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National Agency for Medicines and Medical Devices

Decisions of the NAMMD Scientific Council

Medicinal product batches recalled during the 4th quarter of 2011

Applications for marketing authorisation/marketing authorisation renewal submitted to the NAMMD during the 3rd quarter of 2011

Medicinal products authorised for marketing by the NAMMD during the 3rd quarter of 2011

EMA centrally authorised medicinal products for which the European Commission issued decisions during the 3rd quarter of 2011

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DECISIONS OF THE NAMMD SCIENTIFIC COUNCIL

DECISION

No. 23/13.12.2011
on approval of the Guideline on the bioanalytical method validation

The Scientific Council of the National Agency for Medicines and Medical Devices (NAMMD), established based on Order of the Minister of Health No. 1123/18.08.2010, modified through Order of the Minister of Health No. 1601/28.11.2011, reunited on summons of the President of the National Agency for Medicines and Medical Devices in the ordinary meeting of 05.04.2011, in accordance with Article 12(5) of Government Decision No. 734/2010 on establishment, organisation and operation of the National Agency for Medicines and Medical Devices, as amended, adopts the following

DECISION

Art. 1. – The Guideline on the bioanalytical method validation is approved, according to the Annex which is integral part of this Decision.

Art. 2. – This Decision enters into force on 1.02.2012.

PRESIDENT
of the Scientific Council
of the National Agency for Medicines and Medical Devices,
Acad. Prof. Dr. Leonida Gherasim

ANNEX
(SCD No. 23/13.12.2011.)

GUIDELINE ON BIOANALYTICAL METHOD VALIDATION

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CHAPTER I
INTRODUCTION (BACKGROUND)

Art. 1. – (1) This Guideline represents the Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009), adopted by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency on la 21.07.2011, and shall come into force on 1 February 2012. This Guideline defines the key-elements needed in view of a validation of bioanalytical methods and focuses on the validation of bioanalytical methods so as to obtain strength-related quantity data, employed to determine pharmacokinetic and toxicokinetic parameters.

(2) This Guideline contains recommendations and criteria related to the enforcement of these methods validated during the routine analysis of study samples taken during non-clinical and clinical trials.

Art. 2. – (1) Measurement of drug concentrations in biological matrices (such as serum, plasma, blood, urine, and saliva) is an important aspect of medicinal product development. Such data may be required to support applications for new active substances and generics as well as variations to authorised drug products. The results of animal toxicokinetic studies and of clinical trials, including bioequivalence studies are used to make critical decisions supporting the safety and efficacy of a medicinal drug substance or product. It is therefore paramount that the applied bioanalytical methods used are well characterised, fully validated and documented to a satisfactory standard in order to yield reliable results.

(2) Acceptance criteria wider than those defined in this guideline may be used in special situations. This should be prospectively defined based on the intended use of the method.

CHAPTER II
SCOPE

Art. 3. – (1) This guideline provides recommendations for the validation of bioanalytical methods applied to measure drug concentrations in biological matrices obtained in non-clinical pharmacokinetic studies and all phases of clinical trials. As ligand binding assays differ substantially from chromatographic analytical methods, separate validation recommendations for ligand binding assays are provided.

(2) In addition, specific aspects for the analysis of study samples will be addressed.

(3) Furthermore, this guideline will describe when partial validation or cross validation should be carried out in addition to the full validation of an analytical method.

(4) Methods used for determining quantitative concentrations of biomarkers used in assessing pharmacodynamic endpoints are out of the scope of this guideline.

CHAPTER III
LEGAL BASIS

Art. 4. – (1) This guideline has to be read in conjunction with the Introduction and General principles (4) and Part I and II of Annex I to Directive 2001/83/EC as amended. It applies to Marketing Authorisation Applications for human medicinal products submitted in accordance with Directive 2001/83/EC as amended (transposed in national legislation through Law No. 95/2006 on healthcare reform, Title XVII – The medicinal product, as amended, and Regulation (EC) No. 726/2004, in which the analysis of drug concentrations in a biological matrix is part of the application.

(2) The validation of bioanalytical methods and the analysis of study samples for clinical trials in humans should be performed following the principles of Good Clinical Practice (GCP). Further guidance that will help clinical laboratories develop and maintain quality systems which will comply with relevant European Union Directives, national regulations and associated guidance documents can be found in the "Reflection Paper for Laboratories That Perform the Analysis or Evaluation of Clinical Trial Samples." (EMA/INS/GCP/532137/2010).

(3) Non-clinical (pharmacotoxicological) studies submitted in a marketing authorisation application shall be carried out in conformity with the provisions related to Good Laboratory Practice, Directive 2004/10/EC on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances and Directive 2004/9/EC on the inspection and verification of good laboratory practice (GLP). Normally, the validation of bioanalytical methods used in non-clinical pharmacotoxicological studies that are carried out in conformity with the provisions related to Good Laboratory Practice should be performed following the Principles of Good Laboratory Practice. Aspects of method validation not performed according to GLP should be clearly identified and their potential impact on the validation status of the method indicated. Methods used in pre-clinical studies not required to be performed to GLP should be fit for purpose but not necessarily developed in a GLP facility.

CHAPTER IV
METHOD VALIDATION

IV.1. *FULL VALIDATION OF AN ANALYTICAL METHOD*

Art. 5. – (1) A full method validation should be performed for any analytical method whether new or based upon literature.

(2) The main objective of method validation is to demonstrate the reliability of a particular method for the determination of an analyte concentration in a specific biological matrix, such as blood, serum, plasma, urine, or saliva. Moreover, if an anticoagulant is used, validation should be performed using the same anticoagulant as for the study samples. Generally a full validation should be performed for each species and matrix concerned.

(3) In some cases, it may be problematic for validation purposes to obtain an identical matrix compared to the matrix of the study samples. A suitable alternative matrix may be used, e.g. synthetically prepared cerebrospinal fluid, if justified.

(4) The main characteristics of a bioanalytical method that are essential to ensure the acceptability of the performance and the reliability of analytical results are: selectivity, lower limit of quantification, the response function and calibration range (calibration curve performance), accuracy, precision, matrix effects, stability of the analyte(s) in the biological matrix and stability of the analyte(s) and of the internal standard in the stock and working solutions and in extracts under the entire period of storage and processing conditions.

(5) Usually one analyte or drug has to be determined, but on occasions it may be appropriate to measure more than one analyte. This may involve two different drugs, but may also involve a parent drug with its metabolites, or the enantiomers or isomers of a drug. In such cases the principles of validation and analysis apply to all analytes of interest.

Art. 6. – Reference standards

(1) During method validation and analysis of study samples, a blank biological matrix will be spiked with the analyte(s) of interest using solutions of reference standard(s) to prepare calibration standards, quality control samples and stability samples. In addition, suitable internal standard(s) (IS) can be added during sample processing in chromatographic methods.

(2) It is important that the quality of the reference standard and IS is ensured, as the quality (purity) may affect the outcome of the analysis, and therefore the outcome of the study data. Therefore the reference standards used during the validation and study sample analysis should be obtained from an authentic and traceable source. Suitable reference standards, include certified standards such as compendial standards (EPCRS, USP, WHO), commercially available standards, or sufficiently characterised standards prepared in-house or by an external non-commercial organisation. A certificate of analysis is required to

ensure purity and provide information on storage conditions, expiration date and batch number of the reference standard.

(3) The use of certified standards is not needed for IS, as long as the suitability for use is demonstrated, e.g. lack of analytical interference is shown for the substance itself or any impurities thereof.

(4) When mass-spectrometry (MS) detection is used in the bioanalytical method, a stable isotope-labelled is recommended to be used whenever possible. However, it is essential that the labelled standard is of the highest isotope purity and that no isotope exchange reaction occurs. The presence of any unlabelled analyte should be checked and if relative amounts of unlabelled analyte are detected the potential influence has to be evaluated during method validation.

IV.1.1. Selectivity

Art. 7. – (1) The analytical method should be able to differentiate the analyte(s) of interest and IS from endogenous components in the matrix or other components in the sample. Selectivity should be proved using at least 6 individual sources of the appropriate blank matrix, which are individually analysed and evaluated for interference. Use of fewer sources is acceptable in case of rare matrices. Normally, absence of interfering components is accepted where the response is less than 20% of the lower limit of quantification for the analyte and 5% for the internal standard.

(2) It may also be necessary to investigate the extent of any interference caused by metabolites of the drug(s), interference from degradation products formed during sample preparation, and interference from possible co-administered medications. Co-medications normally used in the subject population studied which may potentially interfere should be taken into account at the stage of method validation, or on a study specific and compound specific base.

(3) The possibility of back-conversion of a metabolite into parent analyte during the successive steps of the analysis (including extraction procedures or in the MS source) should also be evaluated, when relevant (i.e. potentially unstable metabolites e.g. acidic metabolites to ester, unstable N-oxides or glucuronide metabolites, lactone ring structures). The extent of back-conversion should be established and the impact on the study results discussed. It is acknowledged that this evaluation will not be possible early during drug development of a new active substance when the metabolism is not yet evaluated. However, it is expected that this issue is taken into account and a partial validation is performed if relevant as further knowledge regarding metabolism of the active substance is gained during drug development.

(4) It is recognized that in some cases it is very difficult to obtain the metabolites of interest. Alternatively, back-conversion of a metabolite can be checked by applying incurred sample reanalysis. However, in this case potential back-conversion during sample processing cannot be ruled out.

IV.1.2. Carry-over

Art. 8. – (1) Carry-over should be addressed and minimised during method development. During validation carry-over should be assessed by injecting blank samples after a high concentration sample or calibration standard at the upper limit of quantification. Carry-over in the blank sample following the high concentration standard should not be greater than 20% of the lower limit of quantification (LLOQ; see below) and 5% for the internal standard.

(2) If it appears that carry-over is unavoidable, study samples should not be randomised. Specific measures should be considered, tested during the validation and applied during the analysis of the study samples, so that it does not affect accuracy and precision. This could include the injection of blank samples after samples with an expected high concentration, before the analysis of the next study sample.

IV.1.3. Lower limit of quantification

Art. 9. – (1) The lower limit of quantification (LLOQ) is the lowest concentration of analyte in a sample which can be quantified reliably, with an acceptable accuracy and precision. The LLOQ is considered being the lowest calibration standard (see Accuracy and Precision). In addition, the analyte signal of the LLOQ sample should be at least 5 times the signal of a blank sample. The LLOQ should be adapted to expected concentrations and to the aim of the study. As an example, for bioequivalence studies the LLOQ should be not higher than 5% of the C_{max}, while such a low LLOQ may be not necessary for exploratory pharmacokinetic studies.

IV.1.4. Calibration curve

Art. 10. – (1) The response of the instrument with regard to the concentration of analyte should be known, and should be evaluated over a specified concentration range. The calibration standards should be prepared in the same matrix as the matrix of the intended study samples by spiking the blank matrix with known concentrations of the analyte. There should be one calibration curve for each analyte studied in the method validation and for each analytical run.

(2) Ideally, before carrying out the validation of the analytical method it should be known what concentration range is expected. This range should be covered by the calibration curve range, defined by the LLOQ being the lowest calibration standard and the upper limit of quantification (ULOQ), being the highest calibration standard. The range should be established to allow adequate description of the pharmacokinetics of the analyte of interest.

(3) A minimum of six calibration concentration levels should be used, in addition to the blank sample (processed matrix sample without analyte and without IS) and a zero sample (processed matrix with IS). Each calibration standard can be analysed in replicate.

(4) A relationship which can simply and adequately describe the response of the instrument with regard to the concentration of analyte should be applied. The blank and zero samples should not be taken into consideration to calculate the calibration curve parameters.

(5) The calibration curve parameters should be reported (slope and intercept in case of linear fit). In addition, the back calculated concentrations of the calibration standards should be presented together with the calculated mean accuracy values (see definition of Accuracy below). All the available (or acceptable) curves obtained during validation, with a minimum of 3 should be reported.

(6) The back calculated concentrations of the calibration standards should be within ±15% of the nominal value, except for the LLOQ for which it should be within ±20%. At least 75% of the calibration standards, with a minimum of six calibration standard levels, must fulfil this criterion. In case replicates are used, the criteria (within ±15% or ±20% for LLOQ) should also be fulfilled for at least 50% of the calibration standards tested per concentration level. In case a calibration standard does not comply with these criteria, this calibration standard sample should be rejected, and the calibration curve without this calibration standard should be re-evaluated, including regression analysis. In case all replicates of the LLOQ or the ULOQ calibration standard are rejected then the batch should be rejected from the validation, the possible source of the failure be determined and the method revised (if necessary). If the next validation batch also fails, then the method should be revised before restarting validation. Although the calibration curve should preferably be prepared using freshly spiked samples, it is allowed to use previously prepared and stored calibration samples, if supported by appropriate stability data.

IV.1.5. Accuracy

Art. 11. – (1) The accuracy of an analytical method describes the closeness of the determined value obtained by the method to the nominal concentration of the analyte (expressed in percentage). Accuracy should be assessed on samples spiked with known amounts of the analyte, the quality control samples (QC samples). The QC samples should be spiked independently from the calibration standards, using separately prepared stock solutions, unless the nominal concentration(s) of the stock solutions have been established.

(2) The QC samples are analysed against the calibration curve, and the obtained concentrations are compared with the nominal value. The accuracy should be reported as percent of the nominal value. Accuracy should be evaluated for the values of the QC samples obtained within a single run (the within run accuracy) and in different runs (the between-run accuracy).

(3) To enable evaluation of any trends over time within one run, it is recommended to demonstrate accuracy and precision of QC samples over at least

one of the runs in a size equivalent to a prospective analytical run of study samples.

Art. 12. – Within-run accuracy

Within-run accuracy should be determined by analysing in a single run a minimum of 5 samples per level at a minimum of 4 concentration levels which are covering the calibration curve range: the LLOQ, within three times the LLOQ (low QC), around 50% of the calibration curve range (medium QC), and at least at 75% of the upper calibration curve range (high QC). The mean concentration should be within 15% of the nominal values for the QC samples, except for the LLOQ which should be within 20% of the nominal value.

Art. 13. – Between –run accuracy

(1) For the validation of the between-run accuracy, LLOQ, low, medium and high QC samples from at least three runs analysed on at least two different days should be evaluated.

(2) The mean concentration should be within 15% of the nominal values for the QC samples, except for the LLOQ which should be within 20% of the nominal value. Reported method validation data and the determination of accuracy and precision should include all results obtained except those cases where errors are obvious and documented.

IV.1.6. Precision

Art. 14 - The precision of the analytical method describes the closeness of repeated individual measures of analyte. Precision is expressed as the coefficient of variation (CV). Precision should be demonstrated for the LLOQ, low, medium and high QC samples, within a single run and between different runs, i.e. using the same runs and data as for the demonstration of accuracy.

Art. 15. - Within-run precision

For the validation of the within-run precision, there should be a minimum of five samples per concentration level at LLOQ, low, medium and high QC samples in a single run. The within-run CV value should not exceed 15% for the QC samples, except for the LLOQ which should not exceed 20%.

Art. 16. - Between –run precision

For the validation of the between-run precision, LLOQ, low, medium and high QC samples from at least three runs analysed on at least two different days should be evaluated. The between-run CV value should not exceed 15% for the QC samples, except for the LLOQ which should not exceed 20%.

IV.1.7. Dilution integrity

Art. 17. - (1) Dilution of samples should not affect the accuracy and precision. If applicable, dilution integrity should be demonstrated by spiking the matrix with an analyte concentration above the ULOQ and diluting this sample with blank matrix (at least five determinations per dilution factor). Accuracy and

precision should be within the set criteria, i.e. within ±15%. Dilution integrity should cover the dilution applied to the study samples.

(2) Evaluation of dilution integrity may be covered by partial validation. Use of another matrix may be acceptable, as long as it has been demonstrated that this does not affect precision and accuracy.

IV.1.8. Matrix effect

Art. 18. - (1) Matrix effects should be investigated when using mass spectrometric methods, using at least 6 lots of blank matrix from individual donors. Pooled matrix should not be used.

(2) For each analyte and the IS, the matrix factor (MF) should be calculated for each lot of matrix, by calculating the ratio of the peak area in the presence of matrix (measured by analysing blank matrix spiked after extraction with analyte), to the peak area in absence of matrix (pure solution of the analyte). The IS normalised MF should also be calculated by dividing the MF of the analyte by the MF of the IS. The CV of the IS-normalised MF calculated from the 6 lots of matrix should not be greater than 15 %. This determination should be done at a low and at a high level of concentration (maximum of 3 times the LLOQ and close to the ULOQ).

(3) If this approach cannot be used, for instance in the case of on-line sample preparation, the variability of the response from lot to lot should be assessed by analysing at least 6 lots of matrix, spiked at a low and at a high level of concentration (maximum of 3 times the LLOQ and close to the ULOQ). The validation report should include the peak areas of the analyte and of the IS and the calculated concentration for each individual sample. The overall CV calculated for the concentration should not be greater than 15 %.

(4) If the matrix is difficult to obtain, less than 6 different lots of matrix may be used, but this should be justified. However, matrix effects should still be investigated.

(5) If a formulation for injection to be administered to the subjects or animals contains excipients known to be responsible for matrix effects, such as polyethylene glycol or polysorbate, matrix effects should be studied with matrix containing these excipients, in addition to blank matrix. The matrix used for this evaluation should be obtained from subjects or animals administered the excipient, unless it has been demonstrated that the excipient is not metabolised or transformed *in-vivo*. The effect of the excipients can be studied by the determination of the MF or by a dilution study of a study sample with a high concentration with blank matrix not containing the excipient.

(6) In addition to the normal matrix it is recommended to investigate matrix effects on other samples e.g. haemolysed and hyperlipidaemic plasma samples. If samples from special populations (such as renally or hepatically impaired populations) are to be analysed it is also recommended to study matrix effects using matrix from such populations.

IV.1.9. Stability

Art. 19. - (1) Evaluation of stability should be carried out to ensure that every step taken during sample preparation and sample analysis, as well as the storage conditions used do not affect the concentration of the analyte.

(2) Stability should be ensured for every step in the analytical method, meaning that the conditions applied to the stability tests, such as sample matrix, anticoagulant, container materials, storage and analytical conditions should be similar to those used for the actual study samples. Reference to data published in the literature is not considered sufficient.

(3) Stability of the analyte in the studied matrix is evaluated using low and high QC samples (blank matrix spiked with analyte at a concentration of a maximum of 3 times the LLOQ and close to the ULOQ) which are analysed immediately after preparation and after the applied storage conditions that are to be evaluated. The QC samples are analysed against a calibration curve, obtained from freshly spiked calibration standards, and the obtained concentrations are compared to the nominal concentrations. The mean concentration at each level should be within ±15% of the nominal concentration.

(4) Stability of the stock and working solutions should be tested with an appropriate dilution, taking into consideration the linearity and measuring range of the detector.

(5) Stability studies should investigate the different storage conditions over time periods that equal or exceed those applied to the actual study samples. The following stability tests should be evaluated:

• stability of the stock solution and working solutions of the analyte and internal standard,

• freeze and thaw stability of the analyte in the matrix from freezer storage conditions to room temperature or sample processing temperature,

• short term stability of the analyte in matrix at room temperature or sample processing temperature,

• long term stability of the analyte in matrix stored in the freezer. In addition the following tests should be performed if applicable:

• stability of the processed sample at room temperature or under the storage conditions to be used during the study (dry extract or in the injection phase),

• on-instrument (auto sampler) stability of the processed sample at injector or auto sampler temperature.

(6) *Regarding the freeze and thaw stability:* The QC samples are stored and frozen in the freezer at the intended temperature and thereafter thawed at room or

processing temperature. After complete thawing, samples are refrozen again applying the same conditions. At each cycle, samples should be frozen for at least 12 hours before they are thawed. The number of cycles in the freeze-thaw stability should equal or exceed that of the freeze/thaw cycles of study samples.

(7) *Regarding long term stability of the analyte in matrix stored in the freezer*: The QC samples should be stored in the freezer under the same storage conditions and at least for the same duration as the study samples. For small molecules it is considered acceptable to apply a bracketing approach, i.e. in case stability has been proved for instance at -70°C and -20°C, it is not necessary to investigate the stability at temperatures in between. For large molecules (such as peptides and proteins) stability should be studied at each temperature at which study samples will be stored. Study samples may be used in addition to QC samples, but the exclusive use of study samples is not considered sufficient as the nominal concentrations of those samples is not known. The results of the evaluation of long term stability should be available before the study report is issued.

(8) *As regards the stability of stock and working solutions:* it is not needed to study the stability at each concentration level of working solutions and a bracketing approach can be used. It is not needed to study the stability of stable-isotope labelled internal standards if it is demonstrated that no isotope exchange reactions occur under the same conditions as the stability of the analyte was demonstrated.

(9) In case of a multi-analyte study and specific for bioequivalence studies, attention should be paid to stability of the analytes in the matrix containing all the analytes.

(10) Sufficient attention should be paid to the stability of the analyte in the sampled matrix directly after blood sampling of subjects and further preparation before storage, to ensure that the obtained concentrations by the analytical method reflect the concentrations of the analyte in the subject at the moment of sampling. A demonstration of this stability may be needed on a case-by-case basis, depending on the structure of the analyte.

IV.2. PARTIAL VALIDATION

Art. 20. - (1) In situations where minor changes are made to an analytical method that has already been validated, a full validation may not be necessary, depending on the nature of the applied changes. Changes for which a partial validation may be needed include transfer of the bioanalytical method to another laboratory, change in equipment, calibration concentration range, limited sample volume, another matrix or species, change in anticoagulant, sample processing procedure, storage conditions etc. All modifications should be reported and the scope of revalidation or partial validation justified.

(2) Partial validation can range from as little as the determination of the within-run precision and accuracy, to an almost full validation.

IV.3. CROSS VALIDATION

Art. 21. - (1) Where data are obtained from different methods within and across studies or when data are obtained within a study from different laboratories, applying the same method, comparison of those data is needed and a cross validation of the applied analytical methods should be carried out. Differences in sample preparation or the use of another analytical method may result in different outcomes between the study sites. Cross validation should be performed in advance of study samples being analysed if possible.

(2) For the cross validation, the same set of QC samples or study samples should be analysed by both analytical methods. For QC samples, the obtained mean accuracy by the different methods should be within 15% and may be wider, if justified. For study samples, the difference between the two values obtained should be within 20% of the mean for at least 67% of the repeats. The outcome of the cross validation is critical in determining whether the obtained data are reliable and whether they can be compared and used.

V. ANALYSIS OF STUDY SAMPLES

Art. 22. - (1) After full validation of the analytical method, analysis of study or subject samples can be carried out. Before start of the analysis of the study samples the performance of the bioanalytical method should have been verified.

(2) The study samples, QC samples and calibration standards should be processed in accordance with the validated analytical method to ensure the acceptability of the analytical run.

V.1. ANALYTICAL RUN

Art. 23. - (1) An analytical run consists of the blank sample (processed matrix sample without analyte and without IS) and a zero sample (processed matrix with IS), calibration standards at a minimum of 6 concentration levels, at least 3 levels of QC samples (low, medium and high) in duplicate (or at least 5 % of the number of study samples, whichever is higher), and study samples to be analysed. As indicated before the calibration standards and QC samples should have been spiked independently using separately prepared stock solutions, unless the nominal concentration(s) of the stock solutions have been established. All samples (calibration standards, QC samples, and study samples) should be processed and extracted as one single batch of samples in the order in which they intend to be submitted or analysed. A single batch is comprised of samples which are handled at the same time, i.e. subsequently processed without interruption in time and by the same analyst with the same reagents under homogeneous conditions. Analysing samples, which were prepared separately as several batches, in a single analytical run should be avoided. If such an approach cannot be avoided, for instance due to bench-top stability limitations, each batch of samples should include low, medium and high QC samples. Acceptance criteria should be

pre-established in a Standard Operating Procedure (SOP) or in the study plan and should be defined for the whole analytical run and the separate batches in the run.

(2) For bioequivalence studies it is advised to analyse all samples of one subject together in one analytical run to reduce the variability in outcome. The QC samples should be divided over the run in such a way that the accuracy and precision of the whole run is ensured.

V.2. ACCEPTANCE CRITERIA OF AN ANALYTICAL RUN

Art. 24. - Criteria for acceptance or rejection of an analytical run should be defined in the protocol, in the study plan or in a SOP. In case a whole run consist of more batches, acceptance criteria should be applied to the whole run and to the individual batches. The run can be acceptable, although a batch might have to be rejected, as criteria were not met.

Art. 25. - The following acceptance criteria should apply:

(1) Accuracy: The back calculated concentrations of the calibration standards should be within ±15% of the nominal value, except for the LLOQ for which it should be within ±20%. At least 75% of the calibration standards, with a minimum of six, must fulfil this criterion. If one of the calibration standards does not meet these criteria, this calibration standard should be rejected and the calibration curve without this calibration standard should be re-evaluated, and regression analysis performed.

(2) If the rejected calibration standard is the LLOQ, the LLOQ for this analytical run is the next lowest acceptable calibration standard of the calibration curve. If the highest calibration standard is rejected, the ULOQ for this analytical run is the next acceptable lower calibration standard of the calibration curve. The revised calibration range must cover all QC samples (low, medium and high).

(3) The accuracy values of the QC samples should be within ±15% of the nominal values. At least 67% of the QC samples and at least 50% at each concentration level should comply with this criterion. In case these criteria are not fulfilled the analytical run should be rejected, and the study samples re-extracted and analysed.

(4) In the case of the simultaneous determination of several analytes, there should be one calibration curve for each analyte studied. If an analytical run is acceptable for one analyte but has to be rejected for another analyte, the data for the accepted analyte can be used, but the samples should be re-extracted and analysed for determination of the rejected analyte.

(5) If replicate calibration standards are used and only one of the LLOQ or ULOQ standards fails, the calibration range is unchanged.

(6) The overall (mean) accuracy and precision of the QC samples of all accepted runs should be calculated at each concentration level and reported in the analytical report. In case the overall mean accuracy and precision exceeds 15%, this should lead to additional investigations justifying this deviation. In the case of bioequivalence trials it may result in the rejection of the data.

V.3. CALIBRATION RANGE

Art. 26. - (1) If a narrow range of analyte concentrations of the study samples is known or anticipated before the start of study sample analysis, it is recommended to either narrow the calibration curve range, adapt the concentrations of the QC samples, or add new QC samples at different concentration levels as appropriate, to adequately reflect the concentrations of the study samples.

(2) If a narrow range of analysis values is unanticipated, but observed after the start of sample analysis, it is recommended that the analysis is stopped and either the standard calibration range narrowed, existing QC concentrations revised, or QC samples at additional concentrations are added to the original curve before continuing with study sample analysis. It is not necessary to reanalyse samples analysed before optimising the standard curve range or QC concentrations.

(3) The same applies if it appears that a large number of the analyte concentrations of the study samples appear to be above the ULOQ. The calibration curve range should be extended, if possible, and QC samples added or their concentrations modified.

(4) At least 2 QC sample levels should fall within the range of concentrations measured in study samples. If the calibration curve range is changed, the bioanalytical method should be revalidated (partial validation) to verify the response function and to ensure accuracy and precision.

V.4. REANALYSIS OF STUDY SAMPLES

Art. 27. - (1) Possible reasons for reanalysis of study samples and criteria to select the value to be reported should be predefined in the protocol, study plan or SOP, before the actual start of the analysis of the samples. The number of samples (and percentage of total number of samples) that have been reanalysed should be discussed in the study report.

(2) The following are examples of reasons for study sample reanalysis:

• rejection of an analytical run because the run did not fulfil the acceptance criteria with regard to accuracy of the calibration standards and/or the QC samples,

• internal standard response significantly different from the response for the calibration standard and QC samples, if such criteria have been pre-defined in a SOP,

• improper sample injection or malfunction of equipment,

• the obtained concentration is above the ULOQ or below the run’s LLOQ, in runs where the lowest standard sample has been rejected from a calibration curve, resulting in a higher LLOQ compared with other runs,

• identification of quantifiable analyte levels in pre-dose samples or placebo sample,

• poor chromatography.

(3) For bioequivalence studies, normally reanalysis of study samples because of a pharmacokinetic reason is not acceptable, as this may affect and bias the outcome of such a study. In this case, reanalysis might be considered as part of laboratory investigations, to identify possible reasons for results considered as abnormal and to prevent the recurrence of similar problems in the future.

(4) In case of reanalysis because of positive pre-dose samples or because of a pharmacokinetic reason, the reanalysed samples should be identified and the initial value, the reason for reanalysis, the values obtained in the reanalyses, the finally accepted value and a justification for the acceptance should be provided.

(5) Re-injection of samples can be made in case of instrument failure if reinjection reproducibility and on-injector stability have been demonstrated during validation. Re-injection of a full analytical run or of individual calibration standard samples or QC samples, simply because the calibration or QCs failed, without any identified analytical cause, is not acceptable.

(6) The safety of trial subjects should take precedence over any other aspect of the trial. Consequently, there may be other circumstances when it is necessary to re-extract and/or re-analyse specific study samples, for example where an unexpected or anomalous result is identified that may impact on patient safety.

V.5. INTEGRATION

Art. 28. - Chromatogram integration and re-integration should be described in a SOP. Any deviation from this SOP should be discussed in the analytical report. Chromatogram integration parameters and in case of re-integration, initial and the final integration data should be documented at the laboratory and should be available upon request. For further guidance reference is made to the "Reflection Paper for Laboratories That Perform The Analysis Or Evaluation Of Clinical Trial Samples." (EMA/INS/GCP/532137/2010).

VI. INCURRED SAMPLES REANALYSIS

Art. 29. - (1) The use of calibration standards and QC samples during validation may not mimic the actual study samples. Differences for instance in protein binding, back-conversion of known and unknown metabolites, sample inhomogeneity or concomitant medications, may affect the accuracy and precision of the analyte in such samples during processing and storage. It is therefore recommended to evaluate accuracy of incurred samples by reanalysis of study samples in separate runs at different days. The extent of testing depends on the analyte and the study samples, and should be based upon in-depth understanding of the analytical method and analyte. However, as a guide, 10% of the samples should

be reanalysed in case the number of samples is less than 1000 samples and 5% of the number of samples exceeding 1000 samples. Moreover, it is advised to obtain samples around Cmax and in the elimination phase.

(2) The concentration obtained for the initial analysis and the concentration obtained by reanalysis should be within 20% of their mean for at least 67% of the repeats. Large differences between results may indicate analytical issues and should be investigated.

(3) In case incurred sample analysis showed deviating results, this should be investigated, and adequate steps should be taken to minimize inaccuracy (and imprecision).

(4) Incurred sample reanalysis should be done at least in the following situations:

• toxicokinetic studies once per species

• all pivotal bioequivalence trials

• first clinical trial in subjects

• first patient trial

• first trial in patients with impaired hepatic and/or renal function

(5) For animal studies, the incurred sample reanalysis may be done only in early Phase studies, if these are representative for pivotal studies in terms of dose administered and concentrations obtained. Samples should not be pooled, as pooling may limit anomalous findings.

VII LIGAND BINDING ASSAYS

VII.1 METHOD VALIDATION

Art. 30. - Ligand-binding assays (LBA) or immunoassays are especially used for macromolecules. The validation principles and the considerations with regard to analysis of study samples, as indicated before should also be applied in general for ligand-binding assays. However ligand binding assays pose several challenges. Due to the inherent characteristics and complex structure of the macromolecules, the extraction process is problematic and as such these assays are often run without prior separation of the analyte of interest. In addition these assays do not directly measure the macromolecule itself but indirectly measure a binding reaction with reagents employed in the assay. For these reasons, several issues need special attention.

7.1.1. Full Validation

7.1.1.1. Reference standards

Art. 31. - Macromolecules are heterogeneous and their potency and immunoreactivity may vary. The reference material should be well characterised and documented (e.g. certificate of analysis and origin). The purest reference standard available at the time should be procured. It is strongly recommended that the batch of the reference standard used for the preparation of calibration standards and QC samples is the same as used for dosing in the non clinical and clinical studies. In case of change of batch, an analytical characterisation and bioanalytical evaluation should be carried out prior to use to ensure that the performance characteristics of the method are not altered.

7.1.1.2. Specificity

Art. 32. - Specificity of the binding reagent(s) refer(s) to its (their) ability to bind solely to the analyte of interest. Specificity is related to the concept of cross-reactivity. Ideally the binding reagent should be specific such that no cross-reactivity occurs with structurally "related compounds" (e.g. endogenous compounds, isoforms, variant forms of the analyte, or physico-chemically similar compounds) or with anticipated concomitant medication. During method development and validation, frequently these "related molecules" are not available. Evaluation of specificity may be conducted after the original validation is completed as more data on the behaviour of the analyte become available. Specificity should be tested with QC samples by adding increasing concentrations of available "related molecules" or drugs expected to be concomitantly administered, into drug-naive sample matrix (matrix obtained from animals or subjects never exposed to the analyte) and measuring the accuracy of the macromolecule of interest at both LLOQ and ULOQ. The assay acceptance criteria of the QC samples should be within 25% of the nominal values.

7.1.1.3. Selectivity

Art. 33. - Selectivity of a ligand-binding assay is the ability to measure the analyte of interest in the presence of unrelated compounds in the matrix. Generally there is no extraction due to the inherent characteristics of macromolecules. Then, unrelated compounds present in matrix e.g. degrading enzymes, heterophilic antibodies or rheumatoid factor, may interfere with the analyte of interest in the ligand binding assay. Selectivity is tested by spiking at least 10 sources of sample matrix at or near the LLOQ. These sources should include lipemic and haemolysed samples. It is also strongly recommended that sources from relevant disease population be included. Selectivity should be evaluated at the low end of an assay where problems occur in most cases. It may be prudent also to evaluate selectivity at higher analyte concentrations. In cases where interference is concentration dependent, it is essential to determine the minimum concentration where

interference occurs. It may be necessary to adjust the lower level of quantification accordingly, before assay validation. The accuracy should be within 20% (25% at the LLOQ) of the nominal spiked concentration in at least 80% of the matrices evaluated.

7.1.1.4. Carry-over effect

Art. 34. - If robotic liquid handling systems are used, potential for carry-over should be investigated by placing blank samples after samples with a high analyte concentration or calibration standard at the upper limit of quantification.

7.1.1.5. Matrix selection

Art. 35. - The measurement of some macromolecules may not be possible in complex matrices without extraction due to high interferences with high levels of structurally related endogenous compounds. Although the use of extracted matrix (e.g. charcoal, immunoaffinity) or alternative matrix (e.g. protein buffers, dialysed serum) is not recommended, the use of such matrices may be necessary when there is no other strategy to quantify the analyte of interest. The calibration standard curve may be prepared in these surrogate matrices. QC samples should be prepared in the actual sample matrix and the accuracy should be calculated to demonstrate the absence of matrix effect.

7.1.1.6. Minimum required dilution

Art. 36. - Because matrices may exhibit a high background signal, it may be necessary to determine the minimum required dilution. The minimum required dilution is the smallest dilution to which a sample must be diluted in buffer to optimize accuracy and precision in an assay run by reducing the signal to noise ratio. Spiked samples should be prepared in the same matrix as the study samples for determination of the minimum required dilution.

7.1.1.7. Calibration curve

Art. 37. - The response function of the calibration curve is measured indirectly and is generally non linear and often sigmoidal. A minimum of 6 calibration standards should be run at least in duplicate. The calibration standards should be spaced approximately evenly on a logarithmic scale within the anticipated range. In addition to the calibration standards, anchor points outside the range of quantification can be used to facilitate the fitting of the curve. A minimum of 6 independent runs should be evaluated during the validation. The results must be reported in a table to establish the overall robustness of the regression model of the calibration curve. A calibration standard may be excluded from the curve due to a technical error with an assignable cause (e.g. pipetting error). The target back-calculated concentrations of the calibration standards should be within 20% of the nominal value (25% at LLOQ and ULOQ) for at least 75% of calibration

standards. The anchor calibrators do not require acceptance criteria since they are beyond the quantifiable range of the curve.

7.1.1.8. Precision and accuracy

Art. 38. - (1) For the estimation of precision and accuracy QC samples should not be freshly prepared, but should be frozen and treated the same way as for the analysis of study samples. At least 5 QC samples (anticipated LLOQ, less than 3 times the LLOQ, mid, high and anticipated ULOQ) should be used to assess accuracy, precision and the total error of the method. Validation should mimic the actual study samples analysis, i.e. in case a study sample is measured twice (i.e. using 2 wells) as recommended then during validation QCs should be analysed twice (i.e. using 2 wells per QC sample).

(2) Measurements should be made across at least 6 independent assay runs over several days. Regarding within-run and between-run accuracy, the mean concentration should be within 20% of the nominal value at each concentration level (25% at the LLOQ and ULOQ). The within-run and between-run precision should not exceed 20% (25 % at LLOQ and ULOQ). Furthermore the total error (i.e. sum of absolute value of the % relative error and % coefficient of variation) should not exceed 30% (40% at LLOQ and ULOQ).

7.1.1.9. Dilution linearity

Art. 39. - Because the narrow range of the calibration standard curve, it is necessary to demonstrate with QC samples that the analyte of interest, when present in concentrations exceeding the range of quantification (above ULOQ), can be accurately measured by the assay after dilution in blank matrix to bring the analyte concentrations into the validated range for analysis. An additional reason for conducting dilutional experiments is to detect a possible prozone or "hook effect" i.e. a signal suppression caused by high concentrations of analyte. The back-calculated concentration for each dilution should be within 20% of the nominal concentration after correction for dilution and the precision of the final concentrations across all the dilutions should not exceed 20%.

7.1.1.10. Parallelism

Art. 40. - If study samples are available, parallelism between the calibration standard curve and serially diluted study samples should be assessed to detect possible matrix effect or differing affinities for metabolites. A high concentration study sample (preferably close to Cmax) should be diluted to at least three concentrations with blank matrix. The precision between samples in a dilution series should not exceed 30%. In case the sample does not dilute linearly (i.e. in a non parallel manner), a procedure for reporting a result should be defined a priori. If study samples are not available during the validation of the method, parallelism should be evaluated as soon as study samples become available.

7.1.1.11. Stability of the samples

Art. 41. - Stability of the analyte is evaluated using samples of the low and high level QC samples as described before in section 4.1.9. As previously mentioned, the investigation of stability should cover short-term stability at room temperature or sample processing temperature and freeze-thaw stability. In addition, long-term freezer stability should be studied at each temperature at which study samples will be stored. A bracketing approach may be considered. The mean concentration at each level should be within 20% of the nominal concentration.

7.1.1.12. Reagents

Art. 42. - (1) Critical reagents, including binding reagents (e.g. binding proteins, aptamers, antibodies or conjugated antibodies) and those containing enzymatic moieties have direct impact on the results of the assay and therefore their quality must be assured. Accordingly, when changing reagent batches during validation or sample analysis the analytical performance of the method must be verified to ensure that it is not altered compared with the original or previous batch.

(2) Conditions guaranteeing the maintenance of the stability of both non critical reagents (e.g. buffers, diluents or acidification reagents) and more importantly of the critical reagents should be documented in order to ensure that the performance of the method is not affected over time.

7.1.1.13. Commercial kits

Art. 43. - Commercial kits may have been developed for purposes other than to support pharmacokinetics. Therefore, commercial kits need to be revalidated to ensure that the LLOQ and the QC samples in the actual concentration range to be used for sample analysis perform accurately and precisely. The principles of validation listed above apply.

VII.2. PARTIAL VALIDATION AND CROSS-VALIDATION

Art. 44. - All the validation aspects reported in previous sections IV.2 and IV.3 are applicable to ligand binding assays.

7.3. ANALYSIS OF STUDY SAMPLES

7.3.1. Analytical run

Art. 45. - Most often microtiter plates are used for LBA. An analytical run may comprise several individual plates, but each plate should contain an individual set of calibration standards and QC samples to compensate for difference in plate performance. The sample capacity in some platforms may be limited. Then, it may be acceptable that a set of calibration standards be placed in the first and the last

platform and QC samples on every single platform. It is recommended to assay a study sample in replicate, i.e. by using at least 2 wells instead of 1.

7.3.2. Acceptance criteria for study sample analysis

Art. 46. - (1) The back calculated concentrations of the calibration standards should be within 20% of nominal value, except for LLOQ and the ULOQ for which it should be within 25%. At least 75 % of the calibration standards with a minimum of 6, must fulfil this criterion. This requirement does not apply to anchor calibrators.

(2) Each plate should contain at least 3 levels of QC samples (low, medium and high) at least in duplicate.

(3) Also during within study validation, the QCs should mimic the analysis of the study sample with regard to the number of wells used per study sample. At least 67% QC samples and 50% at each concentration level should be within 20% of the nominal value. Exceptions to this criterion should be justified.

7.3.3. Incurred samples reanalysis

Art. 47. - All the considerations regarding the incurred sample analysis reported in previous section 6 are applicable to ligand binding assays. The concentration obtained for the initial analysis and the concentration obtained by reanalysis should be within 30% of their mean for at least 67% of the repeats.

VIII. REPORTS

Art. 48. - Information regarding conducted audits/inspection should be included in the report(s).

VIII.1. VALIDATION REPORT

Art. 49. - (1) Depending on the level of detail of the information provided in the validation report, reference to the SOPs for relevant analysis specific procedures may be sufficient. Otherwise these SOPs should be appended to the report.

(2) All source data should be available in its original format and available on request.

(3) Any deviation from the validation protocol should be recorded.

(4) The validation report should include at least the following information:

• summary of the validation performances,

• details of the applied analytical method and where appropriate, the source of the analytical method (references from literature and/or modifications in the procedure),

• details of the assay procedure (analyte, IS, sample pre-treatment, extraction and analysis),

• reference standards (origin, batch number, certificate of analysis, stability and storage conditions),

• calibration standards and QC samples (matrix, anticoagulant if applicable, preparation, preparation dates, and storage conditions),

• run acceptance criteria,

• analysis:

• table of all analytical runs with analysis dates, whether passed or failed and the reason for the failure

• table of calibration results of all accepted analytical runs, including calibration range, response function, back-calculated concentrations, and accuracy,

• table of QC results of all accepted analytical runs (within- and between-run precision and accuracy); values outside acceptance criteria should be clearly marked,

• stability data of stock solution, working solution, QC, covering the applied storage conditions,

• data on selectivity, LLOQ, carry-over, matrix effect if applicable, dilution integrity;

• unexpected results obtained during validation with full justification of the action taken,

• deviations from method and/or SOPs (description of deviations, impact on study, supportive data).

(5) All measurements with the individual calculated concentrations have to be presented in the validation report.

VIII.2. ANALYTICAL REPORT

Art. 50. - (1) The analytical report should include a reference to the validation report(s) applicable to the analysis of the study samples. Furthermore it should include a detailed description of the analysis of the study samples.

(2) If the analytical report provides detailed information, a reference to the analysis specific SOPs in the analytical report is sufficient. Otherwise, the SOPs should be appended to the analytical report.

(3) All source data should be available in its original format and available on request.

(4) Any deviation from the protocol, analytical procedure or SOPs should also be discussed in the analytical report.

(5) The analytical report should include at least the following information:

• reference standards (origin, batch, certificate of analysis, stability, storage conditions)

• calibration standards and QC samples (storage conditions)

• run acceptance criteria (short description, reference to specific protocol or SOP)

• assay procedure (short description)

• sample tracking (dates of receipt and contents, sample conditions on receipt, storage location and conditions, if applicable)

• study sample analysis:

• content of the analytical run,

• table identifying all analytical runs and study samples, with run dates and results,

• table of calibration results of all (passed) analytical runs,

• table of QC results of all (passed) analytical runs; values outside acceptance criteria should be clearly marked;

• failed analytical runs (identity, assay date, reason for failure),

• deviations from method and/or SOPs (description of deviations, impact on study, supportive data),

• reassay, excluding reassay due to analytical reasons, such as failed run (table of sample identification, reason for re-assay, original and re-assay values).

(6) The results of incurred sample reanalysis may be supplied either in the validation report, in the analytical report or in a stand alone report.

(7) For bioequivalence studies, all chromatograms from the runs which include 20% of the subjects, including the corresponding QC samples and calibration standards should be appended to the analytical study report. For other studies representative chromatograms should be appended to the report. Additional chromatograms should be available on request.

DEFINITIONS

1. Accuracy
The accuracy of an analytical procedure expresses the closeness of the determined value to the value which is accepted either as a conventional true value or an accepted reference value. Accuracy is defined as (determined value/true value)x100%.

2. Analyte
A specific chemical moiety being measured, which can be intact drug, biomolecule or its derivative, metabolite and/or degradation product in a biologic matrix.

3. Analytical run
A complete set of analytical and study samples with appropriate number of calibration standards and QC samples for their validation. Several runs may be completed in one day, or one run may take several days to complete.

4. Analytical procedure
The analytical procedure refers to the way of performing the analysis. It should describe in detail the steps necessary to perform each analysis.

5. Anchor calibrators
Anchor calibrators are standards points outside of the range of quantification, used to assist in fitting the non linear regression of the standard curve in ligand-binding assays.

6. Calibration range
The range of an analytical procedure is the interval between the upper and lower concentration (amounts) of analyte in the sample (including these concentrations) for which it has been demonstrated that the analytical procedure meets the requirements for precision, accuracy and response function.

7. Calibration standard
A matrix to which a known amount of analyte has been added or spiked. Calibration standards are used to construct calibration curves.

8. Carry-over
Carry-over is the appearance of an analyte signal in blank sample after the analysis of samples with a high analyte concentration.

9. Cross validation

Comparison of validation parameters of two bioanalytical methods.

10. Full validation
Establishment of all validation parameters to apply to sample analysis for the bioanalytical method for each analyte.

11. Incurred samples
Study samples from dosed subjects or animals.

12. Incurred sample reanalysis
The analysis of a portion of the incurred samples to determine whether the original analytical results are reproducible.

13. Internal standard
Test compound(s) (e.g. a structurally similar analogue, or stable isotope labelled compound) added to calibration standards, QC samples and study samples at a known and constant concentration to correct for experimental variability during sample preparation and analysis.

14. Lower limit of quantification (LLOQ)
The lower limit of quantification of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined with pre-defined precision and accuracy.

15. Matrix effect
The direct or indirect alteration or interference in response due to the presence of unintended analytes (for analysis) or other interfering substances in the sample.

16. Nominal concentration
Theoretical or expected concentration.

17. Partial validation
Series of analytical experiments where only relevant parts of the validation are repeated after modifications are made to the validated bioanalytical method.

18. Precision
The precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained under the prescribed conditions. Precision is defined as the ratio of standard deviation/mean (%).

19. Quality control (QC) sample
A spiked sample used to monitor the performance of a bioanalytical method and to assess the integrity and validity of the results of the unknown samples analysed in an individual batch.

20. Response function
Response function is a function which adequately describes relationship between instrument response (e.g. peak area or height ratio) and the concentration (amount) of analyte in the sample. Response function is defined within a given range.

21. Selectivity
Selectivity is the ability of the bioanalytical method to measure and differentiate the analyte(s) of interest and internal standard in the presence of components which may be expected to be present in the sample.

22. Specificity
Specificity is the ability to measure the analyte unequivocally in the presence of other compounds, either exogenous or endogenous, in the matrix.

23. Stability
The chemical stability of an analyte in a given matrix under specific conditions for given time intervals.

24. Standard Operating Procedure
Document which describes the regularly recurring operations relevant to the quality of the investigation and enabling to carry out the operations correctly and always in the same manner.

25. Upper limit of quantification (ULOQ)
The upper limit of quantification of an individual analytical procedure is the highest amount of analyte in a sample which can be quantitatively determined with pre-defined precision and accuracy.

DECISION

No. 25/13.12.2011

on approval of amendment of Scientific Council Decision No. 1/22.02.2011 on accreditation of national Good Clinical Practice training providers

The Scientific Council of the National Agency for Medicines and Medical Devices (NAMMD), set up based on Order of the Minister of Health No. 1123/18.08.2010, amended through Order of the Minister of Health No. 1601/28.11.2011, reunited on summons of the President of the National Agency for Medicines and Medical Devices in the ordinary meeting of 13.12.2011, in accordance with Article 12(5) of the Romanian Government Decision No. 734/2010 on establishment, organisation and operation of the National Agency for Medicines and Medical Devices, as amended, adopts the following

DECISION

Art. 1. - The term for enforcement of SCD No. 1/22.02.2011 on accreditation of national Good Clinical Practice training providers is extended to the approval of the norms for enforcement and establishment of a new calendar.

Art. 2. - The NAMMD Scientific Council Decision No. 1/22.02.2011 on accreditation of national Good Clinical Practice training providers is amended on this Decision coming into force.

PRESIDENT
of the Scientific Council
of the National Agency for Medicines and Medical Devices,
Acad. Prof. Dr. Leonida Gherasim

DECISION

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

The Scientific Council of the National Agency for Medicines and Medical Devices, set up based on Order of the Minister of Health No. 1123/18.08.2010, amended through Order of the Minister of Health No. 1601/28.11.2011, reunited on summons of the NAMMD President in the ordinary meeting of 13.12.2011, in accord with Article 12 (5) of Decision of the Government of Romania No. 734/2010 related to the set up, organisation and operation of the National Agency for Medicines and Medical Devices, as amended, agrees on the following

DECISION

Art. 1. – Amendment of Art. 40 of Regulations (Annex to 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), as follows:

„Art. 40. – (1) The application for clinical trial authorisation is accompanied by the form on qualification of each main investigator at the respective investigation site and their undertaking to take part in the clinical trial (according to Annex 5, which is integral part of these regulations);

(2) For clinical trials where the domain of the trial/therapeutic group of the investigational medicinal product is different from the main investigator's speciality, the NAMMD requires the sponsor/the sponsor's representative to submit a written consent of the Specialist Board of the Ministry of Health in the trial domain (after validation of the application for clinical trial conduct authorisation)."

Art. 2. - On this decision coming into force, Scientific Council NAMMD 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 shall be duly amended."

PRESIDENT
of the Scientific Council
of the National Agency for Medicines and Medical Devices,
Acad. Prof. Dr. Leonida Gherasim

DECISION

No. 27/13.12.2011

on approval of the Guideline on the collection, verification and presentation of adverse event/reaction reports arising from 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. 1123/18.08.2010, modified through Order of the Minister of Health No. 1601/28.11.2011, reunited on summons of the President of the National Agency for Medicines and Medical Devices in the ordinary meeting of 07.03.2012, in accordance with Article 12(5) of Government Decision No. 734/2010 on establishment, organisation and operation of the National Agency for Medicines and Medical Devices, as amended, adopts the following

DECISION

Art. 1. – The Guideline on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use is approved according to the Annex which is integral part of this decision.

Art. 2. - On this decision coming into force, NAMMD Scientific Council Decision no. 26/28.09.2007 on approval of the detailed Guideline on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use shall be repealed.

PRESIDENT
of the Scientific Council
of the National Agency for Medicines and Medical Devices,
Acad. Prof. Dr. Leonida Gherasim

ANNEX

GUDELINE

on collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use

CHAPTER I

I.1 Introduction

Article 1. – This guidance is a translation into Romanian and an adaptation of the CT 3 Guidance (2011/C 172/01) on collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use.

I.2 Legal basis

Article 2. – Article 65 of Order of the Minister of Public Health (hereinafter OMPH) 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, transposing 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[1], on request by the European Commission, provides for participation draw and publication by the National Agency for Medicines and Medical Devices (hereinafter NAMMD) of detailed guidance on the collection, verification and presentation of adverse event/reaction reports, together with decoding procedures for unexpected serious adverse reactions; this guidance responds to obligations stipulated in this article.

Article 3. – According to provisions of Article 4(2) of OMPH No. 904/2006 transposing Article 3(1) of Directive 2001/20/EC, all national provisions on the protection of clinical trial subjects have to be consistent with the procedures and time-scales set out in OMPH No. 904/2006, including procedures and time-scales for the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use. This document provides guidance on these aspects.

Article 4. – When applying OMPH No. 904/2006, the NAMMD and the National Ethics Committee on medicinal product study as well as local boards for monocentric trials and persons to whom tasks and functions related to safety reporting have been delegated, should consider this guidance.

I.3.Scope

Article 5. – This detailed guidance addresses the collection, verification and reporting of adverse events and adverse reactions which occur in a clinical trial falling within the scope of OMPH No. 904/2006, i.e. a clinical trial as defined therein and performed in at least one EU Member State.

Article 6. – For more details on the scope of OMPH No. 904/2006, reference is made to section 1.2 of the Scientific Council Decision No. 22/2010 on the Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial[2](hereinafter ‘detailed guidance CT-1’).

[1]OJ L 121, 1.5.2001, p. 34

[2]For the purposes of this document, references to the EU, EU Member States or Member States should be understood to include the EEA or EEA Contracting States, unless indicated otherwise.

I.4. Definitions

Article 7. – The definitions contained in OMPH No. 904/2006 transposing Directive 2001/20/EC, its implementing Commission acts and relevant Commission guidance documents in their current versions also apply in respect of this detailed guidance.

Article 8. – Regarding the terms 'adverse event', 'adverse reaction', 'suspected', 'unexpected', and 'serious', reference is made to the respective sections of this detailed guidance.

Article 9. – For the purposes of this detailed guidance, 'Member State concerned' means the Member State in which the clinical trial has been authorised by the national competent authority and received a favourable opinion of the Ethics Committee.

1.5. Interface with other guidance documents

Article 10.–This detailed guidance is to be read in conjunction with, in particular:

— Scientific Council Decision No. 22/2010 transposing the detailed guidance CT-1, and

— the *Note for guidance on clinical safety data management: Definition and standards for expedited reporting*[3] (hereinafter '*note for guidance ICH E2A'*).

Article 11. – Where appropriate, this detailed guidance reproduces the content of the above-mentioned guidance documents in order to facilitate application of the rules on safety reporting.

CHAPTER II
INTERFACE WITH PHARMACOVIGILANCE RULES

Article 12. – The pharmacovigilance rules laid down in Law No. 95/2006 on healthcare reform, as amended, transposing Directive 2001/83/EC, as amended[4], and 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 (hereinafter '*Regulation (EC) No. 726/2004'*)[5] do not apply to investigational medicinal products ('IMPs') and non-investigational medicinal products[6] ('non-IMPs')[7].

Article 13. – It follows that:

— safety reporting falls *either* under OMPH No. 904/2006*or* under the provisions on pharmacovigilance as set out in Law No. 95/2006and Regulation (EC) No. 726/2004. Adverse reactions may not be reported under both regimes, i.e. OMPH No. 904/2006as well as Regulation (EC) No. 726/2004 and Law No. 95/2006,

— an adverse reaction to an IMP or non-IMP occurring in a clinical trial is only to be reported or followed up in accordance with OMPH No. 904/2006. In applying that Order, this detailed guidance should be complied with.

Article 14. – Thus, the responsibilities of sponsors and investigators as regards safety reporting are determined only by OMPH No. 904/2006.

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[3] OJ C 82, 30.3.2010, p. 1.
[4]CPMP/ICH/377/95 (http://www.ema.europa.eu/pdfs/human/ich/ 037795en.pdf).
[5] OJ L 311, 28.11.2001, p. 67.
[6] OJ L 136, 30.4.2004, p. 1.
[7] For guidance on these terms, see *Guidance on Investigational Medicinal Products (IMPs) and 'non investigational medicinal products' (NIMPs)* (http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm) Art. 697 c) of Law No. 95/2006 as amended, transposing Article 3(3) of Directive 2001/83/EC, See also Article 107(1), 3rd subparagraph of Directive 2001/83/EC, as amended by Directive 2010/84/EU of 15 December 2010

CHAPTER III
RESPONSIBILITIES OF THE INVESTIGATOR AND SPONSOR AS REGARDS MONITORING AND SAFETY REPORTING

Article 15.–The investigator's responsibilities entail:

— reporting of serious adverse events to the sponsor (see Chapter IV),

— reporting of certain non-serious adverse events and/or laboratory abnormalities to the sponsor (see Chapter V).

Article 16. –The sponsor's responsibilities entail:

— recording of adverse events (see Chapter VI),

— reporting of suspected unexpected serious adverse reactions ('SUSARs') to the NAMMD, be it directly or through the Eudravigilance Clinical Trials Module, see section VII.4) and the Ethics Committee (see Chapter VIII),

— informing the investigators (see section VII.10),

— annual safety reporting to the national competent authority and the Ethics Committee (see Chapter VIII).

Article 17. – The sponsor should continuously weigh anticipated benefits and risks of the clinical trial[8], which includes ongoing safety evaluation of IMPs.

Article 18. – The sponsor should arrange for systems and written standard operating procedures to ensure compliance with the necessary quality standards at every stage of case documentation, data collection, validation, evaluation, archiving, reporting and following-up.

Article 19. – Regarding clinical trials with advanced therapy investigational medicinal products, specific guidance is contained in the detailed guidelines on good clinical practice specific to advanced therapy medicinal products[9].

Article 20. – Delegation of tasks does not remove the ultimate responsibility of the sponsor or investigator for the conduct of the clinical trial in accordance with the applicable legislation.

CHAPTER IV
REPORTING OF SERIOUS ADVERSE EVENTS BY THE INVESTIGATOR TO THE SPONSOR

IV.1.Legal basis and purpose

Article 21. – Article 58 of OMPH No. 904/2006, transposing Article 16(1) of Directive 2001/20/EC reads as follows:

'(1) The investigator shall report all serious adverse events immediately to the sponsor except for those that the protocol or investigator's brochure identifies as not requiring immediate reporting.

(2) The immediate report shall be followed by detailed, written reports.

(3) The immediate and follow-up reports shall identify subjects by unique code numbers assigned to the latter.'

Article 22. –The purpose of this obligation is to ensure that the sponsor has the necessary information to continuously assess the benefit-risk balance of the clinical trial, in accordance with Article 23 a) of OMPH No. 904/2006, transposing Article 3(2)(a) of Directive 2001/20/EC.

[8]Art. 7 of Scientific Council Decision No. 39/2006, GCP guideline, transposing section 2.2 of ICH E6 – Good Clinical Practice
[9]EudraLex, volume 10

IV.2. ‘**Serious adverse event**’

IV.2.1. ‘Adverse event’

Article 23. – An ‘adverse event’ is defined in Article 21 lit. m) of OMPH No. 904/2006, transposing Article 2(m) of Directive 2001/20/EC as follows:

‘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 24. – An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product[10].

IV.2.2. ‘Serious adverse event’

Article 25. – A ‘serious adverse event’ is defined in Article 21 lit. o) of OMPH No. 904/2006, transposing Article 2(o) of Directive 2001/20/EC as follows:

‘Any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect’.

Article 26. – These characteristics/consequences have to be considered at the time of the event. For example, regarding a life- threatening event, this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Article 27. – Some medical events may jeopardise the subject or may require an intervention to prevent one of the above characteristics/consequences. Such events (hereinafter referred to as ‘important medical events’) should also be considered as ‘serious’ in accordance with the definition.

Article 28. – Medical and scientific judgment should be exercised in deciding whether an event is ‘serious’ in accordance with these criteria[11].

IV.3. Timelines

Article 29. – The investigator has to immediately report to the sponsor all serious adverse events with the exception of those that are identified as not requiring immediate reporting in the protocol or the investigator’s brochure (‘IB’)[12].

IV.3.1. Immediate reporting and follow-up report

Article 30. – Immediate reporting should allow the sponsor to take the appropriate measures to address potential new risks in a clinical trial. Therefore, the immediate report should be made by the investigator within a very short period of time and under no circumstances should this exceed 24 hours following knowledge of the serious adverse event.

Article 31. – The follow-up report should allow the sponsor to determine whether the serious adverse event requires a reassessment of the benefit-risk balance of the clinical trial, if the relevant information was not already available and provided in the initial report.

IV.3.2. Non-immediate reporting

Article 32.–In cases where reporting is not required immediately (see above under section 4.3) the investigator shall report within the appropriate time frame, taking account of the specificities of the trial and of the serious adverse event, as well as possible guidance in the protocol or the IB[13].

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[10] Section 2.A.1 of the note for guidance ICH E2A

[11] Examples are provided in section 2.B of the note for guidance ICH E2A.

[12] See also sections 2.5 and 2.6 of the detailed guidance CT-1.

[13] See footnote 12.

IV.4. Start and end of reporting serious adverse events to the sponsor

Article 33. – The investigator is responsible for reporting to the sponsor all serious adverse events in relation to subjects treated by him in the clinical trial.

(2) The investigator does not need to actively monitor subjects for adverse events once the trial has ended, unless provided otherwise in the protocol[14].

Article 34. – Serious adverse events occurring to a subject after the treatment of that subject has ended should be reported to the sponsor if the investigator becomes aware of them[15].

CHAPTER V
REPORTING OF NON-SERIOUS ADVERSE EVENTS AND/OR LABORATORY ABNORMALITIES BY THE INVESTIGATOR TO THE SPONSOR

Article 35. – Article 59 of OMPH No. 904/2006, transposing Article 16(2) of Directive 2001/20/EC reads as follows:

'Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations shall be reported to the sponsor according to the reporting requirements and within the time periods specified in the protocol.'

Article 36. – Regarding the definition of adverse event, reference is made to section IV.2.1.

CHAPTER VI
RECORD-KEEPING BY THE SPONSOR

Article 37. – Article 61 of OMPH No. 904/2006, transposing Article 16(4), first sentence of Directive 2001/20/EC reads as follows:

'The sponsor shall keep detailed records of all adverse events which are reported to him by the investigator or investigators.'

CHAPTER VII
REPORTING OF SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS BY THE SPONSOR

VII.1. Legal basis and purpose

Article 38.–Article 62 (1), (2), (4) of OMPH No. 904/2006, transposing Article 17(1)(a), (b) and (d) of Directive 2001/20/EC reads as follows:

'(1) The sponsor shall ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening is recorded and reported as soon as possible to the competent authorities in all the Member States concerned, and to the Ethics Committee, and in any case no later than seven days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days.

[14] For advanced therapy medicinal products there are specific provisions in section VIII of the *detailed guidelines on good clinical practice specific for advanced therapy medicinal products* (http://ec. europa.eu/health/documents/eudralex/vol-10/index_en.htm).

[15] See section 3.E.3 of the note for guidance ICH E2A

(2) All other suspected serious unexpected adverse reactions shall be reported to the competent authorities concerned and to the Ethics Committee concerned as soon as possible but within a maximum of 15 days of first knowledge by the sponsor.

(3) The sponsor shall also inform all investigators.'

Article 39. – Article 64 of OMPH No. 904/2006, transposing Article 17(3)(a) of Directive 2001/20/EC reads as follows:

'The National Medicines Agency shall see to it that all suspected unexpected serious adverse reactions to an investigational medicinal product which are brought to its attention are immediately entered in a European database to which only the competent authorities of the Member States, the Agency and the Commission shall have access.'

Article 40. – The 'European database' referred to Article 64 of OMPH No. 904/2006, transposing Article 17 of Directive 2001/20/EC is the Eudravigilance Clinical Trials Module ('EVCTM')[16].

Article 41. – The purpose of the reporting obligation towards the NAMMD (be it directly or indirectly through the EVCTM, see section VII.4) is to make the NAMMD aware of SUSARs and to collect safety information on the safety profile of an IMP. This, in turn, is intended to give the relevant NAMMD the opportunity to:

— assess, in view of the various reported SUSARs, whether an IMP poses an unknown risk to the subject, and

— take measures to protect the safety of subjects, if necessary.

Article 42. – The purpose of the reporting obligation towards the Ethics Committee (see Chapter VIII) is to make the Ethics Committee aware of SUSARs that have occurred in Romania.

Article 43. – The purpose of the information obligation towards the investigator (see section VII.10) is to inform investigators of safety issues in view of detected SUSARs.

VII.2. Suspected unexpected serious adverse reaction

VII.2.1. 'Adverse reaction' — causality

Article 44. – An 'adverse reaction' is defined in Article 21 n) of OMPH No. 904/2006, transposing Article 2(n) of Directive 2001/20/EC as follows:

'all untoward and unintended responses to an investigational medicinal product related to any dose administered'.

Article 45. – The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.

Article 46. – The definition implies a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.

Article 47. – An untoward and unintended response to a non-IMP which does not result from a possible interaction with an IMP is, by definition, not a SUSAR (see also section VII.6). For possible follow-up action reference is made to section VII.11.3.

VII.2.2. 'Serious' adverse reaction

Article48. – Regarding the criterion of 'seriousness', reference is made to section IV.2.2.

[16] http://eudravigilance.ema.europa.eu/human/index02.asp

VII.2.3. 'Unexpected' adverse reaction

VII.2.3.1. Definition

Article 49. – Article 21 p) of OMPH No. 904/2006, transposing Article 2(p) of Directive 2001/20/EC defines 'unexpected adverse reaction' as follows:

'an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorised investigational product or summary of product characteristics for an authorised product)'.

Article 50. – The term 'severity' is used here to describe the intensity of a specific event. This has to be distinguished from the term 'serious'[17].

Article 51. – Reports which add significant information on the specificity, increase of occurrence, or severity of a known, already documented serious adverse reaction constitute unexpected events[18].

VII.2.3.2. Reference safety information

Article 52. – (1) The expectedness of an adverse reaction is determined by the sponsor in the reference safety information ('RSI').

(2) This should be done from the perspective of events previously observed, not on the basis of what might be anticipated from the pharmacological properties of a medicinal product[19].

Article 53. – (1) The RSI is contained in the Summary of product characteristics ('SmPC') or the IB[20].

(2) The covering letter which is submitted with the application to the NAMMD should refer to the RSI[21].

Article 54. – If the RSI is contained in the IB, the IB should contain a clearly-identified section to this effect. This section should include information on the frequency and nature of the adverse reactions.

Article 55. – If the IMP has a marketing authorisation in several Member States concerned with different SmPCs, the sponsor should select the most appropriate SmPC, with reference to subject safety, as RSI[22].

Article 56. – (1) The RSI may change during the conduct of a clinical trial. This is typically a substantial amendment[23].

(2) For the purpose of SUSAR reporting the version of the RSI at the moment of occurrence of the SUSAR applies[24]. Thus, a change of the RSI impacts on the number of adverse reactions to be reported as SUSARs.

(3) Regarding the applicable RSI for the purpose of the annual safety report, see Chapter VIII.

VII.3. Assessment of seriousness, causality and expectedness

Article 57. – The sponsor is responsible for ensuring that all adverse events are reported which, cumulatively,

— have a reasonable possibility of a causal relationship (see section VII.2.1) to an IMP,

— are 'serious' (see section VII.2.2); and

[17]For examples, see section 2.B of the note for guidance ICH E2A.
[18] For examples, see section 2.C.2 of the note for guidance ICH E2A.
[19]See section 2.C of the note for guidance ICH E2A.
[20] For details, see section II.6 of Scientific Council Decision No. 22/2010, transposing section 2.6 of the detailed guidance CT-1.
[21] For details, see section II.3 of Scientific Council Decision No. 22/2010, transposing section 2.3 of the detailed guidance CT-.
[22]See footnote 21.
[23] For details, see sectionsIII.3and III.4 of Scientific Council Decision No. 22/2010, transposing sections 3.3 and 3.4 of the detailed guidance CT-.
[24]See footnote 21.

— are ‘unexpected’ (see section VII.2.3).

VII.3.1. ‘Seriousness’

Article 58. – The judgement as to whether the event is serious is usually made by the reporting investigator (see section IV.2.2).

VII.3.2. Causality

Article 59. – The assessment of whether there is a reasonable possibility of a causal relationship is usually made by the investigator.

Article 60. – (1) In the absence of information on causality from the reporting investigator, the sponsor should consult the reporting investigator and encourage him to express an opinion on this aspect.

(2) The causality assessment given by the investigator should not be downgraded by the sponsor.

(3) If the sponsor disagrees with the investigator’s causality assessment, the opinion of both the investigator and the sponsor should be provided with the report.

VII.3.3. ‘Expectedness’

Article 61. – Assessment of expectedness is usually done by the sponsor.

Article 62. – The ‘expectedness’ of a serious adverse reaction is assessed in the light of the RSI (see section VII.2.3.2).

Article 63. – If information on expectedness has been made available by the reporting investigator, this should be taken into consideration by the sponsor.

VII.4. SUSARs reported to the NAMMD (directly or indirectly through the EVCTM)

VII.4.1. Introduction

Article 64. – SUSARs have to be reported to the NAMMD.

Article 65. – In addition, EVCTM has to be populated with these reports.

Article 66. – (1) In the future, in order to simplify workflows and to avoid duplicate populating of EVCTM, the reporting of SUSARs to the NAMMD should be made for all SUSARs through the EVCTM .

(2) To this end, the capabilities of EVCTM are currently improved in accordance with section IX.3 towards ‘enhanced functionalities’.

(3) Once the enhanced functionalities have been reached, a ‘final arrangement’ (see section VII.4.3) applies. Until that time, i.e. during the transitional period, a ‘transitional arrangement’ (see section VII.4.2) applies.

Article 67. – The Commission will publicly announce when this final arrangement has been reached, after this has been established jointly by the Commission, the European Medicines Agency (‘Agency’) and the national competent authorities, the NAMMD included.

Article 68. – Regarding reporting to the national competent authority, the NAMMD included, a distinction has to be made between direct and indirect reporting:

— ‘Direct reporting’: the sponsor reports the SUSAR directly as an individual case safety report (‘ICSR’) to the national competent authority in the relevant member state (the NAMMD in Romania)[25],

[25] For details which is the ‘relevant’ Member State, see below.

— 'Indirect reporting'/'Indirect reporting through the EVCTM': the sponsor reports the SUSAR as an ICSR through the EVCTM to the national competent authority in the relevant member state (the NAMMD in Romania)[26].

VII.4.2. SUSARs to be reported and reporting modalities (transitional arrangement)

Article 69. – The transitional arrangement (see section VII.4.1) for reporting SUSARs to the national competent authorities, the NAMMD included, is as follows:

VII.4.2.1. SUSARs to be reported (transitional arrangement)

Article70. – The sponsor of a clinical trial performed in at least one Member State should report the following SUSARs:

— all SUSARs occurring in that clinical trial, irrespective of whether the SUSAR has occurred at a trial site in a Member State or at a trial site in a third country concerned,

— all SUSARs related to the same active substance (regardless of pharmaceutical form and strength or indication investigated) in a clinical trial performed exclusively in a third country or exclusively in another Member State, if that clinical trial, is

— sponsored by the same sponsor, or

— sponsored by another sponsor who is either part of the same mother company or who develops a medicinal product jointly, on the basis of a formal agreement, with that other sponsor[27].

VII.4.2.2. Reporting modalities (transitional arrangement)

Article 71. – In the transitional arrangement, the modalities for reporting are as follows:

(a) Reporting to the NAMMD[28]:

— The SUSARs referred to in section VII.4.2.1, first bullet, are reported to the NAMMD;

— The SUSARs referred to in section VII.4.2.1, second bullet, are reported to the NAMMD, where the NAMMD has authorised the clinical trial with the same active substance.

Article 72. – The reporting of SUSARs to the NAMMD starts with the authorisation of the clinical trial by the NAMMD[29] and ends with the completion of the treatment of all subjects enrolled in Romania.

(b) Populating the EVCTM:

Article 73. – (1) The NAMMD is responsible for ensuring that EVCTM is populated with the SUSARs reported to it, according to this section.

(2) To this end, the national competent authorities may:

— Provide for the national competent authority to populate EVCTM.

— Provide for indirect reporting, or

— Leave it up to the sponsor to choose indirect or direct reporting.

(3) In Romania, SUSAR reporting is performed according to rules related to electronic reporting as posted on the EudraVigilance website, at http://eudravigilance.ema.europa.eu/human/docs/20101210_Romania_SUSAR.pdf.

Article 74. – If the SUSAR has occurred in a third country, and that clinical trial is performed also in the EU, the sponsor should report indirectly through the EVCTM or choose

[26] See footnote 25.

[27] Provision of the IMP or information to a future potential marketing authorisation holder on safety matters should not be considered a joint development.

[28] A list of addressees and databases for the national competent authorities is available here: http://ec.europa.eu/health/human-use/clinical-trials/index_en.htm

[29] For SUSARs occurring prior to the authorisation, see section II. 1.4.2. of Scientific Council Decision No. 22/2010, transposing section 2.1.4.2. of the detailed guidance CT-1.

any one Member State where the national competent authority populates EVCTM and where the national competent authority has authorised the clinical trial.

Article 75. – If the clinical trial is exclusively performed in a third country, and the SUSAR is reported to the national competent authority of a Member State (see section VII.4.2.1, second bullet), the sponsor should report indirectly through the EVCTM or choose any one Member State where the national competent authority populates EVCTM and where the national competent authority has authorised the clinical trial which is performed in the EU.

Article 76. – SUSARs identified after the end of the trial[30] should be reported as well. This should be done by way of indirect reporting through the EVCTM.

VII.4.3. SUSARs to be reported and reporting modalities (final arrangement)

Article 77. – The final arrangement (see section VII.4.1) for reporting SUSARs is as follows:

VII.4.3.1. SUSARs to be reported (final arrangement)

Article 78. – The sponsor of a clinical trial performed in at least one Member State should report the following SUSARs:

— all SUSARs occurring in that clinical trial, irrespective of whether the SUSAR has occurred at a trial site in a Member State or in a third country concerned, and

— all SUSARs related to the same active substance (regardless of pharmaceutical form and strength or indication investigated) in a clinical trial performed exclusively in a third country, if that clinical trial, is

- sponsored by the same sponsor, or
- sponsored by another sponsor who is either part of the same mother company or who develops a medicinal product jointly, on the basis of a formal agreement, with that other sponsor[31].

VII.4.3.2. Reporting modalities (final arrangement)

Article 79. – SUSARs to be reported in accordance with section VII.4.3.1 are reported indirectly to the national competent authorities of all Member States concerned, the NAMMD included, through the EVCTM.

Article 80. – (1) Sponsors may not have the resources and experience for indirect reporting.

(2) Consequently, the sponsor may delegate indirect reporting to another person, for example, where a commercial partner is involved (e.g. the marketing authorisation holder of the IMP), indirect reporting could be delegated to that partner[32]:

Article 81. – (1) SUSARs identified after the end of the trial[33] should be reported as well.

(2) This should be done by way of indirect reporting through the EVCTM.

VII.5. Reporting of SUSARs to the Ethics Committee

Article 82. – The Ethics Committee does not have access to the EVCTM[34].

Article 83. – (1) Sponsors should report to the Ethics Committee issuing the 'single opinion' in accordance with Article 32 and 33 of OMPH No. 904/2006, transposing Article 7 of Directive 2001/20/EC, all SUSARs occurring in the clinical trial concerned, if the SUSARs occurred in Romania.

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[30] On the notion of 'end of trial', see Chapter IV of Scientific Council Decision No. 22/2010, transposing section 4 of the detailed guidance CT-1.

[31] See footnote 28.

[32] See section 5.1. of the Clinical Trials Application Form (http://ec. europa.eu/health/documents/eudralex/vol-10/index_en.htm).

[33] See footnote 31.

[34] Art. 64 of OMPH No. 904/2006, transposing Article 17 (3) a) of Directive 2001/20/EC

(2) It is recommended that all SUSARs arising in other member states and, where necessary, in third countries, to be subject to regular reporting at least every 6 months, as listing accompanied by a brief report by the sponsor, highlighting the main issues of interest; such regular reports should only include SUSARs occurring during the reporting time. A copy of the report should be submitted to the concerned national authority.

Article 84. – The National Ethics Committee and the NAMMD should liaise closely on matters related to subject safety, where necessary.

VII.6. Adverse reactions *not* to be reported as SUSARs

Article 85. – Sections VII.4 and VII.5 contain an exhaustive list of SUSARs to be reported. In particular, there is no need for the sponsor to report as SUSARs:

— adverse reactions related not to an IMP but to a non-IMP received by the subject and without interaction with the IMP (see section VII.2.1),

— SUSARs occurring in a clinical trial performed (partly or exclusively) in the EU for which he is not the sponsor. These SUSARs may come to the attention of the sponsor through individual reports, publications (such as academic literature) or regulatory authorities[35],

— adverse reactions occurring in a third country outside a clinical trial in relation to a medicinal product which is marketed there but which is exclusively used as an IMP in the EU.

Article 86. – These cases are instead addressed through reporting other than SUSAR reporting, as well as follow-up measures (see sections VII.11.3 and VII.11.4).

Article 87. – The rules on pharmacovigilance remain inapplicable in these cases (see Chapter II).

VII.7. Timelines for reporting relevant information on fatal or life-threatening SUSARs

VII.7.1. Reporting of 'relevant information'

Article 88. – The sponsor must report all information that is 'relevant', i.e. the information which is necessary in order to:

— verify whether the anticipated therapeutic and public health benefits continue to justify the foreseeable risks, and

— process the report administratively.

Article 89. – Medical and scientific judgement should be applied in identifying non-relevant and relevant information.

Article 90. – In particular, new administrative information that could impact on the case management is to be considered as 'relevant'. One example is information that may help to detect potential duplicates (e.g. new case identifiers have become known to the sponsor which may have been used in previous transmissions).

Article 91. – It may transpire, after the initial reporting, that the event is not a SUSAR, for example due to lack of causality, seriousness, or expectedness (hereinafter referred to as 'downgrade'). Downgrades should be considered as relevant information.

Article 92. – Examples of non-relevant information are minor changes of dates or corrections of typographical errors in the previous case version.

VII.7.2. Timelines, clock-start

Article 93. – In applying the rules on reporting of relevant information within the timelines the following should apply:

Article 94. – The clock for expedited initial reporting (day 0 = Di 0) starts as soon as the information containing the minimum reporting criteria has been received by the sponsor[36].

[35] Reporting these SUSARs would lead to double-entries as, in a functioning system, those SUSARs would be reported anyway.

Article 95. – For fatal and life-threatening SUSARs, the sponsor should report at least the minimum information as soon as possible and in any case no later than seven days after being made aware of the case.

Article 96. – If the initial report is incomplete, e.g. if the sponsor has not provided all the information/assessment within seven days, the sponsor is to submit a completed report based on the initial information within an additional eight days. In this instance, the receipt date should not be changed with regard to the initial report[37].

Article 97. – If significant new information on an already reported case is received by the sponsor, the clock starts again at day zero, i.e. the date of receipt of new information. This information should be reported as a follow-up report within 15 days[38].

Article 98. – The minimum information includes, at least, all of the following:

— valid EudraCT number (where applicable)[39],

— sponsor study number[40],

— one identifiable coded subject[41],

— one identifiable reporter[42],

— one SUSAR[43],

— one suspect IMP (including active substance name- code)[44],

— a causality assessment[45].

Article 99. – In addition, in order to properly process the report electronically, the following administrative information should be provided:

— the sender's (case) safety report unique identifier[46],

— the receive date of the initial information from the primary source[47],

— the receipt date of the most recent information[48],

— the worldwide unique case identification number[49],

— the sender identifier[50].

Article 100. – For the format and structure of the information, see section VII.9.

VII.8. Timelines for non-fatal and non-life-threatening SUSARs

Article 101. – SUSARs which are not fatal and not life-threatening are to be reported within 15 days.

Article 102. – (1) There may be cases where a SUSAR turns out to be fatal or life-threatening, whereas initially it was considered as non-fatal or not life-threatening.

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[36] If the task has been delegated to another person, the date of receipt by that other person is the clock-start.
[37] In case of electronic transmission of the ICSR, this means that the date specified in the ICH E2B(R2) data element A.1.6 'Receive date' should be the same as the date specified in the ICH E2B(R2) data element A.1.7 'Receipt date'.
[38] In case of electronic transmission of the ICSR this means that the date specified in the ICH E2B(R2) data element A.1.6 'Receive date' should be the same as the date when the initial report was received. In the ICH E2B(R2) data element A.1.7 'Receipt date' the date when significant new information on the case was received by the sponsor should be indicated.
[39] For electronic transmission to be included in the ICH E2B(R2) data element A.2.3.1.
[40] For electronic transmission to be included in the ICH E2B(R2) data element A.2.3.2.
[41] For electronic transmission to be included in the ICH E2B(R2) Section B.1.
[42] For electronic transmission to be included in the ICH E2B(R2) Section A.2.
[43] For electronic transmission to be included in the ICH E2B(R2) Section B.2.
[44] For electronic transmission to be included in the ICH E2B(R2) Section B.4.
[45] For electronic transmission to be included in the ICH E2B(R2) Section B.4.k.18.
[46] For electronic transmission to be included in the ICH E2B(R2) data element A.1.0.1.
[47] For electronic transmission to be included in the ICH E2B(R2) data element A.1.6.
[48] For electronic transmission to be included in the ICH E2B(R2) data element A.1.7.
[49] For electronic transmission to be included in the ICH E2B(R2) data element A.1.10
[50] For electronic transmission to be included in the ICH E2B(R2) data element A.3.1.2.

(2) The non-fatal or non-life- threatening SUSAR should be reported as soon as possible, but within 15 days.

(3) The fatal or life-threatening SUSAR follow-up report should be made as soon as possible, but within a maximum of seven days after first knowledge of the reaction being fatal or life-threatening.

(4) Regarding the follow-up report, see section VII.7.2.9.

Article 103. – 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, while the initial report has not yet been submitted, a combined report should be created.

VII.9. Format of report

VII.9.1. In case of indirect reporting

Article 104. – Regarding the details of reporting indirectly an individual case safety report ('ICSR') through the EVCTM, reference is made to the following documents:

— the current version of the ICH E2B guideline on Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports (hereinafter 'ICH E2B(R2)')[51], and

— The current version of the *Note for guidance EudraVigilance Human — Processing of safety messages and individual case safety reports* (ICSRs)[52].

Article 105. – It should be emphasised that:

— the sponsor should provide, before completing the clinical trials application form[53], information on the IMP in the EudraVigilance Medicinal Product Dictionary ('EVMPD')[54,55],

— the data in free-text fields should be entered in English,

— only reports complying with the validation rules[56] are accepted in EVCTM,

— the data in coded fields should contain internationally agreed terminologies, formats and standards for the conduct of pharmacovigilance.

Article 106. – Regarding initials or names of persons, if these are known to the sender but cannot be reported due to personal data protection requirements, this should be highlighted in the report[57].

VII.9.2. In case of direct reporting

Article 107. – The information should be structured in the same way as for indirect reporting, to enable the NAMMD to populate EVCTM.

Article 108. – This should also apply during the transitional arrangement referred to in section VII.4.2.

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[51] http://www.ich.org/products/guidelines/efficacy/article/efficacy- guidelines.html

[52]Doc. Ref. EMA/H/20665/04/Final Revision 2 of 15 October 2010 (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000199.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800250b3).

[53]http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm

[54] In order to standardise information between clinical trial applications and related SUSARs reported to the competent authorities, a list of all active substances entered in the EudraVigilance Medicinal Product Dictionary, including development substances — codes, will be made available in the public domain for use in completing the clinical trial application form for EudraCT in the relevant fields.

[55] A 'help function' will be available by the Agency for sponsors who have difficulty with accessing or entering information in EVMPD

[56] See *Note for guidance EudraVigilance Human — Processing of safety messages and individual case safety reports (ICSRs)*, Doc. Ref. EMA/H/20665/04/Final Revision 2 of 15 October 2010.

[57] As regards the ICH E2B data elements, the field should be populated by 'PRIVACY'.

VII.10. Informing the investigator

Article 109. – Article 62 (4) of OMPH No. 904/2006, transposing Article 17(1)(d) of Directive 2001/20/EC provides that 'the sponsor shall also inform all investigators'.

Article 110. – (1) The information should be concise and practical.

(2) Therefore, whenever practicable the information on SUSARs should be aggregated in a line listing of SUSARs in periods as warranted by the nature of the research project/clinical development project and the volume of SUSARs generated. This line listing should be accompanied by a concise summary of the evolving safety profile of the IMP.

Article 111. – Regarding blinded treatment allocation, see section VII.11.1.

VII.11. Other issues

VII.11.1. Unblinding treatment allocation[58]

Article 112. – As a general rule only SUSARs on which the treatment allocation of the subject is unblinded should be reported by the sponsor to the NAMMD (be it directly or indirectly through the EVCTM, see section VII.4), as well as the Ethics Committee (see section VII.5).

Article 113. – Investigators (see section VII.10) should only receive blinded information unless unblinded information is judged necessary for safety reasons[59].

Article 114. – The investigator should only unblind the treatment allocation in the course of a clinical trial if this is relevant to the safety of the subject.

Article 115. – (1) As regards the sponsor, when an event may be a SUSAR the blind should be broken by the sponsor only for that specific subject.

(2) The blind should be maintained for persons responsible for the ongoing conduct of the study (such as the management, monitors, investigators) and those responsible for data analysis and interpretation of results at the conclusion of the study, such as biometrics personnel.

(3) Unblinded information should only be accessible to those who need to be involved in the safety reporting to the NAMMD (be it directly or indirectly through the EVCTM), Ethics Committees and Data Safety Monitoring Boards ('DSMB')[60], or persons performing ongoing safety evaluations during the trial.

Article 116.– (1) However, for trials 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.

(2) Under these and similar circumstances, the sponsor should reach agreement in the authorisation process as to which serious events would be treated as disease- related and not subject to systematic unblinding and expedited reporting[61].

Article 117. – For such trials, sponsors are strongly encouraged to appoint an independent DSMB in order to review safety data on the ongoing trial on a regular basis and when necessary to recommend to the sponsor whether to continue, modify or terminate the trial. The composition and operation of the DSMB should be described in the protocol.

Article 118. – (1) In all cases, following unblinding, if the event turns out to be a SUSAR (for example as regards expectedness), the reporting rules for SUSARs apply (see sections above).

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[58] See also section 3.D. of the note for guidance ICH E2A.
[59] More information is contained in section 3.D of the note for guidance ICH E2A.
[60] On DSMBs, see also the EMA guideline on Data Monitoring Committees, Doc. Ref. EMEA/CHMP/EWP/5872/03 Corr (http:// www.ema.europa.eu/pdfs/human/ewp/587203en.pdf).
[61] See section II.5 of Scientific Council Decision No 22/2010, transposingsection 2.5 of the detailed guidance CT-1.

(2) For cases where the SUSAR becomes apparent only after the trial has ended, reference is made to section VII.4.

VII.11.2. SUSARs associated with active comparator or placebo

Article 119. – (1) Comparators and placebos are IMPs[62]. Therefore, SUSARs associated with a comparator product follow the same reporting requirements as for the test IMP.

(2) Events associated with placebo will usually not satisfy the criteria for a SUSAR and therefore for expedited reporting. However, where SUSARs are associated with placebo (e.g. reaction due to an excipient or impurity), the sponsor should report such cases[63].

VII.11.3. Adverse reactions related to non-IMPs

Article 120. – A serious adverse reaction which is related not to an IMP but to a non-IMP is not a SUSAR and not reported as such (see section VII.2.1).

Article 121. – While the legal obligations contained in the rules on pharmacovigilance as set out in Law No. 95/2006 and Regulation (EC) No. 726/2004 do not apply (see Chapter II) to adverse reactions to IMPs or non-IMPs, in cases where the non-IMP is an authorised medicinal product, investigators and sponsors are encouraged to report suspected adverse reactions to the non-IMP to the NAMMD or to the marketing authorisation holder.

VII.11.4. Safety issues not falling within the definition of SUSAR — other measures

Article 122. – Events may occur during a clinical trial which do not fall within the definition of SUSAR and thus are not subject to the reporting requirements for SUSARs, even though they may be relevant in terms of subject safety. Examples[64] are:

— new events related to the conduct of a trial or the development of an IMP likely to affect the safety of subjects, such as:

- a serious adverse event which could be associated with the trial procedures and which could modify the conduct of the trial,
- a significant hazard to the subject population such as lack of efficacy of an IMP used for the treatment of a life-threatening disease,
- a major safety finding from a newly completed animal study (such as carcinogenicity),
- a temporary halt of a trial for safety reasons if the trial is conducted with the same investigational medicinal products in another country by the same sponsor,11

— recommendations of the DSMB, if any, where relevant for the safety of subjects,

— in the case of advanced therapy investigational medicinal products, relevant safety information regarding the procurement or the donor.

Article 123. – These events/observations are not to be reported as SUSARs, but they might require other action, such as:

— urgent safety measures and their notification (Article 10(b) of Directive 2001/20/EC, see also section 3.9 of the detailed guidance CT-1),

— substantial amendments (Article 10(a) of Directive 2001/20/EC; see also section 3.7 of the detailed guidance CT-1), or

[62] Art. 21 d) of OMPH No. 904/2006, transposing Article 2(d) of Directive 2001/20/EC.
[63] The suspected ingredient of the placebo should be specified in the ICH E2B(R2) data element B.4.k.2.2. 'Active substance name'.
[64] For examples, see section 3.A.2 of the note for guidance ICH E2A.

— early termination of the trial (Article 10(c) of Directive 2001/20/EC; see also section 4.2.2 of the detailed guidance CT-1).

Article 124. – Moreover, it is recommended that the sponsor informs the NAMMD and the Ethics Committee of safety issues which might materially alter the current benefit-risk assessment of an IMP while not falling within the actions listed above.

CHAPTER VIII
ANNUAL SAFETY REPORTING BY THE SPONSOR TO THE NAMMD AND THE ETHICS COMMITTEE

Article 125. – Article 63 of OMPH No. 904/2006, transposing Article 17(2) of Directive 2001/20/EC reads as follows:

'Once a year throughout the clinical trial, the sponsor shall provide the Member States in whose territory the clinical trial is being conducted and the Ethics Committee with a listing of all suspected serious adverse reactions which have occurred over this period and a report of the subjects' safety.'

Article 126. – The report is addressed to the NAMMD and the Ethics Committee.

Article 127. - The report should only be submitted to the NAMMD and the Ethics Committee if the treatment of subjects is still ongoing in Romania[65].

Article 128. – (1) For details regarding annual safety reporting, including rules for unblinding, reference is made to the guideline ICH Topic E2F — Development Safety Update Report[66] ('DSUR', hereinafter '*Note for guidance ICH E2F'*).

(2) The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has published 'model DSURs'.

(3) These 'model DSURs' take account of the differing knowledge about a medicine, depending on whether the sponsor holds the marketing authorisation or not[67].

Article 129. – The report should contain, in an appendix, the RSI in effect at the start of the reporting period (see section VII.2.3.2; see also sections 2.6 and 3.20 of the note for guidance ICH E2F).

Article 130. – The RSI in effect at the start of the reporting period serves as RSI during the reporting period[68].

Article 131. – (1) If there are significant changes to the RSI during the reporting period they should be listed in the annual safety report[69,70].

(2) Moreover, in this case the revised RSI should be submitted as an attachment to the report[71], in addition to the RSI in effect at the start of the reporting period (see above).

(3) Despite the change to the RSI, the RSI in effect at the start of the reporting period serves as RSI during the reporting period[72].

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[65]See section 2.3 of the note for guidance ICH E2F.
[66]http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm
[67]http://www.ich.org/products/guidelines/efficacy/article/efficacy- guidelines.html
[68]See section 2.6 of the note for guidance ICH E2F.
[69]See section 3.4 of the note for guidance ICH E2F.
[70]They are typically also substantial amendments; see section 3.4.3.b of the detailed guidance CT-1.
[71]See footnote 69.
[72]This means that the RSI used as the basis for the annual report may not be identical with the evolving RSI which is the basis for SUSAR reporting (see section VII.2.3.2).

CHAPTER IX
FUNCTIONALITIES OF EVCTM

IX.1. Introduction

Article 132. – The EVCTM serves the following purposes:

— provision of an overview of SUSARs relevant for supervising clinical trials in the EU as a whole and in each Member State,

— facilitation of reporting to the NAMMD by way of indirect reporting, in particular in the case of multinational trials,

— facilitation of communication of SUSARs between national competent authorities, the NAMMD included, the Commission and the Agency.

Article 133. – The data contained in the EVCTM are not accessible to persons other than the national competent authorities, the NAMMD included, the Agency and the Commission[73].

Article 134. – The EVCTM is based on pick lists, dropdown menus and dictionaries or automatically generated codes or text. It is acknowledged that not all dictionaries will be available in all official languages and may initially exist only in English. Translations of dictionaries will only be used where the originators of the dictionaries make full and current versions available.

IX.2. Basic functionalities

Article 135. – The basic functionalities of the EVCTM allow for:

— indirect reporting based on the current version of internationally agreed formats,

— generating specific reports integrating statistical methods of signal detection with option of primary filtering on source country, type of report, drug characterisation, the number of the EudraCT European clinical trials database (EudraCT number), sending organisations (national competent authorities, sponsors), date of reporting,

— Querying for:

- number of SUSARs reported for one or more selected IMPs or active substances,
- number of SUSARs reported by age group or indication (if reported) for one or more selected IMPs or active substances,
- number of SUSARs reported for a selected clinical trial based on one or more EudraCT numbers,
- individual case line listings for reactions grouped at any level of the MedDRA hierarchy for one or more selected medicinal products or active substances,

— Static reaction monitoring reports for one or more selected medicinal products or active substances.

IX.3. Enhanced functionalities

Article 136. – After the transitional arrangement (section VII.4.1), EVCTM will have enhanced functionalities in conjunction with EudraCT, allowing the NAMMD and the other competent authorities to receive:

— regular messages on new SUSARs for all relevant IMPs/clinical trials,

[73]See art. 64 of OMPH No. 904/2006, transposing Article 17(3)(a) of Directive 2001/20/EC.

— alerts in respect of SUSARs relevant to Member States for certain types of reactions, trials or populations, or IMPs of interest, and

— reports based on a range of ICH E2B and EudraCT fields.

Article 137. – Detailed technical requirements, as well as an implementation plan for the enhanced functionalities, are going to be published in a separate document.

DECISION

No. 28/13.12.2011

on approval of amendment of NAMMD Scientific Council Decision No. 13/05.04.2011 on approval of guidelines on consultations with target patient groups for the package leaflet and documentation on criteria for certification and inspection by the National Agency for Medicines and Medical Devices of operators performing consultations with target patient groups

The Scientific Council of the National Agency for Medicinal and Medical Devices (NAMMD), set up based on Order of the Minister of Health No. 1123/18.08.2010, amended through Order of the Minister of Health No. 1601/28.11.2011, reunited on summons of the NAMMD President in the ordinary meeting of 13.12.2011, in accord with Art. 12 (5) of Government Decision No. 734/2010 related to the set up, organisation and functioning of the National Agency for Medicines and Medical Devices, as amended, agrees on the following

DECISION

Art. 1. – Amendment of par. 6 of Article 4 of Annex No. 1 to NAMMD Scientific Council Decision No. 13/05.04.2011 on approval of guidelines on consultations with target patient groups for the package leaflet and documentation on criteria for certification and inspection by the National Agency for Medicines and Medical Devices of operators performing consultations with target patient groups is approved as follows:

"5) For medicinal products for human use having a marketing authorisation for which applications in view of safety variations have been submitted, within a year as of their approval, an application concerning the changes in design and wording of the package of medicinal products for human use, as well as changes in leaflet and the Summary of Product Characteristics, other than caused by Type IA, IB and II variations to MA terms, including the outcomes of consultations with target patient groups shall be submitted.

6) For all other medicinal products for human use, irrespective of the time of their authorisation/renewal, an application concerning the changes in design and wording of the package of medicinal products for human use, as well as changes in leaflet and the Summary of Product Characteristics, other than caused by Type IA,

IB and II variations to MA terms, including the outcomes of consultations with target patient groups shall be submitted by 1 June 2012."

Art. 2. – In case of non-compliance with the provisions to Art. 4, points (3), (4), (5) and (6) of Annex 1 to Scientific Council Decision No. 13/05.04.2011, the provisions of Art. 836 (1) i) of Law No. 95/2006 on healthcare reform, Title XVII – The medicinal product, as amended, shall be applied.

Art. 3. – On the coming into force of this Decision, NAMMD Scientific Council Decision No. 16/05.04.2011 on approval of the modification and supplementation of NAMMD Scientific Council Decision No. 13/05.04.2011 on approval of the Guideline on consultations with target patient groups for the package leaflet and documentation on criteria for certification and inspection by the National Agency for Medicines and Medical Devices of operators performing consultations with target patient groups shall be repealed.

PRESIDENT
of the Scientific Council
of the National Agency for Medicines and Medical Devices,
Acad. Prof. Dr. Leonida Gherasim

DECISION

No. 29/13.12.2011

on approval of the update of Annex 1 to Scientific Council Decision No. 33/13.12.2010 on approval of the Regulations for organisation and functioning of the Scientific Council of the National Agency for Medicines and Medical Devices

The Scientific Council of the National Agency for Medicines and Medical Devices (NAMMD), set up based on the Order of the Minister of Health No. 1123/18.08.2010, modified through the Order of the Minister of Health No. 1601/28.11.2011, reunited on summons of the NAMMD President in the ordinary meeting of 13.12.2011, in accordance with Art. 12 (5) of the Government Decision No. 734/2010 on the organisation and functioning of the National Agency for Medicines and Medical Devices, as amended, hereby adopts the following

DECISION

Single article. – The update of Annex 1 to Scientific Council Decision No. 33/13.12.2010 on approval of the Regulations for organisation and functioning of the Scientific Council of the National Agency for Medicines and Medical Devices is approved, in accordance with the provisions of the Order of the Minister of Health No. 1601/28.11.2011.

PRESIDENT
of the Scientific Council
of the National Agency for Medicines and Medical Devices,

Acad. Prof. Dr. Leonida Gherasim

ANNEX 1
to SC Regulation

Proposal/Document/SCD No.

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Crt. No.	NAMMD SC Members	For information/ discussion	Support			Adoption		
			YES	NO	Abstention	YES	NO	Abstention
1.	Acad. Prof. Dr. L. Gherasim							
2.	Dr. Petru Domocoş							
3.	Dr. Nicolae Fotin							
4.	Senior Pharm. Nela Vîlceanu							
5.	Prof. Dr. Ostin C. Mungiu							
6.	Prof. Dr. Dan Cheţa							
7.	Dr. Florian Bodog							
8.	Prof. Dr. Ofelia Crişan							
9.	Prof. Dr. Dragoş Vinereanu							
10.	Prof. Dr. Pharm. D. Lupuliasa							
11.	Dr. Dragoş Damian							
12.	Dr. Radu Răşinar							
13.	Conf. Dr. Eng. Victor Purcărea							
Total								

Medicinal product batches recalled during the 4th quarter of 2011

Crt. No.	Product recalled	Pharmaceutical form	Strength	INN	Manufacturer/MAH	Batch	Grounds for withdrawal	Action proposed	Date of withdrawal
1	Meclodin	vaginal tablets	500 mg/ 200 mg	metronidazole/ clotrimazole	S.C. Arena Group, Voluntari	2840709 (06.2012)	The presence of longitudinal fissures, rugged surface and chipped edges in some tablets	Withdrawal and destruction	01.08.2011
2	Prospan ®	syrup	7 mg/ml	herbs	Engelhard Arzneiminttel, Germany	11F024A	Microbial contamination	Voluntary withdrawal and destruction	02.09.2011
3	Fastum Gel	gel	25 mg/ml	ketoprofen	A. Menarini Manufacturing Logistics and Services/ A. Menarini Industrie Farmaceutiche Riunite S.R.L., Italy	all batches	Secondary packaging and leaflet not updated in accordance with European Commission Decision No. 11/29.11.2010	Withdrawal from wholesale distributors in view of fixing the non-compliance (repackaging/ relabelling)	13.09.2011
4	Bronhosolv	tablets	8 mg	ambroxol	S.C. Laropharm S.R.L. Bragadiru	1010251 (expiry date: 09.2012)	Wrong imprinting of the primary packaging	Withdrawal and destruction	13.10.2011
5	Ambroxol AL	tablets	30 mg	ambroxol	Aliud®Pharma GmbH&CoKg, Germany	81338 (expiry date: 02.2012)	Voluntary withdrawal performed by the MAH in accordance with the Order of the Minister of Health No. 279/30.03.2005	Voluntary withdrawal and destruction	13.10.2011
6	Coldrex Maxgrip	tablets		combinations	GSK Dungarvan, Ireland/ GSK Export Ltd., Great Britain	080467, 080609, 080626, 080742, 080913,081000, 081080, 090036, 090126, 090237, 090383, 080459, 080592, 080669, 080932, 081001, 090154, 090252, 090400	Voluntary withdrawal performed by the MAH in accordance with the Order of the Minister of Health No. 279/30.03.2005	Voluntary withdrawal and destruction	17.10.2011
7	Strepsils Intensiv miere şi lămâie	lozenges		combinations	Reckitt Benckiser Healthcare International Ltd., Great Britain	12X, 10Y, 7AA3, 8AA, 8AA2, 1BB, 3BB, 12BB, 2CC2, 2CC3	Voluntary withdrawal performed by the MAH in accordance with the Order of the Minister of Health No. 279/30.03.2005	Voluntary withdrawal and destruction	19.10.2011

Crt. No.	Product recalled	Pharmaceutical form	Strength	INN	Manufacturer/MAH	Batch	Grounds for withdrawal	Action proposed	Date of withdrawal
8	Propafenon AL	film-coated tablets	150 mg	propafenone	Aliud®Pharma GmbH&CoKg, Germany	73877, 73878, 74281, 74284, 75086, 75087, 75089, 75090, 91210, 91211, 91305, 91306, 91307, 91408, 91409, 91412, 91413, 91514.	Voluntary withdrawal performed by the MAH in accordance with the Order of the Minister of Health No. 279/30.03.2005	Voluntary withdrawal and destruction	26.10.2011
9	Aspirin	tablets	500 mg	Acetylsalicylic acid	Bayer Bitterfeld GmbH, Germany/ Bayer S.R.L.	BTA90HO	Voluntary withdrawal performed by the MAH in accordance with the Order of the Minister of Health No. 279/30.03.2005	Voluntary withdrawal and destruction	01.11.2011
10	Colgate Periogard	oromucosal solution	0.2 %	chlorhexidine	Gabba International, Switzerland/ Gabba International, Switzerland	9314CHG11B (expiry date: 05.2012)	Microbial contamination (Burkhodeira sp.)	Voluntary withdrawal and destruction	01.11.2011
11	Vitamax	soft capsules		combinations	Europharm Romania/ GSK S.R.L. Romania	x 15 capsules: 001-021 x 5 capsules: 001-005	Discontinuation of the reauthorisation procedure on 08.11.2010	Voluntary withdrawal and destruction	21.11.2011
12	Marcofen	capsules	400 mg	ibuprofen	S.C. Europharm S.A.	025, 026, 027, 028,031, 032, 033	Voluntary withdrawal performed by the MAH in accordance with the Order of the Minister of Health No. 279/30.03.2005	Voluntary withdrawal and destruction	28.11.2011

Applications for marketing authorisation/marketing authorisation renewal submitted to the NAMMD during the 3rd quarter of 2011

During the 3rd quarter of 2011, 271 marketing authorisation/renewal applications for medicinal products corresponding to the following therapeutic groups have been received:

A01 – Stomatological preparations
A02 – Drugs for acid related disorders
A03 – Drugs for functional gastrointestinal disorders
A05 – Bile and liver therapy
A06 - Laxatives
A07 – Antidiarrheals, intestinal anti-inflammatory/anti-infective agents
A09 – Digestives, including enzymes
B01 – Antithrombotic agents
B02 - Antihemorrhagics
B05 – Blood substitutes and perfusion solutions
C01 – Cardiac therapy
C03 - Diuretics
C05 - Vasoprotectives
C07 – Beta blocking agents
C09 – Agents acting on the renin-angiotensin system
C10 – Lipid modifying agents
D01 – Antifungals for dermatological use
D05 - Antipsoriatics
D07 – Corticosteroids, dermatological preparations
G01 – Gynecological antiinfectives and antiseptics
G03 – Sex hormones and modulators of the genital system
G04 - Urologicals
H01 – Pituitary and hypothalamic hormones and analogues
J01 – Antibacterials for systemic use
J02 – Antimycotics for systemic use
J05 – Antivirals for systemic use
J07 - Vaccines
L01 – Antineoplastic agents
L02 – Endocrine therapy
L03 - Immunostimulants
L04 - Immunosuppressants
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
N05 - Psycholeptics
N06 - Psychoanaleptics
R01 – Nasal preparations
R02 – Throat preparations
R03 – Drugs for obstructive airway diseases
R05 – Cough and cold preparations
R06 – Antihistamines for systemic use
S01 - Ophthalmologicals
V01 - Allergens
V03 – All other therapeutic products
V08 – Contrast media
V09 – Diagnostic radiopharmaceuticals

Medicinal products authorised for marketing by the NAMMD during the 3rd quarter of 2011

INN	Invented name	Pharmaceutical form	Manufacturer	Country	MA Number		
ACIDUM ACETYLSALICYLICUM	ACID ACETILSALICILIC ACTAVIS 75 mg	gastroresistant tablets	ACTAVIS GROUP PTC EHF	ICELAND	3608	2011	19
ACIDUM ACETYLSALICYLICUM	ACID ACETILSALICILIC ACTAVIS 100 mg	gastroresistant tablets	ACTAVIS GROUP PTC EHF	ICELAND	3609	2011	19
ACIDUM ACETYLSALICYLICUM	ACID ACETILSALICILIC ACTAVIS 150 mg	gastroresistant tablets	ACTAVIS GROUP PTC EHF	ICELAND	3610	2011	19
ACIDUM ACETYLSALICYLICUM	ACID ACETILSALICILIC ACTAVIS 160 mg	gastroresistant tablets	ACTAVIS GROUP PTC EHF	ICELAND	3611	2011	19
ACIDUM IBANDRONICUM	OSAGRAND 150 mg	film-coated tablets	ZENTIVA K.S.	CZECH REPUBLIC	3777	2011	06
ACIDUM IBANDRONICUM	OSAGRAND 3 mg/3 ml	solution for injection	ZENTIVA K.S.	CZECH REPUBLIC	3778	2011	02
ACIDUM RISEDRONICUM	PEXALIT 5 mg	film-coated tablets	DR. REDDY'S LABORATORIES ROMANIA S.R.L.	ROMANIA	3565	2011	02
ACIDUM RISEDRONICUM	PEXALIT 35 mg	film-coated tablets	DR. REDDY'S LABORATORIES ROMANIA S.R.L.	ROMANIA	3566	2011	04
AMBROXOLUM	FLAVAMED COMPRIMATE 30 mg	tablets	BERLIN-CHEMIE AG	GERMANY	3693	2011	03
AMLODIPINUM	AMLODIPINA HELCOR 5 mg	tablets	HELCOR S.R.L.	ROMANIA	3666	2011	02
AMLODIPINUM	AMLODIPINA HELCOR 10 mg	tablets	HELCOR S.R.L.	ROMANIA	3667	2011	02
ATORVASTATINUM	MODLIP 10 mg	film-coated tablets	TORRENT PHARMA S.R.L.	ROMANIA	3648	2011	12
ATORVASTATINUM	MODLIP 20 mg	film-coated tablets	TORRENT PHARMA S.R.L.	ROMANIA	3649	2011	12
ATORVASTATINUM	MODLIP 40 mg	film-coated tablets	TORRENT PHARMA S.R.L.	ROMANIA	3650	2011	12

ATORVASTATINUM	MODLIP 80 mg	film-coated tablets	TORRENT PHARMA S.R.L.	ROMANIA	3651	2011	12
ATORVASTATINUM	ATORVASTATINA MYLAN 10 mg	film-coated tablets	GENERICS (UK) LTD	GREAT BRITAIN	3711	2011	05
ATORVASTATINUM	ATORVASTATINA MYLAN 20 mg	film-coated tablets	GENERICS (UK) LTD	GREAT BRITAIN	3712	2011	05
ATORVASTATINUM	ATORVASTATINA MYLAN 40 mg	film-coated tablets	GENERICS (UK) LTD	GREAT BRITAIN	3713	2011	05
ATORVASTATINUM	ATORVASTATINA MYLAN 80 mg	film-coated tablets	GENERICS (UK) LTD	GREAT BRITAIN	3714	2011	05
ATORVASTATINUM	TORVALIPIN 10 mg	film-coated tablets	ACTAVIS GROUP PTC EHF.	ICELAND	3724	2011	11
ATORVASTATINUM	TORVALIPIN 20 mg	film-coated tablets	ACTAVIS GROUP PTC EHF.	ICELAND	3725	2011	11
ATORVASTATINUM	TORVALIPIN 40 mg	film-coated tablets	ACTAVIS GROUP PTC EHF.	ICELAND	3726	2011	11
ATORVASTATINUM	ATORIS 30 mg	film-coated tablets	KRKA D.D., NOVO MESTO	SLOVENIA	3796	2011	14
ATORVASTATINUM	ATORIS 60 mg	film-coated tablets	KRKA D.D., NOVO MESTO	SLOVENIA	3797	2011	14
ATORVASTATINUM	ATORIS 80 mg	film-coated tablets	KRKA D.D., NOVO MESTO	SLOVENIA	3798	2011	14
ATORVASTATINUM	STATORVA 30 mg	film-coated tablets	MIKLICH LABORATORIOS S.L.	SPAIN	3799	2011	14
ATORVASTATINUM	STATORVA 60 mg	film-coated tablets	MIKLICH LABORATORIOS S.L.	SPAIN	3800	2011	14
ATORVASTATINUM	STATORVA 80 mg	film-coated tablets	MIKLICH LABORATORIOS S.L.	SPAIN	3801	2011	14
BETAHISTINUM	BETAHISTINA LPH 24mg	tablets	LABORMED PHARMA SA	ROMANIA	3723	2011	04
BICALUTAMIDUM	BICATLON 50 mg	film-coated tablets	MEDICO UNO PHARMA KFT.	HUNGARY	3744	2011	16
BILASTINUM	ALIGRIN 20 mg	tablets	MENARINI INTERNATIONAL OPERATIONS LUXEMBOURG S.A.	LUXEMBURG	3795	2011	05
BROMHEXINUM	BROMHEXIN HELCOR 8 mg	tablets	AC HELCOR SRL	ROMANIA	3699	2011	01
CEFIXIMUM	EFICEF 100 mg	capsules	ANTIBIOTICE S.A.	ROMANIA	3762	2011	02

CLARITHROMYCINUM	CLARITROMICINA MYLAN 500 mg	modified release tablets	GENERICS (UK) LTD	GREAT BRITAIN	3690	2011	11
COLECALCIFEROLUM	VITAMINA D3 BIOFARM 20000 IU/ml	oral drops, solution	BIOFARM S.A.	ROMANIA	3663	2011	01
COMBINATIONS	HARMONET 0.075mg/0.020 mg	lozenges	PFIZER EUROPE MA EEIG	AUSTRIA	3697	2011	02
COMBINATIONS (ETINILESTRADIOLUM + DROSPIRENONUM)	PALANDRA 0.03mg/3mg	film-coated tablets	BAYER SCHERING PHARMA AG	GERMANY	3619	2011	04
COMBINATIONS (ETINILESTRADIOLUM + DROSPIRENONUM)	LULINA 0.03 mg/3 mg	film-coated tablets	IVOWEN LIMITED	IRELAND	3779	2011	02
COMBINATIONS (ETINILESTRADIOLUM + DROSPIRENONUM)	BELUSHA 0.02 mg/3mg	film-coated tablets	GEDEON RICHTER ROMANIA S.A.	ROMANIA	3782	2011	02
COMBINATIONS (ACIDUM ACETYLSALICYLICUM+ BISOPROLOLUM)	BETAPRES 5mg/75mg	capsules	PHARMACEUTICAL WORKS POLPHARMA SA	POLAND	3652	2011	11
COMBINATIONS (ACIDUM ACETYLSALICYLICUM+ BISOPROLOLUM)	BETAPRES 10mg/75mg	capsules	PHARMACEUTICAL WORKS POLPHARMA SA	POLAND	3653	2011	11
COMBINATIONS (AMLODIPINUM+ BISOPROLOLUM)	ALOTENDIN 5mg/5mg	tablets	EGIS PHARMACEUTICALS PLC	HUNGARY	3807	2011	04
COMBINATIONS (AMLODIPINUM+ BISOPROLOLUM)	ALOTENDIN 5mg/10mg	tablets	EGIS PHARMACEUTICALS PLC	HUNGARY	3808	2011	04
COMBINATIONS (AMLODIPINUM+ BISOPROLOLUM)	ALOTENDIN 10mg/5mg	tablets	EGIS PHARMACEUTICALS PLC	HUNGARY	3809	2011	04
COMBINATIONS (AMLODIPINUM+ BISOPROLOLUM)	ALOTENDIN 10mg/10mg	tablets	EGIS PHARMACEUTICALS PLC	HUNGARY	3810	2011	04
COMBINATIONS (CANDESARTANUM CILEXETIL+ HYDROCHLOROTHIAZIDUM)	CANDESARTAN/ HIDROCLOROTIAZIDA MYLAN 8 mg/12.5 mg	tablets	GENERICS (UK) LTD	GREAT BRITAIN	3703	2011	15
COMBINATIONS (CANDESARTANUM CILEXETIL+ HYDROCHLOROTHIAZIDUM)	CANDESARTAN/ HIDROCLOROTIAZIDA MYLAN 16 mg/12.5 mg	tablets	GENERICS (UK) LTD	GREAT BRITAIN	3704	2011	15

COMBINATIONS (DORZOLAMIDUM+ TIMOLOLUM)	COSOPT FĂRĂ CONSERVANT 20 mg/ml + 5 mg/ml	eye drops, solution in single dose container	MERCK SHARP & DOHME ROMANIA S.R.L.	ROMANIA	3733	2011	03
COMBINATIONS (IRBERSARTANUM+ HYDROCHLOROTHIAZIDUM)	IRBEZYD COMBI 150 mg/12.5 mg	film-coated tablets	PHARMACEUTICAL WORKS POLPHARMA SA	POLAND	3615	2011	02
COMBINATIONS (IRBERSARTANUM+ HYDROCHLOROTHIAZIDUM)	IRBEZYD COMBI 300 mg/12.5 mg	film-coated tablets	PHARMACEUTICAL WORKS POLPHARMA SA	POLAND	3616	2011	02
COMBINATIONS (IRBERSARTANUM+ HYDROCHLOROTHIAZIDUM)	IRBEZYD COMBI 300 mg/25 mg	film-coated tablets	PHARMACEUTICAL WORKS POLPHARMA SA	POLAND	3617	2011	02
COMBINATIONS (LATANOPROSTUM+ TIMOLOLUM)	XALOPTIC COMBI 50 micrograms/ml + 5 mg/ml	oral drops, solution	PHARMACEUTICAL WORKS POLPHARMA S.A.	POLAND	3692	2011	03
COMBINATIONS (LATANOPROSTUM+TIMOLOLUM)	XALAPROST COMBI 50 micrograms/ml+ 5mg/ml	eye drops, solution	ICN POLFA RZESZOW S.A.	POLAND	3756	2011	03
COMBINATIONS (LOSARTANUM+ HYDROCHLOROTHIAZIDUM)	VALEZAAR PLUS 50 mg/12.5 mg	film-coated tablets	ICN POLFA RZESZOW S.A.	POLAND	3606	2011	01
COMBINATIONS (OLMESARTANUM+ AMLODIPINUM+ HYDROCHLOROTHIAZIDUM)	INOVUM HCT 20 mg /5 mg/12.5 mg	film-coated tablets	MENARINI INTERNATIONAL OPERATIONS LUXEMBOURG S.A.	LUXEMBURG	3739	2011	15
COMBINATIONS (OLMESARTANUM+ AMLODIPINUM+ HYDROCHLOROTHIAZIDUM)	INOVUM HCT 40 mg /5 mg/12.5 mg	film-coated tablets	MENARINI INTERNATIONAL OPERATIONS LUXEMBOURG S.A.	LUXEMBURG	3740	2011	15
COMBINATIONS (OLMESARTANUM+ AMLODIPINUM+ HYDROCHLOROTHIAZIDUM)	INOVUM HCT 40 mg /5 mg/25 mg	film-coated tablets	MENARINI INTERNATIONAL OPERATIONS LUXEMBOURG S.A.	LUXEMBURG	3741	2011	15
COMBINATIONS (OLMESARTANUM+ AMLODIPINUM+ HYDROCHLOROTHIAZIDUM)	INOVUM HCT 40 mg/10 mg/12.5 mg	film-coated tablets	MENARINI INTERNATIONAL OPERATIONS LUXEMBOURG S.A.	LUXEMBURG	3742	2011	15
COMBINATIONS (OLMESARTANUM+ AMLODIPINUM+ HYDROCHLOROTHIAZIDUM)	INOVUM HCT 40 mg/10 mg/25 mg	film-coated tablets	MENARINI INTERNATIONAL OPERATIONS LUXEMBOURG S.A.	LUXEMBURG	3743	2011	15

COMBINATIONS (OLMESARTANUM+ AMLODIPINUM+ HYDROCHLOROTHIAZIDUM))	SEVIKAR HCT 20mg/5 mg/12.5 mg	film-coated tablets	DAIICHI SANKYO EUROPE GMBH	GERMANY	3772	2011	15
COMBINATIONS (OLMESARTANUM+ AMLODIPINUM+ HYDROCHLOROTHIAZIDUM)	SEVIKAR HCT 40mg/5 mg/12.5 mg	film-coated tablets	DAIICHI SANKYO EUROPE GMBH	GERMANY	3773	2011	15
COMBINATIONS (OLMESARTANUM+ AMLODIPINUM+ HYDROCHLOROTHIAZIDUM)	SEVIKAR HCT 40mg/10 mg/12.5 mg	film-coated tablets	DAIICHI SANKYO EUROPE GMBH	GERMANY	3774	2011	15
COMBINATIONS (OLMESARTANUM+ AMLODIPINUM+ HYDROCHLOROTHIAZIDUM)	SEVIKAR HCT 40mg /5 mg/25 mg	film-coated tablets	DAIICHI SANKYO EUROPE GMBH	GERMANY	3775	2011	15
COMBINATIONS (OLMESARTANUM+ AMLODIPINUM+ HYDROCHLOROTHIAZIDUM)	SEVIKAR HCT 40mg/10 mg/25 mg	film-coated tablets	DAIICHI SANKYO EUROPE GMBH	GERMANY	3776	2011	15
COMBINATIONS (PERINDOPRILUM+ INDAPAMIDUM)	PERYL COMBI 2mg/0.625mg	tablets	ICN POLFA RZESZOW S.A.	POLAND	3559	2011	02
COMBINATIONS (PERINDOPRILUM+ INDAPAMIDUM)	PERYL COMBI 4mg/1.25mg	tablets	ICN POLFA RZESZOW S.A.	POLAND	3560	2011	02
COMBINATIONS (PERINDOPRILUM+ INDAPAMIDUM)	DANURIT 4 mg/1.25mg	tablets	GEDEON RICHTER ROMANIA S.A.	ROMANIA	3623	2011	04
COMBINATIONS (PERINDOPRILUM+ INDAPAMIDUM)	DANURIT 2 mg/0.625 mg	tablets	GEDEON RICHTER ROMANIA S.A.	ROMANIA	3624	2011	04
COMBINATIONS (PERINDOPRILUM+ INDAPAMIDUM)	INDAPRIL 2 mg/0.625 mg	tablets	LABORMED PHARMA S.A.	ROMANIA	3661	2011	04
COMBINATIONS (PERINDOPRILUM+ INDAPAMIDUM)	INDAPRIL 4 mg/1.25 mg	tablets	LABORMED PHARMA S.A.	ROMANIA	3662	2011	04
COMBINATIONS (PERINDOPRILUM+ INDAPAMIDUM)	PRICORON COMBI 2 mg/0.625 mg	tablets	ZENTIVA K.S.	CZECH REPUBLIC	3737	2011	04

COMBINATIONS (PERINDOPRILUM+ INDAPAMIDUM)	PRICORON COMBI 4 mg/1.25 mg	tablets	ZENTIVA K.S.	CZECH REPUBLIC	3738	2011	04
COMBINATIONS (VALSARTANUM+ HYDROCHLOROTHIAZIDUM)	VALSARTAN HIDROCLOROTIAZIDA TORRENT 80 mg/12.5 mg	film-coated tablets	TORRENT PHARMA S.R.L.	ROMANIA	3674	2011	03
COMBINATIONS (VALSARTANUM+ HYDROCHLOROTHIAZIDUM)	VALSARTAN HIDROCLOROTIAZIDA TORRENT 160 mg/12.5 mg	film-coated tablets	TORRENT PHARMA S.R.L.	ROMANIA	3675	2011	03
COMBINATIONS (VALSARTANUM+ HYDROCHLOROTHIAZIDUM)	VALSARTAN HIDROCLOROTIAZIDA TORRENT 160 mg/25 mg	film-coated tablets	TORRENT PHARMA S.R.L.	ROMANIA	3676	2011	03
COMBINATIONS (VALSARTANUM+ HYDROCHLOROTHIAZIDUM)	VALSARTAN HIDROCLOROTIAZIDA TORRENT 320 mg/12.5 mg	film-coated tablets	TORRENT PHARMA S.R.L.	ROMANIA	3677	2011	03
COMBINATIONS (VALSARTANUM+ HYDROCHLOROTHIAZIDUM)	VALSARTAN HIDROCLOROTIAZIDA TORRENT 320 mg/25 mg	film-coated tablets	TORRENT PHARMA S.R.L.	ROMANIA	3678	2011	03
COMBINATIONS (OLMESARTANUM+ AMLODIPINUM)	SEVIKAR 20 mg/5 mg	film-coated tablets	TERAPIA S.A.	ROMANIA	3645	2011	11
COMBINATIONS (OLMESARTANUM+ AMLODIPINUM)	SEVIKAR 40 mg/5 mg	film-coated tablets	TERAPIA S.A.	ROMANIA	3646	2011	11
COMBINATIONS (OLMESARTANUM+ AMLODIPINUM)	SEVIKAR 40 mg/10 mg	film-coated tablets	TERAPIA S.A.	ROMANIA	3647	2011	11
ANTI-INHIBITOR COAGULANT COMPLEX	FEIBA NF 500 U FEIBA	powder + solvent for solution for injection	BAXTER A.G.	AUSTRIA	3802	2011	02
ANTI-INHIBITOR COAGULANT COMPLEX	FEIBA NF 1000 U FEIBA	powder + solvent for solution for injection	BAXTER A.G.	AUSTRIA	3803	2011	03
DICLOFENACUM	DICLOSAL 10mg/g	gel	SLAVIA PHARM S.R.L.	ROMANIA	3654	2011	02

DOCETAXOLUM	TAXEGIS 20 mg	concentrate and solvent for solution for infusion	EGIS PHARMACEUTICALS PLC	HUNGARY	3631	2011	01
DOCETAXOLUM	TAXEGIS 80 mg	concentrate and solvent for solution for infusion	EGIS PHARMACEUTICALS PLC	HUNGARY	3632	2011	01
DONEPEZILUM	DONEPEZIL TORRENT 5 mg	film-coated tablets	TORRENT PHARMA S.R.L.	ROMANIA	3633	2011	12
DONEPEZILUM	DONEPEZIL TORRENT 10 mg	film-coated tablets	TORRENT PHARMA S.R.L.	ROMANIA	3634	2011	12
DOPAMINUM	CLORHIDRAT DE DOPAMINA ZENTIVA 5 mg/ml	concentrate for solution for infusion	ZENTIVA S.A.	ROMANIA	3561	2011	02
EPLERENONUM	ERIDANUS 25 mg	film-coated tablets	GEDEON RICHTER ROMANIA S.A.	ROMANIA	3620	2011	02
EPLERENONUM	ERIDANUS 50 mg	film-coated tablets	GEDEON RICHTER ROMANIA S.A.	ROMANIA	3621	2011	02
ESCITALOPRAMUM	ESCITALOPRAM PHARMASWISS 10 mg	film-coated tablets	PHARMASWISS CESKA REPUBLIKA S.R.O.	CZECH REPUBLIC	3684	2011	24
ESCITALOPRAMUM	ESCITALOPRAM PHARMASWISS 15 mg	film-coated tablets	PHARMASWISS CESKA REPUBLIKA S.R.O.	CZECH REPUBLIC	3685	2011	24
ESCITALOPRAMUM	ESCITALOPRAM PHARMASWISS 20 mg	film-coated tablets	PHARMASWISS CESKA REPUBLIKA S.R.O.	CZECH REPUBLIC	3686	2011	28
ESCITALOPRAMUM	ESPROLAN 5 mg	film-coated tablets	MEDANA PHARMA SA	POLAND	3769	2011	06
ESCITALOPRAMUM	ESPROLAN 10 mg	film-coated tablets	MEDANA PHARMA SA	POLAND	3770	2011	06
ESCITALOPRAMUM	ESPROLAN 20 mg	film-coated tablets	MEDANA PHARMA SA	POLAND	3771	2011	06
EXEMESTANUM	XANEPRA 25 mg	film-coated tablets	ROMASTRU TRADING S.R.L.	ROMANIA	3761	2011	02
FINASTERIDUM	BEPRONAL 5 mg	film-coated tablets	FARMACEUTICA REMEDIA S.A.	ROMANIA	3806	2011	06
FLUCONAZOLUM	FLUCONAZOL LPH 50 mg	capsules	LABORMED PHARMA S.A.	ROMANIA	3658	2011	01
FLUCONAZOLUM	FLUCONAZOL LPH 150 mg	capsules	LABORMED PHARMA S.A.	ROMANIA	3659	2011	01
GALANTAMINUM	GALSYA 8 mg	prolonged-release capsules	KRKA D.D. NOVO MESTO	SLOVENIA	3571	2011	18
GALANTAMINUM	GALSYA 16 mg	prolonged-release capsules	KRKA D.D. NOVO MESTO	SLOVENIA	3572	2011	18

GALANTAMINUM	GALSYA 24 mg	prolonged-release capsules	KRKA D.D. NOVO MESTO	SLOVENIA	3573	2011	18
GEMCITABINUM	GEMCITABINA HOSPIRA 38 mg/ml	concentrate for solution for infusion	HOSPIRA UK LTD	GREAT BRITAIN	3689	2011	03
GINKGO BILOBA	FLAVOTAN 80 mg (see C04AXN1)	film-coated tablets	LABORMED PHARMA S.A.	ROMANIA	3668	2011	01
GINKGO BILOBA	FLAVOTAN 120 mg (see C04AXN1)	film-coated tablets	LABORMED PHARMA S.A.	ROMANIA	3669	2011	01
HOMEOPATE	GENTOS	oral drops, solution	RICHARD BITTNER AG	AUSTRIA	3642	2011	03
HOMEOPATE	AFLUBIN	sublingual tablets	RICHARD BITTNER AG	AUSTRIA	3643	2011	04
HOMEOPATE	MASTODYNON	tablets	BIONORICA SE	GERMANY	3764	2011	03
IMUNOGLOBULINĂ UMANĂ NORMALĂ	GAMMANORM 165 mg/ml	solution for injection	OCTAPHARMA (IP) LIMITED	GREAT BRITAIN	3794	2011	06
INDAPAMIDUM	INDAPAMIDA MYLAN 1.5 mg	prolonged-release tablets	MYLAN S.A.S.	FRANCE	3688	2011	04
IRBESARTANUM	DEPALONG 75 mg	film-coated tablets	MEDANA PHARMA S.A.	POLAND	3635	2011	01
IRBESARTANUM	DEPALONG 150 mg	film-coated tablets	MEDANA PHARMA S.A.	POLAND	3636	2011	01
IRBESARTANUM	DEPALONG 300 mg	film-coated tablets	MEDANA PHARMA S.A.	POLAND	3637	2011	01
IRBESARTANUM	IRBESARTAN DR. REDDY'S 7.5 mg	film-coated tablets	DR. REDDY'S LABORATORIES ROMANIA S.R.L.	ROMANIA	3753	2011	14
IRBESARTANUM	IRBESARTAN DR. REDDY'S 150 mg	film-coated tablets	DR. REDDY'S LABORATORIES ROMANIA S.R.L.	ROMANIA	3754	2011	14
IRBESARTANUM	IRBESARTAN DR. REDDY'S 300 mg	film-coated tablets	DR. REDDY'S LABORATORIES ROMANIA S.R.L.	ROMANIA	3755	2011	14
IRBESARTANUM	IRBESARTAN PFIZER 75 mg	tablets	PFIZER EUROPE MA EEIG	GREAT BRITAIN	3791	2011	14
IRBESARTANUM	IRBESARTAN PFIZER 150 mg	tablets	PFIZER EUROPE MA EEIG	GREAT BRITAIN	3792	2011	14
IRBESARTANUM	IRBESARTAN PFIZER 300 mg	tablets	PFIZER EUROPE MA EEIG	GREAT BRITAIN	3793	2011	14
KETOCONAZOLUM	NIZORAL 20 mg/g	cream	JANSSEN PHARMACEUTICA NV	BELGIUM	3804	2011	02
LATANOPROSTUM	GLAUTAN 0.05 mg/ml	eye drops, solution	ROMPHARM COMPANY SRL	ROMANIA	3660	2011	01

LERCANIDIPINUM	LERCANIDIPINA TEVA 10 mg	film-coated tablets	TEVA PHARMACEUTICALS S.R.L.	ROMANIA	3721	2011	13
LERCANIDIPINUM	LERCANIDIPINA TEVA 20 mg	film-coated tablets	TEVA PHARMA-CEUTICALS S.R.L.	ROMANIA	3722	2011	12
LEVETIRACETAMUM	LEVETIRACETAM DESITIN 250 mg	covered granules in single dose envelope	DESITIN ARZNEIMITTEL GMBH	GERMANY	3627	2011	06
LEVETIRACETAMUM	LEVETIRACETAM DESITIN 500 mg	covered granules in single dose envelope	DESITIN ARZNEIMITTEL GMBH	GERMANY	3628	2011	06
LEVETIRACETAMUM	LEVETIRACETAM DESITIN 750 mg	covered granules in single dose envelope	DESITIN ARZNEIMITTEL GMBH	GERMANY	3629	2011	06
LEVETIRACETAMUM	LEVETIRACETAM DESITIN 1000 mg	covered granules in single dose envelope	DESITIN ARZNEIMITTEL GMBH	GERMANY	3630	2011	06
LEVETIRACETAMUM	LEVETIRACETAM TORRENT 250 mg	film-coated tablets	TORRENT PHARMA S.R.L.	ROMANIA	3705	2011	06
LEVETIRACETAMUM	LEVETIRACETAM TORRENT 500 mg	film-coated tablets	TORRENT PHARMA S.R.L.	ROMANIA	3706	2011	06
LEVETIRACETAMUM	LEVETIRACETAM TORRENT 750 mg	film-coated tablets	TORRENT PHARMA S.R.L.	ROMANIA	3707	2011	06
LEVETIRACETAMUM	LEVETIRACETAM TORRENT 1000 mg	film-coated tablets	TORRENT PHARMA S.R.L.	ROMANIA	3708	2011	06
LEVETIRACETAMUM	LEVETIRACETAM PHARMASWISS 250 mg	film-coated tablets	PHARMASWISS CESKA REPUBLIKA S.R.O.	CZECH REPUBLIC	3748	2011	08
LEVETIRACETAMUM	LEVETIRACETAM PHARMASWISS 500 mg	film-coated tablets	PHARMASWISS CESKA REPUBLIKA S.R.O.	CZECH REPUBLIC	3749	2011	08
LEVETIRACETAMUM	LEVETIRACETAM PHARMASWISS 750 mg	film-coated tablets	PHARMASWISS CESKA REPUBLIKA S.R.O.	CZECH REPUBLIC	3750	2011	08
LEVETIRACETAMUM	LEVETIRACETAM PHARMASWISS 1000mg	film-coated tablets	PHARMASWISS CESKA REPUBLIKA S.R.O.	CZECH REPUBLIC	3751	2011	08
LEVETIRACETAMUM	LEVETIRACETAM PHARMASWISS 100mg/ml	oral solution	PHARMASWISS CESKA REPUBLIKA S.R.O.	CZECH REPUBLIC	3752	2011	03
LEVETIRACETAMUM	LERETAN 500 mg	film-coated tablets	LABORMED PHARMA S.A.	ROMANIA	3811	2011	08

LEVETIRACETAMUM	LERETAN 1000 mg	film-coated tablets	LABORMED PHARMA S.A.	ROMANIA	3812	2011	07
LEVOFLOXACINUM	LEVOFLOXACINA BLUEFISH 500 mg	film-coated tablets	BLUEFISH PHARMACEUTICALS AB	SWEDEN	3607	2011	08
LIDOCAINUM	LIDOCAINA MIMER 20 mg/ml	solution for injection	MIMER MEDICAL	SWEDEN	3746	2011	01
LOPERAMIDUM	STOPERAN 2 mg	capsules	US PHARMACIA SP. Z.O.O.	POLAND	3805	2011	01
LORAZEPAMUM	ANXIAR 1 mg	tablets	GEDEON RICHTER ROMANIA S.A.	ROMANIA	3601	2011	01
LORNOXICAMUM	XEFO 4 mg	film-coated tablets	NYCOMED AUSTRIA GMBH	AUSTRIA	3729	2011	07
LORNOXICAMUM	XEFO 8 mg	film-coated tablets	NYCOMED AUSTRIA GMBH	AUSTRIA	3730	2011	07
LORNOXICAMUM	XEFO 8 mg/2 ml	powder + solvent for solution for injection	NYCOMED AUSTRIA GMBH	AUSTRIA	3731	2011	04
LORNOXICAMUM	XEFO RAPID 8 mg	film-coated tablets	NYCOMED AUSTRIA GMBH	AUSTRIA	3732	2011	07
LOSARTANUM	SARLON 50 mg	film-coated tablets	ALKALOID D.O.O.	SLOVENIA	3557	2011	01
LOSARTANUM	SARLON 100 mg	film-coated tablets	ALKALOID D.O.O.	SLOVENIA	3558	2011	01
LOSARTANUM	LOSARTAN TECNIMEDE 50 mg	film-coated tablets	TECNIMEDE-SOCIEDADE TECNICO-MEDICINAL S.A.	PORTUGAL	3576	2011	03
LOSARTANUM	LOSARTAN TECNIMEDE 100 mg	film-coated tablets	TECNIMEDE-SOCIEDADE TECNICO-MEDICINAL S.A.	PORTUGAL	3577	2011	03
MONTELUKASTUM	ASTMASAN 4 mg	granules	SANDOZ S.R.L.	ROMANIA	3567	2011	07
MONTELUKASTUM	TELUMANTES 4 mg	chewable tablets	SIGILLATA LIMITED	GREAT BRITAIN	3625	2011	09
MONTELUKASTUM	TELUMANTES 5 mg	chewable tablets	SIGILLATA LIMITED	GREAT BRITAIN	3626	2011	09
MONTELUKASTUM	MONTELUKAST MYLAN 4 mg	chewable tablets	GENERICS (UK) LTD	GREAT BRITAIN	3709	2011	18
MONTELUKASTUM	MONTELUKAST MYLAN 5 mg	chewable tablets	GENERICS (UK) LTD	GREAT BRITAIN	3710	2011	18
MYCOPHENOLATUM MOFETILUM	MICOFENOLAT MOFETIL TERAPIA 500mg	film-coated tablets	TERAPIA S.A.	ROMANIA	3556	2011	02
OLANZAPINUM	OLANZAPINA LILLY VELOTAB 5 mg	orodispersible tablets	ELI LILLY ROMANIA S.R.L.	ROMANIA	3602	2011	04

OLANZAPINUM	OLANZAPINA LILLY VELOTAB 10 mg	orodispersible tablets	ELI LILLY ROMANIA S.R.L.	ROMANIA	3603	2011	04
OLANZAPINUM	OLANZAPINA LILLY VELOTAB 15 mg	orodispersible tablets	ELI LILLY ROMANIA S.R.L.	ROMANIA	3604	2011	04
OLANZAPINUM	OLANZAPINA LILLY VELOTAB 20 mg	orodispersible tablets	ELI LILLY ROMANIA S.R.L.	ROMANIA	3605	2011	04
OLANZAPINUM	OLANZAPINA LPH 5 mg	film-coated tablets	LABORMED PHARMA S.A.	ROMANIA	3757	2011	03
OLANZAPINUM	OLANZAPINA LPH 10 mg	film-coated tablets	LABORMED PHARMA S.A.	ROMANIA	3758	2011	03
OLANZAPINUM	OLANZAPINA LPH 15 mg	film-coated tablets	LABORMED PHARMA S.A.	ROMANIA	3759	2011	03
OLANZAPINUM	OLANZAPINA LPH 20 mg	film-coated tablets	LABORMED PHARMA S.A.	ROMANIA	3760	2011	03
OLANZAPINUM	OLANZAPINA LILLY 2.5 mg	film-coated tablets	ELI LILLY ROMANIA S.R.L.	ROMANIA	3783	2011	04
OLANZAPINUM	OLANZAPINA LILLY 5 mg	film-coated tablets	ELI LILLY ROMANIA S.R.L.	ROMANIA	3784	2011	04
OLANZAPINUM	OLANZAPINA LILLY 7.5 mg	film-coated tablets	ELI LILLY ROMANIA S.R.L.	ROMANIA	3785	2011	04
OLANZAPINUM	OLANZAPINA LILLY 10 mg	film-coated tablets	ELI LILLY ROMANIA S.R.L.	ROMANIA	3786	2011	04
OLANZAPINUM	OLANZAPINA LILLY 15 mg	film-coated tablets	ELI LILLY ROMANIA S.R.L.	ROMANIA	3787	2011	04
OLANZAPINUM	OLANZAPINA LILLY 20 mg	film-coated tablets	ELI LILLY ROMANIA S.R.L.	ROMANIA	3788	2011	04
OLANZAPINUM	OLANZAPINA LILLY 10 mg	powder for solution for injection	ELI LILLY ROMANIA S.R.L.	ROMANIA	3789	2011	02
OMEPRAZOLUM	OMEPRAZOL JENSON 20 mg	gastroresistant capsules	JENSON PHARMACEUTICAL SERVICES LTD.	GREAT BRITAIN	3578	2011	31
OMEPRAZOLUM	OMEPRAZOL JENSON 40 mg	gastroresistant capsules	JENSON PHARMACEUTICAL SERVICES LTD.	GREAT BRITAIN	3579	2011	31
OMEPRAZOLUM	OMEPRAZOL PFIZER 10 mg	gastroresistant capsules	PFIZER EUROPE MA EEIG	GREAT BRITAIN	3638	2011	15
OMEPRAZOLUM	OMEPRAZOL PFIZER 20 mg	gastroresistant capsules	PFIZER EUROPE MA EEIG	GREAT BRITAIN	3639	2011	19
OMEPRAZOLUM	OMEPRAZOL PFIZER 40 mg	gastroresistant capsules	PFIZER EUROPE MA EEIG	GREAT BRITAIN	3640	2011	15

OMEPRAZOLUM	OMEPRAZOL AUROBINDO 10 mg	gastroresistant capsules	AUROBINDO PHARMA (MALTA) LIMITED	MACEDONIA	3715	2011	15
OMEPRAZOLUM	OMEPRAZOL AUROBINDO 20 mg	gastroresistant capsules	AUROBINDO PHARMA (MALTA) LIMITED	MACEDONIA	3716	2011	19
OMEPRAZOLUM	OMEPRAZOL AUROBINDO 40 mg	gastroresistant capsules	AUROBINDO PHARMA (MALTA) LIMITED	MACEDONIA	3717	2011	15
OXALIPLATINUM	OXALIPLATIN ACTAVIS 5 mg/ml	concentrate for solution for infusion	ACTAVIS GROUP PTC EHF	ICELAND	3641	2011	03
OXALIPLATINUM	OXALIPLATIN EBEWE 5mg/ml	concentrate for solution for infusion	EBEWE PHARMA GES.M.B.H NFG. KG	AUSTRIA	3682	2011	10
PANTOPRAZOLUM	PIROSTOP 20 mg	gastroresistant tablets	M.R. PHARMA GMBH	GERMANY	3687	2011	04
PARACETAMOLUM	PARACETAMOL ACTAVIS 24 mg/ml	oral solution	ACTAVIS GROUP PTC EHF.	ICELAND	3728	2011	06
PERINDOPRILUM	PERINDOPRIL ARGININA GENERICS 2.5 mg	film-coated tablets	GENERICS (UK) LTD	GREAT BRITAIN	3568	2011	10
PERINDOPRILUM	PERINDOPRIL ARGININA GENERICS 5 mg	film-coated tablets	GENERICS (UK) LTD	GREAT BRITAIN	3569	2011	10
PERINDOPRILUM	PERINDOPRIL ARGININA GENERICS 10 mg	film-coated tablets	GENERICS (UK) LTD	GREAT BRITAIN	3570	2011	10
PERINDOPRILUM	PRESTPRIL 4 mg	tablets	LABORMED PHARMA S.A.	ROMANIA	3664	2011	06
PERINDOPRILUM	PRESTPRIL 8 mg	tablets	LABORMED PHARMA S.A.	ROMANIA	3665	2011	06
PIRACETAMUM	NOOTROPIL 800 mg	film-coated tablets	U.C.B. PHARMA S.A.	BELGIUM	3562	2011	03
PIRACETAMUM	NOOTROPIL 1200 mg	film-coated tablets	U.C.B. PHARMA S.A.	BELGIUM	3563	2011	05
PRAMIPEXOLUM	PEXOGIES 0.18 mg	tablets	SYNTHON BV	HOLLAND	3694	2011	02
PRAMIPEXOLUM	PEXOGIES 0.7 mg	tablets	SYNTHON BV	HOLLAND	3695	2011	02
PROMESTRIENUM	COLPOTROPHINE 10mg	vaginal capsules	LABORATOIRE THERAMEX	MONACO	3655	2011	01
PROTOXID DE AZOT + OXIGEN	KALINOX 50 %/50 %	compressed medical gas	AIR LIQUIDE SANTE INTERNATIONAL	FRANCE	3727	2011	12
QUETIAPINUM	QUEPSAN 25 mg	film-coated tablets	PRO. MED. CS PRAHA A.S.	CZECH REPUBLIC	3580	2011	08

QUETIAPINUM	QUEPSAN 100 mg	film-coated tablets	PRO. MED. CS PRAHA A.S.	CZECH REPUBLIC	3581	2011	08
QUETIAPINUM	QUEPSAN 200 mg	film-coated tablets	PRO. MED. CS PRAHA A.S.	CZECH REPUBLIC	3582	2011	08
QUETIAPINUM	QUEPSAN 300 mg	film-coated tablets	PRO. MED. CS PRAHA A.S.	CZECH REPUBLIC	3583	2011	08
QUETIAPINUM	QUEPSAN 400 mg	film-coated tablets	PRO. MED. CS PRAHA A.S.	CZECH REPUBLIC	3584	2011	03
QUETIAPINUM	QUETIAPINE ACCORD 25 mg	film-coated tablets	ACCORD HEALTHCARE LIMITED	GREAT BRITAIN	3590	2011	14
QUETIAPINUM	QUETIAPINE ACCORD 100 mg	film-coated tablets	ACCORD HEALTHCARE LIMITED	GREAT BRITAIN	3591	2011	14
QUETIAPINUM	QUETIAPINE ACCORD 150 mg	film-coated tablets	ACCORD HEALTHCARE LIMITED	GREAT BRITAIN	3592	2011	14
QUETIAPINUM	QUETIAPINE ACCORD 200 mg	film-coated tablets	ACCORD HEALTHCARE LIMITED	GREAT BRITAIN	3593	2011	14
QUETIAPINUM	QUETIAPINE ACCORD 300 mg	film-coated tablets	ACCORD HEALTHCARE LIMITED	GREAT BRITAIN	3594	2011	14
RABEPRAZOLUM	RABEPRAZOL TEVA 10 mg	gastroresistant tablets	TEVA PHARMACEUTICALS S.R.L.	ROMANIA	3679	2011	18
RABEPRAZOLUM	RABEPRAZOL TEVA 20 mg	gastroresistant tablets	TEVA PHARMACEUTICALS S.R.L.	ROMANIA	3680	2011	18
RANITIDINUM	RANITIDINA CLARIS 25 mg/ml	solution for injection/infusion	CLARIS LIFESCIENCES (UK) LTD.	GREAT BRITAIN	3683	2011	03
RISPERIDONUM	RISPOLUX 0.5 mg	orodispersible film	SANDOZ S.R.L.	ROMANIA	3585	2011	11
RISPERIDONUM	RISPOLUX 1 mg	orodispersible film	SANDOZ S.R.L.	ROMANIA	3586	2011	11
RISPERIDONUM	RISPOLUX 2 mg	orodispersible film	SANDOZ S.R.L.	ROMANIA	3587	2011	11
RISPERIDONUM	RISPOLUX 3 mg	orodispersible film	SANDOZ S.R.L.	ROMANIA	3588	2011	11
RIVASTIGMINUM	RIVASTIGMIN WELDING 1.5 mg	capsules	WELDING GMBH & CO KG	GERMANY	3765	2011	10
RIVASTIGMINUM	RIVASTIGMIN WELDING 3 mg	capsules	WELDING GMBH & CO KG	GERMANY	3766	2011	10
RIVASTIGMINUM	RIVASTIGMIN WELDING 4.5 mg	capsules	WELDING GMBH & CO KG	GERMANY	3767	2011	10
RIVASTIGMINUM	RIVASTIGMIN WELDING 6 mg	capsules	WELDING GMBH & CO KG	GERMANY	3768	2011	10
ROSUVASTATINUM	ROSUVASTATINA KRKA 5 mg	film-coated tablets	KRKA D.D. NOVO MESTO	SLOVENIA	3540	2011	11

ROSUVASTATINUM	ROSUVASTATINA KRKA 10 mg	film-coated tablets	KRKA D.D. NOVO MESTO	SLOVENIA	3541	2011	11
ROSUVASTATINUM	ROSUVASTATINA KRKA 15 mg	film-coated tablets	KRKA D.D. NOVO MESTO	SLOVENIA	3542	2011	11
ROSUVASTATINUM	ROSUVASTATINA KRKA 20 mg	film-coated tablets	KRKA D.D. NOVO MESTO	SLOVENIA	3543	2011	11
ROSUVASTATINUM	ROSUVASTATINA KRKA 30 mg	film-coated tablets	KRKA D.D. NOVO MESTO	SLOVENIA	3544	2011	11
ROSUVASTATINUM	ROSUVASTATINA KRKA 40 mg	film-coated tablets	KRKA D.D. NOVO MESTO	SLOVENIA	3545	2011	11
ROSUVASTATINUM	ROSWERA 5 mg	film-coated tablets	KRKA D.D. NOVO MESTO	SLOVENIA	3546	2011	11
ROSUVASTATINUM	ROSWERA 10 mg	film-coated tablets	KRKA D.D. NOVO MESTO	SLOVENIA	3547	2011	11
ROSUVASTATINUM	ROSWERA 15 mg	film-coated tablets	KRKA D.D. NOVO MESTO	SLOVENIA	3548	2011	11
ROSUVASTATINUM	ROSWERA 20 mg	film-coated tablets	KRKA D.D. NOVO MESTO	SLOVENIA	3549	2011	11
ROSUVASTATINUM	ROSWERA 30 mg	film-coated tablets	KRKA D.D. NOVO MESTO	SLOVENIA	3550	2011	11
ROSUVASTATINUM	ROSWERA 40 mg	film-coated tablets	KRKA D.D. NOVO MESTO	SLOVENIA	3551	2011	11
ROSUVASTATINUM	ROMAZIC 5 mg	film-coated tablets	PHARMACEUTICAL WORKS POLPHARMA SA	POLAND	3552	2011	01
ROSUVASTATINUM	ROMAZIC 10 mg	film-coated tablets	PHARMACEUTICAL WORKS POLPHARMA SA	POLAND	3553	2011	01
ROSUVASTATINUM	ROMAZIC 20 mg	film-coated tablets	PHARMACEUTICAL WORKS POLPHARMA SA	POLAND	3554	2011	01
ROSUVASTATINUM	ROMAZIC 40 mg	film-coated tablets	PHARMACEUTICAL WORKS POLPHARMA SA	POLAND	3555	2011	01
ROSUVASTATINUM	ROSUVASTATINA RATIOPHARM 5 mg	film-coated tablets	RATIOPHARM GMBH	GERMANY	3718	2011	30
ROSUVASTATINUM	ROSUVASTATINA RATIOPHARM 10 mg	film-coated tablets	RATIOPHARM GMBH	GERMANY	3719	2011	30
ROSUVASTATINUM	ROSUVASTATINA RATIOPHARM 20 mg	film-coated tablets	RATIOPHARM GMBH	GERMANY	3720	2011	30
SILDENAFILUM	SILAXA 25 mg	film-coated tablets	MEDICO UNO PHARMA KFT.	HUNGARY	3734	2011	05
SILDENAFILUM	SILAXA 50 mg	film-coated tablets	MEDICO UNO PHARMA KFT.	HUNGARY	3735	2011	05
SILDENAFILUM	SILAXA 100 mg	film-coated tablets	MEDICO UNO PHARMA KFT.	HUNGARY	3736	2011	05
SILDENAFILUM	OLVION 50 mg	film-coated tablets	MEDOCHEMIE LTD.	CYPRUS	3780	2011	04
SILDENAFILUM	OLVION 100 mg	film-coated tablets	MEDOCHEMIE LTD.	CYPRUS	3781	2011	04

TELMISARTANUM	TELMARK 20 mg	film-coated tablets	GLENMARK PHARMACEUTICALS S.R.O.	CZECH REPUBLIC	3595	2011	08
TELMISARTANUM	TELMARK 40 mg	film-coated tablets	GLENMARK PHARMACEUTICALS S.R.O.	CZECH REPUBLIC	3596	2011	08
TELMISARTANUM	TELMARK 80 mg	film-coated tablets	GLENMARK PHARMACEUTICALS S.R.O.	CZECH REPUBLIC	3597	2011	08
TELMISARTANUM	TANYDON 20 mg	film-coated tablets	GEDEON RICHTER ROMANIA S.A.	ROMANIA	3598	2011	08
TELMISARTANUM	TANYDON 40 mg	film-coated tablets	GEDEON RICHTER ROMANIA S.A.	ROMANIA	3599	2011	08
TELMISARTANUM	TANYDON 80 mg	film-coated tablets	GEDEON RICHTER ROMANIA S.A.	ROMANIA	3600	2011	08
TELMISARTANUM	ZMERTAN 20 mg	tablets	SIGILLATA LIMITED	GREAT BRITAIN	3700	2011	10
TELMISARTANUM	ZMERTAN 40 mg	tablets	SIGILLATA LIMITED	GREAT BRITAIN	3701	2011	10
TELMISARTANUM	ZMERTAN 80 mg	tablets	SIGILLATA LIMITED	GREAT BRITAIN	3702	2011	10
TERBINAFINUM	TERBINAFINA SCHOLL 1%	cream	SCHOLL CONSUMER PRODUCTS LTD	GREAT BRITAIN	3681	2011	02
TIMOLOLUM	GELTIM 1 mg/g	eye gel in single-dose container	LABORATOIRES THEA	FRANCE	3622	2011	02
TIOTROPIUM	SPIRIVA 18 micrograms	capsules containing inhalation powder	BOEHRINGER INGELHEIM INTERNATIONAL GMBH	GERMANY	3790	2011	08
TOPOTECAMUM	TOPOTECAN ATB 1 mg	powder for concentrate for solution for infusion	ANTIBIOTICE S.A.	ROMANIA	3656	2011	01
TOPOTECAMUM	TOPOTECAN ATB 4 mg	powder for concentrate for solution for infusion	ANTIBIOTICE S.A.	ROMANIA	3657	2011	01
TRIMETAZIDINUM	TRIMELUZINE 35 mg	prolonged-release tablets	LUPIN (EUROPE) LTD	GREAT BRITAIN	3564	2011	24
TRIMETAZIDINUM	TRIMEDAL 35 mg	prolonged-release tablets	ZENTIVA K.S.	CZECH REPUBLIC	3747	2011	28

TRIMETAZIDINUM	TRIMETAZIDINA ATB 35 mg	prolonged-release tablets	ANTIBIOTICE S.A.	ROMANIA	3763	2011	01
COMBINED VACCINE	PEDIACEL	suspension for injection in pre-filled syringe	SANOFI PASTEUR SA	FRANCE	3644	2011	05
HEPATITIS A VACCINE, INACTIVATED	HAVRIX JUNIOR 720 VACCIN HEPATITIC A INACTIVAT, ADSORBIT	suspension for injection	GLAXOSMITHKLINE BIOLOGICALS S.A.	BELGIUM	3696	2011	05
MENINGOCOCCAL POLYSACCHARIDE VACCINE	VACCIN MENINGOCOCIC POLIZAHARIDIC A+C	powder and solvent for suspension for injection	SANOFI PASTEUR S.A.	FRANCE	3698	2011	02
VALSARTANUM	VALSACOR 40 mg	film-coated tablets	KRKA D.D. NOVO MESTO	SLOVENIA	3612	2011	13
VALSARTANUM	VALSACOR 80 mg	film-coated tablets	KRKA D.D. NOVO MESTO	SLOVENIA	3613	2011	13
VALSARTANUM	VALSACOR 160 mg	film-coated tablets	KRKA D.D. NOVO MESTO	SLOVENIA	3614	2011	13
VALSARTANUM	VALSARTAN TORRENT 40 mg	film-coated tablets	TORRENT PHARMA S.R.L.	ROMANIA	3670	2011	02
VALSARTANUM	VALSARTAN TORRENT 80 mg	film-coated tablets	TORRENT PHARMA S.R.L.	ROMANIA	3671	2011	03
VALSARTANUM	VALSARTAN TORRENT 160 mg	film-coated tablets	TORRENT PHARMA S.R.L.	ROMANIA	3672	2011	03
VALSARTANUM	VALSARTAN TORRENT 320 mg	film-coated tablets	TORRENT PHARMA S.R.L.	ROMANIA	3673	2011	03
VANCOMYCINUM	VANCOMICINA PFIZER 500 mg	powder for concentrate for solution for infusion	PFIZER EUROPE MA EEIG	GREAT BRITAIN	3574	2011	01
VANCOMYCINUM	VANCOMICINA PFIZER 1000 mg	powder for concentrate for solution for infusion	PFIZER EUROPE MA EEIG	GREAT BRITAIN	3575	2011	01
VERAPAMILUM	VERAPAMIL ARENA 80 mg	capsules	ARENA GROUP S.A.	ROMANIA	3589	2011	03
ZOLPIDEMUM	ZOLPIDEM PFIZER 10 mg	film-coated tablets	PFIZER EUROPE MA EEIG	GREAT BRITAIN	3618	2011	31
ZOPICLONUM	SONLAX 7.5 mg	film-coated tablets	AS GRINDEKS	LATVIA	3745	2011	03

EMA centrally authorised medicinal products for which the European Commission has issued decisions during the 3rd quarter of 2011

INN	Invented name	Pharmaceutical form	Strength	MA Holding Company	Country	MA Number		
ACIDUM IBANDRONICUM	ACID IBANDRONIC SANDOZ 50 mg	film-coated tablets	50mg	SANDOZ PHARMACEUTICALS GMBH	GERMANY	685	2011	05
BELIMUMABUM	BENLYSTA	powder for concentrate for solution for infusion	120mg	GLAXO GROUP LIMITED	GREAT BRITAIN	700	2011	01
BELIMUMABUM	BENLYSTA	powder for concentrate for solution for infusion	400mg	GLAXO GROUP LIMITED	GREAT BRITAIN	700	2011	01
BOCEPREVIRUM	VICTRELIS	capsules	200mg	MERCK SHARP & DOHME LTD	GREAT BRITAIN	704	2011	01
DABIGATRANUM ETEXILATUM	PRADAXA 150mg	capsules	150mg	BOEHRINGER INGELHEIM INTERNATIONAL GMBH	GERMANY	442	2011	05
DENOSUMAB	XGEVA 120mg	solution for injection	70mg/ml	AMGEN EUROPE B.V.	HOLLAND	703	2011	02
EVEROLIMUS	VOTUBIA	tablets	2.5mg	NOVARTIS EUROPHARM LTD.	GREAT BRITAIN	710	2011	03
EVEROLIMUS	VOTUBIA	tablets	5mg	NOVARTIS EUROPHARM LTD.	GREAT BRITAIN	710	2011	02
EVEROLIMUS	VOTUBIA	tablets	10mg	NOVARTIS EUROPHARM LTD.	GREAT BRITAIN	710	2011	02
IPILIMUMABUM	YERVOY 5mg/ml	concentrate for solution for infusion	5mg/ml	BRISTOL-MYERS SQUIBB PHARMA EEIG	GREAT BRITAIN	698	2011	02
LEVETIRACETAMUM	LEVETIRACETAM TEVA 250 mg	film-coated tablets	250mg	TEVA PHARMA	HOLLAND	701	2011	07
LEVETIRACETAMUM	LEVETIRACETAM TEVA 500 mg	film-coated tablets	500mg	TEVA PHARMA	HOLLAND	701	2011	07
LEVETIRACETAMUM	LEVETIRACETAM TEVA 750 mg	film-coated tablets	750mg	TEVA PHARMA	HOLLAND	701	2011	07
LEVETIRACETAMUM	LEVETIRACETAM TEVA 1000mg	film-coated tablets	1000mg	TEVA PHARMA	HOLLAND	701	2011	07

LINAGLIPTINUM	TRAJENTA	tablets	5mg	BOEHRINGER INGELHEIM INTERNATIONAL GMBH	GERMANY	707	2011	11
NEVIRAPINUM	VIRAMUNE 50mg	prolonged-release tablets	50mg	BOEHRINGER INGELHEIM INTERNATIONAL GMBH	GERMANY	55	2011	01
NEVIRAPINUM	VIRAMUNE 100mg	prolonged-release tablets	100mg	BOEHRINGER INGELHEIM INTERNATIONAL GMBH	GERMANY	55	2011	01
NEVIRAPINUM	VIRAMUNE 400mg	prolonged-release tablets	400mg	BOEHRINGER INGELHEIM INTERNATIONAL GMBH	GERMANY	55	2011	01
PRAMIPEXOLUM	PRAMIPEXOLE ACCORD 0.088 mg	tablets	0.088mg	ACCORD HEALTHCARE LIMITED	GREAT BRITAIN	728	2011	02
PRAMIPEXOLUM	PRAMIPEXOLE ACCORD 0.18 mg	tablets	0.18mg	ACCORD HEALTHCARE LIMITED	GREAT BRITAIN	728	2011	02
PRAMIPEXOLUM	PRAMIPEXOLE ACCORD 0.35mg	tablets	0.35mg	ACCORD HEALTHCARE LIMITED	GREAT BRITAIN	728	2011	02
PRAMIPEXOLUM	PRAMIPEXOLE ACCORD 0.7mg	tablets	0.7mg	ACCORD HEALTHCARE LIMITED	GREAT BRITAIN	728	2011	02
PRAMIPEXOLUM	PRAMIPEXOLE ACCORD 1.1mg	tablets	1.1mg	ACCORD HEALTHCARE LIMITED	GREAT BRITAIN	728	2011	02