPRAZOL TAKEDA 60 mg	modified-release capsules	60mg	TAKEDA PHARMA A/S	DENMARK	6093	2014	02
DICLOFENACUM	DICLOFENAC SINTOFARM 12.5 mg	suppositories	12.5 mg	SINTOFARM S.A.	ROMANIA	6077	2014	02
DIDANOSINUM	DIDANOZINA AUROBINDO 250 mg	gastroresistant capsules	250mg	AUROBINDO PHARMA (MALTA) LIMITED	MALTA	6164	2014	04
DIDANOSINUM	DIDANOZINA AUROBINDO 400 mg	gastroresistant capsules	400mg	AUROBINDO PHARMA (MALTA) LIMITED	MALTA	6165	2014	05
DIVERSE	APA PENTRU PREPARATE INJECTABILE B. BRAUN	solvent for parenteral use		B. BRAUN MELSUNGEN AG	GERMANY	6248	2014	03
DONEPEZILUM	DONEPEZIL TEVA 5 mg	orodispersible tablets	5mg	TEVA PHARMACEUTICALS S.R.L.	ROMANIA	6079	2014	010
DONEPEZILUM	DONEPEZIL TEVA 10 mg	orodispersible tablets	10mg	TEVA PHARMACEUTICALS S.R.L.	ROMANIA	6080	2014	010
DOXAZOSINUM	DOXAZOSIN PFIZER 4 mg	prolonged-release tablets	4mg	PFIZER EUROPE MA EEIG	GREAT BRITAIN	6193	2014	012

EPINEPHRINUM	EPIPEN 150 micrograms	solution for injection in pre-filled pen	150micrograms	MEDA PHARMA GMBH & CO.KG	GERMANY	6111	2014	02
EPINEPHRINUM	EPIPEN 300 micrograms	solution for injection in pre-filled pen	300micrograms	MEDA PHARMA GMBH & CO.KG	GERMANY	6112	2014	02
ESOMEPRAZOLUM	ESOMEPRAZOL LABORMED 20 mg	gastroresistant tablets	20mg	LABORMED PHARMA S.A.	ROMANIA	6220	2014	03
ESOMEPRAZOLUM	ESOMEPRAZOL LABORMED 40 mg	gastroresistant tablets	40mg	LABORMED PHARMA S.A.	ROMANIA	6221	2014	03
ETHAMBUTOLUM	ETAMBUTOL ARENA 250 mg	capsules	250mg	ARENA GROUP S.A.	ROMANIA	6121	2014	01
ETONOGESTRELUM	NEXPLANON 68 mg	implant	68mg	N.V. ORGANON	HOLLAND	6256	2014	01
EXEMESTANUM	AROMASIN 25 mg	lozenges	25mg	PFIZER EUROPE MA EEIG	GREAT BRITAIN	6157	2014	01
EZETIMIBUM	EZETROL 10 mg	tablets	10mg	MERCK SHARP & DOHME ROMANIA S.R.L.	ROMANIA	6315	2014	03
EZETIMIBUM	LIPOBON 10 mg	tablets	10mg	EGIS PHARMACEUTICALS PLC.	HUNGARY	6213	2014	03
EZETIMIBUM	EZETIMIB SANDOZ 10 mg	tablets	10mg	SANDOZ S.R.L.	ROMANIA	6261	2014	029
VIII CLOTTING FACTOR	HAEMOCTIN SDH 250	powder and solvent for solution for injection	50IU/ml	BIOTEST PHARMA GMBH	GERMANY	6199	2014	01
VIII CLOTTING FACTOR	HAEMOCTIN SDH 500	powder and solvent for solution for injection	50IU/ml	BIOTEST PHARMA GMBH	GERMANY	6200	2014	01
VIII CLOTTING FACTOR	HAEMOCTIN SDH 1000	powder and solvent for solution for injection	100IU/ml	BIOTEST PHARMA GMBH	GERMANY	6201	2014	01
FENOFIBRATUM	FENOFIBRAT TEVA 160 mg	film-coated tablets	160mg	TEVA PHARMACEUTICALS S.R.L.	ROMANIA	6099	2014	012
FLECAINIDUM	JUNEFLECAD 50 mg	prolonged-release capsules	50mg	LABORATORIOS LICONSA, S.A.	SPAIN	6186	2014	02

FLECAINIDUM	JUNEFLECAD 100 mg	prolonged-release capsules	100mg	LABORATORIOS LICONSA, S.A.	SPAIN	6187	2014	02
FLECAINIDUM	JUNEFLECAD 150 mg	prolonged-release capsules	150mg	LABORATORIOS LICONSA, S.A.	SPAIN	6188	2014	02
FLECAINIDUM	JUNEFLECAD 200 mg	prolonged-release capsules	200mg	LABORATORIOS LICONSA, S.A.	SPAIN	6189	2014	02
FLUCONAZOLUM	DIFLUCAN 2mg/ml	solution for infusion	2mg/ml	PFIZER EUROPE MA EEIG	GREAT BRITAIN	6166	2014	012
GEMCITABINUM	GEMCITABINA EBEWE 200 mg	powder for solution for infusion	200mg	EBEWE PHARMA GES.M.B.H. NFG. KG	AUSTRIA	6264	2014	02
GEMCITABINUM	GEMCITABINA EBEWE 1000 mg	powder for solution for infusion	1000mg	EBEWE PHARMA GES.M.B.H. NFG. KG	AUSTRIA	6265	2014	02
GEMCITABINUM	GEMCITABINA SUN 200 mg	powder for solution for infusion	200mg	SUN PHARMACEUTICAL INDUSTRIES EUROPE B.V.	HOLLAND	6277	2014	01
GEMCITABINUM	GEMCITABINA SUN 1 g	powder for solution for infusion	1g	SUN PHARMACEUTICAL INDUSTRIES EUROPE B.V.	HOLLAND	6278	2014	01
GEMCITABINUM	GEMCITABINA TEVA 200 mg	powder for solution for infusion	200mg	TEVA PHARMACEUTICALS S.R.L.	ROMANIA	6169	2014	03
GEMCITABINUM	GEMCITABINA TEVA 1000 mg	powder for solution for infusion	1000mg	TEVA PHARMACEUTICALS S.R.L.	ROMANIA	6170	2014	03
GEMCITABINUM	GEMCITABINA TEVA 2000 mg	powder for solution for infusion	2000mg	TEVA PHARMACEUTICALS S.R.L.	ROMANIA	6171	2014	03
GLICLAZIDUM	ESQUEL 80 mg	tablets	80mg	GEDEON RICHTER ROMANIA S.A.	ROMANIA	6075	2014	01
GRANISETRONUM	GRANISETRON TEVA 1mg/1ml	concentrate for solution for infusion/injection	1mg/1ml	TEVA PHARMACEUTICALS S.R.L.	ROMANIA	6088	2014	06
GRANISETRONUM	GRANISETRON TEVA 3mg/3ml	concentrate for solution for infusion/injection	3mg/3ml	TEVA PHARMACEUTICALS S.R.L.	ROMANIA	6089	2014	06

IBUPROFENUM	ALGIN BABY 100 mg/5 ml	oral suspension	100mg/5ml	ZENTIVA, K.S.	THE CZECH REPUBLIC	6254	2014	02
IBUPROFENUM	REUPROFEN 200 mg	film-coated tablets	200mg	AC HELCOR S.R.L.	ROMANIA	6113	2014	02
IBUPROFENUM	REUPROFEN 400 mg	film-coated tablets	400mg	AC HELCOR S.R.L.	ROMANIA	6114	2014	01
IBUPROFENUM	NUROFEN IMMEDIA ULTRA 400 mg	lozenges	400mg	RECKITT BENCKISER HEALTHCARE INTERNATIONAL LTD.	GREAT BRITAIN	6139	2014	06
IBUPROFENUM	NUROFEN EXPRESS 200 mg	lozenges	200mg	RECKITT BENCKISER HEALTHCARE INTERNATIONAL LTD.	GREAT BRITAIN	6140	2014	010
IBUPROFENUM	IBUPROFEN BANNER PT. COPII PESTE 7 ANI 100 mg	chewable soft capsules	100mg	BANNER PHARMACAPS EUROPE B.V.	HOLLAND	6146	2014	016
INDAPAMIDUM	INDAPAMID LPH 2.5 mg	film-coated tablets	2.5 mg	LABORMED PHARMA S.A.	ROMANIA	6303	2014	02
INDAPAMIDUM	INDAPAMID LPH 1.5 mg	prolonged-release tablets	1.5 mg	LABORMED PHARMA S.A.	ROMANIA	6302	2014	02
INDAPAMIDUM	INDAPAMIDA SOPHARMA 1.5 mg	prolonged-release tablets	1.5 mg	SOPHARMA PLC	BULGARIA	6065	2014	01
INTERFERONUM ALFA 2a	ROFERON-A 3 million IU/0.5 ml	solution for injection	3million IU/ 0.5 ml	ROCHE ROMANIA S.R.L.	ROMANIA	6285	2014	01
INTERFERONUM ALFA 2a	ROFERON-A 9 million IU/0.5 ml	solution for injection	9million IU/ 0.5 ml	ROCHE ROMANIA S.R.L.	ROMANIA	6286	2014	01
IRBESARTANUM	IRBESARTAN HF 150 mg	film-coated tablets	150mg	STADA HEMOFARM S.R.L.	ROMANIA	6299	2014	09
IRBESARTANUM	IRBESARTAN HF 300 mg	film-coated tablets	300mg	STADA HEMOFARM S.R.L.	ROMANIA	6300	2014	011
IRBESARTANUM	IRBESARTAN TERAPIA 150 mg	film-coated tablets	150mg	TERAPIA S.A.	ROMANIA	6306	2014	09
IRBESARTANUM	IRBESARTAN TERAPIA 300 mg	film-coated tablets	300mg	TERAPIA S.A.	ROMANIA	6307	2014	09
IRBESARTANUM	IRBESARTAN SANDOZ	film-coated	150mg	SANDOZ S.R.L.	ROMANIA	6308	2014	030

	150 mg	tablets						
IRBESARTANUM	IRBESARTAN SANDOZ 300 mg	film-coated tablets	300mg	SANDOZ S.R.L.	ROMANIA	6309	2014	030
KETOPROFENUM	PROFENID LP 200 mg	prolonged-release tablets	200mg	LABORATOIRE AVENTIS	FRANCE	6215	2014	01
KETOPROFENUM	PROFENID 100 mg intramuscular	powder and solvent for solution for injection	100mg	LABORATOIRE AVENTIS	FRANCE	6214	2014	01
LEVOFLOXACINUM	LEVOFLOXACIN KABI 5 mg/ml	solution for infusion	5mg/ml	FRESENIUS KABI ROMANIA SR.L.	ROMANIA	6167	2014	010
LEVOFLOXACINUM	LEVOFLOXACINA ARENA 250 mg	film-coated tablets	250mg	ARENA GROUP S.A.	ROMANIA	6179	2014	02
LEVOFLOXACINUM	LEVOFLOXACINA ARENA 500 mg	film-coated tablets	500mg	ARENA GROUP S.A.	ROMANIA	6180	2014	02
LINEZOLIDUM	PNEUMOLID 2 mg/ml	solution for infusion	2mg/ml	ALVOGEN IPCO S.AR.L	LUXEMBURG	6301	2014	012
LOPINAVIRUM+ RITONAVIRUM	LOPINAVIR/RITONAVIR TERAPIA 200mg/50 mg	film-coated tablets	200mg/50mg	TERAPIA S.A.	ROMANIA	6293	2014	04
LORATADINUM	SYMPHORAL 10 mg	tablets	10mg	GEDEON RICHTER ROMANIA S.A.	ROMANIA	6076	2014	01
MEMANTINUM	MEMANTINA POLIPHARMA 10 mg	film-coated tablets	10 mg	POLIPHARMA INDUSTRIES S.R.L.	ROMANIA	6069	2014	015
MEMANTINUM	MEMANTINA POLIPHARMA 5mg+10mg+15mg+20mg	film-coated tablets	5mg/10mg/ 15mg/20mg	POLIPHARMA INDUSTRIES S.R.L.	ROMANIA	6071	2014	01
MEMANTINUM	MEMANTINA POLIPHARMA 20 mg	film-coated tablets	20 mg	POLIPHARMA INDUSTRIES S.R.L.	ROMANIA	6070	2014	015
MEMANTINUM	MEMANTINA CHANELLE 10 mg/ml	oral solution	10mg/ml	CHANELLE MEDICAL	IRLANDA	6190	2014	06
MEMANTINUM	MEMANTINA LANNACHER HEILMITTEL 20 mg	film-coated tablets	20mg	LANNACHER HEILMITTEL GES.M.B.H.	AUSTRIA	6295	2014	014
MEMANTINUM	MEMANTINA LANNACHER HEILMITTEL 10 mg	film-coated tablets	10mg	LANNACHER HEILMITTEL GES.M.B.H.	AUSTRIA	6294	2014	014
MEROPENEMUM	MEROPENEM SANDOZ 500 mg	powder for solution for	500 mg	SANDOZ S.R.L.	ROMANIA	6172	2014	02

		injection/infusion						
MEROPENEMUM	MEROPENEM SANDOZ 1g	powder for solution for injection/infusion	1g	SANDOZ S.R.L.	ROMANIA	6173	2014	02
METAMIZOLUM NATRIUM	CENTRALGIN 500 mg	tablets	500mg	CENTROFARM S.A.	ROMANIA	6153	2014	01
METHYLFENIDATUM	MEDIKINET EM 10 mg	modified-release capsules	10mg	MEDICE ARZNEIMITTEL PUTTER GMBH & CO.KG	GERMANY	6241	2014	02
METHYLFENIDATUM	MEDIKINET EM 20 mg	modified-release capsules	20mg	MEDICE ARZNEIMITTEL PUTTER GMBH & CO.KG	GERMANY	6242	2014	02
METHYLFENIDATUM	MEDIKINET EM 30 mg	modified-release capsules	30mg	MEDICE ARZNEIMITTEL PUTTER GMBH & CO.KG	GERMANY	6243	2014	02
METHYLFENIDATUM	MEDIKINET EM 40 mg	modified-release capsules	40mg	MEDICE ARZNEIMITTEL PUTTER GMBH & CO.KG	GERMANY	6244	2014	02
METOCLOPRAMIDUM	METOCLOPRAMID ARENA 10 mg	tablets	10mg	ARENA GROUP S.A.	ROMANIA	6216	2014	01
MISOPROSTOLUM	MISODEL 200 micrograms	vaginal delivery system	200micrograms	FERRING GMBH	GERMANY	6162	2014	03
MOMETASONUM	KALMENTE 50 micrograms/dose	nasal spray, suspension	50micrograms/ dose	ALVOGEN IPCO S.AR.L.	LUXEMBURG	6257	2014	03
MONTELUKASTUM	MONTELUKAST MYLAN 4 mg	chewable tablets	4 mg	GENERICS (UK) LTD	GREAT BRITAIN	6272	2014	019
MONTELUKASTUM	MONTELUKAST MYLAN 5 mg	chewable tablets	5 mg	GENERICS (UK) LTD	GREAT BRITAIN	6273	2014	019
MOXIFLOXACINUM	MOFIL 400 mg	film-coated tablets	400mg	ACTAVIS GROUP PTC EHF.	ICELAND	6159	2014	09
MOXIFLOXACINUM	MOXIFLOXACINA PHARMATHEN 5 mg/ml	eye drops, solution	5mg/ml	PHARMATHEN S.A.	GREECE	6203	2014	01

NALOXONUM	NEXODAL 0,4 mg/ml	solution for injection	0.4 mg/ml	ORPHA-DEVEL HANDELS UND VERTRIEBS GMBH	AUSTRIA	6064	2014	01
NEBIVOLOLUM	NEBIVOLOL TEVA 5 mg	tablets	5mg	TEVA PHARMACEUTICALS S.R.L.	ROMANIA	6132	2014	016
OFLOXACINUM	ZANOCIN 200 mg	film-coated tablets	200mg	RANBAXY (U.K.) LIMITED	GREAT BRITAIN	6230	2014	01
OLOPATADINUM	OLOPATADINA ZENTIVA 1 mg/ml	eye drops, solution	1mg/ml	ZENTIVA K.S.	THE CZECH REPUBLIC	6260	2014	01
OMEPRAZOLUM	OMEZ 40 mg	powder for solution for infusion	40mg	DR. REDDY'S LABORATORIES ROMANIA S.R.L.	ROMÂNIA	6227	2014	01
OXACILLINUM	OXACILINA ATB 500 mg	powder for solution for injection/infusion	500mg	ANTIBIOTICE S.A.	ROMANIA	6119	2014	03
OXACILLINUM	OXACILINA ATB 1000 mg	powder for solution for injection/infusion	1000mg	ANTIBIOTICE SA	ROMANIA	6120	2014	03
OXALIPLATINUM	XOPLAN 5 mg/ml	powder for solution for infusion	5mg/ml	NEOLA PHARMA S.R.L.	ROMANIA	6136	2014	02
OXYBUPROCAINI HYDROCHLORIDUM	OFTACAIN 4 mg/ml	eye drops, solution	4mg/ml	ROMPHARM COMPANY S.R.L.	ROMANIA	6178	2014	01
OXYCODONUM	OXIDOLOR 5 mg	prolonged-release tablets	5mg	LANNACHER HEILMITTEL GES.M.B.H.	AUSTRIA	6280	2014	09
OXYCODONUM	OXIDOLOR 10 mg	prolonged-release tablets	10mg	LANNACHER HEILMITTEL GES.M.B.H.	AUSTRIA	6281	2014	09
OXYCODONUM	OXIDOLOR 20 mg	prolonged-release tablets	20mg	LANNACHER HEILMITTEL GES.M.B.H.	AUSTRIA	6282	2014	09
OXYCODONUM	OXIDOLOR 40 mg	prolonged-release tablets	40mg	LANNACHER HEILMITTEL GES.M.B.H.	AUSTRIA	6283	2014	09
OXYCODONUM	OXIDOLOR 80 mg	prolonged-release tablets	80mg	LANNACHER HEILMITTEL GES.M.B.H.	AUSTRIA	6284	2014	09

PANCREATINUM	MEZYM 25000	capsules with mini-gastroresistant tablets	356.100mg	BERLIN-CHEMIE AG (MENARINI GROUP)	GERMANY	6106	2014	03
PANTOPRAZOLUM	PANTOPRAZOL CIPLA 20 mg	gastroresistant tablets	20mg	CIPLA UK LIMITED	GREAT BRITAIN	6083	2014	01
PANTOPRAZOLUM	PANTOPRAZOL CIPLA 40 mg	gastroresistant tablets	40mg	CIPLA UK LIMITED	GREAT BRITAIN	6084	2014	01
PANTOPRAZOLUM	PANTOPRAZOL MACLEODS 20 mg	gastroresistant tablets	20mg	MACLEODS PHARMA UK LIMITED	GREAT BRITAIN	6217	2014	01
PANTOPRAZOLUM	NOLPAZAL 20 mg	gastroresistant tablets	20mg	KRKA D.D., NOVO MESTO	SLOVENIA	6312	2014	03
PARACETAMOLUM	PARACETAMOL CENTROFARM 500 mg	tablets	500mg	CENTROFARM S.A.	ROMANIA	6152	2014	02
PARACETAMOLUM	PANADOL ARTRO 665 mg	prolonged-release tablets	665mg	GLAXOSMITHKLINE EXPORT LIMITED	GREAT BRITAIN	6231	2014	04
PARACETAMOLUM	PARACETAMOL SANDOZ 10 mg/ml	solution for infusion	10mg/g	SANDOZ S.R.L.	ROMANIA	6274	2014	02
PARICALCITOLUM	PARICALCITOL SANDOZ 2 micrograms/ml	solution for injection	2micrograms/ml	SANDOZ S.R.L.	ROMANIA	6258	2014	02
PARICALCITOLUM	PARICALCITOL SANDOZ 5 micrograms/ml	solution for injection	5micrograms/ml	SANDOZ S.R.L.	ROMANIA	6259	2014	02
PERINDOPRILUM	PRINDEX 4 mg	tablets	4mg	GLENMARK PHARMACEUTICALS S.R.O.	THE CZECH REPUBLIC	6108	2014	06
PERINDOPRILUM	PRINDEX 8 mg	tablets	8mg	GLENMARK PHARMACEUTICALS S.R.O.	THE CZECH REPUBLIC	6109	2014	06
PHENYLBUTAZONUM	FENILBUTAZONA FITERMAN 40mg/g	cream	40mg/g	FITERMAN PHARMA S.R.L.	ROMANIA	6184	2014	02
PIMECROLIMUS	ELIDEL 10 mg/g	cream	10mg/g	MEDA PHARMA GMBH & CO.KG	GERMANY	6063	2014	05
PIPERACILLINUM + TAZOBACTAMUM	PIPERACILLIN/TAZOBACTAM KABI 2g/0.25 g	powder for solution for infusion	2g/0.25g	S.C. FRESENIUS KABI S.R.L.	ROMANIA	6097	2014	06
PIPERACILLINUM + TAZOBACTAMUM	PIPERACILLIN/TAZOBACTAM KABI 4g/0.50 g	powder for solution for	4g/0.50g	S.C. FRESENIUS KABI S.R.L.	ROMANIA	6098	2014	03

		infusion						
PIRACETAMUM	PIRACETAM-RICHTER 800 mg	film-coated tablets	800mg	GEDEON RICHTER ROMANIA S.A.	ROMANIA	6123	2014	01
PIRACETAMUM	PIRACETAM-RICHTER 400 mg	film-coated tablets	400mg	GEDEON RICHTER ROMANIA S.A.	ROMANIA	6122	2014	01
PIROXICAMUM	HOTEMIN	solution for injection	20mg/ml	EGIS PHARMACEUTICALS PLC	HUNGARY	6208	2014	01
RETINOLUM	VITAMINA A FORTE BIOFARM 50000 IU	soft capsules	50000 IU	BIOFARM SA	ROMANIA	6249	2014	01
SALMETEROLUM	AIRFLUSAL FORSPIRO 50 micrograms/ 500 micrograms/dose	single-dose powder for inhalation	500micrograms/ 500micrograms/ dose	SANDOZ S.R.L.	ROMANIA	6124	2014	07
SERTRALINUM	SERTRALINA CEFT 50 mg	film-coated tablets	50mg	CEFT LIMITED	GREAT BRITAIN	6176	2014	013
SERTRALINUM	SERTRALINA CEFT 100 mg	film-coated tablets	100mg	CEFT LIMITED	GREAT BRITAIN	6177	2014	013
TAFLUPROSTUM	SAFLUTAN 15 micrograms/ml	eye drops, solution, single dose vial	15micrograms/ ml	MERCK SHARP & DOHME ROMANIA S.R.L.	ROMANIA	6131	2014	02
TOPIRAMATUM	TORLEPTA 25 mg	film-coated tablets	25mg	GLENMARK PHARMACEUTICALS s.r.o.	THE CZECH REPUBLIC	6194	2014	022
TOPIRAMATUM	TORLEPTA 50 mg	film-coated tablets	50mg	GLENMARK PHARMACEUTICALS s.r.o.	THE CZECH REPUBLIC	6195	2014	022
TOPIRAMATUM	TORLEPTA 100 mg	film-coated tablets	100mg	GLENMARK PHARMACEUTICALS s.r.o.	THE CZECH REPUBLIC	6196	2014	022
TYPE A BOTULINUM TOXIN	XEOMIN 100 UNITATI LD50	powder for solution for injection	100 UNITS	MERZ PHARMACEUTICALS GMBH	GERMANY	6236	2014	05
TYPE A BOTULINUM TOXIN	XEOMIN 50 UNITATI LD50	powder for solution for injection	50 UNITS	MERZ PHARMACEUTICALS GMBH	GERMANY	6235	2014	04

TRAMADOLUM	TRAMADOL RETARD 150 mg	prolonged-release tablets	150mg	KRKA D.D. NOVO MESTO	SLOVENIA	6137	2014	01
TRAMADOLUM	TRAMADOL RETARD 200 mg	prolonged-release tablets	200mg	KRKA D.D. NOVO MESTO	SLOVENIA	6138	2014	01
INACTIVATED HEPATITIS A VACCINE	VAQTA 50 U/ml INACTIVATED HEPATITIS A VACCINE	suspension for injection	50 U/ml	MERCK SHARP & DOHME ROMANIA S.R.L.	ROMANIA	6305	2014	04
INACTIVATED HEPATITIS A VACCINE	VAQTA 25 U/0.5 ml INACTIVATED HEPATITIS A VACCINE	suspension for injection	25 U/0.5 ml	MERCK SHARP & DOHME ROMANIA S.R.L.	ROMANIA	6305	2014	04
VALGANCICLOVIRUM	VALCYTE 450 mg	film-coated tablets	450mg	ROCHE ROMANIA S.R.L.	ROMANIA	6279	2014	01
VORICONAZOLUM	VORICONAZOL SANDOZ 200 mg	powder for solution for infusion	200 mg	SANDOZ S.R.L.	ROMANIA	6262	2014	03

EMA centrally authorised medicinal products for which a marketing price was established in Romania during the 1st quarter of 2014

INN	Invented name	Pharmaceutical form	Strength	Manufacturer	Country	MA number		
BEDAQUILINUM	SIRTURO 100 mg	tablets	100mg	JANSSEN-CILAG INTERNATIONAL NV	BELGIUM	901	2014	01
RIOCIGUAT	ADEMPAS 0.5 mg	film-coated tablets	0.5 mg	BAYER PHARMA AG	GERMANY	907	2014	01
RIOCIGUAT	ADEMPAS 2.5 mg	film-coated tablets	2.5 mg	BAYER PHARMA AG	GERMANY	907	2014	13
RIOCIGUAT	ADEMPAS 1mg	film-coated tablets	1mg	BAYER PHARMA AG	GERMANY	907	2014	04
RIOCIGUAT	ADEMPAS 1.5 mg	film-coated tablets	1.5 mg	BAYER PHARMA AG	GERMANY	907	2014	07
RIOCIGUAT	ADEMPAS 2mg	film-coated tablets	2mg	BAYER PHARMA AG	GERMANY	907	2014	10