

DECISION

no. 23/11.10.2013

on approval of the manner of National Agency for Medicines and Medical Devices handling of applications by a notified body for NAMMD scientific opinion on the quality and safety of an ancillary medicinal substance incorporated, as an integral part, into a medical device

The Scientific Council of the National Agency for Medicines and Medical Devices (NAMMD), established based on Order of the Minister of Health No. 158/18.02.2013, reunited on summons of the NAMMD President in the ordinary meeting of 11.10.2013, in accordance with Article 12 (5) of Emergency Government Decision no. 734/2010 on the organisation and operation of the National Agency for Medicines and Medical Devices, as amended, hereby adopts the following

DECISION

Article 1. – The manner of National Agency for Medicines and Medical Devices handling of applications by a notified body for NAMMD scientific opinion on the quality and safety of an ancillary medicinal substance incorporated, as an integral part, into a medical device (hereinafter “ancillary medicinal substance”) is approved, in accordance with the provisions of the European Guideline on borderline products, included in the Annex., which is integral part of this Decision.

Article 2. - (1) Based on Article 7.4.2. of Annex 1 to Government Decision no. 54/2009 on the conditions for the entry of medical devices on the market (hereinafter “Government Decision no. 54/2009”), the NAMMD hereby responds to applications by a notified body relating to grant of a scientific opinion concerning the quality and safety of an ancillary medicinal substance and of the established clinical risk-benefit balance of incorporation of the substance into the device. When issuing the scientific opinion, the NAMMD considers the manufacturing process and data related to the incorporation of the substance into the device, as determined by the notified body.

(2) The NAMMD scientific opinion shall be established within 210 days following receipt of a valid documentation, according to Article 4.3 of Annex 2 to Government Decision no. 54/2009. This period excludes clock stops.

(3) Should changes occur to the ancillary medicinal substance incorporated as an integral part into a medical device, particularly if related to substance manufacturing process, the NAMMD responds to applications of a notified body relating to grant of a scientific opinion concerning the quality and safety of an

ancillary medicinal substance, according to Article 7.4.4. of Annex 1 to Government Decision no. 54/2009. The NAMMD takes into account the data referring to the usefulness of the incorporation of a substance into a device, as determined by the notified body, to ascertain that respective changes do not have a negative impact upon the established risk-benefit balance concerning the incorporation of the substance into the medical device.

(4) If, following initial consultation, the NAMMD has obtained information about the ancillary medicinal substance, which may have an impact upon the risk-benefit balance concerning incorporation of the substance into the medical device, according to Article 7.4.5. of Annex 1 to Government Decision no. 54/2009, the NAMMD informs the notified body in this respect, by updating the initial scientific opinion, regardless of the potential impact of the respective information upon the risk-benefit balance of incorporation of the ancillary medicinal substance into the medical device.

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

Guideline
on borderline products, drug-delivery products and medical devices incorporating, as an integral part, an ancillary medicinal substance or an ancillary human blood derivative

This Guideline is an adapted translation of the MEDDEV 2.1/3 rev. 3 Guideline of the European Commission (EC) on borderline products, drug-delivery products and medical devices incorporating, as an integral part, an ancillary medicinal substance or an ancillary human blood derivative.

This Guideline is part of a set of Guidelines relating to questions of application of EC Directives on medical devices, namely Directive 90/385/EEC of the Council on Active implantable medical devices and Directive 93/42/EEC of the Council on Medical devices, also including their amendment through Directive 2007/47/EC in force as of 21 March 2010.

All these European Directives are transposed into national legislation through Government Decisions (GD) no. 54/2009 on marketing conditions for medical devices (hereinafter Government Decision no. 54/2009) and Government Decision no. 55/2009 on *active implantable medical devices* (hereinafter Government Decision no. 55/2009). It has been elaborated by an expert group including experts from Member States' Competent Authorities, the Commission's services, as well as industry trade associations. It is therefore intended that the document provide useful guidance, which should assist common positions to be taken throughout the European Union. Due to the participation of the aforementioned interested parties and of experts from Competent Authorities, it is anticipated that these guidelines will be followed within the Member States and, therefore, ensure uniform application of relevant Directive provisions.

The present guideline provides non-exhaustive lists of examples of medical devices, accessories to medical devices and medicinal products. Further examples may be found in the manual on borderline and classification in the Community Regulatory framework for medical devices, published on the European Commission website¹. Particular attention should be given to borderline products (products between medical devices and herbal medicinal products).

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¹ http://ec.europa.eu/consumers/sectors/medical-devices/documents/borderline/index_en.htm

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A. BORDERLINE PRODUCTS: MEDICAL DEVICES / MEDICINAL PRODUCTS

A.1 Introduction

Establishment of the line between Directive 93/42/EEC on medical devices (MD) and Directive 90/385/EEC on active implantable medical devices (AIMD), transposed into national legislation through Government Decision no. 54/2009 and Government Decision no. 55/2009, and by Directive 2001/83/EC on the medical device (MD), transposed into national legislation through Law 95/2006 on healthcare reform, Title XVII - The medicinal product (hereinafter Law 95/2006), is essential in view of accurate implementation of these Directives and accurate enforcement of national legislation.

Thus, there are several provisions in Government Decision no. 54/2009, Government Decision no. 55/2009 and Law 95/2006 referring to the establishment of a line between the two regulations.

However, it was acknowledged that the subject needs further explanation and exemplification through practical Guidelines.

A.2 General principles

Borderline cases are considered to be those cases where it is not clear from the outset whether a given product falls under the provisions of Government Decision no. 54/2009, Government Decision no. 55/2009 or Law 95/2006.

In order to fall under the regulatory scope of Government Decision no. 54/2009, a medicinal product:

- must fulfil the definition of a medical device, and
- must also not be excluded from the scope of Government Decision no. 54/2009.

It is therefore necessary to examine both prerequisites.

As a general rule, a relevant product is regulated either by Government Decision no. 54/2009 or Law 95/2006. The conformity assessment procedure or the marketing authorization procedure to be followed prior to placing a given product on the market will therefore be governed either by Government Decision no. 54/2009 or by Law 95/2006. The procedures of both regulatory acts do not apply cumulatively.

For defined features, however, some cross-references are made within one regime to specific provisions of the other regime.

The definitions of medical device and medicinal product are reproduced here for reference:

A.2.1 Medical device

A.2.1.1 Definition of medical device

Article 2 (1) point 1 of Government Decision no. 54/2009 MDD defines a medical device as:

"Any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

- a) diagnosis, prevention, monitoring, treatment or alleviation of disease,
- b) diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- c) investigation, replacement or modification of the anatomy or of a physiological process,
- d) control of conception,

and, which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but, which may be assisted in its function by such means;"

In deciding whether a product falls under the Government Decision no. 54/2009, particular account will be taken of the principal mode of action of the product.

Typically, the medical device function is achieved by physical means (including mechanical action, physical barrier, replacement of or support to organs or body functions).

The principal intended action of a medical device may be deduced from the scientific data regarding mechanism of action and the manufacturer's labelling and claims.

Although the manufacturer's claims are important, it is not possible to place the product in one or other category in contradiction with current scientific data. Manufacturers may be required to justify scientifically their rationale for the qualification of their product.

The following definitions for pharmacological, immunological or metabolic means are intended only to provide guidance as to the meaning of these terms.

“Pharmacological means” is understood as an interaction between the molecules of the substance in question and a cellular constituent, usually referred to as a receptor,, which either results in a direct response, or, which blocks the response to another agent. Although not a completely reliable criterion, the presence of a dose-response correlation is indicative of a pharmacological effect.

“Immunological means” is understood as an action in or on the body by stimulation and/or mobilisation of cells and/or products involved in a specific immune reaction.

“Metabolic means” is understood as an action, which involves an alteration, including stopping, starting or changing the speed of the normal chemical processes participating in, and available for, normal body function.

Note: The fact that a product is, or is not, itself metabolised does not imply that it achieves, or does not achieve, its principal intended action by metabolic means.

Medical devices may be assisted in their function by pharmacological, immunological or metabolic means, but as soon as these means are not ancillary with respect to the principal intended action of a product, the product no longer fulfils the definition of a medical device. The claims made for a product, in accordance with its method of action may, in this context, represent an important factor for its qualification as a medical device.

This principle can be, for example, illustrated by bone cements. Plain bone cement without antibiotics is a medical device since it achieves its principal intended action (the fixation of prosthesis) by physical means. Bone cements containing antibiotics, where the principal intended action remains fixation of prosthesis, are also medical devices. In this case the action of the antibiotic,, which is to reduce the possibility of infection being introduced during surgery, is clearly ancillary. If however the principal intended action is to deliver the antibiotic, the product no longer fulfils the definition of a medical device.

A.2.1.2 Examples of medical devices

The following examples should, in view of their principal intended action, generally be considered as medical devices subject to relevant criteria being met; the function of some of the devices indicated in these examples may be assisted by the presence of medicinal substances where such substances have an ancillary action to that of the device.

- Bone cements,
- Dental filling materials,
- Materials for sealing, approximation, or adhesion of tissues (e.g. cyanoacrylates, fibrin-based adhesives not of human origin)
- Resorbable materials used in osteo-synthesis (e.g. pins or bone screws manufactured using polylactic acid),
- Sutures, absorbable sutures,
- Soft and hard tissue scaffolds and fillers (e.g. calcium phosphate, bioglass),
- Bone void fillers intended for the repair of bone defects where the primary action of the device is a physical means or matrix, which provides a volume and a scaffold for osteoconduction,
- Intrauterine devices, except products such as intrauterine contraceptives whose primary purpose is to release progestogens,
- Blood bags,
- Systems intended to preserve and treat blood,

Note: Systems intended for the collection, storage and preservation of blood or blood components and as an ancillary function, the treatment of blood or blood components where this effect is achieved outside the human body, are classified as devices provided that any residual material is not intended to achieve its effect when the blood or cells are reintroduced

into the body, e.g. systems incorporating chemicals activated by light to reduce the viral load where the quantity of chemical remaining has no intended effect when transfused.

This note does not cover substances introduced into an extracorporeal circuit.

- Gases and liquids for ocular endotamponades,
- Cell separators, including those incorporating fixed antibodies for cell binding,
- Wound dressings, which may be in the form of liquids, gels and pastes, etc. (e.g. hydrocolloid, hydrogel),
- Haemostatic products, for example patches, plugs and powders where the haemostatic effect results from the product's physical characteristics, or is due to the surface properties of the material. This includes products such as calcium alginate or oxidised cellulose where adhesion of platelets to the surface triggers platelet adhesion and aggregation
- Concentrates for haemodialysis,
- Pressure reducing valves and regulators,
- Irrigation solutions intended for mechanical rinsing (e.g. bladder irrigation solution, ocular irrigation solution),

Note:

If the solution contains a medicinal substance such as chlorhexidine where the principal intended purpose is to provide a local antimicrobial effect, it will be a medicinal product. Solutions incorporating substances for other purposes, e.g. antimicrobial agent for the preservation of the solution remain a medical device.

- Devices such as catheters, guidewires and stents containing or incorporating radio isotopes where the radioactive isotope as such is not released into the body, used for example in cardiology for the prevention of restenosis.

A.2.1.3 Definition of an accessory of a medical device

Article 2. – (1) point 2 of Government Decision no. 54/2009 defines an accessory of a medical device as follows:

”Accessory” means an article, which whilst not being a (medical) device is intended specifically by its manufacturer to be used together with a device to enable it to be used in accordance with the use of the device intended by the manufacturer of the device.

A.2.1.4 Example of accessories of medical devices

The following products fall under the definition of "accessory".

- Contact lens care products (disinfecting, cleaning, rinsing and hydrating solutions including those, which aid the insertion and/or wearing of contact lenses without therapeutic claim),
- Disinfectants specifically intended for use with medical devices (e.g. endoscopes),

Note:

Multipurpose disinfectants or sterilisation agents are not covered by MDD; they are covered by the directive on biocides.

- Lubricants specifically intended for use together with medical devices (e.g. for gloves, endoscopes, condoms),
- Skin barrier powders and pastes or other skin care products specifically intended for use together with ostomy bags,
- Gases used to drive cryoprobes and surgical tools.

A.2.2. Medicinal product

A.2.2.1 Definition of a medicinal product

Article 695 point 1 of Law 95/2006 defines a medicinal product as follows:

“(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or

(b) Any substance or combination of substances, which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.”

This definition comprises two limbs, one relating to presentation and the other to function. A product constitutes a medicinal product if it is covered by one or other or both of those limbs.

Due to the definition of medicinal product, substances used in or administered to human beings to make a medical diagnosis, even if they fulfil their function by physical or chemical means and not by pharmacological, immunological or metabolic means in the sense as described above are considered to be medicinal products.

The definition of medicinal product must be applied case by case and must be read in accordance with the case law of the European Court of Justice.

Article 696(2) of Law 95/2006 provides that “in cases of doubt, where, taking into account all its characteristics, a product may fall within the definition of a ‘medicinal product’ and within the definition of a product covered by other national legislation the provisions of this Title will apply”.

The wording of this Article shows that it only applies if, after a case-by-case assessment, taking in consideration all the characteristics of a product, the product in question may fall within the definition of both, medical device and medicinal product. In such a case, the provisions of Law 95/2006 apply. Government Decision no. 54/2009 on medical devices and Law 95/2006 cannot be applied cumulatively.

In deciding whether a product falls under the scope of Law 95/2006 or the scope of Government Decision no. 54/2009, particular account shall be taken of the principal mode of action of the product.

A.2.2.2 Examples of medicinal products:

The following examples should generally be considered as medicinal products subject to relevant criteria being met:

- Spermicidal preparations,
- Gases intended to be used in anaesthesia and inhalation therapy, (e.g. oxygen, medical air supplied in containers) including their primary containers,

Note: These gases are also used in minimal access surgery. However, a product intended exclusively for minimal access surgery would be a medical device.

- Topical disinfectants (antiseptics) for use on patients,
- Haemostatic and sealant products interacting with the coagulation cascade through a pharmacological process, i.e. where the primary mode of action is not mechanical (such as certain collagens, which have a molecular structure capable of surface independent demonstrated interaction with platelet receptors and therefore achieve platelet adhesion through a pharmacological process).
- Water for injections, IV fluids and other fluids for drug injection and plasma volume expanders,
- In vivo diagnostic agents, e.g. x-ray contrast media, NMR enhancing agents, fluorescent ophthalmic strips for diagnostic purposes, carrier solutions to stabilize micro-bubbles for ultrasound imaging, radiopharmaceuticals for diagnostic use
- Gases for in-vivo diagnostic purposes, including lung function, tests, e.g. carbon dioxide for vascular diagnostic purposes,
- Antacids,
- Fluoride dental preparations,

Note:

Dental preparations with a typical device mode of action, such as cements or varnishes incorporating fluoride, are medical devices, where the fluoride is of ancillary action to that of the device.

- Solutions administered in-vivo to the local circulation for the cooling of organs during surgery,

B. DRUG-DELIVERY PRODUCTS AND MEDICAL DEVICES INCORPORATING AS AN INTEGRAL PART, AN ANCILLARY MEDICINAL SUBSTANCE OR AN ANCILLARY HUMAN BLOOD DERIVATIVE

B1. Introduction

The term "Competent Authority" is used in this document to represent a competent body responsible for the evaluation of applications for medicinal products for human use being placed on the market (i.e. national competent authority designated by the Member States or the European Medicines Agency (EMA)).

This guideline aims to provide interested parties with appropriate guidance on procedural aspects to facilitate the consultation procedure to a Competent Authority by notified bodies on:

- Medicinal products, within the meaning of Article 695 (1) of Law 95/2006 incorporated, as an integral part, in a medical device and, which are liable to act upon the body with action ancillary to that of the device.
- Medicinal product constituents or medicinal products derived from human blood or human plasma, within the meaning of Article 695 (1) of Law 95/2006 incorporated, as an integral part, in a medical device and, which are liable to act upon the human body with action ancillary to that of the device.

These substances are referred to hereinafter respectively as 'ancillary medicinal substances' and as 'ancillary human blood derivatives'.

B.2 Drug-delivery products regulated as medicinal products

This category involves a device that is intended to administer a medicinal product in the case where the device and the medicinal product form a single integral product,, which is intended exclusively for use in the given combination and, which is not reusable.

According to the Government Decision no. 54/2009, this single product is governed by Law 95/2006 but the relevant essential requirements of Annex I of Government Decision no. 54/2009 (Articles 1-3) shall apply as far as the safety and performance-related device features are concerned.

B.2.1 Examples of drug-delivery products regulated as medicinal products

- Prefilled syringes,
- Aerosols containing a medicinal product,
- Nebulizers precharged with a specific medicinal product,
- Patches for transdermal drug delivery,
- Implants containing medicinal products in a polymer matrix whose primary purpose is to release the medicinal product, for example plastic beads containing antibiotic for treating bone infections, or a matrix to release osteoinductive proteins into the surrounding bone,
- Intrauterine contraceptives whose primary purpose is to release progestogens,
- Single-use disposable iontophoresis devices incorporating a medicinal product,
- Wound treatment products comprising a matrix whose primary purpose is the administration of medicinal products, for example wound dressings containing an antimicrobial agent where the primary action of the dressing is to administer the agent to the wound for the purpose of controlling infection,

- Temporary root canal fillers incorporating medicinal products, whose primary purpose is to deliver the medicinal product.

B.3 Drug-delivery products regulated as medical devices

This category concerns a device that is intended to administer a medicinal product within the meaning of Law 95/2006.

In this case, that device is governed by Government Decision no. 54/2009 without prejudice to the provisions of Law 95/2006 with regard to the medicinal product (Article 3 (1) of Government Decision no. 54/2009).

B.3.1 Examples of drug-delivery products regulated as medical devices

- Drug delivery pump,
- Implantable infusion pump,
- Iontophoresis device,
- Nebulizer,
- Syringe, jet injector,
- Spacer devices for use with metered dose inhalers,
- Port systems.

B.4 Medical devices incorporating, as an integral part, an ancillary medicinal substance

Government Decision no. 54/2009 also specifies the case of medical devices incorporating, as an integral part, a medicinal substance with ancillary action (Article 4 (1) of Government Decision no. 54/2009).

This case relates to a device that incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product within the meaning of Article 695 of Law 95/2006 and, which is liable to act upon the body with action that is ancillary to that of the device.

That device shall be assessed and authorised in accordance with Government Decision no. 54/2009.

Note: Any substance incorporated in the device must meet the three following conditions:

- The substance, if used separately, may be considered to be a medicinal product;
- The substance is liable to act upon the human body;
- The action of this substance is ancillary to that of the device.

A medical device incorporates a medicinal substance *as an integral part*, within the meaning of Article 4 (1) of Government Decision no. 54/2009, if and only if the device and the substance are physically or chemically combined at the time of administration (i.e. use, implantation, application etc.) to the patient.

B.4.1 Examples of medical devices incorporating, as an integral part, an ancillary medicinal substance

- Catheters coated with heparin or an antibiotic agent,
- Bone cements containing antibiotic,
- Root canal fillers, which incorporate medicinal substances with ancillary action,
- Soft tissue fillers incorporating local anaesthetics,
- Bone void filler intended for the repair of bone defects where the primary action of the device is a physical means or matrix, which provides a volume and a scaffold for osteoconduction and where an additional medicinal substance is incorporated to assist and complement the action of the matrix by enhancing the growth of bone cells. In such cases, the ancillary nature would be determined by the performance of the matrix on its own and the extent of the enhancement of growth due to the presence of the substance. With reference to the overall purpose of the

product, where the medicinal substance has such an effect that its ancillary nature cannot be clearly established, the product should be considered in accordance with the concept of a drug delivery system,

- Condoms coated with spermicides,
- Electrodes with steroid-coated tip,
- Wound dressings, surgical or barrier drapes (including tulle dressings) with antimicrobial agent,
- Intrauterine contraceptives containing copper or silver.
- Ophthalmic irrigation solutions principally intended for irrigation, which contain components, which support the metabolism of the endothelial cells of the cornea
- Drug eluting coronary stents

It should be noted that the mere coating of a product with a chemical does not imply that the chemical is a medicinal substance. For example, hydroxyapatite, frequently used as coating for orthopaedic and dental implants, is not considered a medicinal substance. Other coatings, which are in use and, which are not medicinal substances are hydromers and phosphorylcholines.

B.5 Medical devices incorporating, as an integral part, an ancillary human blood derivative

The same rule applies when a medical device or an active implantable medical device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product constituent or a medicinal product derived from human blood or human plasma within the meaning of Article 695 of Law 95/2006 and, which is liable to act upon the human body with ancillary action to that of the device.

Such a device shall be assessed and authorised in accordance with Government Decision no. 54/2009.

C. CONSULTATION PROCEDURE ON DEVICES INCORPORATING, AS AN INTEGRAL PART, AN ANCILLARY MEDICINAL SUBSTANCES OR AN ANCILLARY HUMAN BLOOD DERIVATIVE

C.1 Purpose of the consultation procedure on devices incorporating, as an integral part, an ancillary medicinal substance or an ancillary human blood derivative

For devices incorporating, as an integral part, an ancillary medicinal substance, the notified body shall, having verified the usefulness of the substance as part of the medical device and taking account of the intended purpose of the device, seek a scientific opinion from one of the competent authorities designated by the Member States or the EMA acting particularly through its committee in accordance with Regulation (EC) No 726/2004 on the quality and safety of the substance including the clinical benefit/risk profile of the incorporation of the substance into the device (Article 7.4.2. of Annex 1 to Government Decision no. 54/2009).

For devices incorporating, as an integral part, an ancillary human blood derivative, the notified body shall, having verified the usefulness of the substance as part of the medical device and taking into account the intended purpose of the device, seek a scientific opinion from the EMA, acting particularly through its committee, on the quality and safety of the substance including the clinical benefit/risk profile of the incorporation of the human blood derivative into the device (Article 7.4.3. of Annex 1 to Government Decision no. 54/2009).

Note:

The consultation process is only applicable for devices incorporating a substance, which is liable to act upon the body with action ancillary to that of the device.

Therefore, for example, a contact lens solution containing an antiseptic agent, which does not act upon the body with an action ancillary to that of the device but, which aims to preserve the solution does not fall under this procedure.

In accordance with Article 7.4.1. of Annex I to Government Decision no. 54/2009, the quality, safety and usefulness of an ancillary medicinal substance incorporated in a medical device must be verified by analogy with the methods specified in Order of the Minister of Public Health no. 906/2006 on approval of the Analytical, pharmacotoxicological and clinical Rules and protocols in respect of the testing of medicinal products. This is further elaborated in section C.3.

The assessment of "usefulness" and "safety" has a particular implication when applied to a medicinal substance, which has an ancillary action within a device/medicinal product combination.

The aspect of "usefulness" relates to the rationale for using the medicinal substance in relation to the specific intended purpose of the device. It refers to the suitability of the medicinal substance to achieve its intended action, and whether the potential inherent risks (aspects of "safety") due to the medicinal substance are justified in relation to the benefit to be obtained within the intended purpose of the device.

By means of the consultation process, the Competent Authority may make available relevant information concerning risks related to the use of the substance (e.g. resulting from pharmacovigilance).

C. 2 Notified Body actions to initiate consultation process on medical devices incorporating, as an integral part, an ancillary medicinal substance or an ancillary human blood derivative

- a) The Notified Body should ensure that data supplied by the manufacturer in relation to the device and its intended use includes a specific segment regarding the ancillary medicinal substance or the ancillary human blood derivative incorporated in the medical device. Presentation of the data according to the format of the "Notice to Applicants" may facilitate the review by the Competent Authority. (Ref: "The Rules governing medicinal products in the European Union", volume 2B)
- b) This segment should include data concerning the quality, safety and usefulness of the ancillary medicinal substance or of the ancillary human blood derivative, also appropriate details regarding information to be supplied with the device when placed on the market to permit the evaluation of the aforementioned features.
- c) Except for human blood derivatives and for medicinal products, which fall within the scope of the Annex I to Regulation (EC) N° 726/2004 where consultation with EMA is mandatory, it is at the discretion of the manufacturer to choose the Competent Authority in consultation with its Notified Body. The EMA may also be consulted, e.g. where the substance involved was included in a medicinal product, which has been evaluated by the EMA.

C. 3 Documentation to be provided by the Notified Body to the Competent Authority

Because of the wide range of medical devices, which incorporate, as an integral part, an ancillary medicinal substances or an ancillary human blood derivative, a flexible approach to the data requirements is necessary. Nevertheless the information should be based in principle, to the extent relevant, on Annex I to Directive 2001/83/EC, as amended by Commission Directive 2003/63/EC, transposed into national legislation through Order of the Minister of Public Health no. 906/2006 on approval of the Analytical, pharmacotoxicological and clinical

Rules and protocols in respect of the testing of medicinal products, as amended through Order of the Minister of Health no. 615/2010. It is envisaged that, where well-known medicinal substances for established purposes are the subject of the consultation, all aspects of safety and usefulness may not be required and many of the headings will be addressed by reference to literature, including standard textbooks, experience and other information generally available. Nonetheless all headings should be addressed; either with relevant data or justification for absence of data. The latter may be based on the manufacturer's risk assessment.

For new active substances and for known substances in a non-established purpose, comprehensive data is required to address the requirements of Order of the Minister of Public Health no. 906/2006, as amended through Order of the Minister of Health no. 615/2010. The evaluation of such active substances would be performed in accordance with the principles of evaluation of new active substances.

Particular attention should be given to, as relevant:

- The "EMA recommendation on the procedural aspects and dossier requirements for the consultation to the EMA by a Notified body on an ancillary medicinal substance or an ancillary human blood derivative incorporated in a medical device, EMA/CHMP/401993/2005²."

This recommendation is intended to provide the relevant parties with information about procedural aspects of the consultation procedure to the EMA by Notified Bodies on an ancillary medicinal substance or an ancillary human blood derivative incorporated as an integral part in a medical device, as well as guidance on data requirements and format of such applications for consultation;

- Published guidance from national competent authorities on the documentation requirements for consultations.

1) General information

A general description of the medical device including the manufacturer's claim regarding the purpose of the incorporation of the ancillary medicinal substance or the ancillary human blood derivative, together with a critical appraisal of the results of the risk assessment.

2) Quality documentation

a) For the ancillary medicinal substance or the ancillary human blood derivative itself:

- Relevant parts of CTD-Module 3 in accordance with the format of the "Notice to Applicants" (Ref: "The Rules governing medicinal products in the European Union", volume 2B). Relevant parts should be provided, depending on whether the ancillary medicinal substance or the ancillary human blood derivative is an active pharmaceutical ingredient or a formulated medicinal product.

- Information on the active substance may be provided in the form of an Active Substance Master File (ASMF)³, structured according to Module 3.2.S of the CTD-format.

Particular attention should be made to current CHMP quality guidelines on ASMF⁴.

- Where applicable, reference shall also be made to the European Pharmacopoeia (Ph.Eur.) or in the absence of a Ph.Eur. monograph to a national pharmacopoeia of one of the Member States. If no monograph is available from the Member States reference may be to other national monographs or to the manufacturer's specification and methods of analysis.

- CTD-Module 2.3 (Quality Overall Summary) in accordance with the format of the "Notice to Applicants" (Ref: "The Rules governing medicinal products in the European Union", volume 2B)

²<http://www.emea.europa.eu/pdfs/human/regaffair/40199305en.pdf>

³This option does not apply to biological substances.

⁴<http://www.emea.europa.eu/htms/human/humanguidelines/quality.htm>

b) For the ancillary medicinal substance or the ancillary human blood derivative as incorporated in the medical device:

- Qualitative and quantitative particulars of the constituents

A description of the ancillary medicinal substance or the ancillary human blood derivative, and the amount (giving a range where appropriate) of the ancillary medicinal substance or the ancillary human blood derivative incorporated into each medical device. If the medicinal substance or the ancillary human blood derivative is modified during its incorporation into the medical device, relevant information shall be provided.

- **Description of method of manufacture**

An overall description will already form part of the application to the Notified Body; the section dealing with incorporation of the ancillary medicinal substance or the ancillary human blood derivative in the medical device should be provided.

- **Controls of starting materials**

The specification for the ancillary medicinal substance or the ancillary human blood derivative shall be provided.

- **Control tests carried out at intermediate stages of the manufacturing process of the medical device**

This information is only necessary if it is directly relevant to the quality of the ancillary medicinal substance or the ancillary human blood derivative as incorporated in the medical device.

- **Final Control tests of the ancillary medicinal substance or the ancillary human blood derivative in the medical device**

Qualitative and quantitative tests carried out to control the ancillary medicinal substance or the ancillary human blood derivative incorporated in the medical device.

- **Stability**

Information defined to show the ancillary medicinal substance or the ancillary human blood derivative maintains its desired function throughout the defined shelf-life of the medical device including, taking account of the manufacturer's recommended storage conditions, potential interaction with other materials, and potential degradation of the ancillary medicinal substance or the ancillary human blood derivative.

3) Non-clinical documentation

- Non-clinical pharmacology
- Pharmacodynamics

This section should address the intended action of the ancillary medicinal substance or the ancillary human blood derivative in the context of its incorporation into a medical device.

- Pharmacokinetics

It is anticipated that pharmacokinetic studies will not be required in the majority of cases. Some or all of the following are as may need to be addressed as appropriate:

- Description of the pattern of local and systemic exposure to the ancillary medicinal substance or to the ancillary human blood derivative,
- Where the level of exposure fluctuates (AUC), the maximum level and duration of exposure should be considered,

- Where it is considered possible that potential levels of systemic exposure may present a safety concern, maximum peak plasma concentration should be established, taking due consideration of individual variability,

- New active substances will require information on the release from the medical device, and, if relevant, its subsequent absorption, distribution, metabolism and excretion (AUC and eventually metabolites, if relevant).

- Toxicity (including single-dose toxicity, repeat-dose toxicity, genotoxicity, carcinogenicity and reproductive and developmental toxicity, as applicable)

Reference to the known toxicological profile of the ancillary medicinal substance or the ancillary human blood derivative may be provided. In the case of new active substances, the results of toxicity tests should be provided, taking into account relevant CHMP guidelines⁵.

This may include information on toxicity and biocompatibility of the medical device, which may be available from evaluation in accordance with the EN 10993 series of standards.

- Local tolerance

This is of particular relevance since the route of exposure to the ancillary medicinal substance or the ancillary human blood derivative may be different from its conventional application. The relevant results of medical device testing according to EN ISO 10993 should be provided or, where appropriate, information from the scientific literature.

4) Clinical evaluation

Since these medical devices will be class III, clinical data will form part of the information provided to the Notified Body under annex II or III of the applicable Directive, namely in accordance with Annex 10 of Government Decision no. 54/2009 (national legislation). This data will address the requirements for clinical evaluation of the medical device incorporating an ancillary medicinal substance or an ancillary human blood derivative as required by Annex 10 of Government Decision no. 54/2009. This data will address the safety of the medical device in its entirety. The usefulness of the ancillary medicinal substance or the ancillary human blood derivative incorporated in the medical device should be addressed by clinical evaluation or by cross-reference to other sections of the dossier, as applicable.

An appropriate methodology for clinical investigations on medical devices is described in EN ISO 14155-2012 - Clinical investigation of medical devices for human subjects. Good Clinical Practice.

Particular attention shall be given to any specific guidelines (e.g. EMA guideline on the clinical and non-clinical evaluation during the consultation procedure on medicinal substances contained in drug eluting (medicinal substance-eluting) coronary stents⁶, MEDDEV guidance 2.7.1 Appendix 1 – clinical evaluation of coronary stents⁷).

5) Labelling

Details supplied by the manufacturer of labelling or information to be provided with the medical device with regard to the ancillary medicinal substance or the ancillary human blood derivative, is to be supplied to the Competent Authority to assist in the understanding of the safety and usefulness of the ancillary medicinal substance or the ancillary human blood derivative together with the medical device.

C. 4 Consultation process on medical devices incorporating, as an integral part, an ancillary medicinal substance or an ancillary human blood derivative

⁵<http://www.emea.europa.eu/htms/human/humanguidelines/nonclinical.htm>

⁶http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003275.pdf

⁷http://ec.europa.eu/consumers/sectors/medical-devices/files/meddev/cetf_en.pdf

- a) The Notified Body, having requested a Competent Authority to provide an opinion concerning the ancillary medicinal substance or the ancillary human blood derivative
- b) and its application, should, together with the Competent Authority, agree such matters as: time-schedules, modalities to obtain further information, including clock stops, fees and practical arrangements for submission of data.
 - Further details about the procedure to follow for a consultation to the EMA are detailed in the “EMA recommendation on the procedural aspects and dossier requirements for the consultation to the EMA by a Notified body on an ancillary medicinal substance or an ancillary human blood derivative incorporated in a medical device, EMEA/CHMP/401993/2005”⁸.
 - National competent authorities may also have published guidance on the procedure to follow for consultations.
- b) The Notified Body should make available to the competent Authority relevant data as specified in C.3 together with its own verification of the usefulness of the ancillary medicinal substance or the ancillary human blood derivative incorporated in the device.
- c) The Competent Authority should review the data provided by the Notified Body. It should consider the use of the ancillary medicinal substance or of the ancillary human blood derivative by analogy with existing information regarding the known applications and appropriate features of safety, quality and usefulness as they may be relevant to the specific intended purpose of the device incorporating, as an integral part, the ancillary medicinal substance or the ancillary human blood derivative.
- d) During the consultation process the Notified Body concerned may withdraw the request and ask for the opinion of an alternative relevant Competent Authority. In this case, the previously consulted Competent Authority should be informed of the name of the new Competent Authority.
- e) The Competent Authority should inform the Notified Body of its opinion, taking into account the manufacturing process and the data related to the usefulness of incorporation of the ancillary medicinal substance or of the ancillary human blood derivative into the device as determined by the Notified Body (Article 7.4.2 of Annex 1 to Government Decision no. 54/2009).
- f) The scientific opinion on the competent authority must be included in the documentation concerning the device. The opinion of the Competent Authority must be drawn up within 210 days after receipt of a valid documentation (Article 4.3 of Annex 2 to Government Decision no. 54/2009). This time period excludes clock stops.
- g) For medical devices incorporating an ancillary medicinal substance, the notified body will give due consideration to the views expressed in this consultation when making its decision. It will convey its final decision to the Competent Authority concerned (Article 4.3. of Annex 2 to Government Decision no. 54/2009).

⁸<http://www.emea.europa.eu/pdfs/human/regaffair/40199305en.pdf>

- h) The Notified Body should take into account the opinion of the Competent Authority and use its judgement to either approve the product, after consideration of all aspects of risk/benefit in the intended or expected use of the product, or alternatively to reject the product. It may be that certain suggestions from the Competent Authority may be adopted by the manufacturer to render the product acceptable.
- i) The Notified Body should inform the Competent Authority, which was consulted of the decision reached by the Notified Body, and where this decision deviates from the opinion provided by the Competent Authority this will be shown. Where a Notified Body receives a negative opinion from the Medicinal Product Competent Authority, they should consult with the device Competent Authority before issuing a certificate.
- j) For medical devices incorporating an ancillary human blood derivative, the notified body will give due consideration to the opinion of the EMA when making its decision. The notified body may not deliver the certificate if the EMA's scientific opinion is unfavourable. It will convey its final decision to the EMA (Article 4.3. of Annex 2 to Government Decision no. 54/2009).
- k) Where changes are made to an ancillary substance incorporated in a device (in particular related to the source, the manufacturing process, the amount and the method of incorporation), the notified body shall be informed of the changes and shall consult the relevant medicines competent authority (i.e. the one involved in the initial consultation), in order to confirm that the quality and safety of the ancillary substance are maintained. The competent authority shall take into account the data related to the usefulness of the incorporation of the substance into the device as determined by the notified body, in order to ensure that the changes have no negative impact on the established benefit/risk profile of the addition of the substance in the device (Article 7.4.5. of Annex 1 to Government Decision no. 54/2009).
- l) When the relevant medicines competent authority (i.e. the one involved in the initial consultation) has obtained information on the ancillary substance,, which could have an impact on the established benefit/risk profile of the addition of the substance in the medical device, it shall provide the notified body with advice, whether this information has an impact on the established benefit/risk profile of the addition of the substance in the medical device or not. The notified body shall take the updated scientific opinion into account in reconsidering its assessment of the conformity assessment procedure (Article 7.4.5. of Annex 1 to Government Decision no. 54/2009).

D. PROCEDURES FOR THE REPORTING OF ADVERSE INCIDENTS

The regulation of a product as a medicinal product or medical device will determine which procedure should be followed for the reporting of an adverse incident; medicinal products to meet the requirements for pharmacovigilance and medical devices to meet the requirements for medical device vigilance.

Note: Guidelines are available on:

- Medical device vigilance system (MEDDEV. 2.12/1 rev 7)⁹.
- Pharmacovigilance requirements¹⁰.

⁹ http://ec.europa.eu/consumers/sectors/medical-devices/files/meddev/2_12_1-rev_703-2012_en.pdf

¹⁰ http://ec.europa.eu/health/documents/eudralex/index_en.htm