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GUIDELINES RELATING TO THE APPLICATION OF :
THE COUNCIL DIRECTIVE 90/385/EEC ON ACTIVE IMPLANTABLE MEDICAL DEVICES
THE COUNCIL DIRECTIVE 93/42/EEC ON MEDICAL DEVICES

**DEMARCATIION BETWEEN : - DIRECTIVE 90/385/EEC ON ACTIVE IMPLANTABLE MEDICAL DEVICES
- DIRECTIVE 93/42/EEC ON MEDICAL DEVICES**

AND - DIRECTIVE 65/65/EEC RELATING TO MEDICINAL PRODUCTS

AND -- RELATED DIRECTIVES

Foreword

The present Guidelines are part of a set of Guidelines relating to questions of application of EC-Directives on medical devices. They are legally not binding. The Guidelines have been carefully drafted through a process of intensive consultation of the various interested parties (Competent Authorities, Commission services, industries and other interested parties in both the medical devices and the medicinal products sectors) during which intermediate drafts were circulated and comments were taken up in the document. Therefore this document reflects positions taken in particular by the aforementioned interested parties.

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.

Note: This document is a revision of an earlier document published in July 1995 as MEDDEV 14/93 Rev. 4

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A. DEMARCATION BETWEEN MEDICAL DEVICES DIRECTIVES AND MEDICINAL PRODUCTS DIRECTIVES

A.1 Introduction

The determination of the borderline between the Medical Devices Directive 93/42/EEC (MDD) (OJ No.L 169, 12/7/93), the Active Implantable Medical Device Directive 90/385/EEC (AIMD) (OJ No. L189, 20/7/90) and the Medicinal Products Directive 65/65/EEC (MPD) including related directives, was one of the issues discussed at some length during the legislative procedure on the MDD. Therefore, in the MDD several provisions to establish the demarcation between both legal regimes have been laid down. It was recognised that the subject needs to be further explained and illustrated by practical guidance and examples. The present document has no legal force. It has nevertheless been elaborated by an expert group including experts from Member States' competent authorities for both medical devices and medicinal products, the European Commission, as well as industry trade associations. It is therefore intended that the document will provide useful guidance which should assist common positions to be taken throughout the European Union.

For the relevant definitions and legal requirements reference is made to:

Directive 93/42/EEC MDD	Directive 65/65/EEC MPD	Medicinal Products Extension Directives
Article 1 (2a): "medical device"	Article 1(3) : medicinal product	Directive 89/343/EEC relating to radiopharmaceuticals
Article 1 (3): "drug delivery devices"		Directive 89/342/EEC relating to immunological products
Article 1 (4): "devices incorporating medicinal substances with ancillary action"		Directive 89/381/EEC relating to blood products

A.2 General principles

As a general rule a relevant product is regulated either by the MDD or by the MPD. The authorization or conformity assessment procedure to be followed prior to placing a given product on the market will therefore be governed either by the MDD/AIMD or by the MPD. Normally the procedures of both directives do not apply cumulatively. For defined features, however, some cross-references are made within one regime to specific provisions of the other regime (see Article 1(4) in conjunction with Annex I, section 7.4 MDD; Article 1(3) MDD).

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

Medical device (93/42/EEC)

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

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- 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;"

Medicinal product (65/65/EEC)

"Any substance or combination of substances presented for treating or preventing disease in human beings or animals.

Any substance or combination of substances which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings or in animals is likewise considered a medicinal product."

In order to decide which regime applies, the following criteria should be examined:

Step 1. The intended purpose of the product taking into account the way the product is presented (this is likely to establish if either the MDD or the MPD apply, rather than distinguish between the two regimes),

Step 2. The method by which the principal intended action is achieved.

The latter criterion, based on the "principal intended action" is crucial in the definition of a medical device. Typically the medical device function is fulfilled by physical means (including mechanical action, physical barrier, replacement of or support to organs or body functions, ...). The action of a medicinal product is generally achieved by pharmacological, immunological means or by metabolism.

The principal intended action of a product may be deduced from:

- the manufacturer's labelling and claims,
- scientific data regarding mechanism of action.

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 classification of borderline products.

"Pharmacological means", in the context of the MDD and AIMD, 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", in the context of the MDD and AIMD, 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", in the context of the MDD and AIMD, 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.

The fact that a product is itself metabolised does not imply that it achieves 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 any more ancillary with respect to the principal purpose of a product, the product becomes a medicinal product. The claims made for a product, in accordance with its method of action may, in this context, represent an important factor for its classification as medical device or medicinal product.

These principles are illustrated by bone cements and related products which appear in several of the following sections. Plain bone cement without antibiotics is a medical device since it achieves its primary intended purpose (the fixation of a prosthesis) by mechanical means. Bone cements containing antibiotics, where the principal intended purpose remains fixation of a 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 purpose is to deliver the antibiotic, the product would be a medicinal product.

These principles are subject to certain exemptions as a consequence of which a number of products fall within the definition of "medicinal product", 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. This applies, in particular, to antacids, in-vivo diagnostics, and to the products listed in A.4.2 which are "administered to human beings with a view to making a medical diagnosis" or to fulfil another purpose as indicated in the medicinal product definition. Unlike products which, in the absence of Community medical device legislation, had been assimilated to national medicinal product law and which are now regulated by MDD/AIMD (reclassification will take place in those Member States during the transitional period), the grouping as referred to in A.4.2 has been regarded throughout the EU as medicinal products within the meaning of Directive 65/65/EEC. The status of these products as medicinal products is retained as specified under A.4.2

A.3 Examples of medical devices

3.1 The following examples should, in view of their mode of action, generally be considered as medical devices subject to relevant criteria being met; the function of some of the devices indicated in these examples, e.g. bone cement, may be assisted by the presence of medicinal substances where such substances have an ancillary action to that of the device (see also A.5).

- bone cement (see A.5 and A.6),
- dental filling materials (see A.5 and A.6),
- materials for sealing, approximation, or adhesion of tissues (e.g. cyanocrylates, 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. collagen, 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 (see A5 and A6),
- intrauterine devices (see A.5 and A.6),
- blood bags (see A.5),
- systems intended to preserve and treat blood (see A5),

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 intended 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.

- viscoelastic materials with intended use for mechanical/physical purposes such as protection of tissues during and after surgery and separation of tissues. Such materials are also used as synovial fluid replacements where visco-supplementation provides support and lubrication.

Note : Additional pharmacological benefits claimed which are ancillary to the mechanical action do not alter the medical device status. However, certain of these materials such as some hyaluronan based products, where the predominant claims are of a pharmacological nature and not primarily related to any viscoelastic characteristics, are classed as medicinal products,

- gases and liquids for ocular endotamponades,
- cell separators, including those incorporating antibodies for cell marking,
- wound dressings, which may be in the form of liquids, gels and pastes, etc (e.g. hydrocolloid, hydrogel), (see A.4 and A.5),
- 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 those containing collagen, or calcium alginate or oxidised cellulose where adhesion of platelets to the surface triggers platelet adhesion and aggregation (see A.4 and A.5).
- concentrates for haemodialysis,
- pressure reducing valves and regulators,
- irrigation solutions (including those used in the eye) intended for mechanical rinsing (see A5)

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.

3.2 The following products are covered by the MDD because they fall under the definition of "accessory". This is the case if they are intended specifically to be used together with a device to enable the device to be used in accordance with its intended purpose or to enhance the performance of the device.

- contact lens care products (disinfecting, cleaning, rinsing and hydrating solutions including those which aid the insertion and/or wearing of contact lenses without a 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 will be 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,
- challenge tests specifically intended to assess the tolerance to a given medical device, or its constituents (e.g. injectable collagen).
- gases used to drive cryoprobes and surgical tools (see A4)

A.4 Examples of medicinal products

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

4.1. Products which fulfil their primary intended purpose by pharmacological, immunological or metabolic means,

- 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 agents where primary mode of action is not mechanical such as certain collagens which have a molecular structure capable of a surface-independent demonstrated interaction with platelet receptors, and which achieves platelet adhesion through a pharmacological process.
- zinc paste for dermatological use

4.2. The following products are assimilated to medicinal products and therefore dealt with in accordance with 65/65/EC as medicinal products:

- water for injections, IV fluids and plasma volume expanders,
- haemofiltration substitution solutions,
- 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,
- gases for in-vivo diagnostic purposes, including lung function, tests, e.g. carbon dioxide for vascular diagnostic purposes,
- solutions for peritoneal dialysis,
- antacids,
- artificial tears,
- 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 fluorine is of ancillary action to that of the device. Certain products where the claims are primarily cosmetic in nature and where the fluorine level is less than 0.15% are cosmetic products (see 76/768/EEC and amending Directives).

- solutions administered in-vivo to the local circulation for the cooling of organs during surgery;

It should be noted that the Directive 89/343/EEC relating to radiopharmaceuticals applies also to generators, that means any system incorporating a fixed parent radionuclide the daughter radionuclide of which is to be removed by elution or by any other method and used in a radiopharmaceutical (see article 1(2) of Directive 89/343/EEC).

4.3. Agents for transport, nutrition and storage of organs intended for transplantation,

Note: These products are not currently regulated in all Member States as medicinal products. However there was general consensus of public authorities that the medicinal products category is the most appropriate. Some of these products may have a metabolic effect, others however have no such effects.

A.5 Medical devices incorporating a medicinal substance with ancillary action

It follows from the definition of a medical device that devices may incorporate substances as an integral part which, if used separately, may be considered to be a medicinal product. This is specifically addressed in article 1(4) MDD which makes it clear that such products are devices, provided that the action of the medicinal substance is ancillary to that of the device, as reflected in the product claim and as supported by the scientific data provided by the manufacturer of the devices.

Examples of such devices are:

- catheters coated with heparin or an antibiotic agent,
- bone cements containing antibiotic (see A.3 and A.6),
- root canal fillers which incorporate medicinal substances with secondary action (see A.3 and A.6),
- blood bags containing anticoagulant or preservation agents (see A.3),

Note : rule18 of Annex IX of the MDD applies to these products.

- 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, then the product should be considered in accordance with the concept of a drug delivery system (see section A6.2),
- haemostatic devices enhanced by the incorporation of collagen, where the primary action of the device is mechanical even though there may be ancillary action due to the presence of collagen having demonstrable action with platelet receptors resulting in platelet adhesion through a pharmacological process (see also A.3 and A.4),
- condoms coated with spermicides,
- electrodes with steroid-coated tip,
- wound dressings, surgical or barrier drapes (including tulle dressings) with antimicrobial agent (see A.6),
- 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 (see A3).

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.

Note : For the time being, products incorporating medicinal substances of human origin are excluded from the MDD.

A.6 Drug delivery system

6.1. The status of devices for drug delivery is addressed by article 1(3) MDD. A device which is intended to deliver a medicinal product is itself regulated as a medical device. The medicinal product which the device is intended to administer must, of course, be approved according to the normal procedures for medicinal products.

Examples :

- drug delivery pump,
- implantable infusion pump,
- iontophoresis device,
- nebulizer,
- syringe, jet injector.

Note: in a kit comprising an insulin pen and insulin cartridges, the pen is subjected to the MDD whereas the insulin cartridge is a medicinal product.

- spacer devices for use with metered dose inhalers,
- port systems.

6.2. However, if 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, that single product is regulated as a medicinal product (article 1(3), second subparagraph MDD). Examples of such products are :

- prefilled syringes,
- aerosols containing a medicinal product,
- nebulizers precharged with a specific medicinal product, and not for universal application,
- 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 (see also A5)
- 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, (see A.3 and A.5), 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 (see A.3 and A.5).

In such cases the essential requirements of the MDD apply as far as the device related features of the product are concerned (for example as regards the mechanical safety features of a prefilled syringe). The labelling, however, should comply with the requirements of Directive 92/27/EEC applicable to medicinal products.

B. THE CONSULTATION PROCESS FOR DEVICES INCORPORATING A MEDICINAL SUBSTANCE HAVING ANCILLARY ACTION

B.1 Purpose of the consultation procedure

When referring to the appropriate essential requirement in the MDD - Annex 1, section 7.4 -, a Notified Body so concerned has a responsibility to address this requirement by "consulting one of the competent bodies established by the Member States in accordance with Directive 65/65/EEC before taking a decision" (MDD: Annex II section 4.3 and Annex III section 5).

The term "Competent Authority" is used in this document to represent such a competent body within the meaning of Directive 65/65/EEC, and indicates the authority responsible for the evaluation of application for medicinal products being placed on the market (see Annex for list of appropriate Competent Authorities).

In Essential Requirement 7.4 the expression "substance which, if used separately, may be considered to be a medicinal product as defined in Article 1 of Directive 65/65/EEC..." is used. This reflects the fact that in such cases, neither the device incorporating a medicinal substance nor the substance in itself is a medicinal product as defined in Directive 65/65/EEC. This requirement relates to substances which, otherwise, in the context of medicinal products may be an active constituent of a medicinal product and therefore be liable to act upon the body.

It is for this reason that the verification by the Competent Authority of the safety, quality and usefulness of the "medicinal substance" is to be carried out by analogy with the appropriate methods specified in Directive 75/318/EEC as amended by Directive 91/507/EEC.

The assessment of "usefulness" and "safety" has a particular implication when applied to a medicinal substance which is of ancillary purpose within a device/medicinal substance 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).

The ultimate responsibility for the decision, as to whether the pertinent legal requirements are met, belongs to the Notified Body.

The consultation process is only applicable for devices incorporating a medicinal substance as specified in Annex 1, section 7.4 and only where the substance is liable to act upon the body with action ancillary to that of the device. Therefore, a contact lens solution containing an antiseptic agent where the purpose of the antiseptic is to preserve the solution does not fall under this procedure.

In line with Article 22(3) of the MDD, for a device which has already been granted a marketing authorisation as a medicinal product in at least one Member State the consultation procedure will be limited to a simple exchange of letters between the Notified Body and Competent Authority, provided the product is unchanged in all respects, including the information provided with the device.

B.2 Notified Body actions to initiate consultation process

- 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 medicinal substance being incorporated with ancillary purpose. 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", volume 2B)
- b) This segment should include data concerning the safety, usefulness and quality of the medicinal substance, 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) Before consulting a relevant Competent Authority the Notified Body should have come to a preliminary opinion regarding the suitability of the device with ancillary medicinal substance.
- d) It is at the discretion of the Notified Body to choose the Competent Authority with whom he consults from the listed Competent Authorities as indicated in the annex. The European Medicines Evaluation Agency (EMA) may be consulted, where the substance involved has been included in a medicinal product which has been evaluated by the EMA.
- e) The Notified Body may consider it of benefit to utilise, for the consultation, the appropriate Competent Authority previously responsible for a marketing authorisation for a medicinal product which incorporates the medicinal substance involved in the consultation process.

B.3 Documentation to be provided by the Notified Body to the competent authority for medicinal products

Because of the wide range of medical devices which incorporate medicinal substances, a flexible approach to the data requirements is necessary. Nevertheless the information should be based in principle, to the extent relevant, on the annex to Directive 91/507/EEC, which modifies Directive 75/318/EEC, as outlined in (a) to (q) below. It is envisaged that, where well-known medicinal substances for established purposes are involved, all aspects of safety and usefulness may not be required and many of the headings will be addressed by reference to the literature, including standard textbooks, experience and other information generally available. Nonetheless all headings should be addressed.

For new active substances and for known medicinal substances in a non-established purpose, comprehensive data is required to address items (a) to (q) below. The evaluation of such active substances would be performed in accordance with the principles of evaluation of new active substances. The principal headings of Directive 91/507/EEC are given below, together with comments on their applicability to medical devices. This represents a comprehensive checklist covering headings which may be appropriate depending on the circumstances relating to the case in question.

- a) General information

A general description of the medical device including the manufacturer's claim regarding the purpose of the inclusion of the substance, together with a critical appraisal of the results of the risk analysis.

- b) **Qualitative and quantitative particulars of the constituents**
A description of the substance and the amount (giving a range where appropriate) of the medicinal substance incorporated into each medical device. If the substance is modified during its incorporation into the device, relevant information shall be provided.
- c) **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 medicinal substance in the device should be provided.
- d) **Controls of starting materials**
The specification for the medicinal substance shall be provided. Where applicable, reference shall be to the European Pharmacopoeia or in the absence of an EP 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.
For new active substances and certain known substances additional information will be required which may be provided in the form of a Drug Master File. The guideline "Requirements in relation to active substances"¹ may be of assistance in providing circumstances where reference to a Pharmacopoeia monograph may need to be supplemented by further information.
- e) **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 substance as incorporated in the medical device.
- f) **Control tests on finished product**
Qualitative and quantitative tests carried out to control the medicinal substance in the device.
- g) **Stability**
Information defined to show the medicinal substance maintains its desired function throughout the defined shelf-life of the device, taking account of the manufacturer's recommended storage conditions.
- h) **Toxicity**
Reference to the known toxicological profile of the medicinal substance may be provided. In the case of new active substances, the results of toxicity tests, should be supplied. This may include information on toxicity and biocompatibility of the medical device which may be available from evaluation in accordance with the EN 30993 series of standards.
- i) **Reproductive function**
Similar considerations to h) apply.

Sincerely yours, ¹ In "The Rules Governing Medicinal Products in the European Community, Volume III Addendum II".

- j) Embryo/foetal and perinatal toxicity
Similar considerations to (h) apply.
- k) Mutagenic potential
Similar considerations to h) apply.
- l) Carcinogenic potential
Similar considerations to h) apply. The need for data on carcinogenicity should be addressed taking account of available information on the medicinal substance, the results of genotoxicity testing, the chemical structure of the medicinal substance, and the duration of potential exposure to the substance.
- m) Pharmacodynamics
This section should address the intended action of the medicinal substance in the context of its incorporation into a medical device.
- n) Pharmacokinetics
It is anticipated that pharmacokinetic studies will not be required in the majority of cases. Some or all of the following areas may need to be addressed as appropriate:
- description of the pattern of local and systemic exposure to the medicinal substance,
 - where the level of exposure fluctuates, 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 device, and, if relevant, its subsequent distribution and elimination.
- o) Local tolerance
This is of particular relevance since the route of exposure to the medicinal substance may be different from its conventional application. The relevant results of device testing according to EN 30993 should be provided or, where appropriate, information from the scientific literature
- p) Clinical documentation
Since the devices will normally be class III, clinical data will form part of the information provided to the Notified Body under annex II or III. This data will address the safety of the device in its entirety. The usefulness of the medicinal substance in the medical device should be addressed by clinical data or in other sections of the dossier.
An appropriate methodology for clinical investigations on medical devices is described in EN 540.
- q) Labelling
Details supplied by the manufacturer of labelling or information to be provided with the device with regard to the medicinal substance, is to be supplied to the Competent Authority to assist in the understanding of the safety and usefulness of the substance together with the device.

B.4 The consultation process

- a) The Notified Body, having requested a Competent Authority to provide an opinion concerning the medicinal substance 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.
- b) The Notified Body should make available to the Competent Authority relevant data as specified in B.3.
- c) The Competent Authority should verify the data provided by the Notified Body. It should consider the use of the medicinal substance 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 the medicinal substance.
- d) The Competent Authority should inform the Notified Body of its conclusions and advice as to the suitability of the medicinal substance in its proposed use.
- e) The Notified Body should take into account the opinion of the Competent Authority and use its judgement to either approve the drug/device combination, 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.
- f) 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.
- g) 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.

C. CONSULTATION BY COMPETENT AUTHORITIES FOR MEDICINAL PRODUCTS WITH REGARD TO MEDICINAL PRODUCTS WITH DEVICE RELATED FEATURES.

In accordance with Article 1(3) second subparagraph MDD, products placed on the market in such a way that a device and a medicinal product form a single integral product which is intended exclusively for use in the given combination and which is not reusable, that single product shall be governed by Directive 65/65/EEC. In such cases the relevant essential requirements of Annex I MDD shall apply with regard to safety and performance related device features. Examples of such products are listed in A.6.2).

In such cases Competent Authorities responsible for the evaluation of the medicinal products in question would consult, if necessary, one of the Competent Authorities or Notified Bodies for medical devices. This consultation would cover the essential requirements of Annex I MDD for the relevant device features.

D. PROCEDURES FOR THE REPORTING OF ADVERSE INCIDENTS

The classification of the product, 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 (including those referenced under section A5) to meet the requirements for medical device vigilance.

Note : guidelines are available on a medical device vigilance system (ref. MEDDEV. 2.12/1). Guidelines are available on a pharmacovigilance system.

A report should be made to a relevant authority and the authorities will liaise as necessary.

LIST OF ADDRESSES OF COMPETENT AUTHORITIES FOR MEDICINAL PRODUCTS

COUNTRIES	ASSOCIATIONS	ADRESSES	PHONE	FAX
EUROPEAN UNION	European Medicines Evaluation Agency	7 West Ferry Circus, Canary Wharf; UK-London E014 4HB	44/171/418.84.00	44/171/418.84.16
AUSTRIA	Bundesministerium für Arbeit, Gesundheit und Soziales, Gruppe VIII/C	Stubenring, 1 ; A-1010 Wien	43/1/71172-4673 (4674)	43/1/714.92.22
BELGIUM	Farmaceutische Inspectie	Rijksadministratief Centrum, Vesaliusgebouw; B-1010 Brussel	32/2/210.48.96	32/2/210.49.22
DENMARK	Danish Medicines Agency	Frederikssundsvej, 378; DK-2700 Brønshøj	45/44/889.111	45/44/917.373
GERMANY	* Bundesinstitut für Arzneimittel und Medizinprodukte * For blood products : Paul-Ehrlich-Institut, Bundesanstalt für Sera und Impfstoffe	Seestrasse 10-11, Postfach 33 00 13; D-14191 Berlin Postfach 1740; D-63207 Langen	49/30/4548-30 49/6103/770	49/30/4548-3207 49/6103/770123 oder 124
SPAIN	Direccion General Farmacia y Productos Sanitarios; Ministerio de Sanidad y Consumo	Paseo del Prado 18-20; E-28071 Madrid	34/1/596.40.15-16	34/1/596.40.69 (596.15.47) (596.15.48)
FINLAND	National Agency for Medicines, Pharmacological Department	Mannerheimintie 166; PO Box 55; FIN-00301 Helsinki	358/9/396.750	358/9/714.469
FRANCE	Agence du Médicament; Direction de l'Evaluation	143/145 Bd Anatole France; F-93200 Saint Denis	33/1/48.13.21.57	33/1/48.13.24.75 (48.13.20.98)
GREECE	E.O.F. (National Drug Organisation)	Mesogion 284; GR-155 62 Hologos	30/1/652.62.16	30/1/654.55.35
IRELAND	Irish Medicines Board	The Earlsfort Centre, Earlsfort Terrace IRL-Dublin 2	353/1/676.49.71(7)	353/1/676.84.90
ITALY	Direzione Generale del Servizio Farmaceutico - Ministero della Sanità	Viale della Civiltà Romana, 7 I-00144 Roma EUR	39/6/592.58.63	39/6/599.441.17
LUXEMBOURG	Direction de la Santé; Division de la Pharmacie et des Médicaments	10, rue C.M. Spoo L-2546 Luxembourg	352/478.55.93	352/224.458
NETHERLANDS	College ter beoordeling van geneesmiddelen, Ministerie van Welzijn, Volksgezondheid en Cultuur	Postbus 5811 NL-2280 HV Rijswijk (ZH)	31/70/340.72.10	31/70/340.51.55
PORTUGAL	INFARMED - Instituto Nacional da Farmacia e do Medicamento	Parque de Saúde de Lisboa; Av. do Brasil, 53 P- 1700 Lisboa	351/1/790.85.00 (795.78.36)	351/1/795.91.16
SWEDEN	Medical Products Agency	Husarg, 8; S-75103 Uppsala	46/18/174.691	46/1/548.566
UNITED KINGDOM	Medicines Control Agency; Department of Health	1 Nine Elms Lane; UK-London SW8 5NQ	44/171/273.02.00	44/171/273.04.93