

**Necessity of consultation procedures on medical devices  
incorporating a medicinal substance**

Wissenschaftliche Prüfungsarbeit

zur Erlangung des Titels

**„Master of Drug Regulatory Affairs“**

der Mathematisch-Naturwissenschaftlichen Fakultät  
der Rheinischen Friedrich-Wilhelms-Universität Bonn

vorgelegt von

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Bonn 2008

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## List of Abbreviations

A3	Report adopted by a Parliamentary Committee (of the EP)
ABl.	Amtsblatt der Europäischen Gemeinschaften (since 1 February 2003: Amtsblatt der Europäischen Union) [German edition of the OJ]
Abs.	Absatz [clause]
ADD	Addendum
AGMP	Arbeitsgruppe Medizinprodukte [Working Group Medical Devices] (Germany)
AIMDD	Council Directive 90/385/EEC on Active Implantable Medical Devices
ARGMD	Australian Regulatory Guidelines for Medical Devices
BAH	Bundesverband der Arzneimittel-Hersteller e.V. [German Medicines Manufacturers' Association]
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte [Federal Institute for Drugs and Medical Devices] (Germany)
BGBI.	Bundesgesetzblatt [German "Federal Law Gazette"]
BOE	Boletín Oficial del Estado [Official Spanish Gazette]
C3	Documents coming from other institutions, distributed by the EP
CE	– CE marking: an acronym for the French "Conformité Européenne" – Europe / European Legislation: Communauté européenne (in French) Comunidad Europea (in Spanish) [European Community]
CEE	Communauté économique européenne (in French) Comunidad Económica Europea (in Spanish) [European Economic Community]
COM	EU Commission documents intended for other institutions (legislative proposals, communications, reports, etc.)
EC	European Community
EEA	European Economic Area
EEC	European Economic Community
EEG	Europeiska Ekonomiska Gemenskapen [European Economic Community]
EEKH	Egészségügyi Engedélyezési és Közigazgatási Hivatal [Office of Health Authorisation and Administrative Procedures] (Hungary)
EG	Europäische Gemeinschaft (in German) Europeiska Gemenskapen (in Swedish) [European Community]
EGK	Európai Gazdasági Közösség [European Economic Community]
EK	Európai Közösség [European Community]
EMA	European Medicines Agency

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EP	European Parliament
EU	European Union
EüM	Egészségügyi Minisztérium (Hungarian Ministry of Health)
EWG	Europäische Wirtschaftsgemeinschaft [European Economic Community]
GHTF	Global Harmonization Task Force
IMB	Irish Medicines Board
IVDD	Directive 98/79/EC on In Vitro Diagnostic Medical Devices
LVFS	Läkemedelsverkets föreskrifter [Regulations from Medical Products Agency] (Sweden)
MDD	Council Directive 93/42/EEC on Medical Devices
MDEG	Medical Devices Expert Group
MEDDEV	MEDICAL DEVICES guidance document
MHRA	Medicines and Healthcare products Regulatory Agency (United Kingdom)
MPG	Medizinproduktegesetz [The Act on Medical Devices, Medical Devices Act] (Germany)
NB	Notified Body
No.	Number
Nr.	Nummer [number]
OJ	Official Journal of the European Communities (since 1 February 2003: Official Journal of the European Union)
OJ C	OJ C series (communications)
OJ L	OJ L series (legislation)
OTC	Over-the-counter (medicine)
p.	Page
PE	Unique number given to all EP documents
PHMB	Polyhexamethylene biguanide
REV	Revision
S.	Seite [page]
S.I.	Statutory Instrument
SEC	Miscellaneous EU Commission documents
SYN	Cooperation procedure (EU legislative procedure)
TGA	Therapeutic Goods Administration (Australia)
USA	United States of America
ZLG	Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten [Central Authority of the Laender for Health Protection with Regard to Medicinal Products and Medical Devices] (Germany)

# 1 Introduction

Medical devices are mainly regulated by three directives in the European Union: Council Directive 90/385/EEC on Active Implantable Medical Devices (AIMDD), Council Directive 93/42/EEC on Medical Devices (MDD) and Directive 98/79/EC on In Vitro Diagnostic Medical Devices (IVDD) (all as amended). The latest revision of those statutes was the amendment of the AIMDD and the MDD by Directive 2007/47/EC as of 5 September 2007. Member states have to transpose this directive into national law by 21 December 2008. Manufacturers will be required to comply with the amendments by 21 March 2010.

To demonstrate the compliance of a device with the applicable legislation it must bear the CE marking. Medical devices bearing the CE marking have free access to all Member States of the European Union and the European Economic Area (EEA) without any additional certification by Member State authorities. Restriction of the placing on the market and putting into service of CE-marked medical devices is only allowed for safety reasons in application of the safeguard clause, in cases of wrongly affixed CE marking or in case of particular health monitoring measures.

With the CE marking the responsible person declares that the product conforms to the applicable Community legislation and that the relevant conformity assessment procedures have been completed.

Different conformity assessment procedures exist depending on the class of a medical device. Medical devices are divided into four classes according to their complexity and thus the degree of risk inherent in them (I, IIa, IIb and III – I representing the lowest and III the highest risk level).

In particular for combination devices like e.g. devices that contain a medicinal substance incorporated into the device for the purpose of assisting its functioning there are special stipulations as regards the conformity assessment procedure.

Medical devices incorporating a medicinal substance with action ancillary to that of the device (e.g. antibiotic bone cements) would be class III (i.e. high risk) pursuant to classification rule 13 set out in the MDD. Rule 13 currently reads: "All devices incorporating, as an integral part, a substance which, if used separately, can be considered to be a medicinal product, as defined in Article 1 of Directive 2001/83/EC, and which is liable to act on the human body with action ancillary to that of the devices, are in Class III." [1].

Council Directive 93/42/EEC on Medical Devices (as amended) stipulates for such medical device-medicinal substance combinations in section 7.4 of Annex I (Essential Requirements): “Where a device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product as defined in Article 1 of Directive 2001/83/EC and which is liable to act upon the body with action ancillary to that of the device, the quality, safety and usefulness of the substance must be verified by analogy with the methods specified in Annex I to Directive 2001/83/EC.” [1]. This means that the Notified Body carrying out a conformity assessment procedure in respect of such a medical device incorporating a medicinal substance must consult a competent authority for medicinal products on the medicinal aspects of the device (so-called consultation procedure). This proceeding serves to verify the compatibility of the medical device and the medicinal substance.

Particularly with regard to the above stipulation Dr. Ehrhard Anhalt (Bundesverband der Arzneimittel-Hersteller e.V. (BAH) - Bonn) points out a problem in his publication “Bedürfen Medizinprodukte mit Arzneimittelanteil immer eines Konsultationsverfahrens?” [2]. That is to say he highlights a discrepancy in the wording of Council Directive 93/42/EEC on Medical Devices as amended in section 7.4 of Annex I between the English version given above and the German version.

The wording of the German version of this section of the MDD as amended is: „Gehört zu den festen Bestandteilen eines Produkts ein Stoff, der bei gesonderter Anwendung als Arzneimittel im Sinne des Artikels 1 der Richtlinie 2001/83/EG gelten kann und der in Ergänzung zu dem Produkt eine Wirkung auf den menschlichen Körper entfalten kann, sind die Qualität, die Sicherheit und der Nutzen dieses Stoffes analog zu den in der Richtlinie 2001/83/EG Anhang I genannten Verfahren zu überprüfen. [...]” [3].

Dr. Anhalt presents his view that the wording “eine Wirkung auf den menschlichen Körper entfalten kann” in the German version (translated into English: “can act on the human body”) implies, that the medicinal substance in the device may be effective (in the sense of a pharmaceutical or pharmacological action), even it is not effective (from the pharmaceutical point of view) in the device in question for various reasons. One reason for lacking efficacy is e.g. that the concentration of the medicinal substance in the device is insufficient for an ancillary action. As a consequence of this, a consultation procedure concerning the medicinal substance would strictly be necessary with all medical devices incorporating a medicinal substance without exception, i.e. independent of whether or not the concentration of the medicinal substance in the device is a pharmaceutically or pharmacologically active one.

Furthermore, Dr. Anhalt points out that the wording “is liable to act upon” in section 7.4 of Annex I of the English version of the MDD as amended implies that it can be assumed that the medicinal substance in the medical device is effective (in the sense of a pharmaceutical or pharmacological action). Above mentioned wording “is liable to act upon” would read in a more precise translation into German “eine Wirkung entfaltet” and not “eine Wirkung entfalten kann” (the English translation of the last mentioned wording is “may act upon”).

As a consequence of this, only if the concentration of the medicinal substance in the device is adequate for an ancillary action and only if it is pharmaceutically or pharmacologically active, a consultation procedure concerning the medicinal substance would be necessary. But if the medicinal substance in the device does not act in this way, then a consultation procedure would not be necessary.

An example of a product where a consultation procedure is definitely not required is a solution for contact lenses containing a preservative agent. In fact the preservative agent may be considered as a medicinal substance under other circumstances. But the function of this agent in the solution for contact lenses is only the maintenance of certain characteristics of the solution and the agent is not liable to act on the body. With such medical devices the discrepancy shown above is not an issue.

But this discrepancy may be of importance with products like e.g. a saline nasal spray containing dexpanthenole for nurture of the nasal mucosa. In this nasal spray the medicinal substance “dexpanthenole” indeed has an ancillary (nurturing) action, but the spray does not contain a pharmaceutically active concentration of dexpanthenole (i.e. the content of dexpanthenole is comparable to the content of dexpanthenole in cosmetics).

In due consideration of the above particulars the question arises whether for medical devices like such a nasal spray a consultation procedure is necessary or not.

On the one hand it means elaborate efforts to carry out a consultation procedure in respect of a medical device incorporating a medicinal substance. In addition to the standard requirements for a conformity assessment procedure, the device manufacturer must typically submit detailed data on the quality, safety and usefulness of the medicinal substance. Appropriate details that permit the evaluation of the aforementioned features are [4]:

- 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,
- qualitative and quantitative particulars of the constituents,



- description of the method of manufacture dealing with incorporation of the medicinal substance in the device,
- controls of starting materials for the medicinal substance,
- control tests carried out at intermediate stages of the manufacturing process of the medical device (where directly relevant to the quality of the substance as incorporated in the medical device),
- control tests on finished product (qualitative and quantitative tests to control the medicinal substance in the device),
- stability data to show the medicinal substance maintains its desired function throughout the defined shelf-life of the device,
- toxicity data (reference to known toxicological profile of the medicinal substance or in case of new active substances the results of toxicity tests like e.g. reproductive function, embryo-foetal and perinatal toxicity, mutagenicity, carcinogenicity),
- local tolerance,
- pharmacodynamics of the medicinal substance in the context of its incorporation into the device,
- pharmacokinetics (as appropriate),
- clinical documentation (demonstrating the usefulness of the medicinal substance in the device).

On the other hand different national interpretations of the legislative rules on medical devices incorporating ancillary medicinal substances in the European Union can be of consequence for the marketability of this kind of devices. It is thinkable that a consultation procedure was not carried out in respect of such a device during the conformity assessment procedure, because it was not considered necessary having regard to the relevant laws. This product finally bears the CE marking and therefore is allowed to be freely marketed in all Member States of the European Union and the EEA. But if this medical device is marketed in a European country where a consultation procedure during the conformity assessment is considered necessary according to the national interpretation of the relevant laws, the CE marking will be wrongly affixed to this product in this country. In the end this means that the marketing of the device in question will be prohibited there.

On that account this master thesis will further investigate the discrepancy shown above. The English version was the source text of the MDD in the legislative procedure. So it will be examined for selected Member States of the European Union whether section 7.4 of the Essential Requirements (in Annex I to the MDD) and Classification Rule 13 (in Annex

IX to the MDD) as well as their corresponding transposition into national law also differ from the English version of the MDD.

Based thereon, the question will be considered under what circumstances those selected Member States deem it necessary to carry out a consultation procedure with a medical device that contains an integral medicinal substance for the purpose of assisting its functioning. A search on criteria defining under what conditions the integral medicinal substance acts ancillary to the device will be done. A criterion for this could be, for instance, that the concentration of the medicinal substance in the device is a pharmaceutically active one. What other criteria have to be considered in the decision concerning the necessity of a consultation procedure? Or is a consultation procedure concerning the medicinal substance strictly necessary with all medical devices incorporating a medicinal substance with ancillary action without exception? Does Classification Rule 13 in Annex IX of the MDD actually apply to all medical devices incorporating a medicinal substance with ancillary action?

To find answers to those questions the law-making procedure of Council Directive 93/42/EEC will be studied under the aspect of the primary intention of the stipulations concerning devices incorporating, as an integral part, a substance which, if used separately, may be considered to be a medicinal product and which is liable to act upon the body with action ancillary to that of the device. Existing guidances in the EU will also be examined and the common practice and opinions in selected EU countries will be inquired. At the end of this thesis a short global outline will be given in order to get a view of how medical devices incorporating ancillary medicinal substances are regulated outside of the EU.

## 2 Situation in selected EU Member States

### 2.1 Existing laws in the EU

In order to verify whether the discrepancy shown in section “Introduction” concerning the wording of Directive 93/42/EEC as amended also exists with other Member States of the EU, this chapter will examine the situation in some selected Member States particularly with regard to the equivalent wording in section 7.4 of Annex I (Essential Requirements) and the wording of Classification Rule 13.

Spain, France, Sweden, Ireland, United Kingdom, Germany and Hungary are the EU Member States that will be compared by way of illustration.

Because the corresponding national transpositions of above-mentioned directive into current applicable law actually are the crucial points, those will mainly be examined. But Member States have to transpose the amendments introduced by Directive 2007/47/EC into national law by 21 December 2008. And the national transpositions as yet are based on the precursory law. Therefore, the wording of the relevant precursory law will be compared with the current national transposition.<sup>1</sup> This is justifiable, since comparison between Directive 2007/47/EC and the relevant passage of the precursory law (particularly Directive 93/42/EEC) does not reveal essential differences in the crucial passage. There is only one exception, namely Hungary, which will be detailed later on in this chapter.

Table 1 provides an overview of the current applicable national transpositions with regard to section 7.4 of the Essential Requirements (in Annex I to the MDD) and Classification Rule 13 (in Annex IX to the MDD) in the above-mentioned countries. There actually are several regulatory statutes transposing the MDD into national law in the respective countries. But for this particular intention it is sufficient to only consider those statutes that are relevant for the national transposition of those two crucial passages.

Table 2 summarises the wording of the decisive part of section 7.4 of Annex I (Essential Requirements) of the relevant language version of the directive, the wording of the respective transposition into national law and gives a literal English interpretation of the relevant national transposition for the aforementioned selected EU Member States.

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<sup>1</sup> Thanks to Dr. Hans-Peter Leinenbach, Mrs. Gertrud Schneider and Mrs. Timea Spreizer for support in translation of the Swedish, Spanish and Hungarian texts.

Table 1: Overview of current applicable national transpositions with regard to section 7.4 of the Essential Requirements (in Annex I to Directive 93/42/EEC of 14 June 1993 concerning medical devices as amended) and Classification Rule 13 (in Annex IX to Directive 93/42/EEC of 14 June 1993 concerning medical devices as amended) for selected EU Member States ([5], [6], [7], [8], [9], [10], [11])

Country	National transposition
Spain	REAL DECRETO 414/1996, de 1 de marzo, por el que se regula los productos sanitarios - edición actualizada
France	<p>Code de la santé publique Annexes Livre 5 bis: Dispositifs médicaux, dispositifs médicaux de diagnostic in vitro</p> <p>1.) Exigences essentielles de santé et de sécurité applicables aux dispositifs médicaux. (Article Annexe I aux articles R665-1 à R665-47 (version refondue)) A. - Dispositifs médicaux autres que les dispositifs implantables actifs.</p> <p>and</p> <p>2.) Critères utilisés pour la classification des dispositifs médicaux autres que les dispositifs implantables actifs. (Article Annexe IX aux articles R665-1 à R665-47 (version refondue))</p>
Sweden	Läkemedelsverkets föreskrifter (LVFS 2003:11, ändrad genom 2004:11 samt 2007:3) om medicintekniska produkter
Ireland	S.I. No. 252/1994 — European Communities (Medical Devices) Regulations, 1994 (as amended)
United Kingdom	The Medical Devices Regulations 2002 - S.I. 2002/618, as amended PART II General Medical Devices
Germany	Medizinproduktegesetz in der Fassung der Bekanntmachung vom 7. August 2002 (BGBl. I S. 3146), zuletzt geändert durch Artikel 1 des Gesetzes vom 14. Juni 2007 (BGBl. I S. 1066)
Hungary	<p>16/2006. (III. 27.) EüM rendelet az orvostechnikai eszközökről</p> <p>– 1. számú melléklet a 16/2006. (III. 27.) EüM rendelethez Alapvető követelmények A. Az osztályba sorolt eszközök esetében</p> <p>and</p> <p>– 9. számú melléklet a 16/2006. (III. 27.) EüM rendelethez</p>

Table 2: Wording of section 7.4 of Annex I (Essential Requirements) of Council Directive 93/42/EEC of 14 June 1993 concerning medical devices in the language versions relevant for the current national transpositions in the EU Member States Spain, France, Sweden, Ireland, United Kingdom, Germany and Hungary, wording of the respective transposition into national law and literal English interpretation of the relevant national transposition ([5], [6], [7], [8], [9], [10], [11], [12], [13], [14], [15], [16], [17])

Country	Wording of relevant language version of Directive 93/42/EEC	Wording of relevant national transposition	Literal English interpretation of national transposition / Remarks
Spain	Punto 7.4 del anexo I: “Cuando un producto incorpore, como parte integrante, una sustancia que, de utilizarse por separado, pueda considerarse un medicamento con arreglo a la definición del artículo 1 de la Directiva 65/65/CEE y que <b>pueda</b> ejercer en el cuerpo humano una acción accesoria a la del producto, la seguridad, calidad y utilidad de tal sustancia, teniendo en cuenta la finalidad prevista del producto, deberán verificarse por analogía con los métodos apropiados establecidos en la Directiva 75/318/CEE. [...]”	Apartado 1.4 del anexo I: “Cuando un producto incorpore, como parte integrante, una sustancia que, de utilizarse por separado, pueda considerarse un medicamento con arreglo a la definición del artículo 1 de la Directiva 65/65/CEE y que <b>pueda</b> ejercer en el cuerpo humano una acción accesoria a la del producto, la seguridad, calidad y utilidad de tal sustancia, teniendo en cuenta la finalidad prevista del producto, deberán verificarse por analogía con los métodos apropiados establecidos en la Directiva 75/318/CEE.”	Paragraph 1.4 of annex I: Where a device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product as defined in Article 1 of Directive 65/65/CEE and which <b>can</b> act upon the human body with action ancillary to that of the device, the safety, quality and usefulness of the substance must be verified, taking account of the intended purpose of the device, by analogy with the appropriate methods specified in Directive 75/318/CEE.
France	Annexe I, point 7.4: “Lorsqu'un dispositif incorpore, comme partie intégrante, une substance qui, si elle est utilisée séparément, est susceptible d'être considérée comme un médicament au sens de l'article 1er de la directive 65/65/CEE et qui <b>peut</b> agir sur le corps humain par une action accessoire à celle du dispositif, la sécurité, la qualité et l'utilité de cette substance doivent être vérifiées, en tenant compte de la destination du dispositif, par analogie avec les méthodes appropriées contenues dans la directive 75/318/CEE. [...]”	Annexe I-A, point 7.4: “Lorsqu'un dispositif incorpore, comme partie intégrante, une substance qui, si elle est utilisée séparément, est susceptible d'être considérée comme un médicament au sens de l'article L. 5111-1 du code de la santé publique, à l'exception des médicaments dérivés du sang, et qui <b>peut</b> agir sur le corps humain par une action accessoire à celle du dispositif, la sécurité, la qualité et l'utilité de cette substance doivent être vérifiées, en tenant compte de la destination du dispositif, par analogie avec les méthodes appropriées fixées par les articles R. 5117 à R. 5127 du code de la santé publique;”	Annex I-A, point 7.4: Where a device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product as defined in Article L. 5111-1 of the “code de la santé publique”, with the exception of medicinal products derived from blood, and which <b>can</b> act upon the human body with action ancillary to that of the device, the safety, quality and usefulness of this substance must be verified, taking account of the intended purpose of the device, by analogy with the appropriate methods specified in article R. 5117 to R. 5127 of the “code de la santé publique”;

Country	Wording of relevant language version of Directive 93/42/EEC	Wording of relevant national transposition	Literal English interpretation of national transposition / Remarks
Sweden	<p>Punkt 7.4 i bilaga 1:                      “Om en produkt som en integrerad del innehåller ett ämne som, när det används separat, kan betraktas som ett läkemedel enligt definitionen i artikel 1 i direktiv 65/65/EEG, och <b>vars verkan på kroppen</b> understödjer produktens verkan skall produktens säkerhet, kvalitet och användbarhet kontrolleras med de relevanta metoder som anges i rådets direktiv 75/318/EEG och med hänsyn tagen till det avsedda ändamålet med produkten. [...]”</p>	<p>Punkt 7.4 i bilaga 1:                      “Om en produkt som en integrerad del innehåller ett ämne som, när det används separat, kan betraktas som ett läkemedel enligt definitionen i 1 § läkemedelslagen (1992:859) och <b>vars verkan på kroppen</b> understödjer produktens verkan, skall ämnets säkerhet, kvalitet och användbarhet kontrolleras i analogi med bestämmelserna i läkemedelslagen och med hänsyn tagen till det avsedda ändamålet med produkten. [...]”</p>	<p>Point 7.4 of annex 1:                      Where a device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product as defined in § 1 of the medicines law (1992:859), and <b>whose action upon the body</b> supports the action of the device, the safety, quality and usefulness of the substance must be verified, taking account of the intended purpose of the device, by analogy with the provisions of the medicines law.</p>
Ireland	<p>Section 7.4 of Annex I:                      “Where a device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product as defined in Article 1 of Directive 65/65/EEC and which <b>is liable to act</b> upon the body with action ancillary to that of the device, the safety, quality and usefulness of the substance must be verified, taking account of the intended purpose of the device, by analogy with the appropriate methods specified in Directive 75/318/EEC. [...]”</p>	<p>Section 7.4 of Schedule I:                      “Where a device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product as defined in Article 1 of Directive 65/65/EEC and which <b>is liable to act</b> upon the body with action ancillary to that of the device, the safety, quality and usefulness of the substance must be verified, taking account of the intended purpose of the device, by analogy with the appropriate methods specified in Directive 75/318/EEC. [...]”</p>	<p>Corresponding to Annex I of the Directive (stated in the left column).</p>
United Kingdom	<p>Section 7.4 of Annex I:                      “Where a device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product as defined in Article 1 of Directive 65/65/EEC and which <b>is liable to act</b> upon the body with action ancillary to that of the device, the safety, quality and usefulness of the substance must be verified, taking account of the intended purpose of the device, by analogy with the appropriate methods specified in Directive 75/318/EEC. [...]”</p>	<p>Regulation 5 (2):                      “In this Part a reference to a numbered article or Annex is to the article or Annex of Directive 93/42 bearing that number.”                       and:                       Regulation 8 (1) and (2):                      “[...] unless that device meets those essential requirements set out in Annex I which apply to it.”</p>	<p>Corresponding to Annex I of the Directive (stated in the left column).</p>

Country	Wording of relevant language version of Directive 93/42/EEC	Wording of relevant national transposition	Literal English interpretation of national transposition / Remarks
Germany	<p>Anhang I Abschnitt 7.4: „Gehört zu den Bestandteilen eines Produkts ein Stoff, der bei gesonderter Anwendung als Arzneimittel im Sinne des Artikels 1 der Richtlinie 65/65/EWG angesehen werden und der in Ergänzung zu dem Produkt eine Wirkung auf den menschlichen Körper entfalten <b>kann</b>, sind die Sicherheit, die Qualität und der Nutzen dieses Stoffes unter Berücksichtigung der Zweckbestimmung des Produkts mit den geeigneten Verfahren der Richtlinie 75/318/EWG zu überprüfen. [...]“</p>	<p>§ 7: „Die Grundlegenden Anforderungen sind [...] für die sonstigen Medizinprodukte die Anforderungen des Anhangs I der Richtlinie 93/42/EWG des Rates vom 14. Juni 1993 über Medizinprodukte (ABl. EG Nr. L 169 S. 1), zuletzt geändert durch die Richtlinie 2000/70/EG (ABl. EG Nr. L 313 S. 22), in den jeweils geltenden Fassungen.“</p>	<p>§ 7: The Essential Requirements are [...] for the other medical devices the requirements of Annex I of Council Directive 93/42/EWG of 14 June 1993 concerning Medical Devices (OJ EC No. L 169 p. 1), last amended by Directive 2000/70/EG (OJ EC No. L 313 p. 22), as amended.</p> <p>Section 7.4 of Annex I of Directive 93/42/EWG: Where a device incorporates a substance which, if used separately, may be considered to be a medicinal product as defined in Article 1 of Directive 65/65/EWG and which <b>can</b> act upon the human body with action ancillary to that of the device, the safety, quality and usefulness of the substance must be verified, taking account of the intended purpose of the device, by analogy with the appropriate methods specified in Directive 75/318/EWG.</p>
Hungary	<p>I. melléklet pont 7.4: “Abban az esetben, ha az eszköz integráns részként olyan anyagot foglal magában, amely önállóan felhasználva a 65/65/EGK irányelv 1. cikkében meghatározott gyógyszernek tekinthető, és az eszköz hatásának alárendelten <b>felelős a testre gyakorolt hatásért</b>, az anyag veszélytelenségét, minőségét és hasznosságát, figyelembe véve az eszköz rendeltetési célját, a 75/318/EGK irányelvben előírt megfelelő módszerekhez hasonlóan kell igazolni.”</p>	<p>1. számú melléklet A.II. pont 7.4.: “Ha az eszköz integráns részként olyan anyagot is magában foglal, amelyet ha külön használnak, akkor <b>gyógyszernek minősül</b>, és amely az eszközzel együtt használva az eszköz <b>hatását elősegíti</b>, akkor az anyag biztonságát, minőségét és hasznosságát - figyelembe véve az eszköz alkalmazási célját - az emberi alkalmazásra kerülő gyógyszerek forgalomba hozataláról szóló 52/2005. (XI. 18.) EüM rendelet 1. számú mellékletében előírt módon bizonyítani kell. [...]”</p>	<p>Point 7.4. of annex 1, A.II.: Where the medical device also incorporates a substance, which, if used separately, <b>is a medicinal product and which supports the action of the medical device together with the medical device</b>, the safety, quality and usefulness of the substance must be verified, taking account of the intended purpose of the device, as per annex 1 of the decree 52/2005. (XI. 18.) EüM for the placing on the market of medicinal products for human use.</p>

In an analogous manner to table 2, table 3 compares the wording of Classification Rule 13, which is applicable to medical devices incorporating a medicinal substance with action ancillary to that of the device, in the EU Member States Spain, France, Sweden, Ireland, United Kingdom, Germany and Hungary. This comparison is also a decisive factor, because the classification of a medical device defines the possible conformity assessment procedures for CE marking in practice. And the conformity assessment procedure to be followed determines the time, costs and effort that will be needed to place a product on the market.

The summary tables 2 and 3 show that neither section 7.4 in Annex I to the MDD nor Classification Rule 13 are implemented consistently in the selected EU Member States Spain, France, Sweden, Ireland, United Kingdom, Germany and Hungary.

The examination of the transposition of section 7.4 in Annex I to the MDD reveals a varying scheme. On the one hand Spain and France transposed those provisions comparable to Germany (in the sense of “the medicinal substance can act on the body”). On the other hand Sweden, Ireland, United Kingdom and Hungary rather transposed them comparable to the English version of Directive 93/42/EEC, which had been adopted by the Council (in the sense of “the medicinal substance is liable to act on the body”).

The compilation of the transposition of Classification Rule 13 of Directive 93/42/EEC shows both discrepancies between the examined EU Member States and discrepancies between the wording of section 7.4 in Annex I to the MDD and Classification Rule 13 in individual states. While Spain, France and Sweden transposed rule 13 comparable to Germany (in the sense of “the medicinal substance can act on the body”), Ireland, United Kingdom and Hungary rather transposed it comparable to the English version of Directive 93/42/EEC, which had been adopted by the Council (in the sense of “the medicinal substance is liable to act on the body”). Besides this Sweden currently has an inconsistent transposition. On the one hand section 7.4 is rather comparable to the English version of Directive 93/42/EEC, which had been adopted by the Council (in the sense of “the medicinal substance is liable to act on the body”). The word choice “verkan” in the Swedish statute (translated into English: “action” or “effect”) implies that an action in fact takes place (“action” and “effect” are seen as proactive words). On the other hand Classification Rule 13 is rather transposed in the sense of “the medicinal substance can act on the body” in Sweden.

The meaning of the currently effective Hungarian transposition of section 7.4 of Annex I and Classification Rule 13 of Directive 93/42/EEC is not quite consistent with the



information given by the Hungarian competent authority, EEKH, regarding the current practice in Hungary (see chapter 2.4 of this thesis).

In the Hungarian language version of Directive 93/42/EEC given in table 2 and 3 the word “felelős” means “liable” in English, “testre” means “body” and “gyakorolt hatásért” means “effected action”. In the relevant national transposition of section 7.4 given in table 2 the Hungarian “gyógyszernek minősül” signifies “functions as medicinal product”, “hatását” signifies “action”, “elősegíti” signifies “support”. In the relevant national transposition of Classification Rule 13 given in table 3 “kiegészíti” stands for “completes”, “hatását” stands for “action” and “testre” stands for “body”. So Hungary’s currently effective national transposition of section 7.4 of Annex I and Classification Rule 13 of Directive 93/42/EEC is rather comparable to the English version of Directive 93/42/EEC (transposed in the sense of “the medicinal substance is liable to act on the body”).

But the Hungarian language version of Directive 2007/47/EC, which has to be transposed into national law by 21 December 2008, and the aforementioned section 7.4 of Annex I of Directive 93/42/EEC slightly differ. The decisive wording of Directive 2007/47/EK reads: “[...] és alkalmas arra, hogy az eszköz hatásához képest kiegészítő jelleggel hasson az emberi szervezetre [...]” [18]. The literal English interpretation of this text passage is as follows: [...] and which is able to act on the human body by completing the medical device [...]. Those provisions are similar to those currently effective in Spain, France and Germany, which mean “the medicinal substance can act on the body”. The information given by the competent authority, EEKH, regarding the current practice in Hungary would be more consistent with this wording (see chapter 2.4 of this thesis). But this constitutes yet another discrepancy between the English source text and a national language version. Here it remains to be seen how the wording of Directive 2007/47/EK will be actually transposed into Hungarian law.

The decisive point is the practical interpretation of the provisions described in this chapter in the single EU Member States. Also it could be supportive to study case law with regard to the implementation of section 7.4 in Annex I to Directive 93/42/EEC as amended and Classification Rule 13.

This aspect will be dealt with in chapter 2.4 “Common practice and opinions in the EU” of this master thesis.

Another significant matter that should be taken into consideration is the primary intent of the legislative bodies during the legislative procedure of Council Directive 93/42/EEC of 14 June 1993 concerning medical devices. This law-making procedure will be further examined in chapter 2.2 of this thesis.

Table 3: Comparison of the wording of Classification Rule 13 of Council Directive 93/42/EEC of 14 June 1993 concerning medical devices in the language versions relevant for the current national transpositions in the EU Member States Spain, France, Sweden, Ireland, United Kingdom, Germany and Hungary. Wording of the respective transposition into national law and literal English interpretation of the relevant national transposition ([5], [6], [7], [8], [9], [10], [11], [12], [13], [14], [15], [16], [17]).

Country	Wording of relevant language version of Directive 93/42/EEC	Wording of relevant national transposition	Literal English interpretation of national transposition / Remarks
Spain	Regla 13: “Todos los productos que incorporen como parte integrante una sustancia que, si se utilizara independientemente, podría considerarse como un medicamento según la definición que figura en el artículo 1 de la Directiva 65/65/CEE, y que <b>pueda</b> ejercer sobre el cuerpo humano una acción accesoria a la de los productos, se incluirán en la clase III. [...]”	Regla 13.: “Todos los productos que incorporen como parte integrante una sustancia que, si se utilizara independientemente, podría considerarse como un medicamento según la definición que figura en el artículo 1 de la Directiva 65/65/CEE y que <b>pueda</b> ejercer sobre el cuerpo humano una acción accesoria a la de los productos, se incluirán en la clase III.”	Rule 13.: All devices incorporating, as an integral part, a substance which, if used separately, can be considered to be a medicinal product, as defined in Article 1 of Directive 65/65/CEE, and which <b>can</b> act upon the human body with action ancillary to that of the devices, are in class III.
France	Règle 13: “Tous les dispositifs incorporant comme partie intégrante une substance qui, si elle est utilisée séparément, peut être considérée comme un médicament au sens de l'article 1er de la directive 65/65/CEE et qui <b>est susceptible d'agir</b> sur le corps par une action accessoire à celle des dispositifs font partie de la classe III. [...]”	Règle 13: “Tous les dispositifs incorporant comme partie intégrante une substance qui, si elle est utilisée séparément, peut être considérée comme un médicament au sens de l'article L. 511 du code de la santé publique et qui <b>est susceptible d'agir</b> sur le corps par une action accessoire à celle des dispositifs font partie de la classe III ; [...]”	Rule 13: All devices incorporating, as an integral part, a substance which, if used separately, can be considered to be a medicinal product, as defined in article L. 511 of the “code de la santé publique”, and which <b>is able to act</b> on the body with action ancillary to that of the devices, belong to class III.
Sweden	Regel 13: “Alla produkter, i vilka ett ämne är integrerat som om det används separat kan betraktas som ett läkemedel enligt definitionen i artikel 1 i direktiv 65/65/EEG, och som <b>kan</b> ha en verkan på människokroppen som understödjer produktens, tillhör klass III. [...]”	Regel 13: “Alla produkter i vilka ett ämne är integrerat, som om det används separat, kan betraktas som ett läkemedel enligt definitionen i 1 § läkemedelslagen (1992:859) och som <b>kan</b> ha en verkan på människokroppen som understödjer produkten, tillhör klass III. [...]”	Rule 13: All devices incorporating, as an integral part, a substance which, if used separately, can be considered to be a medicinal product, as defined in § 1 of the medicines law (1992:859), and which <b>can</b> have an action on the human body that is ancillary to that of the device, are in class III.
Ireland	Rule 13: “All devices incorporating, as an integral part, a substance which, if used separately, can be	Rule 13.: “All devices incorporating, as an integral part, a substance which, if used separately, can be	Corresponding to Annex IX of the Directive (stated in the left column).

Country	Wording of relevant language version of Directive 93/42/EEC	Wording of relevant national transposition	Literal English interpretation of national transposition / Remarks
	considered to be a medicinal product, as defined in Article 1 of Directive 65/65/EEC, and which <b>is liable to act</b> on the human body with action ancillary to that of the devices, are in Class III. [...]"	considered to be a medicinal product, as defined in Article 1 of directive 65/65/EEC, and which <b>is liable to act</b> on the human body with action ancillary to that of the devices, are in Class III. [...]"	
United Kingdom	Rule 13: "All devices incorporating, as an integral part, a substance which, if used separately, can be considered to be a medicinal product, as defined in Article 1 of Directive 65/65/EEC, and which <b>is liable to act</b> on the human body with action ancillary to that of the devices, are in Class III. [...]"	Regulation 7 (1): "For the purposes of this Part and Part VI, devices are classified as belonging to Class I, IIa, IIb or III in accordance with the classification criteria set out in Annex IX of Directive 93/42 [...]."	Corresponding to Annex IX of the Directive (stated in the left column).
Germany	Regel 13: „Alle Produkte, zu deren Bestandteilen ein Stoff gehört, der bei gesonderter Verwendung als Arzneimittel im Sinne des Artikels 1 der Richtlinie 65/65/EWG angesehen werden kann und der ergänzend zur Wirkung der Produkte auf den menschlichen Körper einwirken <b>kann</b> , werden der Klasse III zugeordnet. [...]"	§ 13 (1): „Medizinprodukte mit Ausnahme der In-vitro-Diagnostika und der aktiven implantierbaren Medizinprodukte werden Klassen zugeordnet. Die Klassifizierung erfolgt nach den Klassifizierungsregeln des Anhangs IX der Richtlinie 93/42/EWG.“	§ 13 (1): Medical devices other than in vitro diagnostic devices and active implantable medical devices are assigned to classes. The classification is carried out according to the classification rules in Annex IX of the Directive 93/42/EWG.  Rule 13 in Directive 93/42/EWG: All devices incorporating a substance which, if used separately, can be considered to be a medicinal product, as defined in Article 1 of Directive 65/65/EWG, and which <b>can</b> act upon the human body with action ancillary to that of the devices, are in class III.
Hungary	13. szabály: "Valamennyi eszköz, amely integráns részként olyan anyagot foglal magában, amely önmagában gyógyszernek tekinthető a 65/65/EGK irányelv 1. cikke értelmében, és az eszköz hatásának alárendelten <b>felelős a testre gyakorolt hatásért</b> , a III. osztályba tartozik."	13. szabály: "Minden olyan eszköz, amely integráns részeként olyan anyagot tartalmaz, amely külön használva gyógyszernek tekinthető, és amely anyag <b>kiegészíti</b> az eszköz <b>hatását</b> az emberi <b>testre</b> , a III. osztályba tartozik. [...]"	Rule 13: All devices incorporating, as an integral part, a substance which, if used separately, can be considered to be a medicinal product, and <b>which completes the action of the devices on the human body</b> , are in class III.

## **2.2 Fact finding from the law-making procedure of Council Directive 93/42/EEC**

The objective of this section is to understand the primary intent of the legislative bodies during the legislative procedure of Council Directive 93/42/EEC of 14 June 1993 concerning medical devices particularly with regard to the provisions laid down for medical devices incorporating a medicinal substance with action ancillary to that of the device. The development of section 7.4 in Annex I, Classification Rule 13 and a relevant recital will be inquired over the course of the interdisciplinary cooperation procedure for establishing this directive.

To have a better survey the Annex of this thesis shows the chronology of the proceeding of Council Directive 93/42/EEC of 14 June 1993 concerning medical devices and the associated documents. The associated documents are both internal documents made available to the author upon request by the institutions involved (European Parliament, Council of the European Union, European Commission) and documents that have been officially published in the Official Journal of the European Communities (OJ). Only those documents of the law-making procedure, which had a significant impact on the concept of the above-mentioned sections, will be considered in the following. And internal documents will only be considered, where there is no equivalent officially published document.

In its primary proposal for a Council Directive concerning medical devices (internal document COM(91) 287 final – SYN 353, [19]) the Commission of the European Communities stated in the “Explanatory Memorandum” concerning the contents of the proposal: “However, a medical device may include a medicinal substance as an integral part in order to increase its effectiveness, e.g. a heparin-coated catheter. Where the action produced by the presence of the medicinal substance is secondary to the principal action of the device, the conformity assessment procedure for authorizing the placing of the product concerned on the market is covered by this proposal for a directive. As far as safety aspects concerning the presence of the substance are concerned, the verifications required are carried out, where appropriate, by analogy to the methods contained in Directive 75/318/EEC.” (*which is the directive concerning the analytical, toxicological-pharmacological and clinical testing of medicinal products, the author*).

But what further details on this issue do exist considering the progress of this law-making procedure?

Table 4 specifies the key items as per the approach given above. The format of the citations in the table indicates author's emphasis. For clearness reasons the format of the original text was not transferred.

Table 4: Significant steps of the interdisciplinary cooperation procedure for establishing Council Directive 93/42/EEC of 14 June 1993 concerning medical devices with regard to the development of provisions laid down for medical devices incorporating a medicinal substance with action ancillary to that of the device ([20], [21], [22], [23], [24], [25])

Phase of law-making procedure  Considered part of 93/42/EEC	Adoption by Commission	EP Committee opinion 1st reading (Committee on the Environment, Public Health and Consumer Protection)	EP Committee report 1st reading (Committee on Economic and Monetary Affairs and Industrial Policy)	EP opinion 1st reading	Adoption common position	Formal adoption by Council
Wording 6 <sup>th</sup> Recital	“[...] medical devices incorporating, <b>inter alia, substances which, if used separately, may be considered to be a medicinal substance</b> within the meaning of Directive 65/65/EEC; whereas, in such cases, if the substances are incorporated in the medical devices <b>to help them operate</b> , the placing of the devices on the market is governed by this Directive; whereas, in this context, in the event of the <b>bioavailability</b> of such substances, the safety, quality and <b>usefulness</b> of the substances must be verified <b>by analogy with</b> the appropriate methods specified in Council Directive 75/318/EEC [...]”	“[...] medical devices incorporating, <b>inter alia, substances which, if used separately, may be considered to be a medicinal substance</b> within the meaning of Directive 65/65/EEC; whereas, in such cases, if the substances are incorporated in the medical devices <b>to help them operate</b> , the placing of the devices on the market is governed by this Directive; whereas, in this context, in the event of such substances <b>being active</b> , the safety, quality and <b>effectiveness</b> of the substances must be verified <b>by analogy with</b> the appropriate methods specified in Council Directive 75/318/EEC [...]”	“[...] medical devices incorporating <b>substances which, while not designed to be administered as a medicinal product, are bioavailable within the meaning of this Directive and if used separately, may be considered to be a medicinal substance</b> within the meaning of Directive 65/65/EEC; whereas, in such cases, if <b>such</b> substances are incorporated in a medical device <b>to improve its safety, quality or performance</b> , the placing of such devices on the market is governed by this Directive; whereas in this context, in the event of the <b>bioavailability</b> of such substances, the safety, quality and <b>usefulness</b> of the substances must be verified <b>by means of control systems which may be analogous to</b> the appropriate methods specified in Council Directive 75/318/EEC [...]”		“[...] medical devices incorporating, <b>inter alia, substances which, if used separately, may be considered to be a medicinal substance</b> within the meaning of Directive 65/65/EEC; in such cases, if the substances incorporated in the medical devices <b>are liable to act upon the body with action ancillary to that of the device</b> , the placing of the devices on the market is governed by this Directive; whereas, in this context, the safety, quality and <b>usefulness</b> of the substances must be verified <b>by analogy with</b> the appropriate methods specified in Council Directive 75/318/EEC [...]”	“[...] medical devices incorporating, <b>inter alia, substances which, if used separately, may be considered to be a medicinal substance</b> within the meaning of Directive 65/65/EEC; whereas in such cases, if the substances incorporated in the medical devices <b>are liable to act upon the body with action ancillary to that of the device</b> , the placing of the devices on the market is governed by this Directive; whereas, in this context, the safety, quality and <b>usefulness</b> of the substances must be verified <b>by analogy with</b> the appropriate methods specified in Council Directive 75/318/EEC [...]”

Phase of law-making procedure  Con- sidered part of 93/42/EEC	Adoption by Commission	EP Committee opinion 1st reading (Committee on the Environ- ment, Public Health and Consumer Protection)	EP Committee report 1st reading (Committee on Econo- mic and Monetary Affairs and Industrial Policy)	EP opinion 1st reading	Adoption common position	Formal adoption by Council
Wording Article 1 (2) (k)	“ <b>bioavailability</b> means the release of <b>a substance</b> into or onto the human body in such a way that the <b>interaction with the body can reasonably be detected.</b> ”	“ <b>“activity”</b> : means the release <b>of a substance</b> into or onto the human body in such a way that the <b>interaction with the body can reasonably be detected.</b> ”	“ <b>“bioavailability”</b> means the release <b>from a device</b> into or onto the human body <b>of a substance liable to be locally or systematically absorbed by the body’s tissue</b> in such a way that a <b>significant inter- action with the body can be detected.</b> ”	“ <b>“bioavailability”</b> means the release <b>from a device</b> into or onto the human body <b>of a sub- stance liable to be locally or entirely absorbed by the body’s tissue</b> in such a way that a <b>significant inter- action with the body can be detected.</b> ”	deleted	deleted
Wording Annex I Section 7.4	“Where a device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product, as defined in Article 1 of Directive 65/65/EEC, and <b>whose action in combination with the device can result in its bioavailability</b> , the safety, quality and usefulness of the substance must be verified, taking account of the intended purpose of the device, by analogy with the appropriate methods specified in Directive 75/318/EEC, as last amended by Directive 89/341/EEC.”					“Where a device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product as defined in Article 1 of Directive 65/65/EEC and <b>which is liable to act upon the body with action ancillary to that of the device</b> , the safety, quality and usefulness of the substance must be verified, taking account of the intended purpose of the device, by analogy with the appropriate methods specified in Directive 75/318/EEC.”
Wording Classification Rule	Rule 13 (initially Rule 12, became Rule 13 through amendments): “All devices incorporating, as an integral part, a substance which, if used separately, can be considered to be a medicinal product, as defined in Article 1 of Directive 65/65/EEC, and <b>whose action in combination with the devices can result in its bioavailability</b> , are in Class III.”					Rule 13: “All devices incorporating, as an integral part, a substance which, if used separately, can be considered to be a medicinal product, as defined in Article 1 of Directive 65/65/EEC, and <b>which is liable to act on the human body with action ancillary to that of the devices</b> , are in Class III.”

As can be seen from table 4, there definitely was need for discussion concerning the passages dealing with medical devices incorporating a medicinal substance with action ancillary to that of the device.

In the first proposal by the Commission [20] the function of the medicinal substance in the medical device was taken as “to help” the device “operate”. According to this proposal the assessment of the ancillary substance was intended to be carried out by analogy with the appropriate methods specified in the relevant directive on medicinal products in case of the “bioavailability” of the integral substance. Considering the corresponding definition of “bioavailability” in article 1 (2) (k) of the Commission’s proposal, this would have meant that a reasonable interaction of this substance with the body was required for this detailed evaluation of the medicinal part of the device. But the term “can reasonably be detected” was not clearly defined in this context.

During the first reading European Parliament called on to amend the Commission’s proposal in its Committee report and the subsequent embodying of its opinion. The function of the medicinal substance in the medical device was voted to be changed from “to help (*the device, the author*) operate” to “to improve its safety, quality or performance”. And the character of the integral substances was specified as “substances which, while not designed to be administered as a medicinal product, are bioavailable within the meaning of this Directive and if used separately, may be considered to be a medicinal substance”. At the same time the definition of the term “bioavailability” was amended. The EP Committee report of the first reading [22] reads: “Aside from this general issue, the directive could be amended so as to reduce administrative formalities in the following areas: - bio-availability should be taken into account only when it is established that there is a significant interaction with the body (Article 1 (2) (k)), [...]” and “The definition of bioavailability in Article 1 (2) (k) is technically unacceptable and causes confusion with the pharmaceutical concept of bioavailability, which is a key term in Community pharmaceutical law. The term must be changed, or the technical definition of bioavailability must be given.”

Hence the European Parliament suggested the following amendment of the definition of “bioavailability” in its adopted text of the opinion of the first reading [23]: “bioavailability’ means the release from a device into or onto the human body of a substance **liable to be locally or entirely absorbed by the body’s tissue** in such a way that **a significant** interaction with the body can be detected.” According to this proposal the assessment of the ancillary substance was still intended to be carried out by analogy with the appropriate methods specified in the relevant directive on medicinal products in case of the “bioavailability” of the integral substance. Considering the proposed amendment of the definition of “bioavailability” in the European Parliament’s opinion this would have meant



that a significant interaction of this substance with the body was required for this detailed evaluation of the medicinal part of the device. But just like the term “can reasonably be detected” was not clearly defined in the Commission’s proposal, the term “significant interaction” was also not clearly defined in this context.

The wording of Annex I Section 7.4 and of the relevant Classification Rule were not under discussion by the time of the adoption of the European Parliament’s opinion. It was adhered to the phrase “whose action in combination with the device(s) can result in its bioavailability”. This is not quite consistent with the above-quoted 6<sup>th</sup> Recital. Following the 6<sup>th</sup> Recital an assessment of the ancillary substance by analogy with the appropriate methods specified in the relevant directive on medicinal products was required “[...] in the event of the bioavailability of such substances [...]”. However, according to Annex I Section 7.4 it is already required in case of the possibility of the bioavailability of the integral medicinal substance (*underline by the author*).

The last crucial step of the law-making procedure of Council Directive 93/42/EEC of 14 June 1993 concerning medical devices is the adoption of a common position by the Council. At this stage of the procedure the phrase “liable to act (up)on the (human) body” could be found for the first time. In the 6<sup>th</sup> Recital the function of the integral substance is specified as “liable to act upon the body with action ancillary to that of the device”. The character of the integral substances is changed again into “substances which, if used separately, may be considered to be a medicinal substance”. At the same time the term “bioavailability” was deleted. The wording of Annex I Section 7.4 and of the relevant Classification Rule were analogously adapted. Thus, all passages discussed so far have got the wording that is still valid even today. The reason for those amendments in the course of the common position and the formal adoption of the directive by the Council are not really traceable.

But an interesting fact that did not come up until this stage of the legislative procedure is the involvement of the competent authority for medicinal products in the assessment of the ancillary substance by analogy with the appropriate methods specified in the relevant directive on medicinal products. The following statement is given in the common position adopted by the Council on 8 February 1993 [26]: “The common position does not call into question the principles underlying the conformity assessment procedures or the criteria for classifying medical devices proposed by the Commission, and takes very large account of the amendments proposed by the European Parliament. [...] In order to ensure the highest level of protection of patients’ health, the common position lays down a more stringent assessment procedure for this type of device (*devices incorporating medicinal substances, the author*) by using the expertise of the bodies responsible for assessing medicinal products. Point 4.3 of Annex II and point 5 of Annex III stipulate that the notified

body responsible for assessing the conformity of devices must consult those bodies, in accordance with Directive 65/65(/EEC, *the author*) on pharmaceutical products, and must give due consideration to the views expressed in such consultations. It is, however, understood that such consultation will not result in twofold assessment of devices, in respect of which certificates are to be issued solely in accordance with the procedures laid down in this Directive.” Up to that specific date this issue had not been addressed. As per the previous concept, the Notified Body should make the assessment of the medicinal part of the device by itself.

Further Council statements of reasons for made amendments in the course of the common position, like the term “liable to act (up)on the (human) body”, could not be found.

Gert H. Schorn, who was involved in the law-making procedure of Council Directive 93/42/EEC as a Member State representative, outlines in his publication “Blick in die Vergangenheit und in die Zukunft” the reason behind the aforementioned final phrasing used in Annex I Section 7.4 [27]. In all language versions of this directive the intention was to take into consideration the possibility that the ancillary substance had not yet been subject to a marketing authorisation procedure in accordance with the applicable pharmaceutical law, but could be a medicinal product in the legal sense. So, with patient protection in mind, the subjunctive was used (may be considered to be ..., can act upon the body). It should also be signified that the criteria for the categorisation of the substance in question are those of the relevant pharmaceutical law. However, this means that some substances only have a pharmacological effect when reaching a defined concentration and dosage, respectively. As a consequence of this, this would also apply to the ancillary substance in a medical device. So far the comments of Gert H. Schorn.

To sum up: The law-making procedure of Council Directive 93/42/EEC of 14 June 1993 concerning medical devices (MDD) does not provide appropriate guidance with regard to the provisions laid down for medical devices incorporating a medicinal substance with action ancillary to that of the device. At the beginning of the procedure the first thoughts went towards the explicit statement that the bioavailability of the integral medicinal substance was the core requirement for the necessity to carry out a consultation procedure on the medicinal aspects of the device. Then the definition of “bioavailability” was improved by introducing the criterion of the absorbance of the substance in question by the body’s tissue. But the term “significant interaction with the body can be detected” was unfortunately not substantiated. In the final stages of the legislative procedure the definitions were, in a sense, widened. In the author’s opinion this is assumedly due to the intent of the Council to ensure the highest level of protection of patients’ health.

The documents of the law-making procedure of the MDD were examined here as far as they were traceable with the Internet and in particular with the services of the EU (EUR-Lex and associated online databases, Regulation 1049/2001 of 30 May 2001 granting a right of access to European Parliament, Council and Commission documents to any Union citizen). The problem inherent in this is that not all documents that are relevant for this legislative procedure might have been found, because not every particular/detail is made available to the public. Also the references in those databases turned out not to be free from errors (e.g. internal document "PE 170 813" was not traceable).

Therefore, the above summary can not be conclusive.

According to the comments of Gert H. Schorn concerning the reason behind the wording of Annex I Section 7.4 of the MDD the concentration of the ancillary substance in a medical device would indeed play a role.

To obtain more information on the interpretation and the implementation of the legal stipulations on medical devices incorporating a medicinal substance with action ancillary to that of the device, the following chapters will examine the current existing soft law referring to this and the practical implementation of the MDD.

### **2.3 Existing soft law in the EU**

This section of the master thesis is dealing with suitable guidance documents that are currently available with regard to the provisions laid down in section 7.4 of Annex I and Classification Rule 13 of Directive 93/42/EEC as amended for medical devices incorporating a medicinal substance with action ancillary to that of the device. Solely those interpretive documents that help on finding out more about the possible criteria defining under what circumstances a consultation procedure is necessary will be considered. And also supportive documents dealing with rule 13 in Annex IX of Council Directive 93/42/EEC as amended will be studied in order to search for information whether this rule actually applies to all medical devices incorporating a medicinal substance with ancillary action, regardless of whether the substance in question has a pharmacological effect or not from the concentration / dose point of view.

On EU level there are two fundamental documents that provide guidance as to the objective of this analysis: the MEDDEV Guideline 2.1/3 [4] and the MEDDEV Guideline 2.4/1 [28] (especially in part 2). The current versions of both guidelines were issued in 2001. Thus, they have not been adapted to the amendments introduced by Directive 2007/47/EC yet. But because there are no essential differences in the crucial passages between this directive and the precursory law, they may nonetheless be consulted for that matter.

MEDDEV Guideline 2.1/3 comments on the term “substance which, if used separately, may be considered to be a medicinal product” in section 7.4 of Annex I as follows: “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.” Besides this, there is only one other relevant statement that deals with the use of the consultation procedure: “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.” But further illustration of the term “liable to act upon the body with action ancillary to that of the device” or more examples are not given here.

MEDDEV Guideline 2.4/1 explicitly states in part 2 in terms of Classification Rule 13: “This rule is intended to cover combination devices that contain a medicinal substance

incorporated into the device for the purpose of assisting the functioning of that device. However this rule does not cover those devices incorporating substances which under other circumstances may be considered as medicinal substances, but which are incorporated into the device exclusively for the purpose at maintaining certain characteristics of the device and which are not liable to act on the body.”

But the guideline only gives one illustrative example of a product that would not fall under this rule, namely the same as in MEDDEV Guideline 2.1/3 (preservation agent containing solution for contact lenses).

Examples of products that would fall under this rule are given more in detail. Those are

- dressings incorporating an antimicrobial agent where the purpose of such an agent is to provide ancillary action on the wound,
- ophthalmic irrigation solutions principally intended for irrigation, which contain components which support the metabolism of the endothelial cells of the cornea,
- antibiotic bone cements,
- condoms with spermicide,
- endodontic materials with antibiotics or
- heparin coated catheters.

These examples are more or less obvious and don't give many reason to discuss. But there are no complex examples given that really could give guidance for border cases.

All described examples and issues within the current MEDDEV Guidelines can not provide comprehensive guidance in terms of possible criteria defining under what circumstances a consultation procedure is necessary. And the information on the scope of Classification Rule 13 is rather general, too. It does not outline complex cases.

On a national level there indeed are some guidance documents dealing with consultation procedures in the framework of conformity assessment of medical devices. They are mainly issued by the competent authorities for medicinal products (e.g. BfArM, MHRA, IMB, Läkemedelsverket). But they do not really make the issue, examined in this master thesis, a subject of discussion.

The regulatory authority of the United Kingdom, the MHRA, states in one of its bulletins [29]: “However there may still be areas where the regulatory classification is unclear, particularly where products incorporate [...] a medicinal product.” But MHRA does not go into further details concerning this conclusion.

One example of a national guidance document that addresses this issue is the German “Arbeitshilfe: Einstufung und Klassifizierung von Medizinprodukten” [Working Aid: Categorisation and Classification of Medical Devices]. It was drawn up by the AGMP Project Team “Abgrenzungs- und Klassifizierungsfragen” [Demarcation and Classification

Issues] and adopted by the “Arbeitsgruppe Medizinprodukte” [Working Group Medical Devices]. The members of both working groups are employed at the different competent authorities of the different federal states of Germany, responsible for the inspection of medical devices manufacturers. Because this document is only available in German language, the following quotations of the relevant statements will be given in the original language and consecutively in a literal English interpretation.

Concerning the applicability of Classification Rule 13 this working aid sets out [30]:

„Die Bewertung des Arzneimittelanteils und die Prüfung der hinreichenden Konzentration für eine ergänzende Wirkung ist Gegenstand des Konsultationsverfahrens [...]. [...] Die Verwendung des Wortes „kann“ unterstreicht schon allein die theoretische Möglichkeit für eine ergänzende Wirkung des Produktes auf den menschlichen Körper. Medizinprodukte, die unter die Richtlinie 93/42/EWG fallen, und einen - in welcher Form auch immer vorliegenden - arzneilich wirksamen Bestandteil enthalten, sind grundsätzlich der Klasse III zuzuordnen. Nur in solchen Fällen, in denen nach dem aktuellen Stand der wissenschaftlichen Erkenntnisse ein Effekt auf den menschlichen Körper zweifelsfrei nicht zu erwarten ist, findet die Regel 13 keine Anwendung. Hierzu kann je nach Einzelfall eine Anfrage nach § 13 Abs. 3 MPG beim BfArM zweckmäßig sein. Im Zweifelsfall ist die Regel 13 anzuwenden.“

[The assessment of the medicinal substance and the verification of the concentration that is adequate for an ancillary action is a subject of the consultation procedure [...]. [...] The use of the word “can” alone emphasises the theoretical possibility of an ancillary action of the product on the human body. Medical devices coming under the Directive 93/42/EWG and incorporating a – in whatever form present – active pharmaceutical ingredient, as a matter of principle are in Class III. Only in those cases, where an effect on the human body is definitely not to be expected according to the current scientific state-of-the-art, rule 13 does not apply. On this it may be appropriate in particular cases to address a question to BfArM pursuant to § 13 section 3 MPG. In case of doubt rule 13 has to be applied.]

This interpretation, that the verification of the concentration that is adequate for an ancillary action of the medicinal substance in the medical device has to be done in the consultation procedure would add up to the situation that a consultation procedure would be necessary in any case. But this is incongruent with the “spirit” of the MDD, namely that the verification of the adequate concentration of the medicinal substance must take place already beforehand by the manufacturer and the other parties involved in the conformity assessment procedure of a medical device (Notified Body, competent authorities, responsible for manufacturers’ surveillance). Everything else would not quite be consistent with the primary intention of this directive, namely the reduction of administrative burden.

„Die medizinische Stellungnahme in einem Konsultationsverfahren [...] soll die

Wirksamkeit der ausgelobten arzneilichen Hilfsfunktion bei dem konkreten Medizinprodukt prüfen, aber nicht, ob das Medizinprodukt eine nicht ausgelobte arzneiliche (Hilfs-)Funktion besitzt [...]“ [2]. This means that the medicinal assessment in the course of a consultation procedure is intended to verify the effectiveness of the claimed ancillary action of the medicinal substance in the concrete medical device. But it is not intended to examine whether the device has a medicinal (ancillary) action that has not been claimed by the manufacturer.

On the other hand the AGMP makes a clear statement as regards the applicability of Classification Rule 13. As quoted above this means that rule 13 does not apply to medical devices incorporating, as an integral part, a substance which, if used separately, can be considered to be a medicinal product, in some cases. Devices falling under rule 13 are classified as Class III, which is the highest risk class with the most extensive conformity assessment procedure. Therefore, if rule 13 does not apply, the device in question will be assigned to a lower class. And this will reduce time and effort that need to be spent for the conformity assessment procedure. In case of doubt the AGMP however recommends to seek advice from the (German) competent authority responsible for both the registration of medicinal products and carrying out consultation procedures. But that means to place the responsibility for classification of a medical device on the regulatory authority for medicinal products. But in fact the manufacturer of the device and the Notified Body are accountable for this classification. Just in 2004 the AGMP arrived at the conclusion that also the concentration of the integral substance might play a role in the decision on the applicability of rule 13. Scientific literature (e.g. Martindale) and commercially available concentrations should be considered [„Bei der Entscheidung könne auch die Konzentration eine Rolle spielen. Heranzuziehen seien wissenschaftliche Literatur (z.B. Martindale) und handelsübliche Konzentrationen.“] [2]. This last comment given in 2004 by the AGMP is more understandable from a practical point of view. Where an effect of the ancillary substance in the device on the human body is definitely not to be expected, the health and safety of the patient or user is not at risk. Thus, there is nothing to be said against the assignment of a lower risk class to such devices in those cases.

In order to sum up the results with respect to existing soft law, on EU level comprehensive guidance dealing with the criteria for the necessity of a consultation procedure or the applicability of Classification Rule 13 in border cases is currently not really available. On a national level only the working aid issued by the AGMP in Germany could be found. This document has a comprehensible approach concerning the interpretation of the applicability of Classification Rule 13. But it rather does not provide guidance for border cases. In fact its present version only advises to consult the regulatory authority for

medicinal products in case of doubt. And the verification of the concentration that is adequate for an ancillary action of the medicinal substance in the medical device is assigned to the regulatory authority for medicinal products, according to this document. In the author's opinion this is not quite consistent with the intention of Directive 93/42/EEC as amended.

In the end, the question is left how the legal provisions are administered in practice. This will be surveyed in chapter 2.4 of this master thesis.



## **2.4 Common practice and opinions in the EU**

To get an idea of the current practice and the current opinions in the EU in view of the necessity of the execution of consultation procedures with medical devices incorporating a medicinal substance with ancillary action, a corresponding survey was conducted.

Some major Notified Bodies, competent authorities of the model countries outlined in chapter 2.1 of this thesis and also a few associations in the field of medical devices were consulted by the author. Because of the current employment of the author, contacting medical device manufacturers was unfortunately not possible.

The involved parties were asked for information as to the practical experience they have gained or their current practice concerning

- the criteria defining under what circumstances a consultation procedure is necessary for medical devices incorporating a medicinal substance with ancillary action
- the applicability of Classification Rule 13 in Annex IX of Council Directive 93/42/EEC as amended or its national transposition, respectively.

The answers that are displayed below are non-binding information. They are just intended to reflect current attitudes. Therefore, it is not relevant to specify the informants.

On the part of the Notified Bodies only 4 out of 11 responded to the questions. One stated that those issues were controversially discussed and it only refers to the MEDDEV documents for guidance; in daily experience the German competent authority for medicines (BfArM) seemed to prefer the strict interpretation that a consultation procedure is necessary in any circumstance. One Notified Body (NB) was involved in drawing up the AGMP Working Aid described in chapter 2.3 of this thesis and solely cited this German document as basis for decision. The third NB recommended to address those questions to the competent authority for medicines. And the last one just pointed out that the answer to those questions is unfortunately not simple and that no clear answer can be given.

As for the medical device associations 3 associations were consulted. The major European association, Eucomed, did not answer. The other 2 replied to the questions, but very different. The second association referred to the “*EMEA RECOMMENDATION ON THE PROCEDURAL ASPECTS AND DOSSIER REQUIREMENTS FOR THE CONSULTATION TO THE EMEA BY A NOTIFIED BODY ON AN ANCILLARY MEDICINAL SUBSTANCE OR AN ANCILLARY HUMAN BLOOD DERIVATIVE INCORPORATED IN A MEDICAL DEVICE*”. But this guidance document is not useful in the context of this master thesis, because it focuses on the format and content of the applications for consultation and outlines the formal workflow. Apart from the hint on this

document, the second association recommended contacting the German association “BAH”. The most detailed feedback was gotten from the third association. They gave the following résumé: “I am not aware of any circumstances in which a manufacturer would be able to avoid consultation with either EMEA (*which is the European Medicines Agency, the author*) or a national medicines competent authority when their product contains a medicinal product. The fact that the substance might be present in amounts that are below the pharmaceutically active level is, I think, immaterial. For instance, in the case of a heparin-coated catheter the heparin is present in order to prevent blood from coagulating on the catheter’s surface rather than for release for any anticoagulation in the general circulatory system. In this instance the heparin certainly has an effect that assists use of the medical device but one would not say that it had an appreciable pharmaceutical effect on the body. The key point with regard to these products is that the substance is there to enhance the usefulness of the medical device; the device is not there to act as a drug-delivery system, e.g. a pre-filled syringe. Given the above, classification rule 13 would apply in all cases where a medicinal product is present.”

On the part of the national competent authorities 5 out of 7 responded.

The Spanish authority just informed that it was not possible for them to reply because of their workload.

The MHRA, the agency of the United Kingdom, gave a reply: “I can confirm that a consultation procedure for a medical device incorporating a medicinal substance which is acting ancillary would always be required. However in some cases where there are no ancillary claims being made for a substance, evidence is available to support that there is no ancillary action and the substance is present for another reason (eg a preservative) then such products may not need a consultation. I can confirm that Rule 13 in Annex IX of Council Directive 93/42/EEC as amended applies to nearly all medical devices incorporating a medicinal substance with ancillary action. The only exception I am aware of is covered by Rule 18 which states that blood bags, by derogation from other rules, are in Class IIb; some of which contain medicinal substances.”

A staff member of the Irish Medicines Board gave her personal opinion on the issue as follows: “You have raised an interesting question. [...] Your key question appears to be whether in all instances it is necessary to treat a medical device-medicinal substance combination as a drug-device combination as per rule 13 of Annex IX and thereby apply section 7.4 on Annex I. Rule 13 states “... as an integral part, a substance which, if used separately, can be considered to be a medicinal product, as defined in Article 1 of Directive 65/65/EEC, and which is liable to act on the human body with action ancillary to that of the devices...”, so in the strictest terms in my opinion the answer to your question

is yes in the vast majority of cases. However, in some instances it may be possible that a substance already classified as medicinal substances may achieve its effect by means other than pharmacological, metabolic or immunological action e.g. it may achieve its effect physically. These are reviewed on a case by case basis by the Irish Medicines Board as to whether they represent drug-device combinations as per rule 13. In order to classify such a product as anything other a drug-device combination the manufacturer must present very clear evidence that the substance in the combination does not achieve any effect by pharmacological, metabolic or immunological means. This can be difficult to clearly demonstrate. In addition, in some instances the actual benefit of placing a substance in the combination may also be questionable. For instance, coating a central venous catheter with an anticoagulant and then claiming that the anticoagulant concentration is so low that it does not have pharmacological, metabolic or immunological action and the anticoagulant is there as a lubricant. Products of this nature are often discussed at the Classification and Borderline Working Group in Brussels.”

The Hungarian competent authority, EEKH, distinguishes two different cases as to the procedure when a device incorporating a medicinal product is intended to be marketed in Hungary. It namely depends on the registered place of business of the manufacturer or for non-EU manufacturers the authorised representative. Where the registered place of business of the manufacturer or for non-EU manufacturers the authorised representative is in Hungary, the Notified Body shall contact the National Institute of Pharmacy and shall initiate consultation process. Where the registered place of business of the manufacturer or for non-EU manufacturers the authorised representative is outside of Hungary in another EU Member State and the conformity assessment procedures have been performed according to MDD in one of the other EU Member States, the Hungarian distributor shall contact the National Institute of Pharmacy for opinion. Otherwise, the National Institute of Pharmacy shall object distribution of the device in question in Hungary. This is required because the legal regulation on the registration of medicines (decree 52/2005. (XI. 18.)EüM on placing on the market of medicinal products for human use) is not a harmonised one. The staff member of the EEKH further stated that the provisions of the Hungarian decree for medical devices did not depend on the concentration of the medicinal substance. The consultation procedure concerning medical devices incorporating a medicinal substance with ancillary action was strictly necessary without exception in Hungary.

A staff member of Läkemedelsverket, the competent authority of Sweden, stated that it was not absolutely necessary to open a consultation procedure with all medical devices incorporating a medicinal substance with ancillary action in all circumstances. But examples of such combination products where it is not (absolutely) necessary to have an

evaluation of the medicinal substance done by the competent authority responsible for medicines were not given. It would play a decisive role in medical devices incorporating a medicinal substance with ancillary action whether or not the concentration of the medicinal substance in the device is a pharmaceutically active one. There were no other criteria that would have to be considered in the decision concerning the necessity of a consultation procedure. A consultation procedure concerning the medicinal substance would not strictly be necessary with all medical devices incorporating a medicinal substance with ancillary action. But the national transposition of classification rule 13 in Annex IX of Council Directive 93/42/EEC as amended would actually apply to all medical devices incorporating a medicinal substance with ancillary action.

Even though the feedback reflects only a cut out of the 27 Member States, this survey at least shows that there is further need for discussion concerning the necessity of the execution of consultation procedures with medical devices incorporating a medicinal substance with ancillary action within the EU. Most of the respondents tended to a very strict interpretation of the existing laws and guidance documents. But there also appears to be at least awareness of border cases, where the interpretation of the existing laws and guidance is not certain.

The actual practice in Hungary is not quite consistent with the wording of the current national law (see chapter 2.1 of this master thesis). And as the statement of the Hungarian authority shows, different interpretation of the existing laws and guidance in the EU in the end can have an impact on the marketability of medical devices incorporating a medicinal substance with ancillary action.

Also, different interpretation of the existing laws and guidance in the EU in view of the necessity of the execution of consultation procedures on medical devices incorporating a medicinal substance with ancillary action leads to medical devices manufacturers using “loopholes”. In the introduction the example of a saline nasal spray containing dexpanthenole for nurture of the nasal mucosa is given. Such a product was subject to a conformity assessment procedure including a consultation procedure in one EU Member State. In the end the manufacturer of the saline nasal spray containing dexpanthenole withdrew from the procedure in this Member State. Instead of this, another manufacturer in another EU Member State, where a consultation procedure was not deemed necessary for this product according to the national interpretation of the relevant laws, performed the “common” conformity assessment procedure and placed this CE-marked product on the market. [Dr. E. Anhalt, personal communication, September 2008].

A written example of the outcome of a contemporary discussion in the EU about a border case is the classification of single-use examination gloves coated with PHMB (polyhexamethylene biguanide), a broad spectrum bactericide.

Those devices are a subject of the “MANUAL ON BORDERLINE AND CLASSIFICATION IN THE COMMUNITY REGULATORY FRAMEWORK FOR MEDICAL DEVICES” [31]. This manual is issued by the European Commission’s Medical Devices Expert Group (MDEG) on Borderline and Classification. The group consists of Member States, industry and other stakeholders representatives in the area of medical devices.

This manual sets out that classifying these gloves as Class III (i.e. high risk) medical devices would appear the most appropriate. The given rationale is that PHMB, if used separately, is a medicinal product. And what’s more, if the intended use of these gloves is to examine a wound or mucous membrane, there is a risk that PHMB is liable to act on the patient’s body with an action ancillary to that of the device. From MDEG’s point of view this intended use will lead to a considerably increased risk of action of PHMB on the patient.

Swissmedic, the Swiss Agency for Therapeutic Products, explicitly advises in its official periodical [32] that Class I medical devices, as a basic principle, may contain preservative agents, flavours and other adjuvants. However, they may not contain concentrations that might act on humans with a pharmaceutical action. Otherwise, they would be Class III according to Classification Rule 13 in Annex IX of the MDD.

This is an example for the approach that the concentration of the ancillary substance in a medical device indeed is a factor.

Further details of the current practice and the current opinions in the EU in view of the necessity of consultation procedures on medical devices incorporating a medicinal substance with ancillary action may be obtained from case law. But a research in German jurisdiction and in European jurisdiction furnished no results. No relevant law cases could be found in respect thereof.

As a summary, the survey and the example taken from the MDEG manual show the tendency to the view that in any case a consultation procedure should be carried out for medical device-medicinal substance combinations with ancillary action of the medicinal component to the device and only in some Member States any exemption is strongly being examined on a case by case basis. Both the response of the Swedish competent authority and the information from Swissmedic are examples of a different view. As can be seen from the example of Hungary, different interpretation of regulations causes

increased administration effort (Hungarian distributor shall contact the National Institute of Pharmacy for opinion). In the end this can have an impact on the marketability of a medical device and lead to market distortion.

Helpful case law as a basis for discussion could not be furnished.

Furthermore, it turned out to be complex to gather representative and comprehensive information of the factual current practice and the current opinions in the EU in view of the necessity of the execution of consultation procedures on medical devices incorporating a medicinal substance with ancillary action. This is on the one hand owing to the fact that much information on the Internet unfortunately is only available in the particular national language. If information in English is obtainable, the information content will be reduced to a minimum. The topics covered on the English section are often not so extensive like the topics covered on the national language section (e.g. Sweden). So all the more important is the direct exchange of information with the competent authorities.

On the other hand from the author's point of view this is due to a certain lack of sensitivity to this problem among experts of the Notified Bodies, competent authorities and medical device associations. They rather tend to the view that in any case a consultation procedure should be carried out for medical device-medicinal substance combinations with ancillary action of the medicinal component. This appears mainly to be for safety reasons in order to protect patients' health. Safeguarding health of patients and users is a basic and incontrovertible necessity with medical devices. But for medical device manufacturers it would be essential to only have reasonable and science-based obstacles to marketing. Some respondents pointed out that there indeed are decisions on a case by case basis. But this adds up to uncertainty of operations on the part of the manufacturers and constitutes higher administrative burden. On this problem it is desirable to have more – as practical as possible – consistent and generally accepted rules and standards. Therefore, there is need for discussion with all involved parties.

For instance in the case of the example of a saline nasal spray containing dexpanthenole for nurture of the nasal mucosa in a concentration that is comparable to that in cosmetics it is not quite comprehensible if a consultation procedure is deemed necessary. For cosmetics, there is no procedure comparable to the consultation procedure on medical devices incorporating a medicinal substance with ancillary action.

After all it means elaborate efforts to carry out a consultation procedure in respect of a medical device incorporating a medicinal substance.

### 3 Short outline of the situation in Non-EU Countries

In present times there is increasing globalisation and an increasing number of global players. On account of this it is important not only to have a look at single regions of the world, but also to get an idea of the global attitude.

This is also important for medical device manufacturers. They are confronted with a great deal of various legal requirements they have to fulfil in order to be able to place their products on the international market. The more different the prerequisites for marketing are, the higher are time, effort and cost that need to be spent.

The following short outline on the basis of a review given by the GHTF (Global Harmonization Task Force) will exemplify the regulatory environment of the so-called “combination products”. The term “combination product” does not exist in European legislation as to medical devices. But in countries outside Europe where the term “combination product” is defined medical device-medicinal substance combinations with ancillary action of the medicinal component to the device are assigned to this product category.

The aim of the GHTF is to harmonise national medical device regulatory systems. The members of this partnership belong to regulatory authorities and regulated industry of the European Union, United States, Canada, Australia and Japan. Currently there also are three Liaison Body members. On 8 May 2007 the Combination Products Ad Hoc Working Group within GHTF began its work.

In the course of the 12<sup>th</sup> GHTF Steering Committee Meeting held on 7-8 May 2007 in Irvine, California, USA, Ms. Olson presented the results of a side-by-side comparison of the regulatory environment of combination products. The results of this comparison will be recapitulated in brief here [33].

#### 1) Australia:

- No term “combination product”, definition and regulation as Class III medical devices with ancillary medicine components
- Considers combinations of drugs and devices
- Implementation of procedures that specifically require non-primary component consultations
- Committee where combinations can be referred if the lead agency is unclear

#### 2) Canada:

- Definition of term “combination product” exists

- Considers combinations of drugs and devices
  - Implementation of procedures that specifically require non-primary component consultations
  - No unique procedure for determining the lead agency or authority for combination products
- 3) EU:
- No term “combination product”, definition and regulation as Class III medical devices with ancillary medicine components
  - Considers combinations of drugs, devices or biologics
  - No unique procedure for determining the lead agency or authority for combinations
- 4) Japan:
- Regulation as drug or device, depending on the main purpose
  - Considers combinations of drugs, devices or biologics
  - No unique procedure for determining the lead agency or authority for combinations
- 5) USA:
- Definition of term “combination product” exists
  - Considers combinations of drugs, devices or biologics
  - Office of Combination Products in the Commissioner’s Office to refer combination products
  - Implementation of procedures that specifically require non-primary component consultations

The list shows that there is a quite heterogeneous approach.

Some countries have defined a specific term “combination product” (Canada, USA), other countries or regions don’t have. Australia and Canada have provided a regulatory basis for the combination of drug and device, the EU and USA for combinations of drugs, devices, and / or biologics. Japan regulates the entire combination that may consist of drugs, devices, and/or biologics completely either as drug or as device depending on the main intended use. USA have established the Office of Combination Products, where combination products are referred to. Australia has established a Committee, where in case of doubt a combination product can be referred to. This is not the case for Japan, Canada and the EU where the manufacturer must initially determine the lead agency or



authority by itself. Australia, Canada and the USA have implemented specific procedures for non-primary component consultations. Japan solely regulates either drugs or devices. The proceeding in the EU is most likely comparable to the procedures of Australia, USA and Canada (for Class III medical devices with ancillary medicine components the Notified Body consults the national or European medicines agency).

For Australia, Canada and the USA, who have implemented specific procedures for non-primary component consultations, the same question like that examined in chapter 2 of this master thesis with regard to the EU comes up. Namely, what regulatory framework is given with regard to the necessity of performing a consultation procedure with medical devices incorporating an ancillary medicinal substance? Or, in other words, are there exemptions that a medical device containing a substance, that can also be used in a drug product, needs no consultation procedure before putting it on the market?

As for Australia, it is stated in the Therapeutic Goods (Medical Devices) Regulations 2002 [34] in clause 7.4 of Schedule 1 that “[...] If a medical device incorporates, or is intended to incorporate, as an integral part, a substance that, if used separately, might be considered to be a medicine that is intended to act on a patient in a way that is ancillary to the device [...] the safety and quality of the substance must be verified in accordance with the requirements for medicines; and [...] the ancillary action of the substance must be verified having regard to the intended purpose of the device. [...]”.

The relevant guidance document “Essential principles of safety and performance” [35] is currently in draft status. It comments on this clause that the manufacturer of such a device has to prove that both components of the device “function together to achieve the intended purpose”. And he must show that “the medicine meets all the necessary Australian regulatory requirements to be supplied as a medicine”.

As for Canada and the USA, they defined the term “combination product” and established specific rules for this kind of medical device. There are no directly comparable counterparts of the Australian Essential Principles or the European Essential Requirements. But both are members of the GHTF and as such take into account the “Essential Principles of Safety and Performance of Medical Devices” issued by the GHTF. And also because an increasing number of countries adopts the position of the GHTF, this view is not immaterial.

Clause 5.7.4 of the “Essential Principles of Safety and Performance of Medical Devices” [36] issued by the GHTF reads: “Where a device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product / drug

as defined in the relevant legislation that applies within that jurisdiction and which is liable to act upon the body with action ancillary to that of the device, the safety, quality and usefulness of the substance should be verified, taking account of the intended purpose of the device.”

Also the GHTF has generated a document dealing with the “Principles of Medical Devices Classification”. Classification Rule 13 that applies to medical devices incorporating medicinal substances in an ancillary role reads [37]: “All devices incorporating, as an integral part, a substance which, if used separately, can be considered to be a medicinal product, and which is liable to act on the human body with action ancillary to that of the devices, are in Class D (*i.e. highest risk class, the author*).” Additionally, there is a note that those products may require additional conformity assessment procedures pursuant to regional or national requirements of medicinal product competent authorities.

The sense of those provisions of the GHTF is near to the provisions in the European Directive 93/42/EEC.

The proceedings in the single countries are even more complex than could be presented here. But this would go beyond the scope of this master thesis. Further information concerning the criteria for the necessity of the above-mentioned specific non-primary component consultations in Australia, Canada and the USA could not be gotten on the Internet. But the decision whether a consultation procedure is necessary or not is finally with the authorities everywhere.

This review shows that the regulatory environment of medical devices incorporating a medicinal substance with ancillary action is quite heterogeneous. To harmonise those different requirements is a challenging project of the GHTF. But this task makes sense, because harmonisation of this issue will reduce administrative burden of medical device manufacturers and facilitate international trade in the end.

Due to the fact that the EU is a member of the GHTF the final outcome of the work of the Combination Products Ad Hoc Working Group within GHTF will have to be considered in the European procedural methods in the distant future. Thus, the progress of this harmonisation should be further followed up.

## 4 Conclusion and Outlook

What is clearly demonstrated in this thesis is that there indeed are different interpretations and stipulations as to the execution of consultation procedures on medical devices incorporating a medicinal substance with ancillary action. And there definitely is need for discussion as to this issue in the author's opinion.

After all, "Different interpretations of (*European, the author*) Community legislation [...] can put public health at risk and distort the internal market. Both issues are of great concern to Member States and the Commission." [31].

Neither section 7.4 of the Essential Requirements (in Annex I to Directive 93/42/EEC as amended) nor Classification Rule 13 (in Annex IX to Directive 93/42/EEC as amended) are implemented consistently in the considered EU Member States Spain, France, Sweden, Ireland, United Kingdom, Germany and Hungary.

The examination of the law-making procedure of Council Directive 93/42/EEC of 14 June 1993 concerning medical devices (MDD) reveals little information on the primary intent of the legislative bodies as to the stipulations in question. The efficacy of the medicinal part of the device as a prerequisite for the necessity to carry out a consultation procedure was reduced in the end. But the examined documents of the legislative procedure absolutely show that one of the initial rationales during development of the MDD was a reduction of complexity and that it aimed at avoiding the implementation of superfluous formalities. At the same time, patients' safety should in no case be put at risk and the highest level of protection of patients' health should be ensured.

Considering the comments of Gert H. Schorn, who was involved in the law-making procedure of the MDD as a Member State representative, the concentration of the ancillary substance in a medical device would indeed have to be considered and would be a factor in the decision on the necessity of a consultation procedure.

In the author's opinion this is not opposed to the aim of the MDD to ensure the highest level of protection of patients' health.

On EU level the current applicable MEDDEV Guidelines (2.1/3 and 2.4/1 – part 2) do not really give comprehensive guidance dealing with the criteria for the necessity of a consultation procedure or the applicability of Classification Rule 13 in border cases in the author's opinion.

On a national level there indeed are some guidance documents dealing with consultation procedures in the framework of conformity assessment of medical devices, but they do not really make the issue examined here a subject of discussion. Only the German “Arbeitshilfe: Einstufung und Klassifizierung von Medizinprodukten” [Working Aid: Categorisation and Classification of Medical Devices] issued by the AGMP contains a clear statement as regards the applicability of Classification Rule 13. Namely that rule 13 does not apply to medical devices incorporating ancillary medicinal substances in certain cases. AGMP is a working group of the competent authorities of the different federal states of Germany, responsible for the inspection of medical devices manufacturers. But because in the present version this Working Aid only advises to consult - in case of doubt - the regulatory authority for medicinal products - which is different from the authorities inspecting the manufacturers - it does not provide guidance for border cases.

The examination of common practice and opinions in the EU showed the tendency to the view that in any case a consultation procedure should be carried out for medical device-medicinal substance combinations with ancillary action of the medicinal component to the device. The response of the Swedish competent authority and the information from Swissmedic represent a different point of view. As can be seen from the example of Hungary, different interpretation of regulations causes increased administration effort (Hungarian distributor shall contact the National Institute of Pharmacy for opinion). In the end this can have an impact on the marketability of a medical device and lead to market distortion.

The regulatory environment of the so-called “combination products”, where medical device-medicinal substance combinations with ancillary action of the medicinal component pertain to, showed that the sense of the provisions of the GHTF (Global Harmonization Task Force) with regard to such products is near to the provisions in the European Directive 93/42/EEC. But the proceedings in the single countries are even more complex than could be presented here and are quite heterogeneous in detail. To harmonise those different requirements is a challenging project of the GHTF. The final outcome of the work of the Combination Products Ad Hoc Working Group within GHTF will have to be considered in the European procedural methods in the distant future. Thus, the progress of this harmonisation should be further followed up. In the distant future harmonisation of this issue will reduce administrative burden of medical device manufacturers and facilitate international trade in the end.

To get a really comprehensive picture of the situation concerning the necessity of consultation procedures on medical devices incorporating a medicinal substance, the situation in the other EU Member States and also the situation with Active Medical Devices would have to be examined.

Also it would have been helpful to have information on the experiences of medical device manufacturers on this issue and more feedback and more detailed information on the points examined here.

But it turned out to be complex to gather information as to the items under examination, as described in section 2.4 of this master thesis.

To avoid the shown discrepancies, further interpretation, discussion and guidance as to the necessity of consultation procedures on medical devices incorporating a medicinal substance with ancillary action is needed in the author's opinion. Perhaps this could be implemented in the course of the review of the MEDDEV Guidelines (2.1/3 and 2.4/1) that is due because of the coming into force of Directive 2007/47/EC or because both guidelines were issued already in 2001.

Also, to reach full harmonisation on EU level at the first step, the wording of section 7.4 of the Essential Requirements (in Annex I to the MDD as amended) and Classification Rule 13 (in Annex IX to the MDD as amended) - and, consequently, their corresponding transposition into national law - should be adapted to the meaning of the source text (English version of the MDD). Here the author can only subscribe to the view of Dr. Ehrhard Anhalt (Bundesverband der Arzneimittel-Hersteller e.V. (BAH) - Bonn) given in his publication "Bedürfen Medizinprodukte mit Arzneimittelanteil immer eines Konsultationsverfahrens?" [2]. This would mean that a pharmaceutical effect of the medicinal substance in the device analogous to the effect of a medicinal product containing the medicinal substance in question is the crucial factor. But not merely an effect that is comparable to, for instance, a cosmetic product [2]. In the author's opinion this would not be opposed to the aim of the MDD, that is ensuring the highest level of protection of patients' health.

To implement this proposed harmonisation on EU level in the framework of the transposition of the amendments introduced by Directive 2007/47/EC into national law appears to be virtually impossible. Indeed, the European Commission has launched a pilot "pre-adoption screening procedure" that will allow the commission, member states, industry and individuals to participate in the national implementation process of Directive 2007/47/EC [38]. They can submit their draft national legislation for screening, which is then published on the Commission's website for comments. But this page was accessed on 22 September 2008 and only showed the draft legislation of Malta and Belgium. And

the directive must be transposed into national law by 21 December 2008. So there is not much time left. Moreover, there would ideally be need of a selective measure initiated by a key organisation like e.g. the Commission.

But there would be the possibility to implement this proposed harmonisation on EU level in the framework of the so-called “recast”. This is a public consultation that has been initiated by the European Commission with the objective of improving weaknesses in the current regulatory system for medical devices [39].

With this prospective revision of the medical devices directives the EU appears to be on the right path. A prerequisite for success of this goal is dialogue with all parties involved. The aim of this review should continue to be guaranteeing the highest level of patients’ health. But at the same time it should also be aimed for establishing a transparent, unambiguous system that only demands the essential and justifiable obligations according to the current state-of-the-art.

In the course of globalisation and harmonisation efforts of the GHTF it would be all the more important not to go for an individual programme within EU, but to play an increased part in this issue on GHTF level (e.g. the Combination Products Ad Hoc Working Group within GHTF) and head for a global settlement.

## 5 Summary

The European legislation foresees a special proceeding for medical devices incorporating, as an integral part, a substance which, if used separately, may be considered to be a medicinal product as defined in Article 1 of Directive 2001/83/EC and which is liable to act upon the body with action ancillary to that of the device. The Notified Body carrying out a conformity assessment procedure in respect of such a medical device consults a competent authority for medicinal products on the medicinal aspects of the device, which is called consultation procedure. This is to verify the compatibility of the medical device and the medicinal substance. This means that the manufacturer of such a medical device incorporating a medicinal substance with ancillary action has to spend a lot of time, effort and money, because the manufacturer must - in addition to the standard requirements for a conformity assessment procedure - typically submit detailed data on the quality, safety and usefulness of the incorporated medicinal substance.

This master thesis further investigates a problem that was pointed out by Dr. Ehrhard Anhalt (Bundesverband der Arzneimittel-Hersteller e.V. (BAH) - Bonn) in his publication "Bedürfen Medizinprodukte mit Arzneimittelanteil immer eines Konsultationsverfahrens?" [2] with regard to those stipulations. He highlighted a discrepancy in the wording of section 7.4 of Annex I between the English version and the German version of Council Directive 93/42/EEC on Medical Devices as amended (MDD). As a consequence of the wording of the German version, a consultation procedure concerning the medicinal substance would strictly be necessary with all medical devices incorporating a medicinal substance without exception, i.e. independent of whether or not the concentration of the medicinal substance in the device is a pharmaceutically or pharmacologically active one. As a consequence of the wording of the English version, only if the concentration of the medicinal substance in the device is adequate for an ancillary action and only if it is pharmaceutically or pharmacologically active, a consultation procedure concerning the medicinal substance would be necessary. But if the medicinal substance in the device does not act in this way, then a consultation procedure would not be necessary. After all, different national interpretations of the legislative rules on medical devices incorporating ancillary medicinal substances in the European Union can be of consequence for the marketability of this kind of devices. On that account this master thesis further investigates the discrepancy shown above. It examines for selected Member States of the European Union (Spain, France, Sweden, Ireland, United Kingdom, Germany and Hungary) whether section 7.4 of the Essential Requirements (in Annex I to the MDD) and Classification Rule 13 (in Annex IX to the MDD) as well as their corresponding transposition into national law also differ

from the English version of the MDD. The question is considered under what circumstances those selected Member States deem it necessary to carry out a consultation procedure on a medical device that contains an integral medicinal substance for the purpose of assisting its functioning. A search on criteria defining under what conditions the integral medicinal substance acts ancillary to the device was done. The law-making procedure of Council Directive 93/42/EEC is studied under the aspect of the primary intention of the stipulations concerning devices incorporating, as an integral part, a substance which, if used separately, may be considered to be a medicinal product and which is liable to act upon the body with action ancillary to that of the device. Existing guidances in the European Union (EU) are examined and the common practice and opinions in the selected EU countries are inquired. At the end of this thesis a short global outline is given in order to get a view of how medical devices incorporating ancillary medicinal substances are regulated outside of the EU.

What is clearly demonstrated in this thesis is that there indeed are different interpretations and stipulations as to the execution of consultation procedures on medical devices incorporating a medicinal substance with ancillary action. And there definitely is need for discussion. Thus, to avoid such discrepancies, further interpretation, discussion and guidance as to the necessity of consultation procedures on medical devices incorporating a medicinal substance with ancillary action is needed in the author's opinion. For instance, this could take place in the framework of the so-called "recast" of the medical devices directives in the EU.



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## 7 Annex

**Chronology of the law-making procedure of Council Directive 93/42/EEC of 14 June 1993 concerning medical devices and associated documents that were evaluated for the purposes of this master thesis ([19], [20], [21], [22], [23], [24], [25], [26], [40], [41], [42], [43], [44], [45], [46], [47], [48])**

**Cooperation procedure, number: 1991/0353/SYN**

Date	Stage of procedure and European Institution involved	Document identifier	Document title
25-07-1991	Adoption by Commission	OJ C 237, 12.9.1991, p. 3–40 and alike COM(91) 287 final – SYN 353	Proposal for a Council Directive concerning medical devices
30-08-1991	Transmission to Council		
11-09-1991	Transmission to European Parliament (EP)		
12-09-1991	Consultation of Economic and Social Committee (ESC) by Council		
12-09-1991	Consultation of European Parliament (EP) by Council		
	European Parliament – Committee on Economic and Monetary Affairs and Industrial Policy	PE 153.198 PE 153.198/Corr. PE 153.198/corr. 2	Draft Report on the Commission proposal for a Council directive concerning medical devices (COM(91) 0287 final – SYN 353)
29-01-1992	Economic and Social Committee (ESC) opinion	OJ C 79, 30.3.1992, p. 1-3	Opinion on the proposal for a Council Directive concerning Medical Devices
26-02-1992	EP Committee opinion 1st reading (Committee on the Environment, Public Health and Consumer Protection)	PE 154.107	Draft Opinion for the Committee on Economic and Monetary Affairs and Industrial Policy on the proposal from the Commission for a Council Directive concerning medical devices COM (91) 0287 final – SYN 0353 – C3-0331/91
15-04-1992	EP Committee report 1st reading (Committee on Economic and Monetary Affairs and Industrial Policy)	A3-0178/92 (= PE 153.198/fin.)	Report of the Committee on Economic and Monetary Affairs and Industrial Policy on the Commission proposal for a Council directive concerning medical devices (COM(91) 0287 final – C3-0331/91 – SYN 353)

Date	Stage of procedure and European Institution involved	Document identifier	Document title
13-05-1992	EP opinion 1st reading	OJ C 150, 15.6.1992, p. 103-118	
13-05-1992	Commission position on EP amendments on 1st reading		
28-07-1992	Adoption amended proposal by Commission	COM(92) 356 final – SYN 353 and alike OJ C 251, 28.9.1992, p. 40-50	Amended proposal for a Council Directive relating to the medical devices
28-07-1992	Transmission amended proposal to Council		
29-07-1992	Transmission amended proposal to EP by Council		
17-12-1992	Political agreement on a Common Position by Council		
08-02-1993	Adoption common position by Council	OJ C 71, 13.3.1993, p. 1 and 4327/1/93 + ADD 1	Establishing by the Council of common positions under the cooperation procedure provided for by Article 149 (2) of the Treaty establishing the European Economic Community and Common Position adopted by the Council on 8 February 1993 with a view to the adoption of the Directive concerning Medical Devices
05-03-1993	Transmission to EP declaration on common position by Commission	SEC(93) 362 final – SYN 353	Communication from the Commission to the European Parliament [...] concerning the common position adopted by the Council on 8 February 1993 with a view to the adoption of the Directive concerning medical devices
10-03-1993	EP receipt of common position		
21-04-1993	EP opinion 2nd reading	OJ C 150, 31.5.1993, p. 116 (Decision A3-0088/93)	Decision on the common position established by the Council with a view to the adoption of a Directive concerning medical devices
21-04-1993	Commission position on EP amendments on 2nd reading		
01-06-1993	Adoption re-examined proposal by Commission	COM(93) 241 final – SYN 353	Re-examined proposal for a Council Directive relating to medical devices
01-06-1993	Transmission re-examined proposal to Council		
01-06-1993	Transmission re-examined proposal to EP		
14-06-1993	Formal adoption by Council	OJ L 169, 12.7.1993, p. 1-43	Council Directive 93/42/EEC of 14 June 1993 concerning medical devices

Table modified from:  
[http://ec.europa.eu/prelex/detail\\_dossier\\_real.cfm?CL=en&DosID=104269](http://ec.europa.eu/prelex/detail_dossier_real.cfm?CL=en&DosID=104269)

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