Comparison of the Regulatory Environment to Authorise so-called Combination Products Consisting of a Drug and a Medical Device in the US and the EU

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Remarks

As the denotation of certain technical terms is different in US and EU but have similar meaning, the most common term will be used for descriptions concerning both regions with the following exception: if the term is directly used in relation to cited or referenced law or guideline the regional appropriate term is applied. Drug is synonymously used for medicinal product; device for medical device; combination product for drug-device combination product; medical products cover articles regulated as drug, biologic or device.

The thesis is written in British English with exception of cited US American references.

LIST OF ABBREVIATIONS

AAMI	Association for the Advancement of Medical Instrumentation
ACS	Adsorbable Collagen Sponge
ADME	Absorption, Distribution, Metabolism and Excretion
AIMD	Active Implantable Medical Devices Directive
ANDA	Abbreviated New Drug Application
ASTM	American Society for Testing and Materials
ATC	Anatomical-Therapeutic-Chemical
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte; Federal Institute of Drug and Devices (Germany)
BLA	Biologics License Application
BMS	Bare Metal Stents
CA	Competent Authority
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CE	Conformité Européenne (European Conformity)
CEN	Comité Européen de Normalisation (Eur. Committee for Standardization)
CEP	Certificate of Suitability
CETF	Medical Devices Clinical Evaluation Task-Force
CGMP	Current Good Manufacturing Practice
CFR	Code of Federal Regulation
CHMP	Committee for Medicinal Products for Human Use (previous CPMP)
CMC	Chemistry, Manufacturing and Control
CTD	Common Technical Document
DCP	Decentralised Procedure
DDD	Degenerative Disk Disease
DES	Drug-eluting Stents
DMF	Drug Master File
EC	European Commission
EDQM	European Directorate for the Quality of Medicines
EMEA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FAQ	Frequently Asked Questions
FD&C Act	Food, Drug and Cosmetic Act

FDA	Food and Drug Administration
FDAMA	Food and Drug Administration Modernization Act
GCP	Good Clinical Practice
GHTF	Global Harmonization Task Force
GMP	Good Manufacturing Practice
GLP	Good Laboratory Practice
ICA	Intercenter Agreements
ICH	International Committee of Harmonization
IDE	Investigational Device Exemption
IFG	Informationsfreiheitsgesetz (German Freedom of Information Law)
IMB	Irish Medicines Board
INN	International Nonproprietary Names
IND	Investigational New Drug
ISO	International Organisation for Standardisation
ITF	Innovative Task Force
IVD	*In vitro* Diagnostics
HAS	Human Serum Albumin
MAA	Market Authorisation Application
MD	Medical Devices
MDEG	Medical Device Expert Group
MDUFMA	Medical Device User Fee and Modernization Act
MEDDEV	Medical Devices (Guidance document)
MEB	Medicines Evaluation Board (The Netherlands)
MOA	Mode of Action
MPA	Medical Products Agency (Sweden)
MS	Member States
MRP	Mutual Recognition Procedure
NME	New Molecular Entity
NB	Notified Bodies
NBOG	Notified Body Operation Group
NCA	National Competent Authority
NDA	New Drug Application
NOAEL	No Observed Effect Level
NtA	Notice to Applicants
OCP	Office of Combination Products
PAR	Public Assessment Report

PHS Act	Public Health and Welfare Service Act
PK	Pharmacokinetic
PMA	Premarket Application
PMMA	Polymethyl Methacrylate
PMOA	Primary Mode of Action
PTCA	Percutaneous Transluminal Coronary Angioplasty
Q&A	Questions and Answers
QA	Quality Assurance
QS	Quality System
RFD	Requests for Designation
SDS PAGE	Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis
SOP	Standard Operation Procedure
SME	Small and Medium-sized Enterprises
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
U.S.C.	United States Code
US	United States of America
USP	US Pharmacopeia
WHO	World Health Organization

1. INTRODUCTION

The thesis intends to provide an overview of the regulatory environment for the development and authorisation of medical products combining drugs with devices complemented by marketed product examples. These so-called combination products are licensed and regulated under the provisions of pharmaceutical or medical device legislation. Combination products are a heterogeneous product class; well-known examples represent prefilled syringes, antibiotics-containing bone cements, coated catheters, (not reusable) integral drug-containing delivery systems as insulin pens or inhalators and coronary drug-eluting stents (DES). Currently DES are the most successful combination products. In 2006, five years after placing the first DES on the market around four million DES were implanted worldwide[1].

The rationale for any combination of medical products is to improve safety, efficacy or to create new therapeutic opportunities under this provisions. The benefit of the drug-device combination product concept is based on combined pharmaceutical properties with physical/chemical means and vice versa to achieve the intended therapeutic purpose. Mostly this is found realised by targeted drug delivery systems to improve the side effect profile and patient compliance, by ancillary pharmaceutical properties which support the therapeutic effect of the device or by a joint cumulative action of combined components to attain the desired action.

The thesis starts with an overview on the legal basis, definitions and justification of combination products, regulatory procedures and relevant guidelines for the development both in the United States (US) and European Union (EU). After providing the regional backdrop a selection of marketed combination products will be presented for both regions as case reports. Publicly available assessment reports and labelling information of marketed combination products will be used to highlight differences of the regulatory environment and product evaluation by health authorities. In addition, as the information on combination products authorised as medical devices and consultation procedures is limited or not published due to current applicable confidentiality provisions in medical device legislation in the EU a survey was performed to request missing information from six national agencies in the EU and the central European Medicines Agency, EMEA. Based on the legal provisions and guidelines, the assessment reports, the labelling of marketed combination products and the results of the survey will be used to draw up a conclusion onto current authorisation requirements. Identified regional differences for the authorisation of combination products are used to provide an exemplary present status and an outlook on future regulatory developments. The thesis may be used as a starter to get a basic principle overview on the legal provisions and requirements of combination products from pharmaceutical developer's perspective and to aid adequate development by a company unfamiliar with the particularities of this product type.

2. COMBINATION PRODUCTS

The authorisation of combination products is based on regional differently legislation, provisions and guidelines which could lead to the consequence that a product is regulated as drug in the EU and as medical device in the United States (US) which make parallel developing of such a product in these two regions to a challenging task. However, apart

from the distinct legislation, different definitions and regulatory guidelines, both regions also share some similar rules and provisions as basic principles.
In general, for both regions combination products can be characterized as a product combining drugs and medical devices used for the prevention, treatment, healing or diagnosis of diseases or body function. The regulation for licensing and postmarketing measures for combination products follow either the one applicable for drugs or medical devices depending on the primary mode of action to achieve the intended (therapeutic) purpose. Consequently, the lead review and licensing will be with the relevant drug or device authority and the ancillary component will be evaluated by the respective other authority, during a premarket consultation procedure, if required. However, next to a common basis, also fundamental regional differences exist. The definition of a drug-device combination product is clearly defined and commonly used in the US whereas in the EU it is not. In the EU, the term combination product is rather related to fixed combination, a combination of two or more active ingredients in one formulation. Fixed combination of active pharmaceutical ingredients and combination of two devices will not be considered in the thesis as they do not apply to the definition addressed in the thesis. A conclusive overview on different categories of combined medical products and corresponding terminology in the EU and the US is provided in Table 1.

The term “combination product” is defined in US regulations as a single entity comprised of two or more regulated components combined as a drug-device, biologic-device, drug-biologic, or drug-device-biologic. Depending on the combined components and their primary mode of action the combination product will be either regulated as drug, biologic or device. In the US combining of drugs, biological products and devices by crosslabelling or copackaging of the components are considered as combination products as well.
No definition of the term “combination product” used in the context of the thesis is given in the European pharmaceutical legislation but two basic two-tiered approaches are defined in the medical device legislation. (i) Drug delivery devices are regulated as devices but if, however, it is forming a single integral product it becomes a medicinal product. (ii) Devices incorporating medicinal substances with ancillary action are regulated as medical device. For simplification and consistency reasons the term combination product will be used throughout this thesis in the sense of drug-device combination for the general chapters and also applies to the EU and the US region, if not indicated otherwise.

The number of guidelines interpreting the legal provisions of combination products in particular is limited. Hence, to a certain extent depending on the product and components, the development and dossier documentation requirements of combination products must follow both, the applicable pharmaceutical guidelines and essential requirements for devices by recognised standards. The review of the dossier will be either performed by the health authorities for drugs or devices under consideration of the opinion of the regulatory counterpart in course of a consultation procedure if required and applicable. An overview of the regulatory environment of combination products in the US and EU is provided in appendices 7.1 and 7.2.

Looking at the opportunities and market for combination products, both have grown continuously in the recent years. Moreover, human tissue engineered products, nanotechnology and biomarkers are likely to be incorporated in future. In the past

combination products were often relative simple products such as drug delivery systems (prefilled syringes or transdermal patches) for targeted administration of drugs[2] or drug-coated devices (heparin-coated catheter or steroid tipped pacing wires) to improve intended purpose of the device. Innovative new technologies in the combination product sector offer the chance for improved therapies or even the cure of diseases with currently unmet medical need. At present, existing technologies have been modernized/improved e.g. by drug-eluting stents to prevent restenosis of artheriosclerotic coronary vessel or matrices impregnated with osteoinductive proteins to replace autografts in orthopedic surgery. Prospectively the innovation will continue with products such as implantable devices with feedback systems using biosensors or human tissue engineered products incorporated in devices are already being developed. In the EU, by adoption of the new regulation on advanced therapies, a combined advanced therapy medicinal product was recreated combining tissue/cells with devices to build a new regulatory framework.

Table 1: Overview and terminology of different categories of combination products

Combination Products[A]					
	parts/ components/ constituents	**EU**		**US**	
		Product type	**Lead review**	**Product type**	**Lead review**
1a	**Drug-Device**	Medical device and medicinal product form a single integral product[B] ⇒ Medicinal product	NCA, EMEA	Drug-device combination product ⇒ Drug	CDER
		Or		Or	
1b		Medical device containing a medicinal product with ancillary action ⇒ Medical device	Notified Body	Device-drug combination product ⇒ Device	CDRH
2a	**Biologic-Device**	Medical device and medicinal product form a single integral product[B] ⇒ Medicinal product	EMEA	Biologic-device Combination product ⇒ Biologic	CBER
		Or		Or	
2b		Medical device containing a medicinal product with ancillary action ⇒ Medical device	Notified Body	Device-biologic combination product ⇒ Device	CDRH
3a	**Drug-Biologic**	Fixed combination ⇒ Fixed combination medicinal product[C]	NCA, EMEA	Drug-biologic combination product[D] ⇒ Drug	CDER
				Or	
3b		Fixed combination ⇒ Fixed combination medicinal product[C]	NCA, EMEA	Biologic-drug combination product ⇒ Biologic	CBER

[A] highlighted in grey different categories of combination products which will be presented in the thesis
[B] which is intended exclusively for use in the given combination and which is not reusable
[C] Art 10b of Directive 2001/83/EC
[D] for example a monoclonal antibody combined with a chemotherapeutic drug

Combination Products[A]					
	parts/ components/ constituents	EU		US	
		Product type	Lead review	Product type	Lead review
4	Drug-biologic-device	No combination		Drug-biologic-device combination product ⇒ any of above	CDER, CBER, or CDRH
5	Cell/Tissue-Device	Cellular or tissue part incorporate as integral part a device ⇒ Combined advanced therapy medicinal product [A]	EMEA	Combination product [B] ⇒ tissue-device, tissue-drug	CDER, CBER, or CDRH
6	Drug-Drug	Fixed combination ⇒ Fixed-combination medicinal product[C]	NCA or EMEA	Fixed combination [D] ⇒ Drug	CDER
7	Device-Device	Medical device	NB	Device	CDRH

Table 1. Seven different product combinations are listed in the table, differentiated by the region and kind of combination indicating the type of authorisation and reviewing agencies or Centers. The categories 1 and 2 (both EU and US), as well as 3 and 4 (US only) are drug/biologic-device combination products in context of this thesis. The terminology of drug-device combination products is regionally different. In the EU combination products are either a medical device containing a medicinal product with ancillary action or a medicinal product, which forms a single integral product, not reusable and only intended to be used in the given combination. The latter is regulated as medicinal product. In the US a combination product is defined as a single entity comprised of two or more regulated components combined as a drug-device, biologic-device, drug-biologic, or drug-device-biologic, which will be either regulated as drug, biologic or device depending on combined components and the primary mode of action of the combination product. Only combination products regulated as such in their region will be described in this thesis and are marked in the table in grey. In addition, fixed combination, and advanced therapies with cell/tissue-devices are indicated for information but beyond the scope of this thesis. Note: listing of possible combination does not claim to be exhaustive.

2.1 Definition of Combination products in US

The term "combination product" is precisely defined in the Code of Federal Regulation (CFR) 21CFR chapter I part 3 section 3.2(e) [3] as a single entity comprised of two or more regulated components combined as a drug-device, biologic-device, drug-biologic, or drug-device-biologic. The premarket review and licensing will be performed by one of three US health agency's evaluation Centers for human medical products.

2.1.1 Legislation of Drugs, Biologics and Devices in the US

Marketing of drugs and devices for human and veterinary use is restricted to authorised products according to applicable US acts and regulations. US laws are adopted by the legislative branch in the Congress and published in United States Code (U.S.C.). Regulations are adopted by the executive branch (Department and Agencies) and are

[A] Art. 2 1(d) of Regulation (EC) 1394/2007
[B] no official source for definition of HCT/P containing combination products could be found
[C] Art 10b of Directive 2001/83/EC
[D] 21CFR300.50

published in the CFR. The relevant legislation for drugs, biological products (biologics) or medical device in US is laid down in Federal Food, Drug and Cosmetic Act (FD&C Act), Public Health and Welfare Service Act (PHS Act) and applicable regulations. Both acts and regulations have legal binding character but regulations provide more detailed information than the law. Relevant guidances are issued by individual agencies to interpret laws and reflect current regulatory thinking; they are not binding but indicate the expectations of regulatory agencies. Non-binding interpretation of law is also published by dockets in the Federal Register.

- FD&C Act Chapter V –Drugs and Devices Subchapter A --Drugs and Devices - Part A - Drugs and Devices [4].
- CFR Title 21 Subchapter D --Drugs for Human Use Part 314 Applications for FDA to Market a New Drug[5]
- CFR Title 21 Subchapter H --Medical Devices Part 814 Premarket Approval of Medical Devices[6]

Licensing of Biologics are regulated by separate and parallel law and regulation:

- PHS Act Title 42 Chapter 6a Subchapter II Part F Section 262 Regulation of biological products[7].
- CFR Title 21 Subchapter F – Biologics Part 601 Licensing[8]

There is a long history of amendments to the FD&C Act, which should be taken into consideration. Three amendments with implication for combination products are given below:

- Safe Medical Devices Act of 1990 [9]
- Food and Drug Administration Modernization Act (FDAMA) of 1997 [10]
- Medical Device User Fee and Modernization Act (MDUFMA) of 2002[11]

2.1.2 What is a Combination Product in the US?

With the amendment of the FD&C Act by the Safe Medical Devices Act of 1990 the Food and Drug Administration (FDA) secretary was enforced to designate products that are combinations of drug, device or biological product to the relevant Center for premarket reviewing according to "the primary mode of action" (PMOA). Subsequently, by 21CFR3 Section 3.2(e)[3] a combination product was defined to include:

(1) "A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity;"

(2) "Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;"

(3) "A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, …or"

A fourth claim covers investigational combination products. Prior to 1990 combination products were regulated on a case by case decision.

Drug-drug, device-device, or biologic-biologic combinations do not meet the definition of a combination product. A single formulation containing two or more drugs is regulated as a fixed combination[12]. *In vitro* diagnostic tests are no combination products either. To illustrate the different combination products defined under 21CFR3.2(e) FDA provides the examples in their Q&A document [13] as listed in Table 2. However, the definition and examples in the CFR does not provide the appropriate licensing route. This could be taken from intercenter agreements (ICA), jurisdictional updates or published designation decisions (chapter 2.1.3).

Table 2: Examples of combination products in the US

Definition	Examples of combination products
21CFR3.2(e)(1):	• Monoclonal antibody combined with a therapeutic drug • Device coated or impregnated with a drug or biologic o drug-eluting stent; o pacing lead with steroid-coated tip; o catheter with antimicrobial coating; o condom with spermicide o skin substitutes with cellular components; o orthopedic implant with growth factors • Prefilled syringes, insulin injector pens, metered dose inhalers, transdermal patches
21CFR3.2(e)(2):	• Drug or biological product packaged with a delivery device • Surgical tray with surgical instruments, drapes, and lidocaine or alcohol swabs
21CFR3.2(e)(3) or (e)(4):	• Photosensitizing drug and activating laser/light source • Iontophoretic drug delivery patch and controller

Table 2: Different examples of combination products categorised according to the definitions of combination products in the CFR, which does not specify the licensing route.

To determine the composition of a combination product the single components must be defined to statutory terms of drug, biologic or device. The terminology of drug and device are defined in FD&C Act Section 201 (g) and (h). Drugs and devices are separately defined but share similar clauses. The term „drug" is defined as an article and the term "devices" as an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article. Both drugs and devices are (i) officially recognized in the US Pharmacopeia (USP) or National Formulary and (ii) intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease (or other conditions) in man or other animals and (iii) intended to affect the structure or any function of the body of man or other animals. The main difference in the definition of drugs and devices is based in the clause in Section 201 (h)(3) that the principal intended purpose of the device as being not chemically or dependent upon being metabolised.
With regard to this key determinant it is interesting to note, that there are continued activities of a working group exploring the development of a definition of "chemical action," contained in the statutory definition of a device. The clarification of the term should be helpful to sponsors and FDA in determining whether a product meets the definition of a drug or a device[A].

[A] http://www.fda.gov/oc/combination/report2006/activities.html [21.04.2008]

Biological products are defined in the PHS Act Sec. 262(a) as a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine for prevention, treatment, or cure of a disease or condition of human beings.
For the sake of completeness, some products are used together in a way that does not meet the regulatory definition of a combination product, but that may raise similar development or regulatory issues as the concomitant use of medical products that are not "individually specified" in the product labelling as well as combinations with other types of FDA-regulated articles, such as dietary supplements, cosmetics or foods[A].

2.1.3 FDA Drugs, Biologics and Device Evaluation Centers

Table 3: FDA Centers for medical products for human use

	CDER	CBER	CDRH
Products	• Drugs • Therapeutic proteins: o Monoclonal antibodies *in vivo* use o Cytokines, enzymes, novel proteins o Immunomodulators o Growth factors	• Blood and blood products • Vaccines and vaccine safety • Cellular and gene therapies • Tissues • Xenotransplantation • Devices • Allergenics	• Medical devices • Radiation-emitting products
Scope of the Center	• New drug development & review • Generic drug review • OTC review • Post drug approval process	• Review new biol. products • Surveillance biol. products .. and more	• Device review to research or market • surveillance • GMP
Reviews & Approvals	• NDA • BLA • ANDA	• Biological Device • BLA • Biological NDA and ANDA	• PMA (Class III) • 510(k) (Class II) • Class I

Table 3: Regulated products, scope and types of licenses granted by the three medical Centers. Review and approvals of investigational drugs, biologics and devices not indicated.

The US Food and Drug Administration (FDA) is the scientific, regulatory and public health agency which authority is derived from multiple laws and regulation (e.g. FD&C Act, PHS Act, etc.). The FDA consists of six Centers of which three Centers, the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER) and the Center for Devices and Radiological Health (CDRH) are responsible for licensing and post approval activities of drugs, biologics, and devices for human use.

As more drug and biological products are developed for a broader range of illnesses the FDA initiated the transfer of certain product oversight responsibilities from the CBER to the CDER which provided the opportunity to further develop and coordinate scientific and regulatory activities for both efficient and consistent agency action[14]. On June 30, 2003, FDA transferred most of the therapeutic biological products that had been reviewed and

[A] http://www.fda.gov/oc/combination/other_combinations.html [12.04.2008]

regulated by the CBER to the CDER. CDER now has regulatory responsibility, including premarket review and continuing oversight, over the transferred products[15].

2.1.3.1 Office of Combination Products

The understanding of the regulatory particularities of combination products and different regional requirements have a decisive impact for a conclusive and successful development. Frequently innovation goes along with small enterprises or spin-offs, which have a vital interest to get a grip on regulatory implication of their product, as they have neither a broad development department nor sufficient financial resources for a delayed authorisation.
By the Medical Device User Fee and Modernization Act (MDUFMA) in 2002 FDA was requested by the Congress to establish the Office of Combination Products (OCP) to ensure that the regulation of combination products is clear, consistent and predictable. Six specific duties were assigned to this office. The OCP is responsible for assignment of products to one of the agency's three human medical product Centers, CBER, CDER or the CDRH that will be reviewing the products. Secondly, the OCP is coordinating the timely and effective premarket review and coordinating reviews involving more than one agency Center. Moreover, the OCP is ensuring the consistency and appropriateness of postmarketing regulations, is involved in assignment of dispute resolution, is reviewing and updating agreements, gives guidance to the assignment of combination products and issues annual reports to the Congress on the impact of the office. Aside from that, the OCP can also be contacted for informal consultations.
The assignment and reviewing of the combination products by one of the Centers will be based on the primary mode of action (PMOA). The 21CFR part 3 Section 3.2(k) also defines a mode of action (MOA) because combination products will typically have more than one mode of action but the relevant decision-making criterion remains to be the PMOA, which is defined in 21CFR part 3 Section 3.2(m) as:

- *"Primary mode of action is the single mode of action of a combination product that provides the most therapeutic action of the combination product. The most important therapeutic action is the mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product."*

If the most relevant therapeutic action of a combination product cannot be determined with reasonable certainty, the assignment is based on a two-tiered algorithm which is part of the proposed regulation. In some situations, it is not possible to determine, with reasonable certainty, which one mode of action will provide a greater contribution than any other mode of action to the overall therapeutic effects of the combination product (21CFR Section 3.4(b)). In such a case the combination product will be assigned to the Center that regulates other combination products that present similar questions of safety and effectiveness or the most expertise to the most significant questions, if the first clause is not applicable. In August 2005 by the Federal Regulation Dockets No. 2004N-0194[16] the final rule of 21CFR3 "Definition of Primary Mode of Action of a Combination Product" was published including comments and examples for the assignment of combination products which should be used for interpretation of the regulation and to aid decisions on borderline cases of combination products.
Before establishing the MDUFMA in 2002, which describes the principle of the PMOA and transfer of the assignment to the OCP, the regulatory responsibility for cases of doubt

of drugs, devices or combination products was governed by a decision of the ombudsman and by intercenter agreements (ICA) which still provide non-binding guidance on some combination product assignments. Since the ICAs had already been issued in 1991 and not been updated, FDA's current thinking is more reflected by jurisdictional updates of the classification and assignment of product classes, jurisdictional determination of 140 capsular descriptions of selected Requests for Designation (RFD) decisions, and redacted RFD decision letters[A]. If the classification or assignment of a combination product is unclear or in dispute a RFD should be requested early in the product's development as soon as sufficient data are available and before the NDA is filed.
Coronary DES represent a descriptive example on practicing the PMOA principle, RFD decisions and ICAs. After receiving several RFDs for drug-eluting cardiovascular stents the FDA has issued a jurisdictional update by stating that the PMOA of DES is related to the physical functions of the uncoated stent, while the drug component has a secondary role in preventing restenosis. This is consistent with the basic ICA between the CDRH and the CDER assigning the review responsibility to the CDRH for devices incorporating a drug component with the combination product having the primary intended purpose of fulfilling a device function. Accordingly, the FDA has assigned the responsibility for premarket review and regulation of DESto the CDRH and clarified that for human drugs Current Good Manufacturing Practices (CGMP) applies to the manufacture of the drug component of the combination product[17]. However, drug-eluting devices to prevent restenosis of vascular grafts[A] or drug-eluting disc/wafers for chemotherapy of brain tumors are regulated as drugs[16].
The FDA OCP website[A] is a useful source for combination product developers by providing current information on combination products including guidance and FAQ documents, examples for approved combination products and jurisdictional updates.

Table 4: **Selected guidance documents for Combination Products in US**

Author & Release	Title of the guidance
FDA OCP, CDER, CBER, CDRH, Sep 2006	Guidance for Industry and FDA Staff. Early Development Considerations for Innovative Combination Products[18]
FDA OCP	Submission and Resolution of Formal Disputes Regarding the Timeliness of Premarket Review of a Combination Product[19]
FDA OCP Aug 2005	Guidance for Industry and FDA Staff. How to Write a Request for Designation (RFD)[20]
FDA OCP Sep 2004	Draft: Guidance for the Industry and FDA. Current Good Manufacturing Practice for Combination Products[21]

Only few guidance documents refer directly to the scientific and technical issues to be considered when drug, device, and/or biological product constituents are combined as a combination product[B, 18]. As an aid to sponsors and manufacturers seeking to develop a combination product, the OCP has compiled a list of guidance documents on its website selected from those issued by CBER, CDER and CDRH that could be of interest for the applicant [B]. Some documents are general in nature to explain the regulatory approaches of individual FDA review Centers, while others specifically address combination products or cover a broad product class but address combination product issues within the document.

[A] http://www.fda.gov/oc/combination/ [12.01.2008]
[B] http://www.fda.gov/oc/combination/guidance.html [12.01.2008]

The listed documents are intended only to serve as a starting point for obtaining information on the regulation of combination products (Table 4). The guidance documents for the development and testing of drugs, devices, and biological products as individual products should be taken into consideration if otherwise only insufficient information how to develop the combination product could be obtained.
A single marketing application is sufficient for most combination products. However, a sponsor may choose to submit two applications in order to receive some benefit (e.g., new drug product exclusivity, orphan status). In other cases, FDA may determine that two separate marketing applications are necessary, when one of the individual constituent parts of a combination product is already approved for another use. FDA encourages applicants to discuss this issue with the lead reviewing Division and/or the OCP if applicable[18].

2.1.3.2 Intercenter Consultation Process

The regulatory responsibility and lead review for the combination product will be assigned by the OCP to one of the FDA's three human medical product Centers, CBER, CDER or CDRH according to the combination product's PMOA. The responsible lead Center often consults or collaborates with other agency Centers to review the information in the submitted dossier for market authorisation or investigational application (IND, IDE) if a required expertise is not resident in the reviewing Center. The intercenter consultation or collaboration process is detailed for FDA employees by a Standard Operating Procedure[22] (SOP) issued by the OCP to ensure an appropriate handling, timelines and consistency of the intercenter reviews of combination products. The legal provisions of the reviewing lead Center remain unchanged by the consultation with regard to timeliness and responsibility of the review. A consultative review of a premarket approval (PMA) application or investigational application of products other than combination products could be performed if required. An example for the composition and tasks of a combination product review team is given by the CDRH/CDER team evaluating drug-eluting stents[23] (Table 5).

Table 5: CDRH/CDER review team for drug-eluting stents

CDRH Review Team	CDER Review Team
Lead Reviewer	Project Manager
Clinical Reviewer	Clinical Reviewer
Engineer review team	Drug review team
• Mechanical • Electrical/software • Biocompatibility/sterility/shelf life	• Chemistry • Pharmacology • Toxicology • Microbiology
Branch chief	Supervisory Chemist
Deputy division director	Supervisory pharmacologist
Other division senior management	Other division senior management

Table 5: The CDRH/CDER review teams, which have been established at the FDA in 2000-2001 to meet the growing demand for reviewing drug-eluting stent applications. Currently, the CDER has a dedicated combination product team based in the Cardiorenal Drugs devision[23].

It is important to engage another Center in a consultative or collaborative review as early in the review process as possible. In the best case, intercenter interaction on combination products should begin during the pre-submission process. The structure of the consultation

dossier is obviously not strictly defined and it was criticized that the information covering the device portion is often scattered in many different sections of the submission, and the sponsor is advised to provide a stand-alone section of the NDA or BLA containing all device-related information, which would also facilitate the consulting process [A].

2.2 Definition of Combination Products in the EU

The term combination products is differently defined and used in European pharmaceutical legislation as combination of two or more active substances in a single formulation also named fixed combination medicinal product[B] [C]. However, the scope of the thesis is the regulatory environment of combination products consisting of a drug and medical device constituent.

2.2.1 Legislation of Medicinal Products and Medical Devices in the EU

Basically, the definition of drug-device combination products originates from and is part of two European Council Directives on active implantable medical devices (AIMD) and medical devices (MD), both last amended by Directive 2007/47/EC[24] in September 2007. The MD Directives were developed and adopted together with a third Directive on *in vitro* diagnostics (IVD) between 1987 and 1998[D] to harmonise the essential requirements and standards of MDs, and to improve the industrial manufacturing as initiated by the Council Resolution on the New Approach[25]. The Directives represent the common legal basis for placing MDs onto the European market after their transposition into national law of the Member States (MS).

- Council Directive AIMD 90/385/EEC[26]
- Council Directive MDD 93/42/EEC[27]
- Directive IVD 98/79/EC[28]

The confirmation of conformity of a MD with the legal requirements in one European country allows the marketing of the product in the whole EU after affixing the CE (Conformité Européenne) marking. By the need to define MDs, a demarcation between MDs and medicinal products was established and a definition of products combining medicinal products and MDs was included which provides the primary legal basis for their regulation.
The Council Regulation (EEC) No 2309/93[29], updated by Regulation (EC) No 726/2004 [30], represents the currently valid legislation for the authorisation and supervision of medicinal products for human use in the European Community and is the legal basis for the pharmaceutical Directive 2001/83/EC[31] (Community Code).

- Regulation (EC) No 726/2004
- Directive 2001/83/EC

Very recently, with the amendment of the Directive 2001/83/EC and the Regulation (EC) No 726/2004 by the Regulation (EC) No 1394/2007[32] on advanced therapies among gene therapy and somatic cell therapy medicinal product and tissue engineered product, a new

[A] http://www.fda.gov/oc/combination/perspectives.html [17.03.08]
[B] Art. 10b of Directive 2001/83/EC as amended
[C] CPMP/EWP/240/95 Rev. 1 Draft Guideline on Fixed Combination Medicinal Products
[D] DGRA presentation 2005 Dr. Ehrhardt Anhalt

type of combination product was created for the authorisation of cells or tissues containing devices.

2.2.2 What is a Combination Product in the EU?

The definitions of drug-device combination products represent rather two basic two-tiered approaches, drug delivery devices and devices incorporating medicinal substances with ancillary action, leading to two types of combination products and three possible regulatory authorisation pathways. In Directive 93/42/EEC[A] it is stated in;

- Art. 1(3) *"…for devices intended to administer a medicinal product.., that the device shall be governed by the present Directive,..;"*
- *"If, however, such a device… and the medicinal product form a single integral product which is intended exclusively for use in given combination and which is not reusable, that single product shall be governed by Directive 2001/83/EC. …."*
- in Art. 1(4) *"Where a device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product within the meaning of Article 1 of Directive 2001/83/EC and which is liable to act upon the body with action ancillary to that of the device, that device must be assessed and authorized in accordance with this Directive."*

In other words, drug-device combination products are either regulated (i) as separate products each under the relevant legal provisions in case of medicinal products administrated by drug delivery devices, (ii) as medicinal product if, however, they form a single integral product intended for use in a given combination or (iii) as devices, if they incorporate a medicinal substance with ancillary action. The latter phrase should be completed by the legally non-binding comment given in the guideline MEDDEV 2.1/3: as soon as it is not more ancillary with respect to the principal purpose of a product, the product becomes a medicinal product.
With the amendment of both Council Directives by the Directive 2000/70/EC in November 2000 and insert of Art. 1 Section 4 a, the legal provisions were also made to include human blood derivatives as constituent of the device with ancillary action as well. According to Art. 1 sentence 5 (f) (g) of 93/42/EEC the following products are excluded from the MD Directives: Transplants or tissues or cells of human origin (except for those listed in sentence 4a) and those of animal origin, unless a device is manufactured utilizing animal tissue which is rendered non-viable or non-viable products derived from animal tissue.
Before a proper designation of the regulatory pathway of the product can be made the components must be classified as medical device or medicinal product according to their definition laid down in Council Directive 93/42/EEC Art. 1 sentence 2(a) and Directive 2001/83/EC Art. 1 sentence 2(a)(b) as amended by Directive 2004/27/EC[33], respectively, and detailed in Table 6. The key question for a correct assignment concerns, whether the component exerts its principal intended action by pharmacological, immunological or metabolic means and determination of the component's properties and nature with regard to this will turn the balance for the categorisation as medicinal substance or as medical device. Important to note here is, that in the US drugs are also defined by demarcation from devices but, however, this drugs simply need to show properties of chemical action and metabolic degradation (chapter 2.1.2).

[A] Art. 1(3) second paragraph in 90/385/EEC not stated and subsequently no option for AIMD

Table 6: Definition of medical devices and medicinal products in the EC Directives

Dir. 93/42/EEC Art. 1 sentence 2(a)	Dir. 2001/83/EC Art. 1 sentence 2(a)(b)
"*medical device means any instrument, apparatus, appliance, software, material or other article whether used alone or in combination…: …and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means;"*	*(a) Any substance or combination of substances … for treating or preventing disease in human beings; or* *(b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting and modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis."*

Another element to alleviate the decision on which legislation is applicable in special cases was introduced with the amendment of the Council Directive 93/42/EEC by Directive 2007/47/EC in September 2007, which specifies in Art. 1 sentence 5(c)[A]:

- "*In deciding whether a product falls under that Directive or this Directive particular account shall be taken of the principal mode of action of the product*".

In particular, if the medicinal product has ancillary action to that of the device, the determination of the principle mode of action could become an important decision-making criterion. Summarising it could be stated, if the principal mode of action of the combination product for intended use could not be described as pharmacological, immunological or metabolic action the regulatory pathway to licence this combination product will follow applicable Directives and guidelines for medical devices. By the amendment of the European MDs Directives, the rationale for a decision on borderline cases converged to the existing US legislation with the PMOA as described in chapter 2.1.3.1.

Another justification for classification and regulation of drug-device combination product as medicinal products can be drawn from Art. 2(2) of the Directive 2001/83/EC amended by 2004/27/EC, where it is stated:

- *"In cases of doubt, where, taking into account all its characteristics, a product may fall within the definition of a "medicinal product" and within the definition of a product covered by other Community legislation the provisions of this Directive shall apply."*

The rationale for the above-mentioned clause in the amendment came from the emergence of new therapies and the growing number of so-called "borderline" products between the medicinal product sector and other regulated products, which require a modified definition for medicinal products by the type of action that the medicinal product may exert on physiological functions[33]. However, if a product could be clearly defined be other product categories Directive 2001/83/EC does not apply. The Medical Device Expert Group[B] (MDEG) regularly confers and provides advice on borderline and classification issues[C] to support case-by-case decision by concerned national competent authorities (CA).

[A] Art. 1 6 (a) 90/385/EEC, respectively
[B] chaired by the Commission and composed of representatives from all MS, EFTA and other stakeholders
[C] http://ec.europa.eu/enterprise/medical_devices/borderline_classification_en.htm [16.04.2008]

However, the conclusions are not legally binding since only the European Court of Justice can give an authoritative interpretation of the Community law.

With the amendment of Directive 2001/83/EC and Regulation (EC) No 726/2004 by Regulation (EC) No 1394/2007 on advanced therapies, a new type of combination product of cells or tissues containing devices was introduced and termed as „combined advanced therapy medicinal product“. In 2006 the Innovative Task Force (ITF) was established as an internal EMEA horizontal cross-sectorial group, for the EMEA-wide coordination in the areas of interest, focussing on emerging therapies and borderline products and to providing a forum for an early dialogue with applicants in particular for Small and Medium-sized Enterprises (SMEs)[34]. The ITF provides regulatory and scientific advice on new medicinal products for emerging therapies and borderline products and their eligibily for EMEA procedures. Next to gene therapy products, novel routes of administration and delivery systems, new development strategies or manufacturing approaches it should be emphasised that borderline therapeutics including the combination of medicinal products and devices are within the scope of ITF. Regarding the coordination of the applicable regulatory pathway the ITF and OCP have similar function as long as the product are eligible for EMEA procedures.

2.2.2.1 Two Types of Combination Products in the EU

A comprehensive source for interpretation of the definitions and provisions of the MD directives are provided by MD guidelines MEDDEV, in particular 2.1/3, 2.4/1 and 2.1/1. The main categories of combination products as defined in the MD Council Directives 93/42/EEC and 90/385/EEC are further on specified and exemplified in the MEDDEV 2.1/3 rev 2 - guideline. The following examples in Table 7 were selected for illustration and should be taken into consideration in comparison to the definition and examples according to the US regulation presented in Table 2.
The intrathecal infusion pump Medtronic SynchroMed II and ziconotide (Prialt®) are examples to administer a medicinal product by a CE marked drug delivery device (Table 7 a). In addition, the metallic scaffold LT-CAGE™ and InductOS® (chapter 3.2.3.2) also represent a drug delivery systems whereas InductOS® itself, containing a carrier and growth factor, is an example for an integral product (Table 7 h). Septocoll®, a gentamicin-containing collagen fleece is licensed as Class III medical device containing a medicinal product with ancillary action (Table 7r; chapter 3.2.5.2), which can also be authorised as medicinal product if the primary action is controlling the infection (Table 7k). DESsuch as CYPHER™ or TAXUS™ (chapter 3.2.1) are indicated for the treatment of coronary artery lesions, which represent medical devices containing a medicinal product with ancillary action.
The guideline MEDDEV 2.1/3 outlines that the principal intended action of a product may be deduced from the proposed labelling, claims and scientific data regarding the mechanism of action. However, it is not possible to place the product in contradiction to current scientific data and manufacturers should justify scientifically their rationale for classification of borderline products.

Table 7: Categories and examples of combination products in the EU

Definition/Category	Examples of combination products in MEDDEV 2.1/3
Art. 3 of Dir. 93/42/EEC Drug delivery system	a) implantable infusion pump, b) iontophoresis device, c) nebulizer, d) syringe, jet injector.
Art. 3 of Dir. 93/42/EEC Medical device and medicinal product form a single integral product[A]	e) aerosols containing a medicinal product, f) nebulizers precharged with a specific medicinal product, g) patches for transdermal drug delivery, h) plastic beads containing antibiotic for treating bone infections, or a matrix to release osteoinductive proteins i) intrauterine contraceptives releasing progestogens, j) single-use disposable iontophoresis devices incorporating a medicinal product, k) wound dressings containing an antimicrobial agent with the primary action of controlling infection,
Art. 4 of Dir. 93/42/EEC Medical devices incorporating medicinal substances with ancillary action	l) catheters coated with heparin or an antibiotic agent, m) bone cements containing antibiotic, n) blood bags containing anticoagulant or preservation agents, o) haemostatic devices with collagen p) condoms coated with spermicides, q) electrodes with steroid-coated tip, r) wound dressings with antimicrobial agent, s) intrauterine contraceptives containing copper or silver

Table 7: Categories of combination products as defined in the MD Council Directives 93/42/EEC and 90/385/EEC which are exemplified in the MEDDEV 2.1/3 rev 2 - guideline. The category of the combination product implies the regulatory pathway. Note the different allocation of wound dressings containing antimicrobial agents indicated in k and r depending on the primary action.

2.2.3 European Regulatory Authorities for Drugs and Devices

The decision and appropriateness of the selected regulatory pathway and authorisation for the combination product has to be justified by the sponsor or manufacturer, respectively. Common requirements for the assessment and licensing of medicinal products and medical devices must be followed, but certain particularities of drug-device combination products should be taken into consideration with regard to seeking an scientific opinion from the national competent authority (NCA) or Notified Bodies (NBs), respectively, in context of a consultation procedure.

Before placing a medicinal product onto the market of European MSs an authorisation under one of two three kind of market authorisation application (MAA) is required: the decentralized procedure (DCP), mutual recognition procedure (MRP) or the centralised procedure (CP). The MAA will be reviewed by one of the governmental agencies with mutual recognition by the NCAs of concerned MS or by the central European agency, EMEA. The centralized procedure, which is solely performed by the EMEA is mandatory for biotechnology products and certain therapeutics and allows marketing of medicinal

[A] which is intended exclusively for use in the given combination and which is not reusable

products in all European MSs with a single license. However, in the case when the medical device and medicinal product form a single integral product, the CA responsible for the evaluation of the medicinal product would consult, if necessary, one of the CA or NB for medical devices to cover the review of the Essential Requirements in Annex I of the relevant MD Directives.

Before medical devices can be placed on the European market the product must pass a conformity assessment procedure at an appropriate certified NB [A] or CA for devices to proof compliance with the Essential Requirements of Annex I of applicable MD Directives [27, 26]. NBs are independent, private institutions which have been certified and accredited according to applicable provisions by public institutions as e.g. in Germany the Central Authority of the Laender for Health Protection with regard to Medicinal Products and Medical Devices [B](ZLG). NBs carry out tasks pertaining to the conformity assessment procedure for products falling under the provision of free movement of goods[C] in the EU when a third party is required. Subsequently, the conformity compliance of the product must be declared by affixing the CE marking [D] and depicting the identification number of the responsible NB. Oversight and approval by an independent regulatory Body is required for all except Class I products. If the medical device contains a medicinal product with ancillary action, the NB must initiate a consultation process with the CA/EMEA to assess the quality and safety of the substance including the clinical risk/benefit profile of the incorporation of the substance into the device. In contrast to the consultation procedures initiated by the CAs, consultation procedures on the medicinal substance with ancillary action are mandatory for the responsible NB. Accredited NBs in the EU are listed on the NANDO website [E].

2.2.3.1 Medical Device Classes and Conformity Assessment Procedures

Combination products that will be authorised as medical devices must follow the authorisation procedure by the classification and conformity assessment procedures of devices at a certified NB. The adequate classification of the product is essential for the correct selection of the valid conformity assessment procedure to achieve the marketability of the product. The explanation for classification of the combination product is required to initiate the consultation procedure with the NCA as described in chapter 2.2.3.2. Medial devices are categorised in four Classes (I, IIa, IIb, III) according to the degree of invasiveness, part of the body affected by the use of the device, duration of the contact to the patient and classification as inactive/active device.
The manufacturer should determine the medical device class of their product by following the decision trees in MEDDEV 2.4/1 - guideline [35, F] and relevant rules in Annex IX of Directive 93/42/EEC. However, all combination products authorised as medical device are in the highest category, Class III according to rule 13 Annex IX of Directive 93/42/EEC

[A] http://ec.europa.eu/enterprise/newapproach/nando/index.cfm?fuseaction=directive.main# [26.01.2008]
[B] Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten (ZLG).
[C] According Articles 28, 29 and 30 of the EC Treaty
[D] except devices intended for clinical investigation and custom-made devices acc. Art. 4 93/42/EEC as amended.
[E] http://ec.europa.eu/enterprise/newapproach/nando/index.cfm?fuseaction=directive.main# [26.01.2008]
[F] Not applicable for classifying of active implanatable medical devices

and MEDDEV 2.4/1 - guideline. Medical devices as part of drug delivery function system to administer a medicinal product may be eligible for a lower classification. Depending on the the classification of the device, the manufacturer must show compliance of the product with the Essential Requirements of Annex I and relevant conformity assessment procedures as laid down in Annexes II to VII of MD Directives[A]. The higher the class, the more stringent the assessment.

Table 8: Conformity assessment procedures depend on the device class

Requirements pursuant 93/42/EEC and guidelines [36, 37]	**Medical Device**		
	Class IIa	**Class IIb**	**Class III**
Annex II: Full quality assurance system Design, production & final inspection Audit by NB (ISO 9001 with ISO 13485:2003)	Yes	Yes	Yes + Design dossier
Design dossier examination by NB	No	No	Yes
	Or	**Or**	**Or**
Annex III: EC-type examination by NB	No	Yes and IV or V or VI	Yes and IV or V
Annex IV: Examination and testing of each product/batch by a NB	Yes or V or VI	Yes or V or VI	or V
Annex V: Production quality assurance. Audit of production & final inspection by NB (ISO 13488:2003)	Yes or IV or VI	Yes or IV or VI	or IV
Annex VI: Product quality assurance. Audit of final inspection by NB (ISO 13488:2003)	Yes or IV or V	Yes or IV or V	No
Annex VII: Technical file	Yes	Yes	Yes

Table 8: For compliance of the device with the conformity requirements of their class indicated provisions and standards must be addressed in the application. Multiple conformity assessment routes are possible. Requirements for Class I devices are not shown. A technical file has to be lodged at the relevant NB and is required for all classes including Class I. The design dossier represents the technical file of Class III devices.

Class I products imply a low level of risk. The conformity assessment to ensure that the product complies with relevant Essential Requirements of Annex I will solely be performed under the responsibility of the manufacturer who must issue a self-declaration of conformity (Directive 93/42/EEC Annex VII) thereafter. In addition, for sterile products and devices with a measuring function the manufacturer must apply to a NB for the certification of the aspects of manufacture relating to sterility or metrology. Except for the self-certification of Class I products the manufacturer must consult a NB to assess and verify the conformity of the established quality system, the manufacturing (and) the product with auditing and testing requirements as well as development and clinical data applicable for the relevant device class as indicated in Annex X and VII, respectively. Class IIa products are low-medium risk devices and Class IIb products are medium-high risk devices. Class III devices are high risk (balloon catheters, prosthetic heart valves).

[A] Different annexes are applicable for AIMDs and IVDs

There are two conformity assessment routes for the manufacturer of a Class III device to comply with the Essential Requirements of Annex I (see Table 8). Either the responsible NB must carry out an audit of a full quality assurance (QA) system at the manufacturing site (Annex II; ISO 9001 with ISO 13485:2003) or a type-examination (Annex III) plus one of the following two options apply: (i) examination and testing of each product or homogeneous batch of products by a NB (Annex IV) or (ii) audited QA system for the production & final inspection of products (ISO 13488:2003). In addition, the manufacturer must also submit a design dossier to the NB for approval (Annex II Section 4). The audited and approved QA system will ensure that the devices are in compliance with the technical file (Annex VII).

2.2.3.2 Consultation Procedure

According to Annexes II and III of the MD Council Directives, the NB need to consult one of the NCAs or the EMEA (mandatory for human blood derivates) before taking a decision on medial devices incorporating medicinal substances with ancillary action. The objective of the consultation procedure is to verify the safety, quality and usefulness of the medicinal substance, taking into account the intended purpose[A] of the device, by analogy of appropriate methods specified for medicinal products in Directive 2001/83/EC, as amended. Guidelines from NCAs and the EMEA have been issued to provide detailed information on the consultation procedure for ancillary medicinal substance use in a medical device, Table 9. If existing, the NB should follow the guideline of concerned CA and the applicant and/or manufacturer under consideration of the MEDDEV 2.1/3 rev 2 - guideline.

Table 9: Guidelines on consultation procedures

Agency & Release	Title
IMB (IE) January 2008	Draft Guide to Drug Device Consultations [38]
EMEA June 2006	Draft EMEA/CHMP/401993/2005 Guideline on the procedural aspects and dossier requirements for the consultation to the EMEA by a Notified Body on an ancillary medicinal substance use in a medical device [39]
BfArM (DE)	Hinweise zur Durchführung von Konsultationsverfahren und Einreichung von Unterlagen für Medizinprodukte mit die Wirkung des Produktes ergänzendem Arzneimittelanteil. [40]
MHRA (GB) June 2003	Guidance for Notified Bodies. Devices which incorporate a medicinal substance. Consulting the MHRA. MHRA Guidance Note. 18 [41].
European Commission July 2001	MEDDEV 2.1/3 rev 2 Guidelines relating to the application of: The Council Directive 90/385/EEC on active implantable medical devices the Council Directive 93/42/EEC on medical devices[42]
MEB (NL)	Procedure & dossier requirements [43]

Prior to the consultation the NB is responsible to provide a scientific explanation for the classification and verification of the usefulness of the medicinal substance in the medical device. A presubmission meeting to seek regulatory advice can be requested with the

[A] underlined wording excluded in 2007/47/EC

EMEA or the central German CA BfArM[A], but is mandatory at the central Irish Medicines Board (IMB). Because of the wide range of medical devices, which incorporate medicinal substances, a flexible approach to the data requirements is necessary. The required information will depend on the medical device, intended use and the following conditions: (i) the medicinal substance has obtained a marketing authorisation as a medicinal product in one of the European MSs which complies with the current requirements, (ii) the medicinal substance itself has not been authorised as a medicinal product, but belongs to a licensed substance class, or (iii) the medicinal substance is a new class and currently not authorised. In the first instance the procedure may be limited to a simple exchange of letters between the NB and the concerned CA, provided the product is unchanged in all aspects including the information provided with the device (applies to MHRA and BfArM). For the second and third case more comprehensive information will be required and should be based in principle, to the extent relevant, on Annex I to Directive 2001/83/EC as amended by Commission Directive 2003/63/EC. The consultation dossier shall be provided according to the format and content of the MEDDEV 2.1/3 rev 2 – guideline (Section B3 a to q, see chapter 2.4.3.2) or according to the Common Technical Document (CTD) structure in NtA Vol. 2B (BfArM, MHRA). Well-known medicinal substances for established purposes may not require all aspects of safety and usefulness and many of the headings will be addressed by reference to the literature, however all headings should be addressed in the documentation.
Organisational arrangements on the consultation procedure such as time schedules, submission date of the dossier, clock stops and fees will provided by the concerned CA. After reviewing the dossier the CA will prepare an assessment report and provide it to the NB. With Directive 2007/47/EC the assessment period was fixed to 210 days after receipt of a valid application. By taking into account the assessment of the CA, the NB will use its judgement to grant or reject the combination product. The NB may certify a CE mark for a medical device without positive opinion from the CA but the guidelines recommend contacting the CA for medical devices before issuing the certificate. For human blood derivates as medicinal substances with ancillary action the NB may not issue a CE marking without favourable opinion from the EMEA[B].
Prior to the amendment of the Directive 90/385/EEC in September 2007 by the Directive 2007/47/EC no consultation procedure was in place for AIMDs incorporating a medicinal product constituent with ancillary action. After the revision, the same consultation procedures as described above were implemented for combinations either regulated under the Directives 90/385/EEC (AIMD) or 93/42/EEC (MD). If changes are made to the medicinal product constituent after the CE mark was certified to the medical device, the NB shall consult the relevant CA, in order to confirm that the quality and safety of the ancillary substance are maintained.
Whereas consultation procedures are mandatory for ancillary medicinal substance in a medical device for the NB before taking a decision, there is no obligation if a medical device and medicinal product form a single integral product (MEDDEV 2.1/3 rev 2 – guideline Section C). The optional approach for combination products authorised as medicinal product might be the reason why no consultations procedure with a NB was

[A] BfArM personnel communication Dr. Stephan
[B] 93/42/EEC and 90/385/EEC as amended, Annex II and III, section 4.3 and 5, respectively

performed by the EMEA or one of four European NCAs (BfArM, MEB, IMB, MPA) between 2004 and 2007 [A].

2.3 Authorisation of Combination Products

The legal basis for the authorisation of combination products and applicable guidelines for the development programme to collect required data will be outlined in the next chapters. An overview of the different regulatory environment of combination products is provided in appendices 7.1 and 7.2. Only a few guidelines were exclusively issued for combination products and therefore the requirements for their authorisation are often based on guidance issued for drugs and medical devices. Different institutions such as representatives from national authorities, industry and trade association started activities to harmonise requirements to authorise medicinal products or medical devices. Two major associations resulted from such initiatives should be mentioned in particular. The “International Committee of Harmonization" (ICH) was founded in 1990 to increase international harmonisation of technical requirements to ensure that safe, effective, and high quality medicines are developed and registered in the most efficient and cost-effective manner. The Global Harmonization Task Force (GHTF) was conceived in 1992 in an effort to respond to the growing need for international harmonization in the regulation of medical devices.

2.3.1 US Acts and Regulations

There is no special type of marketing application for combination products in US[86]. Combination products are either authorised as a drug, a biologic or a device. In the development programme three legal frameworks may be considered to collect the required data for a successful application for authorisation, since each of the above mentioned products have their own types of application for authorisation and QA regulations[86]. The type of product and appropriate regulatory pathway (defined by PMOA and designation of the product; see chapter 2.1.3) will determine the specific requirements to place the combination product on the market. Consequently the use of applicable guidelines or standards to describe the manufacturing, analytics/controls, safety and clinical testing of the product will ensure proper development of the product in a given indication and represents the prerequisite for a successful application of the combination product and authorisation as drug, biologic or device.

2.3.1.1 Combination Products Authorised as Drugs or Biologics

Drugs

The FD&C Act specifies in Section 505 the content of NDAs as whether (i) the drug is safe for use and effective in use, (ii) list of components, (iii) composition of such drug, (iv) a full description of the methods, and the facilities and controls used for, the manufacture, processing, and packing of the drug, (v) samples of the drug if requested by the Secretary and (vi) specimens of the labelling for the drug.

[A] according to information obtained in frame of performed survey and sent questionnaire of the author

Further on, the 21CFR314[5] "Application for FDA Approval to Market a new Drug" specifies the content of a new drug application (NDA) in Section 314.50 and Section 314.126 which provides the primary basis for determining whether there is "substantial evidence" to support the claims of effectiveness for new drugs by adequate and well-controlled studies in human.

Biologics

The legal basis of a MAA approval of a biological product is laid down in PHS Act § 262 "Regulation of Biological Products". The application must demonstrate that the biological product is safe, pure and potent; and the manufacturer facility meets the standards designed to assure that the biological product continues to be safe, pure, and potent.

Further on, in 21CFR601 "Licensing" specifies the content of application for biologics licenses and primary base for effectiveness of the new biologic. The applicant shall submit data from nonclinical laboratory and clinical studies to demonstrate the safety, purity and potency. A full description of manufacturing methods, data establishing stability of the product through the dating period; representative sample(s) of the product, summaries of results of tests performed on the lot(s), as well as specimens of the labels, enclosures and containers must be presented. In addition, 21CFR601.25 details the meaning of effectiveness by referencing to the prerequisites for drugs laid down in 21CFR314.126. Proof of effectiveness shall consist of data generated in controlled clinical investigations.

2.3.1.2 Combination Products Authorised as Devices

The Medical Device Amendments of 1976 to the FD&C Act established three regulatory classes for marketing of medical devices. The three classes are based on the degree of control necessary to assure that the various types of devices are safe and effective as laid down in FD&C Act Section 513 and detailed in 21CFR860.3[44]. Appropriate classification is relevant for combination products as they can be classified as Class II or III.

Class I products have to meet general controls only, whereas Class II products require a premarket notification submission (510k) and performance standards have to be met, Class III products are subject of a PMA by a FDA review. The requirements for Class II and III devices include clinical data to demonstrate the safety and effectiveness of the device as described in FD&C Act Section 513 (2) and (3). However, if there is sufficient scientific evidence about the effectiveness of the device under the conditions of use prescribed the device may be authorised without investigation described in paragraph 513 (3A).

- *"(2) For purposes of this section and sections 514 and 515[A], the safety and effectiveness of a device are to be determined …"*
- *"(3)(A) Except as authorized by subparagraph (B), the effectiveness of a device is, for purposes of this section and sections 514 and 515, to be determined, in accordance with regulations promulgated by the Secretary, on the basis of well-controlled investigations, including 1 or more clinical investigations where appropriate, by experts qualified by training and experience to evaluate the effectiveness of the device, … under the conditions of use prescribed, recommended, or suggested in the labeling of the device."*

[A] Performance standards and premarket approval

The provisions for a premarket notification submission (510k, Class II) and PMA (Class III) with respect to performance standards are provided in FD&C Act Sections 514 and 515.

- *"SEC. 514 Performance standards. (a) Provisions of Standards (1) The special controls required by section 513(a)(1)(B) shall include performance standards for a class II device if the Secretary determines that a performance standard is necessary to provide reasonable assurance of the safety and effectiveness of the device. …"*

The requirements of the PMA for Class III devices are laid down in FD&C Act Section 515(c) "Application for Premarket Approval". Basically, the applicant must submit (i) all reports to show whether or not the device is safe and effective, (ii) a full statement of the components, ingredients and principles of operation, (iii) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and, when relevant, packing and installation of the device, (iv) adequate information to show that the device fully meets relevant performance standard or a justification for any deviation, (v) samples of the device and (vi) specimens of proposed labelling for the device.

The CFR PMA application (21CFR814.20[6]) provides detailed guidance on the procedure and content of the dossier, which can be summarised as follows:
A summary to gain a general understanding of the data and information in the application including the indication for use, device description, summary of the non-clinical laboratory and clinical studies and conclusion. A complete description of the device, properties of the device with relevance of intended use, principles of operation and quality controls. Reference to any performance standard with regard to radiation control. Nonclinical laboratory studies with the device including microbiological, toxicological, immunological, biocompatibility, stress, wear, shelf life, and other laboratory or animal tests as appropriate. Results of the clinical investigations involving human subjects with the device. A justification to show that data from a single investigator are sufficient to ensure reproducibility of test results if the PMA is supported solely by data from one investigation. A bibliography of all published reports, whether adverse or supportive, that concern the safety or effectiveness of the device. One or more samples of the device and its components, if requested by FDA. Copies of all proposed labelling for the device.
To ensure that the medical device will be safe and effective and otherwise in compliance with the FD&C Act the manufacturer has to establish a quality system and design controls as laid down in 21CFR820 "Quality System Regulation". Details of the requirements concerning the quality system will be determined by applicable norms. Extensive guidance documents on pre- and postmarket provisions of devices are available on the CDRH website[A]. The requirements for a premarket notification submission 510(k) can be found in 21CFR807 Subpart E.

2.3.2 EU Regulations and Directives

Combination products in EU are either authorised as medicinal products or medical devices and the development programme must consider applicable pharmaceutical and medical device legislation and guidelines to collect the required set of data for a successful

[A] http://www.fda.gov/cdrh/devadvice/ [26.04.2008]

market authorisation application. The type of product and appropriate regulatory pathway determine the specific requirements to place the combination product on the market (see chapter 2.2.2). Consequent use of applicable guidelines or standards to describe the manufacturing, analytics/controls, safety and clinical testing of the product will ensure proper development of the product in a given indication. In total two regulatory pathways can be distinguished by the following directives, but a third option discharges in two separate market licenses as drug and device. The mandatory combined use must be described in the labelling of at least one product but may not be required mutually (see chapter 3.2.3.2).

For combination products authorised as medicinal products or medicinal biological products the Council Regulation (EEC) No 2309/93[29] updated by Regulation (EC) No 726/2004 represents the valid legislation for authorisation and supervision of medicinal products for human use in the European Community. Directive 2001/83/EC amended by Commission Directive 2003/63/EC[45] with its Annex I provides a detailed description of the required documentation for a MAA of a medicinal product. Further on, the Commission Directives 2003/94/EC[46] and 2005/28/EC[47] provide principles and guidelines of good manufacturing and good clinical practice of investigational medicinal products and Directive 2001/20/EC[48] laid down the good clinical practice in the conduct of clinical trials.

For combination products authorized as medical devices, Council Directives 93/42/EEC and 90/385/EEC amended by Directive 2007/47/EC are applicable. For the determination of the type of combination product or device, respectively, the guidelines MEDDEV 2.1/3 rev.2[42] and 2.1/2 rev 2[49] should be consulted and read under consideration of the definitions in Annex IX of Council Directive 93/42/EEC.

2.3.2.1 Device and Medicinal Product Form a Single Integral Product

The first option to authorise a combination product - as medicinal product - is justified in Art. 1 (3) of Directive 93/42/EEC. When a medical device and medicinal product form an integral product the product must comply with the requirements for quality, safety and efficacy as laid down in the medicinal products Directive 2001/83/EC and, in addition, the safety and performance-related features of the medical device part must comply with Essential Requirements of Annex I of Directive 93/42/EEC as amended. In such cases the CA responsible for the evaluation of the medicinal product would consult, if necessary, one of the CAs or NBs for medical devices to cover the review of the essential requirements in Annex I of the relevant MD Directive.

With regard to the MAA for a medicinal product it shall contain the following particulars and documents as described in Directives 2001/83/EC and 2003/63/EC Annex I. The following abridgement is taken from Directive 2001/83/EC Art. 8:

"… 3. The application shall be accompanied by the following particulars and documents, submitted in accordance with Annex I:…

- *(c) Qualitative and quantitative particulars of all the constituents of the medicinal product, …*
- *(d) Description of the manufacturing method.*
- *(e) Therapeutic indications, contraindications and adverse reactions.*
- *(f) Posology, pharmaceutical form, method and route of administration and expected shelf life.…*

- *(h) Description of the control methods employed by the manufacturer.*
- *Results of:*
  - *a. - pharmaceutical (physico-chemical, biological or microbiological) tests,*
  - *b. - pre-clinical (toxicological and pharmacological) tests,*
  - *c. - clinical trials.*

(ia) A detailed description of the pharmacovigilance and, where appropriate, of the risk-management system which the applicant will introduce. …

(j) A summary, in accordance with Article 11, of the product characteristics, …"

In addition, special provisions shall be taken into account for human blood derivates and plasma as laid down in Directive 2001/83/EC amended by Directive 2002/98/EC in Title X and XI to ensure batch consistency and viral safety.

2.3.2.2 Devices Incorporating Medicinal Substances with Ancillary Action

The second possibility to authorise a combination product - as medical device - concerns medical devices incorporating medicinal substances with ancillary action as defined in Art. 1 (4) or (4a) of Council Directives 93/42/EEC and 90/385/EEC. In this case the quality, safety and usefulness of the medicinal product component must be verified by analogy with the methods specified in Annex I to Directive 2001/83/EC as described in Annex I Essential Requirements Section 7.4 of Directive 93/42/EEC.

In practice, the dossier of the product will be evaluated by the NB according to MD directives and the substance component by CA/EMEA in analogy with the methods specified in Annex I to Directive 2001/83/EC. After verification of the usefulness of the substance as part of the medical device, the NB initiates a consultation process with the NCA or EMEA (see chapter 2.2.3.2) to assess the quality and safety of the substance including the clinical risk/benefit profile of the incorporation of the substance into the device. The manufacturing process and the data related to the usefulness of incorporation of the substance into the device as determined by the NB should be taken into account by the agency[24].

Which authority is responsible for the consultation will depend on the type of medicinal substance. A consultation procedure could be requested from each European NCA if no restrictions apply. The central European agency may be consulted when the medicinal product component falls under provisions of Regulation (EC) No 726/2004 but is mandatory in case of human blood products[26, 27]. All combination products authorised as medical device are classified as Class III devices according to rule 13 Annex IX of Directive 93/42/EEC as amended and the MEDDEV 2.4/1 - guideline.

2.3.2.3 Drug Delivery Device Systems

Drug delivery systems which are non-integral and reusable, may be authorised with separate licenses for each product, one for the medical device and another for the medicinal product according to Art. 1(3) of Council Directives 93/42/EEC or 90/385/EEC (and Directive 2001/83/EC). In this case the term "combination product" is not used in EU. However, both products must be developed and licensed according their applicable directives and guidelines. The products must also be tested in combination (e.g. insulin pen and cartridge) to demonstrate compatibility and compliance with established

specifications[A, B]. Accordingly, the labelling of the medicinal product (Section 4.2 posology and methods of administration) must contain a generic remark that the medicinal product can only be administrated by a drug delivery system e.g. implanted infusion pump or iontophoresis device. In case the use is limited to a certain brand or model of device the information on the device must be mentioned in Section 4.1 therapeutic indication (see chapter 3.2.3.2 InductOs®).

2.4 Development of Combination Products

Currently, a few general guidelines for combination products exist. Some of these cover certain types of combination products, e.g. drug-eluting stents. Hence, the requirements for pharmaceutical products and devices established by harmonised and regional guidelines and standards should be taken into consideration for the development of the relevant constituents.
The development programme depends on whether the combined constituents obtained an authorisation and are marketed as single medical products with established safety and efficacy/effectiveness for other purposes or if the combination product contains new products as constituents. Available information should be used to streamline the overlapping aspects of the development and to prevent duplication of data. Although this information is often helpful, it should be recognized that it is the combination product that is being developed and not just the constituent part[18]. Because of the complexity of combination products, no development paradigm exists and both guidelines and standards established either for drugs or devices must be taken into consideration. The development of the production process as well as required documentation and data for the application for authorisation of the combination product constituents must comply with pharmaceutical and device legislation as presented in chapter 2.3.

2.4.1 Guidelines and Standards for Drugs and Devices

Both, initiatives of the pharmaceutical and medical device sectors developed international guidelines and standards to harmonise pre- and postapproval requirements to place products earlier on the market without unnecessary delay and duplication of required clinical studies.

2.4.1.1 ICH Guidelines for Development of Drugs in the US and the EU

The extent of quality, preclinical and clinical data to support a marketing authorisation and to assist for various stages of the clinical development of a pharmaceutical product was harmonised among the regions of Europe, USA and Japan with implementation of international standards and adoption of harmonised guidelines by the ICH[50] to prevent unnecessary duplication of animal studies as well as clinical trials in human.

[A] Council Directive 93/42/EEC Annex I paragraph 7.3
[B] CPMP/ICH/367/96 ICH Topic Q6A Specifications 3.3.2.3 Parenteral Drug Products j) Functionality testing of delivery systems

2.4.1.1.1 Quality Topics

It is recommended to develop the production process and to collect quality data for the medicinal product constituent by following the relevant ICH guidelines. Currently the following quality topics have been harmonised by these guidelines: Stability: Q1A - Q1F; Analytical Validation: Q2; Impurities: Q3A - Q3C; Pharmacopoeias: Q4, Q4A, Q4B; Quality of Biotechnology Products: Q5A - Q5E; Specifications: Q6A, Q6B; Good Manufacturing Practice: Q7; Pharmaceutical Development: Q8 and Quality Risk Management: Q9.

2.4.1.1.2 Safety Topics

The scope, timing and duration of required non-clinical safety studies to support the conduct of human clinical trials and recommendation for marketing approval for pharmaceuticals are outlined in the ICH M3 guideline[51]. The non-clinical safety study recommendations include single and repeated dose toxicity studies (both prior phase I clinical studies), genotoxicity studies (AMES, micronucleus test) (prior phase I), reproduction toxicity, local tolerance studies (prior phase I) separately or in combination with safety pharmacology and pharmacokinetic (Absorption, Distribution, Metabolism and Excretion; ADME) studies (both prior phase I). Indicated non-clinical studies are prerequisite to start the clinical phase I studies. The different requirements with respect to the duration of repeated dose toxicity studies to support phase I, II, III trials in US, phase I, II, trials in EU or phase III trials in the EU and marketing applications in all regions should be taken into consideration. In general preliminary evidence of established safety of the combination product could be expected with data from completed acute and chronic toxicity studies to support first exposure to humans.
An assessment of the carcinogenic potential is required for drugs that pose a special cause for concern (substance class or positive results in genotoxicity studies) or are intended for long-term use. Other preclinical studies may be necessary with respect to the intended use, formulation, and route of administration or results from conducted studies. For the development of biotechnological products, particular considerations have to be taken into account which are discussed in ICH S6 [52].

2.4.1.1.3 Efficacy Topics

Design and conduct of clinical studies to investigate the efficacy of the medicinal product component should follow the ICH guidelines. However, authorisation procedure related specialities, disease-specific guidelines or existing region-specific requirements should be taken into consideration as well. Currently the following topics have been adopted in several ICH guidelines: Clinical Safety, Clinical Study Reports, Dose-response Studies, Ethnic Factors, Good Clinical Practice, Clinical Trials, Guidelines for Clinical Evaluation by Therapeutic Category, Clinical Evaluation and Pharmacogenomics.
The first human exposure studies are generally single dose studies, completed by dose escalation and short term repeated dose studies, followed by dose escalation and short term repeated dose studies to evaluate pharmacokinetic (PK) parameters and tolerance (Phase I studies -- human pharmacology studies). These studies are often conducted in healthy volunteers but may also include studies in patients (Phase II studies -- Therapeutic

Exploratory studies). This is followed by confirmatory clinical trials to investigate the efficacy and safety in patient populations (Phase III -- therapeutic confirmatory studies)[51].
The applicant should identify the appropriate clinical settings for the product in a meeting with the CA with respect to (i) surrogate or clinical endpoints, (ii) placebo/comparator controlled trials, (iii) superiority versus equivalence and (iv) novel or me-too product.
Often surrogate parameters (e.g. blood pressure) are used to determine the success of the therapy instead of firm clinical endpoints (e.g. reduction of mortality has a too wide time horizon in not life-threatening diseases. Acceptance of surrogate endpoints in the clinical dossier should be either proven by applicable guidelines or by addressed to the authorities prior start of a clinical trial. Another point is the design as placebo-controlled or comparator-controlled trials. The latter probably represents the ideal control in terms of bias but is unethical if an existing therapy is withheld to patients. New therapies must consider sufficient sample size and alpha error to show superiority over existing therapies but a similar product of an established product class only needs to demonstrate equivalence.
Especially for combination products some study endpoints can only be tested in animals but not in human for ethical reasons, for example if it would be required to remove an implant to examine surrounding tissue for histocompatibility.

2.4.1.2 Guidelines and Standards for Medical Devices in the US and the EU

The medical device sector also harbors international initiatives to harmonise their pre- and postapproval requirements. The GHTF represents an international initiative of representatives from medical device regulatory authorities and trade associations in the EU, in the US, Canada, Japan and Australia to promote harmonisation and standardisation of regulatory requirements for medical devices. A number of guidelines with respect to premarket issues, clinical evidence and evaluation, quality management systems, auditing and postmarket issues have been adopted for medical devices[53] which can be also considered for development and authorisation of combination products. It is of interest to note, that the current European regulatory system largely reflects work carried out in GHTF Study groups.
The International Organization for Standardization (ISO) is the world largest standards developing organisation which is a non-governmental institution comprised of a network of the national standards institutes of 157 countries[A]. Many medical device standards are ISO norms. For example, ISO 14971:2007 specifies a process for a manufacturer to identify the hazards associated with medical devices, including *in vitro* diagnostic (IVD) medical devices, to estimate and evaluate the associated risks, to control these risks, and to monitor the effectiveness of the controls.
In the US, the FDA CDRH has an active programme of evaluating and recognising consensus standards and maintains a searchable standard database[54, 55]. For example, the ASTM International (American Society for Testing and Materials) should be mentioned as an international standards organization that develops and publishes voluntary consensus technical standards.
The lists of harmonized European standards, which provide presumption of conformity with the obligatory essential requirements laid down in the MD Directives, are published in

[A] http://www.iso.org/iso/home.htm

the Offical Journal of the European Community and can be obtained from the European Commission (EC) website[A]. For example, certain requirements for cardiac and vascular implants are specified in EN 14299:2004 or biological evaluation of medical devices - Part 18: Chemical characterization of materials (ISO 10993-18:2005). Standards are chargeable and were adopted by the European Standards Bodies. One relevant body is the European Committee for Standardization (CEN, Comité Européen de Normalisation), which is developing European standards based on voluntary agreement between all parties, not only for medical devices.
Other standards, norms or protocols issued and published from international industry trade organisation, medical professional associations of physicians or the WHO (World Health Organization) may be taken into consideration, if necessary.

2.4.1.3 Quality Assurance for Drugs and Devices in the US and the EU

QA systems are mandatory for the production of pharmaceutical products or medical devices but are of different scope and design.
The principles and guidelines of good manufacturing practices (GMP) for drugs have been laid down in FD&C Act Section 520, and three regulations (chapter 2.4.2.1), and in the Commission Directive 2003/94/EC[46] to ensure consistent, unchanged quality of a human medicinal product and starting material during manufacturing, storage, and distribution in accordance with provisions made in Directive 2001/83/EC Art. 46 and 47. All manufacturers should operate an effective quality management system of their manufacturing operations, which requires the implementation of a pharmaceutical QA system. The Art. 2 (6) of Commission Directive 2003/94/EC defines GMP as “part of QA which ensures that products are consistently produced and controlled in accordance with the quality standards appropriate to their intended use“. The principles and guidelines of GMP are detailed in ICH harmonized guideline ICHQ7[56] and in the Commission guidelines on GMP on medicinal products including biological products Volume 4[57].
The QA system of medical devices is currently described by the standard EN ISO 13485. So far, an explicit guideline for QA systems for combination products has only been issued in form of a draft version in US (see chapter 2.4.2.1).

2.4.2 Guidances on Combination Products in the US

Two guidance documents are addressing combination products in particular; one is referring to GMP requirements[21] (see chapter 2.4.2.1) and another is initially discussing the scientific and technical information that may be necessary for investigational or marketing application for these combination products[18]. The existing guidance for the constituent parts are a good starting point to consider the type of development issues raised by the constituents but an adaptation to address the specific nature of the respective combination product is required. The manufacturer should be aware that changes in the manufacturing of the single constituents or composition of the product could affect the safety and efficacy of the combination product as a whole. This might render already generated preclinical and clinical data as not being viable for the dossier any longer[18].

[A] http://www.newapproach.org/Directives/Default.asp [20.03.08]

For example, preclinical requirements and safety testing for pharmaceutical products is different from preclinical/non-clinical studies conducted for devices. In conclusion it is likely that neither isolated approach would sufficiently address the relevant preclinical requirements for the single constituents nor the combination product and the manufacturer/applicant must deploy an own development pathway to address the preclinical issues. Currently recognised consensus standards for devices may be appropriate for testing of the device constituent of many combination products and can be retrieved from the CDRH website[54]. However, these standards may be adopted or even new methodologies may be developed for certain combination products, if required.

Manufacturing

Combination products containing new products as constituent, require a basic testing of the single constituents before the development of the combination product as a whole can be started. When combined constituents are licensed and marketed as single medical products it is often very helpful to consider the relevant data as a starting point to establish safety and effectiveness for its use in the combination product.

Moreover the relevant information on quality of the combination product for the NDA could be provided by referencing to existing applications (NDA, BLA, PMA or 510(k)) or submission of a drug master file[A] and/or device master file[B] of product constituents. An authorisation letter from the owner of the referenced material must accompany the submission. The extent of information for the combination product constituent will vary from case to case but missing information can be submitted by a supplement of the existing master file. The manufacturing, scale-up and quality management of a combination product require a thorough development and realisation. FDA encourages the consideration of manufacturing issues posed by the scientific and technical aspects of the drug, biological product and device constituent's parts, and of the combination product as a whole[18]. The following quality issues should be considered in particular.

Drug device interaction

The compatibility of physical or chemical combined components is an important aspect. The physiochemical properties of the components must be chemically stable and resistant to any adverse interaction both during storage and use to maintain the product quality.

In particular the following potential interactions should be investigated as far as possible: (i) leachables/extractables of the device material into the drug or biologic substance, (ii) changes in the stability or activity of the drug constituent when used together with an energy emitting device, when administrated by the device or used as a coating on the device, (iii) drug adhesion to the device that could change the dosing, and (iv) inactive breakdown products or manufacturing residues from device manufacturing. A similar consideration should be given to the effects a drug may have on the device constituent. Some drugs/biologics may alter the material of the device but others not.

For example as in the case of drug-eluting stents, the polymer to control the continuous release of the active ingredient from the device (stent) must be investigated by appropriate tests to support the chosen formulation. For excipients which are being used the first time in a human drug product, used in a new route of administration or is critical for controlled

[A] http://www.fda.gov/cder/guidance/dmf.htm [22.03.2008]
[B] http://www.fda.gov/cdrh/dsma/pmaman/appdxc.html#P7_2 [22.03.2008]

drug release the same level of quality and quantity of testing data as drug substance itself must presented to FDA[103].

Stability
The effect of manufacturing methods on the interaction of constituents and their properties should be taken into consideration. The stability of the combination product as a whole may be different than that of the separate constituents[18].

Terminal Sterilisation
During entire manufacturing process of the combination product the drug substance must be stable and remain chemically unchanged. Compatibility and suitability of the chosen sterilisation process should be investigated. Medical devices are often sterilised by ethylene oxide, which may chemically interact with the medicinal product component causing degradation or potential toxic by-products[103]. For constituent parts manufactured under aseptic conditions appropriate manufacturing methods should be implemented to ensure aseptic control of the combination products.

Preclinical testing
The diversity of combination products is high and different physicochemical and pharmacological properties, shape and size but also different modes of administration must be taken into consideration for appropriate preclinical studies. It is critical to consider what information is necessary to characterize the safety and efficacy when the drug constituent is a new molecular entity (NME) or biologic. In this case the preclinical investigations will start with the NME alone and provide the basis for clinical studies and the combination of the NME with the device constituent. For example, certain conventional pharmacology and toxicology studies[58] may be necessary to establish the safety profile of the new drug or biologic before the clinical investigation of the combination product can be started[18].
If a combination product contains a drug or device constituents approved for another use the applicant/manufacturer should address the potential changes for the established safety, efficacy and dosing by the new combination in additional tailored preclinical or clinical studies. This can mean that *in vivo* pharmacokinetic studies must be performed to consider and evaluate (i) changes in formulation, strength, route of administration or delivery mode, (ii) new dosage, new patient population or (iv) new indication. Dose ranging or dose finding studies[59] may be appropriate to determine dose adjustments for safety/effectiveness when therapy is targeted to a local site. Acute and repeat dose toxicity studies may be appropriate to determine the NOAEL (no observed effect level) and the toxicity profile of the combination product[18]. Typical toxicity studies for a drug component with an existing marketing authorisation could be seen in the case of drug-eluting stent approval which contained a local, regional and systemic effects studies scheduled with evaluation after 1, 3 and 6 months[18].
A different situation concerns licensed drug delivery systems, which are developed for a new target organ. A licensed intravenous drug delivery catheter may need biocompatibility studies to establish the safety of the device material for the use in the neural tissues. However, permanent implants may require a different extent of toxicity data than topical drug delivery systems.

Biocompatability
Biocompatability is a central requirement for medical devices[6] which must also be demonstrated for combination products containing a device constituent. Permanent implanted products placed in the body and coming into contact with blood must be tested for biocompatibility prior to any studies in humans with relevant standards as for example the EN ISO 10993 series[76]. Typically combination products or devices having contact to blood must be at least be tested for cytotoxicity, sensitisation, acute toxicity, genotoxicity and hemocompatibility. The type of the product and indication should be taken into consideration as for example cytotoxicity could be expected for chemotherapeutic substances and cytotoxicity testing would not be required. Hence, discussion of the study design with the FDA in a pre-IND meeting would be helpful to define an appropriate non-clinical development programme (chapter 2.4.4.2).

PK and animal studies
Pharmacokinetic (PK) studies must be performed to quantify the plasma levels and duration of the drug exposure to the body, which describe the safety profile of the product to support a study in humans. The dosage of the drug used in combination products is often low and may be difficult or even impossible to analyse. In this case, *in vivo* or *in vitro* release profiles of the active ingredient from the combination product could provide sufficient safety data to support the first trial in humans. The approval of DESwas e.g. based on *in vitro* PK studies quantifying drug resolution rates[18].
Besides safety testing to support initiating a clinical trial in human proof-of-concept studies in an animal model is the second main goal in animal testing. As the sponsor may be asked by the FDA how the therapeutic doses in human trials have been chosen, it would be useful to determine a low dose as subtherapeutic and a high dose as toxic level in animal models and consequently establish a safety margin between therapeutic and toxic dose[18].

Animal models
Unfortunately it is very difficult to obtain informative results on effectiveness due to the lack of appropriate disease models in animals and distinct human pathophysiology. Even if such animal models exist the correlation between human and animal effectiveness data could be weak. In particular for combination products, it is very difficult to reproduce the complex biological interactions between the drug and the local, tissue-related or systemic environment. Hence, in general FDA considers safety data from acute and chronic toxicity studies with preliminary evidence as sufficient to start clinical studies of combination products[18].

Clinical Investigation
Data on safety and effectiveness of the combination product must be collected by appropriate clinical investigation to support the NDA/PMA application. Prior to starting the clinical investigation programme and the distribution of an unauthorised medical product the manufacturer/applicant must file an Investigational New Drug (IND) or Investigational Device Exemption (IDE) with the relevant FDA Center by providing an appropriate study protocol and evidence that the product is reasonably safe for initial use in humans (chapter 2.4.4.1). However, the FDA emphasises that existing regulations for INDs and IDEs provide a great flexibility into consideration how to address the issues posed by a particular medical product[18]. In general, under consideration of the science and technology

of the combination product, the clinical questions arise about the (i) sample size, (ii) statistics, (iii) (surrogate) endpoints, (iv) and measuring of drug levels in areas typically not accessible, or (v) techniques to evaluate drug-device interactions[18]. Specific safety monitoring in the clinical study may be appropriate to obtain data on the novel aspect of the combination product, e.g. local toxicity. It may also be necessary to evaluate the human factors of device use on the safety and effectiveness of the combination product as early as possible in order to identify possible design features that may need modification. The clinical development plan and protocol for the combination product should be discussed with the relevant FDA Centers in the IND/IDE process.

2.4.2.1 Current Good Manufacturing Practice (CGMP) Regulations

In cooperation with the concerned FDA Centres OCP has released a draft guidance document in September 2004 dedicated to the GMP of combination products[21]. The draft guidance[A] entitled "Current Good Manufacturing Practice for Combination Products" provides provisions to the manufacturer to ensure (i) that the product is not adulterated; (ii) the product possesses adequate strength, quality, identity, and purity; and (iii) the product complies with performance standards as appropriate for the marketed combination product. The CGMP draft guidance refers to four existing current good manufacturing practice regulations and other applicable standards for products that may be constituent parts of a combination product in order to ensure regulatory compliance of the entire product. Moreover, the draft also provides a definition for constituent parts: A constituent part of a combination product is an article in a combination product that can be distinguished by ist regulatory entity as a drug, device, or biological product.

- Current good manufacturing practice (CGMP) in manufacturing, processing, packing, or holding of drugs (21 CFR part 210[60]) and current good manufacturing practice in manufacturing for finished pharmaceutical (21 CFR part 211[61])
- GMP requirements for biological products included in 21 CFR subchapter F Biologics (21 CFR part 600-680 [62])
- Quality system (QS) regulation[B] (21 CFR part 820 [63])

In the CGMP draft guidance FDA recognises that there is considerable overlap in the GMP and QS regulation but however each set of the regulations is somewhat different because each is fitted to the characteristics of the type of products for which they were designed. So far the FDA has not finalised the draft guidance on CGMP although a proposed rule was predicted for spring 2007.
Until the finalisation of the CGMP guidance each constituent part of a combination product remains subject only to its governing current good manufacturing practice regulations, when marketed separately and when manufactured separately as constituent parts of a combination that will later be combined. Combination products that are produced as a single entity or co-packaged (21 CFR 3.2 (e)(1), (2)) both, the drug/biologic and device provisions of the current GMP regulations are applicable during and after joining the constituent parts together. For example, the constituents of drug-eluting stents, the bar

[A] The terms "current good manufacturing practices" and "good manufacturing practices" are equivalent. Current good manufacturing practices is preferentially used in US regulations and guidelines and was kept.
[B] Subchapter H Medical Devices

metal stent and the drug, are manufactured under respective CGMP regulations of each constituent until the constituents are joined together. Thereafter, both sets of current GMP regulations apply to the combined product.
However, it should generally not be necessary for manufacturers of single entity or co-packaged combination products to maintain two separate manufacturing systems for ensuring compliance with both GMP and QS regulation. FDA believes that compliance with both sets of regulations can generally be achieved by following one set because under a more general requirement in one set of regulations, it will be possible to develop and implement a practice that complies with a more specific requirement in the other set of regulation[A]. In addition and depending on the type of combination product, it may be necessary to consider other specific requirements to ensure regulatory compliance with both the GMP and QS regulations (e.g. aseptic controls).

In contrast, combination products consisting of constituent parts that are separately marketed but intended to be used together (21 CFR 3.2 (e)(3), (4)) in their labelling, manufacturing of each constituent part is subject to its respective current GMP regulations, and is not subject to both sets of regulations. For example, in case of the photodynamic therapy system, which consists of a separately marketed photosensitising drug and laser device, the laser would be subject to QS regulation and the drug would be subject to GMP regulation.

2.4.3 Guidelines on Combination Products in the EU

As outlined in chapter 2.2 medical products combining a drug and device can be developed and authorised in two different manners in the EU.

2.4.3.1 Device and the Medicinal Product Form a Single Integral Product

When the medicinal product forms a single integral product, it shall be governed by Directive 2001/83/EC. In addition, the safety and performance-related features of the medical device constituent must comply with Essential Requirements of Annex I of Directive 93/42/EEC as amended, which is further outlined in chapter 2.4.3.2.2.
A comprehensive source on the content and formal requirements of medicinal products during the development to collect the data for the dossier of different type of products and indications can be retrieved from the European Commission and EMEA websites.

- Notice to Applicants Vol 3: Guidelines on quality, safety and efficacy of medicinal products for human use[B]
- CHMP Guidelines on quality, safety and efficacy[C]

The European Commission, in consultation with the CAs of the MSs and the EMEA, has prepared this Notice to Applicants (NtA). The CHMP guidelines have been prepared in consultation with authorities of the EU MSs by EMEA's CHMP and should be taken into consideration for the development of the medicinal product and preparing the marketing authorisation application. The guidelines are intended to provide a basis for the practical

[A] current applicable GMP and QS requirements are presented in table 1 of the CGMP draft guidance for combination products
[B] http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol3_en.htm [02.05.2008]
[C] http://www.emea.europa.eu/htms/human/humanguidelines/background.htm [02.05.2008]

harmonisation of the requirements set out by EU MSs and EMEA and to demonstrate quality, safety and efficacy according to the EC Directives. However, the content of documentation need to be in conformity with the current state-of-art scientific knowledge. Further details on the development of medicinal products are beyond the scope of this thesis.

2.4.3.2 Devices Incorporating a Medicinal Product with Ancillary Action

The requirements of a combination products regulated as medical devices with regard to the incorporated medicinal substance with ancillary action is basically defined in Council Directive 93/42/EEC as amended, in Annex I Essential requirements paragraph 7.4 where it states, that the quality, safety and usefulness of the substance (medicinal product constituent) must be verified in analogy to the methods[A] specified in Annex I of Directive 2001/83/EC. In other words, the provisions and guidelines for medicinal products apply (see chapter 2.4.3.1). But normally the procedures of both Directives do not apply cumulatively.
The required documentation, also termed "consultation dossier", as it represents the documentation prepared by the manufacturer and forwarded by the NB to the CA in the frame of the consultation procedure, are specified in the MEDDEV 2.1/3 rev 2 – guideline Section B.3. The content-related information could be considered as outdated as the referenced Directive 75/318/EEC was repealed by Directive 2001/83/EC. However, Section B.3 paragraph (a) "General information" to (q) "Labelling" of this guideline provide additional comments which should be taken into consideration and to be used for the interpretation of applicable guidelines. Helpful remarks on data requirements and applicable guidelines with regard to the medicinal product constituent are also provided with the draft guideline CHMP/4011993/2005[39] for consultation to the EMEA.

The appropriate technical requirements of the medical device and QA system which needs to be established, depends on the classification of the device and are laid down in the Council Directives 93/42/EEC and 90/385/EEC. Medical devices incorporating a medicinal product with ancillary action are Class III devices and must show compliance with Annex I (essential requirements), Annex II (EC declaration of conformity, full quality assurance system), Annex III (EC-type examination) and Annex X (clinical evaluation) of Directives 93/42/EEC. The documentation must describe the design, manufacture and performances of the medical device and is also termed "design dossier" (technical file in case of Class I/II devices). The NB must examine the application during the conformity assessment procedure and, if the product conforms to the relevant provisions issue an EC design-examination certificate.

[A] Interestingly the wording of paragraph 7.4 before amending 93/42/EEC by 2007/47/EC in 2007 could be interpreted as less stringent: „ ..taking account of the intended purpose of the device, by analogy with the appropriate methods .."

2.4.3.2.1 Consultation Dossier

Because of the wide range of medical devices, which incorporate medicinal substances, a flexible approach to the data requirements is necessary. Two different types of applications exist which have a considerable effect on the extent of documentation to be submitted.

1) A bibliographical data application[A, B] is possible when known medicinal substances are concerned with well-established medicinal use within the Community for at least ten years according to Art. 10a Directive 2001/83/EC. All aspects of safety and usefulness may not be required and many of the headings in MEDDEV 2.1/3 rev 2 – guideline Section B.3 will be addressed by reference to the literature, including standard textbooks, experience and other information generally available.

2) For new active substances and for known medicinal substances in a non-established purpose, comprehensive data is required in a full application. The evaluation of such active substances would be performed in accordance with the principles of the evaluation of new active substances according to Directive 2001/83/EC as amended and applicable guidelines.

During development of the medicinal substance or product, the following topics should be considered and addressed in the consultation dossier:

Manufacturing with respect to incorporation of the medicinal product constituent

With respect to the manufacturing of the medicinal product constituent and its incorporation, the amount of the substance processed into each medical device should be determined. If the substance is modified during its incorporation into the device more relevant information is required.

Specification and quality of starting materials

The specification for the medicinal product constituent shall be provided according to CPMP/ICH/367/96[64]. Regarding the quality of the medicinal product constituent comprised of inorganic or organic substances or herbal drugs three ways are feasible to provide required information according the guideline CHMP/QWP/297/97 Rev 1 corr[65]. Firstly, the specification and batch results for the medicinal substance shall be provided by and in compliance with references to the European Pharmacopoeia[C] or (if not available) to a national pharmacopoeia of one of the MSs, or - if no EU monograph is available - to other national monographs (e.g. USP). In case the Certificate of Suitability (CEP) does not address all relevant parameters the applicant should supply additional data (e.g. stability, particle size, polymorphism).

Secondly, for new active substances, full details of chemistry, manufacturing process, quality controls during manufacture and process validation will be required, which may be provided in the form of a Drug Master File (DMF). The information should be presented in the CTD format and comprises of two separate parts, the applicants part and the restricted part (manufacturer). Thirdly, for new active substances, full details of chemistry, manufacturing process, quality controls during manufacture and process validation

[A] the term bibliographical data application not explicitly mentioned in MEDDEV. Mixed data or abridged application might also be considered.

[B] referencing to the dossier of an originator is not feasible. NB would have to submit a complete dossier[39]

[C] the CEP should be included in the dossier together with a written assurance that no significant changes in the manufacturing method have taken place after the certificate was issued.

(CPMP/ICH/281/95 and CPMP/ICH/381/95[66]) as outlined in the guidelines 3AQ5a[67] and CPMP/QWP/130/96[68]. Full description of the chemistry, manufacturing and controls applies also to new biotechnological/biological products with the following general guidelines on quality (3AB1a[69]), on cell substrate used for production (CPMP/ICH/294/95 [70]), specification (CPMP/ICH/365/96; ICH Q6B[71]) and stability CPMP/ICH/138/95 [72] need to be considered. Further guidance exists on quality and certain product types as for example monoclonal antibodies and allergens.

In process controls and control tests of the finished product
In process controls during manufacturing of the medical device shall be established and carried out if it is directly relevant to the quality of the incorporated medicinal substance.
Control tests on the finished product by qualitative and quantitative tests to determine the identity, purity, content, release, validation and batch results[A] shall be established and carried out to control the medicinal substance in the device.

Stability
To ensure desired functioning throughout the use-by date of the device, the stability testing of the medicinal product shall be established to justify the shelf-life and storage conditions. Several guidelines on stability testing of new drug substances (CPMP/ICH/2736/99 [73]), existing active substances (CPMP/QWP/122/02 [74]) and on in-use-stability (CPMP/QWP/122/02[75]) exist and should be taken into account where applicable. Data on content and purity of the medicinal product constituent shall be collected by validated stability assays.

Toxicity
The following aspects may be investigated by appropriate animal testing and must be addressed in the consultation dossier. The toxicity of the medicinal substance may be presented by referencing to the known toxicity profile or must be investigated in appropriate preclinical studies for the safety of new substances and prior to clinical studies in humans. Information on the toxicity and biocompatibility of the device in accordance with the standard 10993 series[76] may be included. Similar considerations also apply to the reproductive function, embryo/foetal and perinatal toxicity, mutagenic potential and carcinogenic potential.

Pharmacodynamics and Pharmacokinetics
The pharmacodynamics of intended action of the medicinal substance should be described in the context of its incorporation into a medical device. With regard to pharmacokinetics not all aspects will be relevant in most cases but the following aspects should be addressed. The pattern of local and systemic medicinal substance exposure should be described. If potential levels of systemic exposure may present a safety concern, maximum peak plasma concentration should be established. In addition, new active substances will require information on the release from the device, and, if relevant, its subsequent distribution and elimination from the body.

Local tolerance

[A] Seminar Medizinprodukte mit Arzneimittelanteil. Bonn 2006. Dr. Stephan, BfArM

Since the route of exposure to the medicinal substance may be different from its conventional application the impact on local tolerance may be investigated. Information on the local tolerance of the device in accordance with the standard 10993 series may be included or taken from the scientific literature.

Clinical evaluation
An European Commission guideline on the evaluation of clinical data was published with MEDDEV 2.7.1[77] and harmonized standards for clinical investigations on medical devices are described in ISO 14155-1:2003[78] and ISO 14155-2:2003[79]. Medical devices incorporating a medicinal product with ancillary action will normally be Class III products. The clinical data will form part of the information provided to the NB under Annex II or III of Directive 93/42/EEC. This data will address the safety of the device in its entirety. The usefulness of the medicinal substance in the medical device should be addressed by clinical data or in other Sections of the dossier. With the amendment of the MD Council Directives by Directive 2007/47/EC clinical data have now become a more strict requirement (Annex I Essential Requirements Section 6a); demonstration of conformity with the essential requirements must include a clinical evaluation in accordance with Annex X. Clinical data are relevant to the various aspects of the clinical safety and performance of the device and can be based on (i) published and/or unpublished data on market experience of the device; or a similar device for which equivalence to the device in question can be demonstrated; or (ii) a prospective clinical investigation(s) of the device concerned; or (iii) results from a clinical investigation(s) or other studies reported in the scientific literature of a similar device for which equivalence to the device in question can be demonstrated[77]. Equivalence, with regard to the literature route, must be demonstrated in all the following essential characteristics with the device, which is the subject of the published reports. The devices should have similarity with regard to the clinical, technical and biological parameters with special attention to the performance, principles of operation and materials[77].

Labelling
The labelling should be composed to assist in the understanding of the safety and usefulness of the medicinal substance together with the device.

2.4.3.2.2 Design Dossier

The manufacturing of medical devices follows a particular concept by design and compliance with performance standards, which is the fundamental distinction to pharmaceutical products. Inherent safety by appropriate design and construction has the highest priority for the medical device as outlined in Annex I Part I General Requirements Section 2 of Directives 93/42/EEC and 90/385/EEC as amended. The device must achieve performance standards intended by the manufacturer and suitable for intended use with regard to Art. 1 (2) of Directive 93/42/EEC. The list of harmonized standards, according to Art. 5 of Directives 93/42/EEC and 90/385/EEC, covering the essential requirements of the medical products or procedures are published in the Offical Journal of the European Communities and can be retrieved from the European Commission website[A].

[A] http://www.newapproach.org/Directives/Default.asp [20.03.08]

Part II of the Annex I of Directive 93/42/EEC outlines the design and construction requirements to guarantee the charaterististics and performance of the devices and their chemical, physical and biological properties (Section 7) in particular with regard to toxicity, biocompatibility of the material and compatibility to administrated medicinal products (Section 7.3). In addition, data on risk of infection, tissue from animal origin, sterilization and information (instruction and label) and others are also mentioned in part II. A list of headings to be addressed in a Class III product design dossier is annexed in appendix 7.3. The risk analysis, chemical, physical properties of the combination product, shelf life, instruction for use and patient leaflet will be addressed in both, the consultation and design dossier[A].
Furthermore, an appropriate QA systems and/or testing of each product/batch must be established and audited by the NB according to 93/42/EEC Annexes II to V (see chapter 2.2.3.1) before the conformity certificate can be issued.
According to Annexes II and III a statement indicating whether or not the device incorporates, as an integral part, a substance or a human blood derivative referred to in Section 7.4 of Annex I and the data on the tests conducted in this connection is required to assess the safety, quality and usefulness of that substance or human blood derivative, taking account of the intended purpose of the device.
Data on the intended use, preclinical evaluation and adopted safety principles become mandatory as part of the EC declaration of conformity (Annex II) and EC-type examination (Annex III) with MD Council Directives amendment 2007/47/EC. The EU MSs shall transpose the provisions of Directive 2007/47/EC until end of 2008 in national law, which shall become legally binding on 21. March 2010.

2.4.3.3 Drug Delivery Systems

For combination products consisting of a medical device used to administer a medicinal product (chapter 2.3.2.3), both products require their own development programmes leading to two separate licenses.
It should be emphasized that mutual compatibility, performance criteria and specification must be established in combination. The device must be designed and manufactured in such a way as to be compatible with the medicinal products concerned according to the provisions and restrictions governing these products and that their performance is maintained in accordance with the intended use[B]. In addition, the specification of the medicinal product, administrated by the device, should have test procedures and acceptance criteria related to the functionality of the delivery system, e.g. parenteral formulations packaged in pre-filled syringes or autoinjector cartridges may include controls and/or parameters of the device[C]. However, in case of pre-filled syringes where the syringe represents a Class I device, the manufacturer performs the conformity assessment of the syringe without consultation of a NB as for all Class I devices.
With regard to drug delivery systems and the MAA of the concerned medicinal product the application must contain data on the reproducibility of the dose delivery from the device in Section 3.2.P.2.4 Container Closure System, compatibility of the drug product with dosage

[A] Seminar Medizinprodukte mit Arzneimittelanteil. Bonn 2006. Dr. Schübel TÜV Süd
[B] Council Directive 93/42/EEC Annex I paragraph 7.3
[C] CPMP/ICH/367/96 Q6A Specifications 3.3.2.3 Parenteral Drug Products: j) Functionality testing of delivery systems

devices in Section 3.2.P.2.6 Compatibility and other information on the device could be described in Module 3.2.R Regional Information[80].

2.4.4 General Requirement to Conduct Clinical Trials in the US and the EU

Presentation of clinical data by bibliographic data or the conduct of clinical trials is a general requirement to obtain an authorisation for medical products inclusively of combination products but two regional diverging approaches exist. The IND application in the USA focuses on a new drug, and supports its development, including the design of necessary clinical studies. The Directive 2001/20/EC and clinical trial application (CTA) focuses on the proper conduct of clinical studies, with new or authorised drugs[A] rather than drug development.

2.4.4.1 Investigational New Drug and Investigational Device Exemption

Prior to start of the clinical development programme of a combination product the sponsor has to file an IND application for a new drug or biologic or approved products supposed to be used outside the granted label. The entire process of application and required development programme is laid down in IND Regulations 21CFR312[81].
In case the combination product will be assigned to the CDRH and regulated as a device an approved IDE is required. An IDE [82] allows the investigational device to be used in a clinical study to collect safety and effectiveness data required to support a PMA application or premarket notification 510(k) submission. Only a small percentage of 510(k)s requires clinical data to support a marketing clearance by the FDA.
In most cases one investigational application is submitted for the clinical investigation of the combination product as a whole. By assignement of the combination products to one of the three applicable FDA Centers and from jurisdictional point of view the sponsor must follow the formal IND or IDE process but typically needs data to support both processes.

2.4.4.2 Contacts with US Agency FDA

The manufacturer/applicant has the opportunity to request for milestone/collaboration meetings with the responsible FDA Centers CDER, CBER and CDRH throughout the development process and submission of investigational and marketing application. At a very early stage of development and before beginning the official IND/IDE process the sponsor could start informal “pre-pre-IND/IDE” discussion with the FDA after submitting preclinical study drafts to discuss key consideration for preclinical testing programme or study designs.
Pre-IND/IDE meeting of the sponsor with the relevant Centers of the agency are optional parts of the formal IND process but highly recommended to facilitate a common understanding on the development programme of the product, especially for combination products. Typically, these meeting are face-to-face meetings between the sponsor, representatives of the FDA review team from CDER, CBER or CDRH and OCP. The main topics of the meeting will include confirmation of the jurisdictional determination of the combination product, required preclinical testing programme for both, the device and the

[A] DGRA presentation 2006 Prof. Seitz

drug part of the combination product, animal studies and planned design of clinical trial(s). Typically the milestone meetings are concerning an "End-of-Phase I Meeting" to discuss Phase I results, and an "End-of-Phase II Meeting" to discuss the further development and the design of the pivotal Phase III protocol as well as a variety of other meetings, e.g. Special Protocol Assessment. Novel products are often discussed in public hearing of the Advisory Committee to evaluate issues as safety or efficacy with experts in the field.

2.4.4.3 General Requirement to Conduct Clinical Trials in EU

The Directive 2001/83/EC contains the European legal framework on authorisation and supervision of medicinal products and a detailed guidance on clinical testing by the amendment of Directive 2005/28/EC and 2001/20/EC. In EU a clinical trial has to be approved by the concerned NCA of each country while the trial will be performed before the recruitment of patients or volunteers can be started.
Clinical trials with medical devices follow the Council Directives 93/42/EEC and 90/385/EEC Annex X and VII, respectively, and applicable standards as ISO 14155-1:2003[78] and ISO 14155-2:2003[79].

2.4.5 Aspects of Labelling for Combination Products in the US and the EU

Labelling US
Labelling of combination products is a challenging task for industry and authorities to reflect the relevant safety and effectiveness results of both components. The instructions-for-use labelling for the combination product will represent a compromise of standard drug and device labelling requirements. Labelling of novel combination products will by performed in close relationship between the applicant and the FDA to develop an appropriate labelling 102.

Labelling EU
As for all Class IIb and III medical devices, also drug-device combination products authorized as a medical device must be accompanied by the information needed to use the device safely and properly, and the name and address of the manufacturer. The information comprises the details on the label and the data in the instructions for use. With regards to devices incorporating human blood derivates with ancillary action (Art. 1 4(a) of MDD and AIMDD), the package labelling must indicate that the device contains a human blood product. Furthermore the instructions for use of MDs must indicate if a medicinal substance, or human blood derivates were incorporated into the device as an integral part in accordance with Section 7.4 annex I.
In case of AIMDs with intended use as a drug delivery system (separate license for the drug and device) adequate information regarding the medicinal products that the device in question is designed to administer should be included.
For medicinal products developed, tested and authorised to be used in combination with a certain medical device, the device will be indicated in the Summary of Product Characteristics (SmPC). If the medicinal products and a certain medical devices can only be given in combination to achieve the therapeutic effect, the device will be mentioned in the SmPC Section 4.1 (therapeutic indication) and the medicinal product can not be used in combination with any other, even similar devices, without being an off-label use. Hence, to

avoid costs for unnecessary line extensions with other or modified devices the information on the device used in combination with the medicinal product should be provided in Section 4.2 (Posology and methods of administration; see chapter 3.2.3.2). However, the indication claims for both products should be concurrent.

3. RESULTS: AUTHORISED COMBINATION PRODUCTS

3.1 Publicly Available Information on Approved Combination Products

To complete the picture of the regulatory environment, marketed combination products will be presented by their type of authorisation and publicly available information such as assessment reports, SmPC, labelling and patient information leaflets. Prior to this, the provisions and sources to obtain these information on medical products in the US and the EU will be detailed. Further on, as information on medical devices is very strictly handled in the EU, the results of a survey are included, which was performed at six European NCAs and the EMEA requesting data on performed consultations and the assessments of the dossiers (questionnaire included in appendix 7.4). Indicated internet sources and the extent of information available served to retrieve the information described in chapter 3.2, but are not suitable to provide a comprehensive overview on available pharmaceutical or medical device information services by regulatory bodies or other institutions.

3.1.1 Legal Provisions and Sources in the US

Basic product information, information on therapeutic indications, supporting documentation for product licensing, annual work programmes of the FDA Centers and many more topics are easily publicly available via the internet to inform the interested citizens. The legal basis was laid down in the Freedom of Information Act in 1996 [83] and specified for drugs, biologics and medical devices in 21CFR314.403[84], 21CFR601[8] and 21CFR814.9[85], respectively.
The responsible FDA Centers CDER, CBER and CDRH provide detailed information on approved medical products and their assessment as NDAs, BLAs and PMAs or 510(k)s on their websites. The extent of available information depends on the date of approval, type of product, supplement or new application and reviewing Center. For example, the CDER website provides three search options to retrieve product information, approval letters, label and reviews of the application from the drug database[A, B, C]. Since CBER is responsible for reviewing different types of application of BLAs, NDAs/ANDAs for biological products and PMAs or 510(k)s for biological devices, the information on approved products are listed under the product category[D]. The CDRH website supports the search for PMA approvals and 510(k) clearance information as well as for device

[A] http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm [02.02.2008]
[B] http://www.fda.gov/cder/orange/default.htm [02.02.2008]
[C] List of Drugs, Medical Devices, Biologics and Veterinary drug product legacy information from February 1991 through September 1996. http://www.fda.gov/cder/da/ddpa.htm [02.02.2008]
[D] http://www.fda.gov/cber/products.htm [02.02.2008]

classification and recognized consensus standards[A]. Hence, publicly available information from the Centers range from FDA press releases, approval letters and package leaflets up to detailed scientific review packages (Table 10). Many more product-related information such as warning letters or transcripts of Advisory Committee meetings can be retrieved from FDA websites but is beyond the scope of the thesis. Information on combination products and their assessment can be obtained from the product databases of the FDA Centers responsible for the lead review and issuing of the license (see above). Unfortunately, there is no explicit search term for combination products or performed consultation procedures to perform a focussed search. Currently, 26 approved combination products are published on the OCP website[B] but the list is not comprehensive and information on products authorized as NDAs is limited to the FDA approval press releases.

Table 10: Type and source of product information at FDA Centers

	CDER	CBER	CDRH
Basic items	• drug name & company • application no. • active ingredient • dosage form & strength • marketing status • FDA action date	• drug name & company • application no. • active ingredient • indication • FDA action date	• device name & applicant • application no. • classification • date received/approved • Docket Number/Notice • Advisory Committee • Expedited Review • statement/supplement • postapproval study • supplements
Review and approval	• approval letters • package insert • labelling • reviews • information for patients	**BLA** • approval letters • summary • labelling • reviews • information for patients **Biological PMA/510(k)** - see right column	**PMA** • approval letters • package insert • summary safety & effectiveness • consumer information **510(k)** • notification letter • 510(k) summary
Divers	• Chemical type • Review classification • others	• Product/Manufacturer Lists • others	• Standards • Device classification • others

Table 10: Used terms on the websites may vary depending on the Center, product, application date and type.

3.1.1.1 OCP Annual Performance Reports

By enforcement of MDUFMA the OCP was required to draw up and publish (i) the numbers and types of reviewed combination products and the timeliness, (ii) the number of premarket reviews and consulted agency Centers and (iii) the improvements in the consistency of postmarket regulation of combination products in annual reports. Up to now the OCP has issued three full annual reports, for 2004[C], 2005[D] and 2006[E], to present annual performance assessments for combination products by timeliness of their assignments and

[A] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/search/search.cfm [02.02.2008]
[B] http://www.fda.gov/oc/combination/approvals.html [02.02.2008]
[C] http://www.fda.gov/oc/combination/report2004/ [28.03.2008]
[D] http://www.fda.gov/oc/combination/report2005/ [28.03.2008]
[E] http://www.fda.gov/oc/combination/report2006/ [28.03.2008]

review and other activities. Unfortunately, content-related information of approved combination products is not part of the reports as for example practiced in the annual reports of Office of Device Evaluation or website of CDER Drug and Biologic Approvals.

Table 11: Combination product application in 2004, 2005 and 2006

No.	Description	# 2004	# 2005	# 2006
1	Convenience kit or package	4	8	2
2	Prefilled drug delivery device/system	15	9	11
3	Prefilled biologic delivery device/system	0	1	1
4	Device coated/impregnated/otherwise combined with drug	55	57	60
5	Device coated or otherwise combined with biologic	5	8	7
6	Drug/biologic combination	0	0	0
7	Separate products requiring mutually conforming label	8	5	2
8	Possible combination based on mutually conforming labelling of separate products	3	0	1
9	Other type of combination product	5	3	5
	Totals	**95**	**91**	**89**

Table 11: Authorisation application in 2004[A], 2005[A] and 2006 differentiated by nine categories of combination products. The majority of combination products are represented by category 4 Device coated/impregnated/otherwise combined with drug. Investigational submissions for INDs, IDEs and HDEs were excluded.

The OCP developed a classification of combination products in nine categories (Table 11) to aid FDA reviewers in classifying products under review[86, 13]. The number of applications for authorisation is about ninety with a slight decreasing tendency in the last two years. The majority of combination product applications are represented by category no. 4 (devices coated/impregnated/otherwise combined with drug), which were 58%, 63%, and 67% of all authorisation applications in 2004, 2005, and 2006, respectively. However, it is not indicated elsewhere in the annual reports how many of the applications successfully passed through the review process.

Table 12: Requests for intercenter consultative or collaborative review

Consulting Center		CBER			CDER			CDRH			Total		
		04	**05**	**06**	**04**	**05**	**06**	**04**	**05**	**06**	**04**	**05**	**06**
Primary assigned Center	**CBER**	-	-	-	4	9	7	16	36	33	20	45	40
	CDER	2	-	2	-	-	-	57	36	62	59	36	64
	CDRH	9	9	10	122	185	221	-	-	-	131	194	231
	Totals	11	9	12	126	194	228	73	72	95	210	275	335

Table 12: The majority of intercenter consultation concerned combination products assigned as devices in which CDRH requested consultation from CDER. The number of requests is not directly comparable to the number of combination product applications reported in the previous chapters as some applications were associated with multiple consulting requests or were unrelated to an application in 2006. Updated numbers from the next annual report were not available for 2004 and 2005 as in Table 11.

The FDA is receiving significantly more combination product applications for review[B] based on a 10% increase of investigational application (249 to 275[A]). The number of

[A] updated numbers for 2004 and 2005 were taken from the next annual report
[B] assumption of author: investigational (IDE, IND) or marketing authorisation application

applications for marketing authorisations for combination products remained almost unchanged (Table 11). Taking the numbers of intercenter consultations from the annual reports, which is not limited to combination products only, the requests are continuously increasing with 31% in 2005 and 22% in 2006 (210 to 275 to 335, Table 12).

3.1.2 Legal Provisions and Sources in the MSs of the EU

Fundamentally, the availability and re-use of public sector information supports the content and spirit of the treaty for the establishment of an internal market in the European Community with undistorted competition. The Directive 2003/98/EC[87] provides a basic framework and set of rules governing the re-use and the practical means of facilitating re-use of existing documents held by public sector bodies of the MSs and is not limited to medical products. This Directive applies to documents that are made accessible for re-use when public sector bodies license, sell, disseminate, exchange or give out information. However, the Directive does not apply to documents for which third parties hold intellectual property rights and does not affects the protection of individuals. It also does not contain an obligation to allow re-use of documents. The decision whether or not to authorise re-use will remain with the Member States or the public sector body concerned. Accordingly, the German BfArM responded, that the survey of the author would be handled persuant to the national freedom of information act (Informationsfreiheitsgesetz, IFG[88]). The IFG came into force on 1 January 2006.
The following legal provisions were implemented to make information on authorised medicinal products in the EU publicly available. According to Art. 21 (3) and (4) of Directive 2001/83 as amended, the relevant CAs need to publish a Public Assessment Report (PAR) of marketing authorisations of medicinal products issued via the MRP or the DCP. The EMEA provides available information on the products assessed by the Committee for Medicinal Products for Human Use (CHMP) at the end of the centralised evaluation process pursuant to Art. 13(3) of Regulation (EC) No 726/2004.
With regard to information on licensed medical products, NBs or NCAs for devices performing the conformity assessment represent the regulatory bodies for publishing relevant information, but restrictions apply as described in chapter 3.1.2.2.

3.1.2.1 Information on Medicinal Products from NCAs and the EMEA

The internet websites of NCAs – amongst others – inform or provide access to general news on pharmaceutical products and applicable regulations and guidelines, maintain or provide links to databases to search for approved medicinal products in the MS, drug safety information, internet portals for electronic submissions. Specific information on medical devices for interested citizens is not supported and restricted to manufacturers or authorities with regard to notification obligation and surveillance of medical devices.
The European or Public Assessment Reports (EPARs; PARs) on approved medicinal products indicating the data which served as the basis for granting of the marketing authorisation are available on the internet websites of the CAs. In general the EPAR or PAR consists of information about the initial procedure, SmPC, product information leaflet, labelling and scientific discussion subdivided in an introduction, quality, non-

[A] not shown, for reference: http://www.fda.gov/oc/combination/report2005/overview.html

clinical and clinical aspects part, overall conclusions and steps taken after authorisation. Any commercially confidential information is excluded from the report before publishing. Another useful information source on medicinal products authorised via the MRP is the product index MRI[A] of the Head of Agencies website or the Eudrapharm database[B].

Table 13: Type and source of product information in EU MS

	EMEA[C]	BfArM/DIMDI[D]	MHRA[EF]	MEB[G]
General	• Product name • MAH • Active substance • INN • Pharmaco-therapeutic Group • ATC Code • Therapeutic indication • Date MA • Orphan designation	Comprehensive pharmaceutical and bibliographic information system with different access levels for the public and professionals (in parts subject to fees)	Pharmaceutical and device information system for the public and professionals (in parts subject to fees)	• MA number • Product name • Active subst. • Dosage form • Country of origin • Legal status • Approval date • MAH
Review & Approval	• Summary for the public • Presentations • EPAR	No information	• PIL • SmPC • PAR (30.10.2005)	• SmPC • Package leaflet • PAR

Table 13: Selected European agencies and internet-based medical information services. Only internet information platforms without fees are considered.

3.1.2.2 No Information on Medical Devices from Notified Bodies

NBs are nationally accredited organisations under private law responsible for issuing certificates and CE marking of devices including medical devices. No information on the approval or even name of any certified device is made public by NBs. Since NBs are private institutions, documents of their assessments do not belong to public sector information and applicable provisions do not need to be respected. The NBs reason their refusal by the confidentiality clause according to Art. 15/20 of the Council Directives 90/385/EEC and 93/42/EEC and decline inquiries for information on products or performed consultation procedures[H].

Databases for medical devices have been established for the notification obligations of manufacturers, test laboratories and NBs for the following purposes as laid down in MDs Directives 93/42/EEC Art. 14, 14a: notification on the first placing on the market and safety officer, incidents, clinical investigations with medical products, information relating to granted or denied certificates for medical devices and the classification and demarcation of medical devices. The central European database EUDAMED on medical devices is exclusively accessible to NCAs. However, the patient information leaflet on the medicinal

[A] http://www.hma.eu/mri.html [04.02.2008]
[B] http://eudrapharm.eu/eudrapharm/selectLanguage.do [04.02.2008]
[C] http://www.emea.europa.eu/htms/human/epar/a.htm [04.02.2008]
[D] http://www.dimdi.de/dynamic/de/index.html [04.02.2008]
[E] http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=342 [04.02.2008]
[F] http://emc.medicines.org.uk/ [04.02.2008]
[G] http://www.cbg-meb.nl/CBG/en/human-medicines/geneesmiddeleninformatiebank/default.htm [04.02.2008]
[H] personal communication Dr. Schübel TÜV Süd

substance of medical devices containing medicinal substances with ancillary action can be found on pharmaceutical database websites such as the Red List[A] and MEB but no public information system for medical devices exists so far. Hence, information on combination products authorised as medical device is very limited. With the amendment of the confidentiality clause in Art. 15/20 of Directives 93/42/EEC and 90/385/EEC by Directive 2007/47/EC, a summary of information and data related to the device needs to be made publicly available. The new provisions are not yet in force but must be transposed into national law until 21 December 2008 and become legally binding on 21 March 2010.

3.1.2.3 Results of the Survey on the Consultation Procedure

In the frame of the survey conducted, the following information on performed consultation procedures and assessed medical products was obtained from the agencies. The number of consultation procedures on medicinal product constituent of medical devices incorporating a medicinal product with ancillary action is shown in Table 14. Although information on performed evaluations with regard to the medicinal product constituent was inquired in the questionnaire, no data were provided by the agencies due to confidentiality reasons with one exception. The German BfArM responded to the questionnaire in a detailed manner and provided two consultation reports. Regarding combination products in which the medical device and medicinal product form a single integral product, it seems that not a single consultation procedure has been performed by NCAs or the EMEA. However, the responses could not be interpreted unambiguously. At the IMB in Ireland a consultation service for NBs on medicinal substances was not in place until the latter part of 2007. Although the central British and French CAs confirmed receipt of the request and their competence, they did not return the requested information or an official decision within the timeframe of four months.

Table 14: Consultation procedures at NCAs and the EMEA between 2001 and 2007

Competent Authority	Consultation procedures							
	2001	2002	2003	2004	2005	2006	2007	Total
MEB (NL)	3	8	6	10	13	13	n.i.	53
BfArM (DE)	1*	8*	10*	20	10	2	3	54
IMB (IE)	n.i.	n.i.	n.i.	0	0	0	0	0
MPA (SE)	n.i	n.i	n.i	1	3	1	1	6
EMEA	n.a.	0	0	0	1	1	1	3

Table 14: Consultation procedures on medical devices incorporating medicinal substances with ancillary action performed at indicated European NCAs and the EMEA between 2001 and 2007. The data was collected by a survey performed in the context of this master thesis. It is not indicated for the NCAs whether the numbers covers all performed consultations or those with positive evaluation only. Consultation procedures by the EMEA are positive opinions. However, the number of positive opinions on performed consultation procedures obtained from Dr. Neugebauer is not consistent with the one published. *numbers taken from BfArM presentation.

European Medicines Agency (EMEA, Great Britain London)

The EMEA has been consulted by NBs on the quality, safety and usefulness of a device incorporating a medicinal product derived from human blood according to Directive 2000/70/EC. In these consultation procedures the evaluation focuses only on the medicinal

[A] http://www.rote-liste.de/Online/login_html [22.04.2008]

product constituent in the context of its use in the device. The NBs evaluate the entire product regulated as device. The positive opinion of the medicinal product constituent assessment during the consultation will only be published in the monthly CHMP reports after successful CE marking of the device. At present, four human serum albumin (HAS) containing media received a positive opinion; no other medicinal product was indicated. The reverse case, contacting of NBs by the EMEA to evaluate the device-related features of a medicinal product forming a single integral product with a device constituent, did not occur yet.
In the frame of the survey no assessment reports of the consultation dossier were provided by the EMEA, justified by the confidentiality of the documents as their disclosure would undermine the protection of commercial interests[A]. The author concludes that this justification is not valid as the request excluded personal and confidential information and suggested to black out confidential information. In addition, the EMEA consultation guideline explicitly mentions that a public report on the consultation procedure at the EMEA by NBs on ancillary medicinal substances used in medical devices will be published on the EMEA website at the time the device obtains the CE mark[39]. This has not yet been established, unless "publishing of a public report" simply means merely stating the medicinal product constituent, the review time, the date, the product and the company concerned.

Medicines Evaluation Board (MEB, The Netherlands)
The MEB only completed a limited part of the questionnaire justified by confidentiality towards the NBs to which the advice has been provided in the respective consultation procedure. Between 2001 and 2006 the MEB received 54 valid requests for consultation procedures of which 24 were positively and, six negatively, while 23 are still pending or indefinite to be continued after a negative opinion was given. The number of requests for consultation, given in brackets, concerned the following therapeutic categories: cardiovascular (17), skin/dermatological (12), orthopedic (6), contraception (5), surgery (4), dental (3), and miscellaneous (6). No product types were mentioned in the response although it was inquired.

Medical Product Agency (MPA, Sweden)
In total only six consultation procedures with two different types of combination products were performed at the MPA; four concerned DESand two human albumin containing *in vitro* media (via the EMEA). The MPA provided a very general response by a brief statement that the assessment will be performed according to MEDDEV 2.1/3 rev.2 and European DMF concerning the quality, safety and clinical usefulness.
Currently MPA is working on the implementation of Directive 2007/47/EC into national legislation, which will be published in December 2008.

Federal Institute for Drugs and Medical Devices (BfArM, Germany)
The German BfArM responded in detail to the questionnaire by providing an overview and attached two consultation reports on a gentamicin-containing bone cement (3.2.4.3) and a lubricant combining an antiseptic and local anaesthetic with confidential parts shown blackened. The consultation dossier of the latter was denied twice due to deficiencies in the

[A] Regulation No 1049/2001 Article 3.2a.

pharmaceutical quality and a missing pharmacological-toxicological expert report. As both medicinal substances, lidocain and chlorhexidin, are well established substances, bibliographic data to document the safety and usefulness were accepted. Inadequate labelling information with regard to mentioned counter measures to be taken in case of side effects was criticised.
There are no current activities at the BfArM concerning Art. 20 of Directive 2007/47/EC.

Table 15: Types of combination products assessed by BfArM and MPA

Product type	2004	2005	2006	2007
Drug-eluting stent	- (1)	1 (2)	-	- (1)
Antibiotic-containing bone cement	1	1	-	2
Antibiotic-containing wound patch	9	2	-	-
Antibiotic-coated catheter	1	-	-	-
Antibiotic-coated nails	-	3	-	-
Intrauterine pessar	4	-	-	-
Optalmic gel	-	-	1	-
Antibiotic-containing lubricant	1	3	-	1
Peloid-containing essential oils	-	-	1	-

Table 15: BfArM and MPA (in brackets) kindly provided an overview of performed consultation procedures and assessed combination product types as requested in the survey. MPA's involvement in the assessment two human albumin solutions via the centralised procedure is not indicated.

3.2 Case Reports of Marketed Combination Products

Five product types are presented in detail to illustrate the regional differences of the dossier requirements, assessment, and licensing of combination products. However, chosen examples do not claim to be representative to serve as a generalisation of the requirements to authorise combination products in the US or the EU.

3.2.1 Drug-Eluting Stents are Regulated as Devices

Stents are implantable stiff bar metal or plastic mesh tubes used as scaffold to reopen narrowed vessels caused by arteriosclerotic plaque deposits. Besides the coronary bypass surgery, the implanting of stents into the arteriosclerotic coronary vessels by percutaneous transluminal coronary angioplasty (PTCA) represents a possible interventional therapy of coronary heart disease to effectively restore blood flow in the ischemic heart. Late thrombosis events and restenosis of bare metal stents (BMS) are commonly observed side effects impairing a successful long-term therapy. Coating of the stent surface with the anti-coagulant heparin[89] or radioactive stents were developed to improve the late side effects. DES were shown to be a potential alternative solution to prevent a restenosis and several DES models are presently marketed by Cordis Corporation (CYPHER™), Boston Scientific Corporation (TAXUS™), and Medtronic Inc. (Endeavor™). They have shown a significant reduction of restenosis by the local intervascular release of anti-proliferative drugs from the implanted stent coating. However, following DES implantation the anti-platelet and anticoagulation therapies are still required.
After the first DES application had been granted, guidelines for intravascular stents were issued by the EMEA and the CDRH to provide consistent advice on the requirements and to meet the growing demand of DES applications in both regions[90, 91, 92]. A number of

applicable standards could be retrieved from the CDRH guidance but represent no integral part of the European guideline and the following chapters.

3.2.1.1 CYPHER™ CE marked in the EU

Sirolimus is naturally occurring cyclosporine, firstly approved to prevent renal transplant rejection and marketed by Wyeth Pharmaceuticals as Rapamune since 1999 in the US. The European MAA was granted in 2001 via the centralised procedure[A]. Due to the proven cytostatic properties of sirolimus, to inhibit T-lymphocyte activation and smooth muscle and endothelial cell proliferation, it had been chosen by Cordis Corporation as a coating for coronary stents to prevent restenosis caused by neointimal hyperplasia observed with bar metal stents.
As published by Cordis Corporation in April 2002[93], the CYPHER™ Sirolimus-Eluting Stent received the CE mark in the indication for de novo and restenotic coronary artery lesions and based on the stainless steel Bx VELOCITY™ Stent coated with a sirolimus-containing polymer. The European Class III device marketing license is based on a comprehensive and favourable review of functional test data, preclinical and long-term clinical data. One pivotal clinical trial had been performed with 238 patients in EU, Brazil and Mexico (RAVEL[94]) demonstrating sustainability of a low incidence of major adverse cardiac events and maintenance of zero restenosis during the one-year follow-up[93]. No additional information by public assessment reports on CYPHER™ or DES in general could be obtained from European or national databases, websites of agencies or by the survey performed.

Presently, with the draft guideline on DES released by the CHMP and the Efficacy Working Party in March 2007[91], regulatory aspects and consistent information of required non-clinical and clinical data for the development of DES are available. The guideline aims at assisting applicants and the NBs in the consultation procedure to the regulatory bodies of the MSs or the EMEA regarding the assessment of the safety and usefulness applied to medicinal substances. It also clarifies that DES could be considered as Class III medical devices incorporating medicinal substances with ancillary action.
In the case of active implantable and Class III devices, evidence of the clinical performance and safety of a medical device is provided by means of clinical data. Clinical data could be provided by bibliographic data under consideration of equivalence with the device in question. The requirements to collect non-clinical and clinical data will also depend on the knowledge on the ancillary medicinal substance in the first place. Hence, different scenarios are distinguished, i.e. primarily (1) the medicinal substance of the combination is known to the CA and already registered in the setting of a DES; (2) the medicinal product of the combination is known to the CA but not registered in the setting of a DES; (3) the medicinal product of the combination is a new active substance and therefore not known to the CA neither as a medicinal product nor in the setting of a DES. Secondly, comparable medicinal substance release characteristics and stent/polymer combination or medicinal substance release characteristics must also be considered. These different possibilities of the DES raise important questions on the amount of data needed

[A] Council Regulation (EEC) No 2309/93 superseded by Regulation (EC) 726/2004

for adequate evaluation to establish the safety and usefulness. The guideline continues to outline the applicable requirements for each above-mentioned category and subcategory.

3.2.1.2 CYPHER™ PMA Approval in the US

Although the RAVEL study suggested that the CYPHER™ stent showed promise and was sufficient for the granting of the CE mark in EU, the FDA decided that it was not large enough to assess the patients most likely to benefit from the device. The FDA requested a larger US study (SIRIUS[95]) with 1058 patients to evaluate the product's safety and effectiveness in a much broader population. Finally, the FDA approved the CYPHER™ stent in April 2003, based on biocompatibility, *in vivo* PK, *in vitro* engineering testing, coating characterisation, CMC, sterilization, stability, *in vivo* animal tests and three clinical studies (first-in-man, RAVE and SIRIUS trials), which provided reasonable assurance of safety and effectiveness.
The regulatory status of coronary DES was clarified and the RFD decision letters of the paclitaxel or sirolimus DES were published on the OCP website. The FDA has confirmed that the CDRH is responsible for the premarket review and regulation of coronary DES. The inspections of the manufacturing facilities were found to be in compliance with relevant device GMP regulations and pharmaceutical CGMP regulations.

Performance standards
The relevant *in vitro* engineering testing was conducted on the uncoated, bare versions of the Bx VELOCITY™ Stent in accordance with the FDA "Guidance for the Submission of Research and Marketing Applications for Interventional Cardiology Devices: Intravascular Stents", May 1995[A]. Supplementary *in vitro* engineering tests were also performed on the coated CYPHER™ Stent.

Analytical tests and specifications
A series of analytical methods was developed to characterise and set of initial specifications for the CYPHER™ Stent coating. ICH Guidelines were followed for the testing routinely performed on the CYPHER™ Stent as part of CMC release testing, where applicable. The release testing included analysis of the polymer, drug identity, drug content and/or impurities and uniformity, residual solvents, *in vitro* elution and particulates.

Stability
The stability testing to establish package integrity and functional testing of the stent system was conducted on the aged product. In addition, appropriate engineering tests were repeated on the aged product and compared to baseline. The stability test parameter concerned the drug identity assay, degradants, *in vitro* elution, particulates, sterility, drug content uniformity, residual solvents and endotoxins. The data generated support a shelf life of 6 months. A GLP polymer stability study was conducted to establish the chemical stability of the main inactive ingredients in the CYPHER™ Stents, following ISO 10993-13. The CYPHER™ Stent System is sterilized using ethylene oxide sterilization, and was validated per AAMI/ISO 11135:1994.

[A] could not be retrieved

Biocompatibility
The biocompatibility testing was performed pursuant to ISO 10993 – 1 and "Guidance for the Submission of Research and Marketing Applications for Interventional Cardiology Devices: Intravascular Stents". The genotoxicity, carcinogenicity, and reproductive toxicity of CYPHER™ Stents were not evaluated. Formal carcinogenicity testing was not required because sirolimus does not remain on the product longer than six months.

Preclinical testing
In support of the application and with regard to the preclinical and clinical toxicology testing of sirolimus, the drug substance and polymer information was referenced to studies conducted by Wyeth-Ayerst and SurModics Inc.'s Device Master File, respectively. The pharmacokinetics of sirolimus as delivered by the CYPHER™ Stent had been determined in patients with coronary artery disease after implantation.
Detailed arterial histopathology and histomorphometry are not obtainable through human clinical trials, so a series of *in vitro and in vivo* animal studies were conducted to evaluate the safety, efficacy (proof of concept) and overall product performance. These studies served as the basis for the dose selection for the CYPHER™ Stent used in the clinical studies. The intravascular safety and biocompatibility of sirolimus-eluting stents were evaluated in a series of animal studies in a porcine model of stent-mediated vascular injury. The results of these tests supported the safety and biocompatibility of the CYPHER™ Stent.

Clinical testing
The safety and efficacy evidence for the CYPHER™ Stent came from three clinical studies investigating the performance of the CYPHER™ Stent in patients with symptomatic ischemic disease due to *de novo* lesions in native coronary arteries. The SIRIUS and RAVEL trials were multi-center, double-blind, randomized clinical trials that compared the CYPHER™ Stent to a control consisting of an uncoated stainless steel stent. The SIRIUS trial was a large study with a primary clinical endpoint of target vessel failure at 9 months, which was significantly reduced in comparison to control. Clinical outcomes through 12 months were consistent with the 9 month outcomes. The incidence of major adverse cardiac events in these patients was statistically significantly lower than that of patients who received an uncoated stent. The RAVEL trial was a smaller study with a primary angiographic endpoint of late loss at 6 months, which was significantly reduced in comparison to control. Clinical outcomes at 24 months were also significantly improved.

Advisory Committee and FDA approval
At the Advisory Committee meeting performed by the Circulatory Systems Devices Panel the CYPHER™ Stent System was recommended for PMA approval. CDRH followed the recommendation of the panel under the condition to submit 5 year follow-up data on patients enrolled in the pivotal, supportive and feasibility studies.
This PMA application was designated for expedited review on 28 June 2002 by CDRH since it was determined that the CYPHER Stent could represent a breakthrough technology which offers a viable alternative to the FDA approved technologies for treating occlusive coronary artery disease. This PMA application sought approval for the first drug-eluting coronary stent system.

3.2.1.3 Regulatory Aspects on Drug-eluting Stents

A comparison of the authorisation of the DES Cypher™ provides a quite objective snap shot on the regulatory requirements in the EU and the US since it concerns the identical product, company and indication, possibly similar data packages submitted, first in class product and both, known and authorised drug and device constituents. However, the extent of publicly available information is very unbalanced due to the restrictive EU medical device publicy information policy. The present guidelines on DES in the EU and the US were not in place at the time when the products had been developed and licensed and, therefore could not be used for a direct comparison.
The assignement and classification of DES as Class III device was identical for both regions. Obviously, the main difference in the authorisation of Cypher™ concerns the number of studies and sample size of the pivotal study required for approval. The European NB was satisfied with one confirmatory study including 238 patients, whereas the FDA requested a larger pivotal US trial with 1058 patients to determine the patient population most likely to benefit from the device. Similar patient numbers were required for later PMA approval of the paclitaxel DES from Boston Scientific Corporation in 2004. In this context it should be noted that in 2005 Medtronic's DES Endeavor™ obtained CE marking and access to the European market with 1197 patients participating in ENDEAVOR II study. Another aspect of FDA's request for a second larger study might be the fact that the RAVEL study was performed outside the US, although foreign studies are accepted if they meet the requirements detailed in 21CFR312. One pivotal trial with 238 patients might be at the very lower end and could possibly be justified by focussing on rather performance-related than efficacy oriented clinical data evaluation[77].
Recently in 2008, a new European guideline on clinical evaluation of coronary stents was drafted by the Medical Devices Clinical Evaluation Task-Force (CETF) to outline in particular the clinical requirements and expectation for this product type. However, it will also have a general scope on clinical evaluation of devices since it is planned to add this guideline as an annex to the already existing MEDDEV 2.7.1 guideline " Evaluation of Clinical Data"[96]. Together with the introduction of a clinical evaluation in Section 5a/6a of Annex I of the MD Council Directives after the amendment with Directive 2007/47/EC this might contribute to strengthen the requirement for clinical data for medical devices in the EU.
Despite the doubtless success of DES also criticism has arisen when late thrombosis events were noticed with these products. After placing on the market, safety issues with respect to small but increased rates of late stent thromboses and non-cardiac mortality were observed in patients treated with DES in comparison to patients treated with bare-metal stents (BMS). An FDA Advisory Committee meeting in 2006 investigating the reported safety issues and concluded that the DES safety concerns do not outweigh their benefits compared to BMS, but off-label use is associated with an increased risk of stent thrombosis, death and myocardial infarction compared to on-label use of DES. The panel recommended at least 12 months of dual antiplatelet therapy for off-label uses of DES and called for larger and longer premarket clinical trials and longer follow-up for post-approval studies[A].

[A] FDA Clinical Overview for Panel Packet DES Thrombosis Panel December 7-8, 2006. www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4253b1_01.pdf [06.04.2008]

3.2.2 HAS-containing Media are Licensed as Medical Devices

For assisted reproduction technologies HAS-containing media have been licensed as medical devices in the EU and the US for cultivation of gametes and blastocyst stages. In the EU HSA from blood donation is a blood product and in context of its use as ancillary medicinal substance the NB must seek a scientific opinion by consulting with the EMEA on the quality and safety of the substance including the clinical risk benefit profile of incorporation according to Annex I's Essential Requirements Section 7.4 of Directive 93/42/EEC before the NB may issue a conformity certificate for licensing of the device. All devices incorporating a medicinal product from human blood derivates with ancillary action are Class III products whereas in the US the HSA-containing product EmbryoAssist™ from MediCult a/s is a Class II product and licensed by premarket notification 510(k) clearance by the CDRH showing substantial equivalence to legally marketed predicate devices.
The EMEA issued four positive opinions on HSA-containing media (chapter 3.1.2.3) with regard to albumin as medicinal product constituent but no information on the assessment is available. However, at least the product information is published on the websites of the relevant companies MediCult a/s, Irvine Scientific and Vitrolife Sweden AB.
In contrast, the FDA 510(k) notification summary of EmbryoAssist™ provides some remarks on safety and effectiveness but must be read in conjunction with the summaries of essentially similar predicate devices previously approved. Biocompatibility testing had been performed with predicate devices. Stability, cytotoxicity and batch testing parameters are presented for EmbryoAssist™. Design and results of nonclinical and clinical studies are briefly discussed in the clinical documentation. No remarks on performed consultation procedures with either the CBER or CDER were found; it is not even clear whether it is considered as combination product or biological device (Table 10).

3.2.3 Devices coated with Growth Factor in Orthopaedic Surgery

An interesting example for different regulatory pathways of combination products is a growth factor-coated device consisting of a recombinant growth factor, a collagen sponge as carrier and a metal scaffold. The combination product is authorized in the indication of surgical treatment of degenerative disk disease (DDD) as medical Class III device in the US, branded as InFUSE™ Bone Graft/ LT-CAGE™ Lumbar Tapered Fusion Device [A]. In contrast, in the EU the product is authorised and marketed as drug with the brand name InductOs®.
The fusion of spinal segments using an autogenous bone with interbody fusion cages is a standard care for surgical treatment of DDD. Recombinant human bone morphogenic protein 2 (rhBMP-2) has the potential to provide significant medical benefit in spine fusion surgery as a direct replacement for autogenous bone graft harvested from the iliac crest. The use of rhBMP-2 requires a carrier to deliver the protein to the site and retain it there long enough to allow bone formation. The potential benefit for the patient is relief from the symptoms of DDD, achieved without the additional pain and morbidity associated with autograft harvesting. The osteoinduction properties of rhBMP-2 without metal scaffold are

[A] classification as filler, recombinant human bone morphogenetic protein, collagen scaffold with metal prosthesis, osteoinduction

also used for the healing of tibia shaft fractures administered adjunct to the surgical standard therapy.

3.2.3.1 InFUSE™ Bone Graft/LT-CAGE™ PMA Approval in the US

Initially, InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device obtained the PMA approval in the US in 2002 for the treatment of DDD by lumbar spine fusion. Later in 2004, InFUSE™ Bone Graft without the cage received a second license for the treatment of acute tibia fractures.
InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device consists of three components: (i) rhBMP-2 lyophilisate, (ii) an absorbable collagen sponge (ACS) and (iii) a metal spinal fusion device (cage), which is not included in the kit. The LT-CAGE™ and ACS are medical devices separately approved by the FDA. The InFUSE™ Bone Graft is a matter of combination product according to 21CFR3.2(e)(2), and the InFUSE™ Bone Graft/LT-CAGE™ according to 21CFR3.2(e)(3) respectively. For authorisation of the InFUSE™ Bone Graft/ LT-CAGE™ Lumbar Tapered Fusion Device the following data and studies had been presented in the PMA.

Performance standards of the cage and data on the active agent rhBMP-2
The description of the design characteristics and mechanical performance of the LT-CAGE™ was presented in the PMA and described in the summary of safety and effectiveness data. Surprisingly the CMC part for the active agent rhBMP-2 only consists of a very basic description of the protein characteristics, recombinant expression in CHO cells and the content of excipients.

Preclinical testing
Non-clinical studies with the implant comprised safety studies, ADME studies, and tumor biology, systemic toxicity, and reproductive toxicity studies. The biocompatibility of rhBMP-2/ACS was evaluated in a series of studies testing systemic, intracutaneous toxicity, dermal irritation, contact sensitization, cell lysis or toxicity, hemolysis and cellular mutagenicity. Three preclinical studies were performed investigating the effectiveness of rhBMP-2/ACS in promoting interbody fusion of the lumbar spine to support intended use.

Clinical investigation and PMA approval
One pilot study and one pivotal study with 278 patients on drug to show comparability to established the autologous graft surgical standard therapy was sufficient and the basis for approval. The PMA was favourably reviewed at the Orthopedic and Rehabilitation Devices Advisory Panel meeting in 2002. The FDA approved the PMA under the following conditions: the applicant was requested to investigate effects of rhBMP-2 on tumor progression, embryonic development in rabbits and collect long-term safety and effectiveness data by a postapproval study with six years follow-up data. With regard to antibody testing, the development of a new validated rhBMP-2 ELISA to detect all isotypes and neutralizing antibodies was also requested from the sponsor. Additional analytical assays i.e. silver stained SDS PAGE, Edmans test and glycoform analysis had to be added to the release specification of the rhBMP-2 device component. The sponsor's

manufacturing facilities were inspected and found to be in compliance with the Quality Systems Regulation (21CFR820). No information was given with regard to the pharmaceutical CGMP regulation.

InFUSE™ Bone Graft in the indication of acute tibia fractures

Relevant non-clinical data of rhBMP-2/ACS (see above) were also included the PMA application of InFUSE™ Bone Graft in the indication of acute tibia fractures. In addition, pharmacological studies have shown that rhBMP-2/ACS can induce bone and repair defects in various animal models. For the PMA one single pivotal multinational clinical study (control, 0.75 or 1.50 mg/ml rhBMP-2) with 150 patients per treatment arm in the indication of acute open tibial shaft fractures was performed against the standard therapy. A significant reduction of secondary intervention was chosen as primary endpoint of the study. InFUSE™ Bone Graft was also favourably evaluated by the Advisory Panel and approved by CDRH under the same condition as in combination with the LT-CAGE™ . With regard to performed consultation procedures, no information is available whether the CBER[A] was involved in the evaluation of the device or rhBMP-2 component at all. However, in contrast to the second indication, treatment of DDD by spine fusion, it took $3^{1/2}$ years from PMA filing until final approval, which could not explained by available information.

3.2.3.2 InductOs® Approved via the European Centralized Procedure

The order and type of regulatory approvals of InductOs® was different in the EU. Initially, InductOs® was authorised as a medicinal product for the treatment of tibial shaft fractures in 2002. Since rhBMP-2 (INN dibotermin alfa; ATC: M05BC01) is produced by recombinant expression, the MAA via the centralized procedure at the EMEA was mandatory according to Regulation EC 726/2004[B]. Later in 2005, the market authorisation of InductOs® was extended to include a second indication for the treatment of lumbar spine fusion only to be used in combination with the LT-CAGE® Lumbar Tapered Fusion Device which is indicated in the labelling.

Quality information

The data provided in the scientific discussion as part of the EPAR on chemical, pharmaceutical and biological information on the active substance and finished product was presented according to Annex I of Directive 2003/63/EC. Analytical methods for development and release of the active substance had been qualified and validated in concordance with applicable guidelines. With respect to the collagen matrix, the ACS is listed under excipients[C]. Information on setting of specification, viral safety and issued TSE CEP and shelf life is detailed for ACS. Dibotermin alfa has also been characterized in combination with ACS. The specification and release criteria of the finished product have also been set for dibotermin alfa in combination with the ACS matrix.

[A] until October 2003 therapeutic proteins were still with CBER
[B] superseded EEC 2309/93
[C] ACS manufacturered by Integra LifeScience Corp. changed to the CE marked product Helistat as indicated in the scientific discussion of the type II variation.

Preclinical studies
Extensive toxicology and pharmacological studies were performed with both dibotermin alfa alone and dibotermin alfa/ACS in combination. Local tolerance and evaluation of the biocompatibility of medical devices prior clinical studies according to ISO 10993 Part I revealed no adverse effect. The osteoinductive effect of dibotermin alfa/ACS was studied by three dental-craniofacial studies and 1.5 mg/ml found as most effective bone inductive concentration.

Clinical studies
No formal PK studies had been performed in healthy volunteers since such trials were not feasible for the intended use of the product. Several small scale studies to investigate appropriate methodology, endpoints and choice of patient population were performed. One dose-finding and one pivotal multinational phase III clinical study (control, 0.75 or 1.50 mg/ml rhBMP-2) with 150 patients per treatment arm in the indication of acute open tibial shaft fractures was performed against the standard therapy. The study met the primary endpoint, significant reduction of secondary intervention to promote fracture healing within 12 months and was accepted as single pivotal trial for the marketing authorisation. The sponsor agreed to the following commitments (i) to conduct a controlled trial of InductOs® (plus standard care) versus standard care in patients treated with reamed IM nails and (ii) to investigate long term risks of dibotermin alfa/ACS, especially for the development of malignancies and antibodies.

Extension of the marketing authorisation of InductOs®
The extension of the market authorisation of InductOs® for the indication of anterior lumbar spine (L4-S1) fusion as a substitute for autogenous bone graft in adults with DDD, who have had at least 6 months of non-operative treatment for this condition, was submitted as type II variation in the EU.

LT-CAGE is a CE marked device
The quality data of LT-CAGE® drawn up in the scientific discussion only concerned a short technical description of the device and references to applicable standards including a statement that technical drawings and the package insert were part of the submission. The proprietor of the LT-CAGE® is Medtronic Sofamor Danek.
It was stated that the package insert is in compliance with Directive 93/42/EEC and subject of annual reviews by the designated NB, but no information was provided whether the regulatory body was involved in the evaluation of the device with regard to the use in combination with InductOs®. The CHMP proposed to remove LT-CAGE® Lumbar Tapered Fusion Device from Section 4.1 “Therapeutic indications” (label claim) of the SmPC, as it blocks the use of other devices. Nevertheless, the mandatory use together with the device but must be mentioned in the Section 4.2. “Posology and methods of administration” of the SmPC.

Non-clinical and clinical studies
Since the formulation of InductOs® is identical to that described in the original MAA non-clinical studies were focussed on spinal fusion efficacy and safety. Six nonclinical studies had been performed; two of them allowed direct comparison of dibotermin alfa/ACS to autografts. One pilot study, one pivotal study with 145 patients on drug and one supportive

study using the laparoscopic approach to show comparability to established autologous graft surgical standard therapy were the basis for the line extension[A].

3.2.3.3 Regulatory Perspectives on Devices coated with Growth Factor

At first, no information could be retrieved from the assessment reports for both territories with regard to performed consultation procedures to assess the drug/device component from the complementary body. The extent of collected preclinical data and clinical studies was very similar if not the same for the authorisation of the product in both regions. In contrast, the extent of the quality data with regard to dibotermin alfa/ACS was unbalanced, less information was required for the PMA approval of Infuse™ as a device in the US and considerable data for the authorisation of InductOS® as medicinal product in the EU, probably reflecting the different requirements and focus for licensing of drugs and devices. What is the statutory and scientific rationale for the different regulatory paths?
The single components of the combination product with regard to their intended use could be clearly differentiated by physical and pharmacological actions: The growth factor represents a drug as it induces bone formation by pharmacological ligand-receptor interactions. The spine fusion device stabilises neighbouring vertebral bodies to be fused in purely physical manner. The ACS is functioning as carrier to retain the growth factor at the site of the bone defect or interbody fusion. The regulatory perspective in the US results from the PMOA concept. Two modes of action can be identified from the overall therapeutic goal of the treatment: (i) maintenance of the intervertebral spacing by physical means and (ii) encourage of bone formation. The FDA attributes the PMOA to the device component's action to mechanically maintain spacing and stabilisation of spines, which could not be achieved by the growth factor alone[16, 97]. The bone formation within and around the cage is considered to play a secondary role. The EU legislation and the MEDDEV 2.1.3 guidance differentiate two basic approaches: either the device is intended to administer a drug (drug delivery system) or it contains a medicinal product with ancillary action. According to the MEDDEV 2.1.3 guideline the primary action[B] is considered as decision criteria in this case. The predominant device mode of action of the product is similarly recognised as in the US but the final conclusion in the EU is different as the ancillary action of the medicinal product could not clearly be established[42] as detailed in the following explanation. Initially, the guideline also considers the repair of bones by bone fillers, which provides a volume or scaffold for osteoconduction, as physical means and which represents the primary action whereas an additional incorporated medicinal substance is to assist and complement the action of the matrix by enhancing the growth of bone cells. But, if the medicinal substance has such an effect that its ancillary nature cannot be clearly established, then the product should be considered in accordance with the concept of a drug delivery system[42]. Finally, this simply means that the growth factor is regulated as medicinal product and the spinal cage (scaffold) as device and two authorisations are required as realised with licensing of InductOS® and LT-CAGE®. Moreover, the same product could also serve as an example for the second type of

[A] identical studies as for the PMA approval in US but differentiated by surgical approach
[B] MEDDEV 2.1/3 rev2 section A3, A5 and A6; after coming into force 2007/47/EC the term in Art. 1 5(c) could be referenced "prinicipal mode of action"

combination product considered in the EU, when the device and the medicinal product form a single integral product which is intended exclusively for use in the given combination and which is not reusable. This single product is regulated as a medicinal product. InductOS® consisting of dibotermin alfa and the collagen sponge as carrier of the growth factor for the treatment of acute tibial shaft fractures could be considered as such an integral product. However, since the ACS carrier is listed under Section 6.1 "List of excipients" in the SmPC of InductOS® this presumption can be excluded.
In conclusion, different interpretation of legal provisions in both regions resulted in two different licenses but the impact on the development was probably limited as submitted data were sufficient for a PMA approval as well as an authorisation as drug. The chosen example may be a borderline case, which has a basis for both regulatory pathways and may be appropriate as long as the set of data and reviewing do not drop behind the requirements of a single authorisations or neglect testing of combined products. It should also be kept in mind that the history of authorised products/devices may have had an influence to regulate a follow-on product replacing autografts by a growth factor. The recombinat expression of dibotermin alfa does the rest.

3.2.4 Antibiotic-containing Bone Cements

Polymethyl methacrylate (PMMA) bone cements was introduced in the 1960s for fixation of total hip arthroplasty replacement components. Although the use of PMMA bone cements has enabled long-term survival of joint arthroplasty implants, there has been concern about aseptic loosening[98]. Hence, the development and use of antibiotic-containing cements may be advantageous over conventional cements. Both, plain and antibiotic-containing bone cements are regulated and licensed as devices.
The regulatory pathway of antibiotic-containing bone cements in US is well-defined by the intercenter agreement between CDER and CDRH from October 1991 classifying the primary intended purpose of bone cements containing antimicrobial agents as of fulfilling a device function and assign the regulatory responsibility to CDRH. The intercenter consultation is only required if a drug or the chemical form of the drug has not been legally marketed in the US as a human drug for the intended therapeutic effect[99].
A similar benchmark was set in the EU and is detailed in the MEDDEV 2.1.3 – guideline in Section A2. In addition, the guideline clarifies when the product starts to be considered as a medicinal product. Bone cements containing antibiotics, where the principal intended purpose remains fixation of a prosthesis, are also medical devices. In this case the action of the antibiotic, which is to reduce the possibility of infection being introduced during surgery, is clearly ancillary. If, however, the principal intended purpose is to deliver the antibiotic, the product would be a medicinal product (see chapter 3.2.5.1).

3.2.4.1 Simplex™ P with Tobramycin

The Simplex™ P with Tobramycin license was granted by premarket notification 510(k) clearance by CDRH in 2003 based on substantially equivalence to authorised and marketed Simplex™ P bone cement. The FDA had reclassified licensing requirements of PMMA bone cements from PMA (Class III) to 510(k) notification (Class II). The reclassification of PMMA bone cements into Class II is supported by special control guidance[100] to aid the

development and detail the requirements of these products. Hence the required set of data is limited and focused on the drug cement interaction and antibiotic release.
The 510(k) Summary of Safety and Effectiveness of Simplex™ P briefly describes the components of the PMNA bone cement and the relevant USP monographs. The evaluation of safety and mechanical properties of Simplex™ P with Tobramycin was based on bibliographic data, additional unpublished details from contacted authors and arthroplasty registries data, that are relevant to the safe use of this product as the bone cement without antibiotic supplement is licensed and used in clinical practice for many years. By extensive *in vitro* and *in vivo* testing a balance between antibiotic release and mechanical integrity without threats of systemic toxicity or compromised mechanical function was achieved. Preclinical studies investigated the antibiotic release from cement polymerized *in situ* in rabbits by measuring local antibiotics concentrations as well as systemic levels. The values predicted by the model correlate very well with the clinical data reported by several clinicians.

3.2.4.2 Refobacin® Plus Bone Cement

A similar PMMA-based gentamicin-containing bone cement, Refobacin® Plus Bone Cement is marketed by Biomet Europe in the EU as a medical device since 2006 for implantation of endoprostheses with an anti-infective protection or exchange of untightened endoprostheses caused by a bacterial infection. Besides that the package leaflet contains information on content, indication, contraindication, adverse events and general remarks, no data on performed clinical studies or other requirements to support the CE marking could by retrieved from publicly available sources.

3.2.4.3 Consultation Procedure on Bone Cement at the BfArM

An assessment report of a gentamicin-containing bone cement was obtained from the BfArM in frame of the performed survey at six European Cas and the EMEA. The assessment of the consultation dossier by the agency evaluated the pharmaceutical quality, preclinical and clinical information. Finally, the consultation dossier was positive evaluated after adequately responding to ascertained deficiencies. The assessment and comments of BfArM with regard to submitted pharmaceutical quality data by the applicant based on the requirements and headings according to MEDDEV 2.1/3 – guideline Section B.3. The starting material was presented as open part of the DMF of the gentamicin manufacturer together with a CEP from the European Directorate for the Quality of Medicines (EDQM). The BfArM confirmed that the toxicological profile of gentamicin is known but requested further information with regard to the formation of antibiotic resistence. It is not apparent whether the applicant provided bibliographic data or/and conducted own clinical studies for the clinical evaluation of the product. The BfArM concluded from the data of several studies that only a low level of gentamicin is released and systemically available and subsequently the potential toxic risks are kept as low as possible. However, BfArM requested more information on later time intervals of gentamicin release from the cement and its effect on the body with regard to toxicity and the development of resistance. In addition, it was also required to include more details on possible adverse reaction with regard to hypersensitivity, nephrotoxicity and ototoxicity in the product information.

3.2.5 Gentamicin-impregnated Collagen Fleeces

Gentamicin-collagen fleeces are primarily used for orthopaedic, intraabdominal, and cardiothoracic surgeries or wound infections following surgical procedures or traumatic events. The intended therapeutic use of presented products are haemostasis and prevention or cure of wound infection. The first effect could be attributed to collagen as haemostasis inducting substance and the latter to the broad-spectrum antibiotic gentamicin. Impregnated collagen has a dual function as drug delivery system targeting high local anti-infective gentamicin concentration and haemostasis to local site of surgical intervention. The benefit of combining gentamicin with collagen fleeces is that a high local concentration required to prevent bacterial growth and development of resistance is achieved while serum levels do not exceed toxicity thresholds. Hence, a high systemic exposure with an antibiotic agent is avoided which otherwise would be necessary for an anti-infective therapy.
According to the explanation in the MEDDEV 2.1.3 - guideline exemplified by wound dressings containing an antimicrobial agent in Sections A5 and A6 the primary intended action will determine the authorisation as medical device or medicinal product. Summarised, as long as the intended purpose of the incorporated antibiotic is ancillary the product is regulated as device, but if the primary action is to administer the antibiotic agent for the purpose of controlling the infection, the product will be regulated as medicinal product. The collagen fleeces presented in the following chapters are examples for practicing of both regulatory pathways. Depending on the source from which the collagen was obtained additional documents and data may be required. Collagen from ruminant animals will also need a TSE CEP and viral safety data.

3.2.5.1 Sulmycin® Implant E authorised as Medicinal Product in Germany

Sulmycin® Implant E, a gentamicin-impregnated collagen fleece represents a combination of two active medicinal substances, which were actually excluded from the scope of thesis. Since such a product type could also be authorised as a “fixed combination” medicinal product or medical device containing a medicinal product with ancillary action (Septocoll® , see next chapter 3.2.5.2) depending on the primary purpose and the indicated therapeutic use in the SmPC, Sulmycin® Implant E was included to show the key issues.
The Sulmycin® Implant E (Collatamp® G[A]) has been licensed as medicinal product and is marketed by Eusa Pharma in Germany for the supporting treatment of ulcerous inflammation of bone and bone marrow after surgery reconstruction and soft tissue surgery[B]. Since the SmPC indicates two active substances, gentamicin and collagen, Sulmycin® Implant E must be considered as a “fixed combination” medicinal product according to Art 10b of Directive 2001/83/EC. The SmPC provides only very little data on pharmacokinetics and safety. The collagen from equine tendons is completely resorbed and replaced by body tissue. The systemic gentamicin plasma level is below the 1-2 mg/l base level of systemic aminoglycosid therapies which is considered as a concentration with less adverse reactions. Only acute toxicity was investigated in several species, which can

[A] approved and marketed in 42 countries in Europe, North America, South America, Central America, Africa, the Middle East and Asia under several tradenames. http://www.innocoll-pharma.com/index.htm
[B] http://www.eusapharma.com/collatamp.html [04.04.2008]

probably be explained by the initial national market authorisation in 1985 and the renewal in 1996, respectively, with the applicable requirements at that time. The highest toxicity was observed with intravenous administration in mice with a LD50 of 75 mg/kg bodyweight. No data on collagen are provided, as it is an abundant protein very unlikely to exert toxic effects. In addition, no data have been collected on mutagenicity, cancerogenicity, and embryotoxicity of collagen. Clinical studies with Gentamicin-impregnated collagen fleeces have been performed since end of the eighties but their results were not included into the SmPC yet. Hence, there is no information available to what extent clinical studies were considered for the initial market authorisation and the renewal.

3.2.5.2 Septocoll® E Authorised as Medical Device in the EU

In contrast, another gentamicin-impregnated collagen fleece, Septocoll® E has been placed on the EU market in 2000 by Biomet Europe as a Class III medical device in the indication of haemostasis of wounds after surgery. The composition of the device is specified in the patient information leaflet with gentamicinsulfat, gentamicincrobefat and collagen from equine tendons. The therapeutic use is indicated as haemostasis and based on the physiological properties of collagen; the treatment of inflammation is not covered by the indication. Nevertheless the gentamicin concentration is even higher as in Sulmycin® Implant E and contains two gentamicin salts facilitating a rapid and protracted antibiotic release. The medical use of Septocoll® also includes the treatment of contaminated wounds and as a result is not limited to the prevention of infections. No information on safety and usefulness or efficacy is provided in the patient information leaflet and it is not possible to retrieve the data which were required for granting the CE mark. However, the company`s website listed various publications of clinical studies with the product.

3.2.5.3 Regulatory Perspectives on Antibiotic-impregnated Collagen Fleeces

Sulmycin® Implant E and Septocoll® E are clearly differing in the claimed therapeutic indication. Sulmycin® Implant E can be used for the treatment of ulcerous inflammation of bone and bone marrow after surgery reconstruction whereas Septocoll® E is lisensed for haemostasis after surgery. The different labelling is the consequence of chosen regulatory pathways and vice versa. The anti-inflammatory properties by pharmacological or immunological means are attributed to medicinal products and represent the key feature for the demarcation against devices according to Directive 93/42/EEC. In contrast the MEDDEV 2.1/3 - guideline defines haemostasis as being a physical property and assign haemostatic medical products including collagen to be regulated as devices.
Finally, this also means that the manufacturer of the device Septocoll® E can not claim any anti-infective properties of the product[A]. However, due to the similar composition an interchangeable use of both products in similar surgical intervention may occur. The gentamicin-impregnated collagen fleeces is a model case where different indications in the labelling despite a similar composition of the products facilitate the authorisation of a product either way as medicinal product or as medical device in the same country. In addition, Septocoll® E can be marketed as medical device with one single license

[A] Seminar Medizinprodukte mit Arzneimittelanteil. Bonn 2006. RA Markus Ambrosius

throughout the EU whereas Sulmycin® Implant E is marketed in 27 European countries under several licenses and trade names[A].
Interestingly, gentamicin-impregnated collagen fleeces are marketed in European countries since almost 20 years but in the US Collatamp® G is still an IND. The sponsor Innocoll Incorporation has currently started the second of two planned phase III trials to show the efficacy by incidence of surgical wound infections at day 60 in patients undergoing cardiac or open colorectal surgery in the US [B]. Accordingly, the product is developed as a drug and has to meet the relevant requirement of a NDA in the US. These facts are quite in contrast to the intercenter agreement between the CDER and the CDRH which classified the primary intended purpose of wound dressing with antimicrobial agent as of fulfilling a device function[99]. Obviously in this case, controlling of the infection is the PMOA and explains the assignment of Collatamp® as IND.

4. DISCUSSION

General
In principle the definition and the determination of the regulatory pathway to authorise products combining drugs and devices started from the medical device legislation. Different legislations, provisions and regional backdrops contribute to the different regulatory environments for the authorisation of combination products in the US and the EU. This is rather a slightly different perspective on drugs or devices than difference purely related to combination products itself which do not possess own laws and form a part in the medical device and pharmaceutical legislation.

US and EU legislation remarks
In 1990, with the amendment of the FD&C Act by the Safe Medical Device Act combination products were obligingly designated as comprising of drug-device, drug-biologic, biologic-device and drug-biologic-device either (i) physically, chemically, or otherwise combined or mixed and produced as a single entity or (ii) copackaged or (iii) crosslabeled products for its intended use in combination. Based on the decision criterion "PMOA", it is determined whether the premarket review and authorisation is that of a drug, a device, or a biological product, resulting in three regulatory pathways.
The establishment of an internal medical market in the EU has also entailed an appropriate legislation with three MD Directives to start onward from 1990 with the harmonisation of the essential requirements and standards to place medical devices onto the European market after implementation into national law. First, the European approach to define combination products might be seen as sophisticated in contrast to the straightforward approach in the US. The definition of medical devices and the demarcation to medicinal products by the Council Directives 90/385/EEC and 93/42/EEC also provides the basis for the regulation of combined medical devices and medicinal products by two basic two-tiered approaches. (i) Drug delivery devices are regulated as devices but if, however, it is forming a single integral product intended for use in given combination and not reusable

[A] it could not be clarified whether Innocoll is marketing Collatamp® G in some European countries as medicinal product and in other as medical device. Germany, Netherlands, Portugal and Greece have licenses of the product as a medicinal product.
[B] http://clinicaltrials.gov/ct2/show/NCT00600925?term=collagen+fleeces&rank=5 [02.05.2008]

then it shall be governed as medicinal product according to the pharmaceutical Community Code Directive 2001/83/EC. (ii) Devices incorporating medicinal substances with ancillary action are regulated as medical device but as soon as the medicinal substance is no longer ancillary with respect to the principal purpose of a product, the product becomes a medicinal product. Human blood derivates were added as medicinal products with ancillary action to be regulated as medical device by the aforementioned amendment of the Council Directives in November 2000. Although the term "principle intended action" is already used in the European Commission guideline MEDDEV 2.1/3 the legal definition "principal mode of action" will become more constitutional force with the amendment of the MDs Council Directives and the European provisions converge to a statutory decision criteria for the combination product assignment in the US. The term "combination product" has a different definition and common use in the EU where it is generally considered as a combination of two or more active ingredients in one formulation; also defined as a "fixed combination medicinal product". The different legal framework and definition, the diversity of European regulatory bodies for devices and the resulting region-specific particularities might raise unnecessary obstacles for a broader understanding to develop a certain combination product in both regions. However, despite the differences, drug-device combination products show also common or overlapping principles in the US and the EU, which should be used by the manufacturer for the assignment and development of these products.

Consultation procedure

In the EU medical devices can be marketed in all MS with a single licence from one of the certified national NBs or NCAs for medical devices. NBs are nationally accredited private organisations responsible for the conformity assessment and CE marking of Class II/III devices prior to marketing. In case of combination products regulated as such, the NB is obliged to consult a NCA or the EMEA to seek an opinion on the safety and usefulness of the drug with ancillary action. Taking the consultation statistics obtained in the context of the performed survey, European NCAs are regularly assessing drug components in consultation procedures. So far, consultative assessments performed by the EMEA concerned only four combination products containing human blood derivates, for which the involvement of the EMEA is mandatory. Hence at present, no medicinal product previously authorised via the centralised procedure, as for example sirolimus in DES, was assessed in a consultation procedure by the EMEA as a constituent of a combination product. The reverse case of consultations concerns NCAs or the EMEA consulting the regulatory body for medical devices to assess the relevant essential requirements with regard to safety and performance-related device features when drug delivery devices form a single integral product and must be regulated as medicinal products. Considering the responses from the survey this is a rarely or even not practiced option and also it is not mandatory.

As a result of the confidentiality clause described in Art. 15/20 of the device Council Directives no information on the conformity assessment nor opinion of consultated authority is currently publicly available and could also not be retrieved by request for information referring to re-use of public sector information according to Directive 2003/98/EC with exception of the German BfArM. This is undoubtfully still a major obstacle for a proven consistency with regard to requirements for authorisation and transparency of the review of combination products as well as devices in comparison to the

situation in the US and at least in the present thesis and view from public interest. The publishing of a summary with information and data related to the device will firstly become mandatory after implementation of the Directive 2007/47/EC into national law and legally enforced as of March 2010.
The European information policy and obligations in the pharmaceutical sector is already more advanced since public assessment reports on approved medicinal products indicate the data which served as a basis for granting the marketing authorisation. This must be made publicly available since the Regulation (EC) No 726/2004 and Directive 2001/83/EC have been enforced. However, device-related information of combination products regulated as medicinal product is still very limited.
Considering the number of regulatory bodies responsible for licensing of the combination products in the EU, heterogeneous institutions such as NBs, NCAs of currently 27 MSs, and the EMEA, it requires a substantial effort to establish a transparent review process and consistent decisions. In contrast, in the US the single licensing agency FDA with three medical Centers, CDER, CBER and CDRH contributes to more strutuctured clarity and consistency. The criticism about differing performances led to the creation of the Notified Body Operation Group (NBOG) in the EU in 2001, which issued a key guidance for certifying these third party NBs, and is currently working on a European guidance for NBs in addition to the existing GHTF documents[101]. The differences in the assessment of medical devices between regulatory bodies of the existing EU and the May 2004 EU accession countries from central and eastern Europe, due to already existing national laws in force for the regulation of medical devices before the European directives had been adopted and/or had to be implemented in the MS legislations will probably disappear by continued activities of NBOG and the review of the MD Council Directives by Directive 2007/47/EC.
The regulatory responsibility and lead review for the combination products in the US will be assigned by the OCP to one of the FDA's three human medical product Centers (CBER, CDER or CDRH) according to the combination product's PMOA. The responsible lead Center may consult with another Center to review submitted applications. A European equivalent to the OCP does not exist and - due to the sovereignity of each European country to authorise medical devices - improbable to be established at all. However, requests for demarcation of drugs and devices and clearance of the applicable regulatory pathway could be requested from NCAs or the EMEA in the frame of scientific advice procedures.

US and EU guideline remarks

On the grounds of harmonised pharmaceutical ICH guidelines and GHTF device standards the requirements for authorisation of drugs and devices have converged but still remaining regional differences could have an impact on the development and authorisation of the product. The European Commission MEDDEV 2.1/3, EMEA/CHMP consultation guideline and the FDA guidance on innovative combination products established general guidelines describing the particularities and requirements of combination products. In addition, guidelines on particular combination products (e.g. on DES) and the consultation procedure have been released to indicate the current requirements, procedures and expectations of the authorities to license these kinds of products.
An important difference concerns the GMP and QA requirements for pharmaceuticals and devices. Manufacturing of drugs follow quality testing and controls; manufacturing of

devices rather follows a design and performance related approach covered by relevant standards for different product types. The question mark is over which GMP and QA system must be realised for the relevant combination product. In cooperation with the CDER, CBER and CDRH, the OCP has already drafted a CGMP guidance for combination products, which outlines the requirements and current thinking of the authorities.

Typical requirements and challenges of combination products

The manufacturers have to deal with some particularities of combination products concerning the drug-device interaction, stability, sterilisation, preclinical testing, biocompatibility and clinical testing. The requirements have a device-related starting point and similar characteristics in both regions. The combined components must be chemically stable and resistant to any adverse interaction. Also drugs can impair the performance of a device, e.g. insulin crystals caused a leakage at the titanium sealing of a drug delivery pump[2]. The stability of the combination product as a whole must be investigated and cannot only be deduced from the single components. Stability of therapeutic proteins in drug delivery pumps concerns physical and chemical stability. Lack of physical stability may lead to soluble aggregates, which in turn could lead to formation of antibodies[2]. The components must endure the chosen terminal sterilisation process chemically unchanged. Preclinical and safety testing for drugs is different from that applied to devices; it should be considered, that it might be necessary to deploy own pathways to address specific preclinical issues. Biocompatibility must be demonstrated for device constituents and - dependent on duration - placing in the body and contact sites. Animal PK studies must be performed to determine the drug exposure to the body and to support initiation of studies in human. Since drug levels released from combination products may be low and difficult to analyse, *in vitro* release profiles may have to be established[18, 23].

General dossier requirements of drugs and devices

The extent of the data to be submitted with the application will depend on the regulatory status of the drug and device component, the market experience of the single components and the chosen regulatory pathway. Available data and documentation of a previously approved drug or device could be referenced for the dossier if the legal prerequisites are established. For example the drug substance paclitaxel in TAXUS™ stents to prevent coronary restenosis was previously approved by the FDA for the treatment of cancer. For the safety and effectiveness of the TAXUS™ the FDA evaluated data from only 1000 patients, but for an investigational drug clinical data from up to 2000 patients would be expected[18]. It should be noted that the requirements for drugs and devices to demonstrate safety and efficacy are different. In general, two pivotal studies are expected for unapproved drugs, if not otherwise specified, whereas one pivotal study would be sufficient for a new device to meet the authorities' expectations[18]

Due to the different nature of the products and gathered experience all three relevant FDA Centres have a different focus and expectations concerning the extent and type of quality data to conclude a positive review and granting the license. Both centres CDER and CBER, responsible for evaluating medicinal products carefully, assess any changes that may affect product strength, quality, purity or potency and may request appropriate product testing before granting a market authorisation. In contrast, CDRH focus more on risk assessment and proper administrative design controls to ensure the quality of the manufacture of the product. Hence, the responsibility and liability of CDRH-controlled

products is shifted to the applicant, but changes of the approved product will be easier with respect to number of required variations post authorisation[102, 103]. Due to the different regulation and procedures CDER/CDBR have different and higher expectations and testing performance standards than the CDRH[103]. It can be assumed that this also applies to regulatory bodies of medical devices and pharmaceutical CAs in the EU.

Licensing of DES in the EU and the US

The main difference in the authorisation of DES in the EU and the US concerns the significant lower requirements with regard to the size of clinical studies, 238 versus 1058 patients. It remains speculative whether in general lower patient numbers are acceptable for licensing in the EU or if it is justified by combining separately approved drugs and devices as components of a new product. However, as the same is true for the US, increased patient numbers could be considered as a basic requirement for the PMA approval in the US. Stricter requirements with regard to quality, preclinical and clinical testing are demanded by the authorities for the authorisation of pharmaceutical products compared to those of medical devices, which make development, and licensing of devices less burdensome, costly and time-consuming.

Lincensing of HAS-containing media

Devices incorporating human blood derivates with ancillary action are Class III products whereas in the US the HSA-containing product EmbryoAssist™ from MediCult a/s is a Class II and is licensed by 510(k) premarket notification clearance showing substantial equivalence to legally marketed predicate devices by CDRH.

All devices incorporating medicinal substances with ancillary action are Class III products according to Council Directive 93/42/EEC Annex IX rule 13, but drug delivery devices, either authorised as medicinal product or by two separate licenses may also be categorised in a lower class. In the US medical devices containing a drug can be licensed as Class III or II product if the product type had been reclassified and the new product shows substantial equivalence in the 510(k) premarket notification as in case of antibiotic-containing bone cements (chapter 3.2.4.1).

Devices coated with growth factors in orthopaedic surgery

InFUSE™ and InductOs® serve as examples for authorisations of combination products under two different regulatory pathways with a similar set of data as far as it could be judged from the public assessment reports. The decision criterion for the different designation is reasonable with the interpretation of PMOA and determination of the level ancillary or secondary action. In contrast to FDA's RFD decision[97] and the PMA approval of InFUSE™, the European relevant guideline concludes that the product should be considered as a drug delivery system if the ancillary nature could not be established, which is regulatory-wise practiced with InductOs®. The case conclusively demonstrates that it is advisable to contact the relevant authority early to be timely prepared for the consequences of different regulatory paths, for example establishing of the appropriate QA systems and postapproval requirements.

Gentamicin-impregnated collagen fleeces

Gentamicin-impregnated collagen fleeces are primarily used in surgeries or for traumata to achieve haemostasis and concomitant prevention or treatment of microbial infections.

Sulmycin® Implant E is licensed in Germany as a medicinal product (fixed combination) for the treatment of ulcerous inflammation after surgery. Controling the infection is the primary intended action of Sulmycin® Implant E, which is a pharmacological property defining an authorisation as medicinal products. In contrast Septocoll® was licensed as Class III medical devise in Germany incorporating a medicinal product with ancillary action to achieve haemostasis after surgery. The possible treatment of contaminated wounds is not excluded but gentamicin-resistant infections are contraindicated. Septocoll® is an example for haemostasis being considered as primary physical action and gentamicin's anti-infective pharmacological properties are secondary for the intended purpose. These product types are clearly an example for consequences of different regulatory pathways for the labelling. It also demonstrates the blur distinction between being either drug or device, a drug-device combination products or a fixed combination if the intended purpose and effect/properties of the contained substance could be attributed to pharmacological, immunological, metabolic or physical means.
Hence, in some selected cases changing the focus of intended purpose in the label has significant impact on applicable regulatory pathways and can be used for placing a product on the market either as drug or device.

5. CONCLUSION AND OUTLOOK

General
The regulatory environment for drug-device combination products in the US and the EU is an implicit part of the legislations and guidelines to regulate and classify drugs and devices. Regional and product-specific differences of the medical products determine the applicable regulatory pathway and requirements to authorise combination products. Understanding of the key elements and consequences will facilitate a smooth and less burdensome development to obtain the authorisation of the product and earlier placing on the US and EU market.
Since combination products are authorised as drugs/biologics or devices, a key element for their regulation concerns the decision criterion for either of both development and authorisation paths. Different approaches have been realised; a rather general straight-on definition in the US opposes a sophisticated and fine-tuned European legal provision. In the US definition of combined products and the determination of the PMOA is the controlling element, whereas in the EU drug delivery devices and devices incorporating a drug with ancillary action represent the central approach assisted by design, use and the principle intended (mode[A]) of action. Biologics are included in the European definition of medicinal substances for drugs. Hence, the term "combination products" is differently defined and used in both regions. The consequence is, that a combination product could be regulated as a drug in one region and as a device in another, or some possible compositions are considered as drug-device combination in the US and a fixed combination in the EU (e.g. drug-biologic). A descriptive examples for such a situation are represented by growth factor coated surgical devices and antibiotic-impregnated collagen fleeces (chapter 3.2.3 and 3.2.5).
Both approaches have their advantages and disadvantages. The concept of combination products could probably be applied easier to new drugs and devices and advanced

[A] Art. 5(c) of Directive 2007/47/EC

technology with the general US definition. The European approach could be considered as elaborated and self-explanatory which allows a precise regulatory-wise assignement of currently marketed products but new approaches and technologies may not fit well with the existing legislation.
The Regulation (EC) No 1394/2007 on advanced therapies introduced among others a new type of combination product for authorisation of cells or tissues containing devices. Recently, also Directive 2007/47/EC amended MD Council Directives to improve consistency of the legal framework in the light of scientific and technological progress as well as technical changes in providing a time frame for consultation procedures, strengthen preclinical and clinical testing and to make publicy information on devices mandatory.

Consultation procedure
In the US a clear structured intercenter cooperation procedure is established, organised by the OCP, to perform consultative/collaborative review process on investigational and premarket applications which is not limited to combination products and is frequently used. All possible kinds of combination products and variants of intercenter consultations are practiced between the FDA Centers with CDRH contacting CDER in the first rank by ~ 200 consulation in 2005 and 2006. In contrast consultation procedures in the EU are solely conducted for one single category of combination products: when devices are incorporating a drug with ancillary action. Consultations are not practiced for the evaluation of device-related features at NBs when devices and drugs form an integral product which are regulated as drugs, although consultations would be possible as described in the MEDDEV 2.1/3 rev. 2 - guideline. No annual overview of performed consulations exists in the EU, as there is no responsible institutional body to collect the data, but from the survey it could be estimated that in total a three digit number will not be exceeded, since authorities with as many application as the BfArM and MEB had significantly less than 20 consultations per year.

Combination products
Five marketed combination product types, drug-eluting stents, albumin-containing media, devices with coated growth factor, antibiotic-containing bone cements and gentamicin-impregnated collagen fleeces were selected to illustrate different authorisation pathways, the data necessary to obtain a license and the relevant criteria to support a decision for regulation of the combination product as drug or device. Different regional determinations of the regulatory path are not limited to combination products. This can also be found with separately licensed drugs and devices developed according to national legislation.
Combination products have some particularities to be considered regarding their development: drug-device interaction, stability, sterilisation, preclinical testing and biocompatibility. Each product must address these issues and probably deploy an own development path if necessary. Nevertheless, the extent of the data to be submitted with the application will depend on the regulatory status of the drug and device components and market experience and the chosen/applicable regulatory pathway.
In general, the licensing of devices might be easier than that of pharmaceutical products, and the expectations from regulatory authorities for devices in the EU are less than those of US bodies, supported by a comparison of approval times by Ralph Jugo[104]. This assumption could be deduced and confirmed, at least from the example of DES. All three currently marketed DES were primarily developed with less number of patients in the EU.

A somewhat reverse situation could be found with INFUSE™, which was licensed as a device in the US whereas for the EU an authorisation as drug was required. A similar set of data was sufficient although the EMEA also recognised the device-orientated development in the scientific discussion of the line extension for the treatment of DDD. However, with the introduction of the clinical evaluation in Annex I of Directive 2007/47/EC the required extent may change soon and contribute to strengthen the requirement for clinical data evaluation for medical devices in general. In general, a combination product developing company has no choice than to follow the regulatory pathway applicable for their product and indication but the antibiotic-containing collagen fleeces may represent the rare case in which a medical product with similar composition but minor different intended purpose and labelling can be placed on the market either as a drug or a device. However, the appropriateness of the selected regulatory pathway has to be justified by the manufacturer.

Approach to identify the regulatory pathway for a new combination product

A developer facing the task to plan the development of a product potentially being a combination product should identify whether a similar (authorised) product with cleared regulatory status exists and should use this information to decide if it is also applicable to the own product. In case this comparison does not suffice the designation of the product as drug or device; in the US the determination of the PMOA for intended purpose should be followed under consideration of ICA, jurisdictional updates and published RFD decision to allocate the regulatory pathway of the product, preferably before a formal RFD is requested at the OCP. In the EU the situation is slightly different due to the drug-delivery-device and drug with ancillary action approaches. The intended purpose of the product - taken into account the way the product is presented - and the method by which the principle intended action is achieved, will advise which might be the applicable pathway. Prior to a consultation procedure the demarcation and clearance of the applicable regulatory pathway could be requested from NCAs or the EMEA by a request for scientific advice. In addition product examples are described in the demarcation guideline MEDDEV 2.1/3 rev.2.

The relevant product information in support of such a decision could be retrieved from the proposed labelling, claims and scientific data regarding the mechanism of action and are applicable for both regions. Nevertheless, contacting the authorities early is recommended if in doubt of the proper assignment of the regulatory pathway of the product in question. Regional differences will remain but convergance of medical legislation and guidance will continue to relieve the global development.

Targeted drug delivery

The concept of delivering a drug directly to a specific tissue, organ or region of intended action is the classic approach of drug-device combination products with arising new opportunities for drug delivery systems such as intrathecal infusion of local anaesthetic, drug-eluting discs or DES. Established therapies with classic drug-delivery devices such as antibiotic-containing bone cements or collagen fleeces represent an archetype of drug delivery devices. The main benefit is a high local drug concentration at the target site, while low concentration remain in the circulation in comparison for example to conventional parenteral systemic antibiotic therapies[105], analgesic or chemotherapies. Shorter hospitalization periods and improved side effect profile are the benefit for the patients.

New technologies are chances for combination products

Combining medical products to improve existing therapies and create opportunities for new therapies will continue to be a growing market. New technologies are currently emerging such as nanotechnology, chip-based drug delivery systems[2], and cell/tissue incorporating devices which prepare the ground of an exciting and challenging work area for developers and regulators. The FDA expects that many future nanotechnology products will be combination products and the OCP is providing assistance for these novel innovative products. In the EU the challenges of new therapeutics may be encountered by establishing of the EMEA ITF to coordinate the regulatory path for new medicinal products for emerging therapies and borderline products including combination of drugs and devices, cell-based gene therapy, therapeutic nanoparticles and others[34]. Confidentiality arrangements between the FDA and the EMEA already proved to be a suitable international forum for discussing new developments in this field. Taken together, innovative medical technologies dispose a promising future for combination products with continued challenges for developers, regulators and assessors finally serving public health.

6. SUMMARY

This thesis presents the regulatory environment of medical products combining drugs and/or biologics and devices, so-called combination products to provide an overview and insight for their authorisation in the US and the EU, to aid the development of such products by companie's unfamiliar with the particular requirements and illustrating the pharmaceutical developer's perspective. The current status of applicable legislations and guidelines have been compared and by means of five types of combination product, exemplified with marketed products and concluded with an outlook on future trends and provisions.

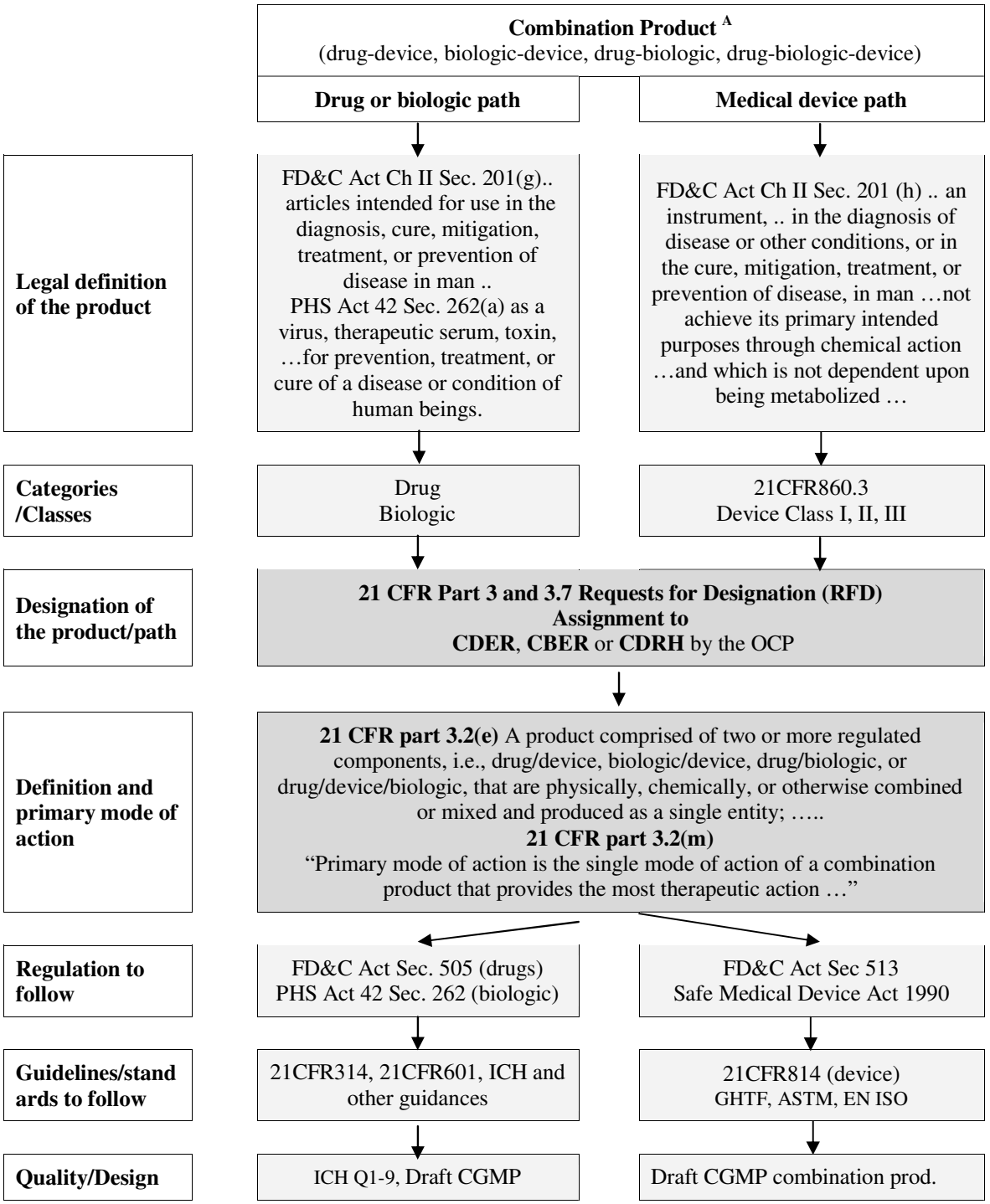
For both regions – US and EU – legal basis of drug-device combination products originates from medical device law. These products are either regulated as drug/biologic or device, but the term is defined and used differently. In the US drug-device combination products are plainly designated as drug-device, drug-biologic, biologic-device and drug-biologic-device containing products regulated by assignement to one of three responsible FDA medical product Centers, based on the product's primary mode of action. In contrast, the European medical device legislation provides two conditional clauses differentiating between devices for drug delivery or devices incorporating drugs with ancillary action. The design, use or the impact of the drug on the intended purpose of the combination product determine the authorisation as drug or device. In the EU, the term "combination product" is also often used for fixed combinations which refers to one or more combined active ingredients in one formulation and which represents no integral part of this thesis.

Drugs and devices both have their own regulatory guidelines and/or standards to follow which will also also apply for products combining drug and devices. However, often combination products have to deploy their own development strategy and only few guidelines are available for them in particular. Drug-eluting stents, albumin-containing media, devices coated with growth factor, antibiotic-containing bone cements and collagen fleeces are presented with their regional differences and regulatory status as far as possible by publicly available information. However, the highlighted products may not be considered as representative for typical drug-device combination products but demonstrate

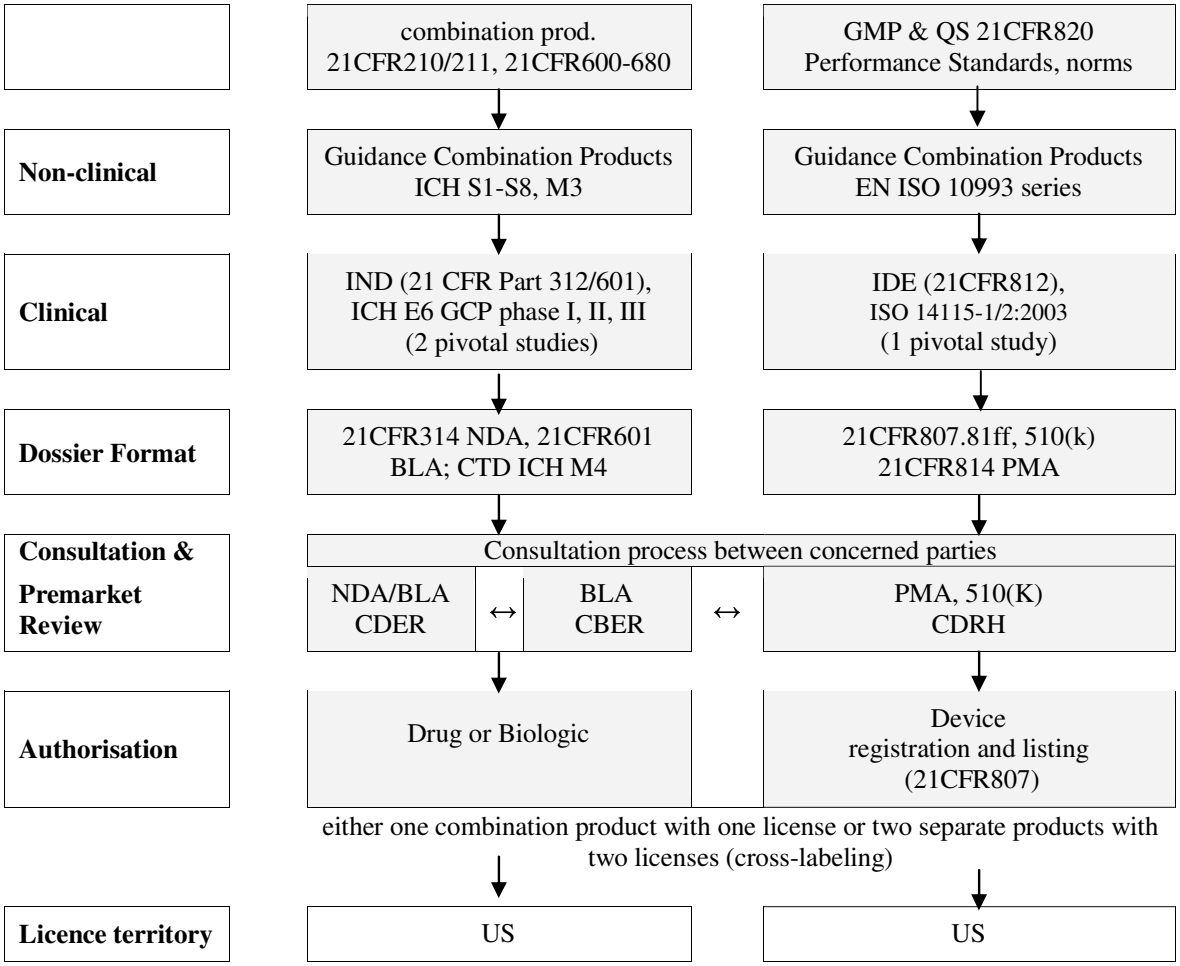
why a product could be regulated as either a device in one region or as a drug in another. In addition, a survey was performed at six European NCAs and the EMEA to obtain missing information on conducted consultation procedures and the assessment of drug-device combination products authorised as drugs or devices.
The next generation of innovative combination products, as for example cell/tissue containing devices and therapeutic nanoparticles, will create new opportunities for novel therapies and dispose the next challenges for developers and regulators to serve the public health.

7. APPENDICES

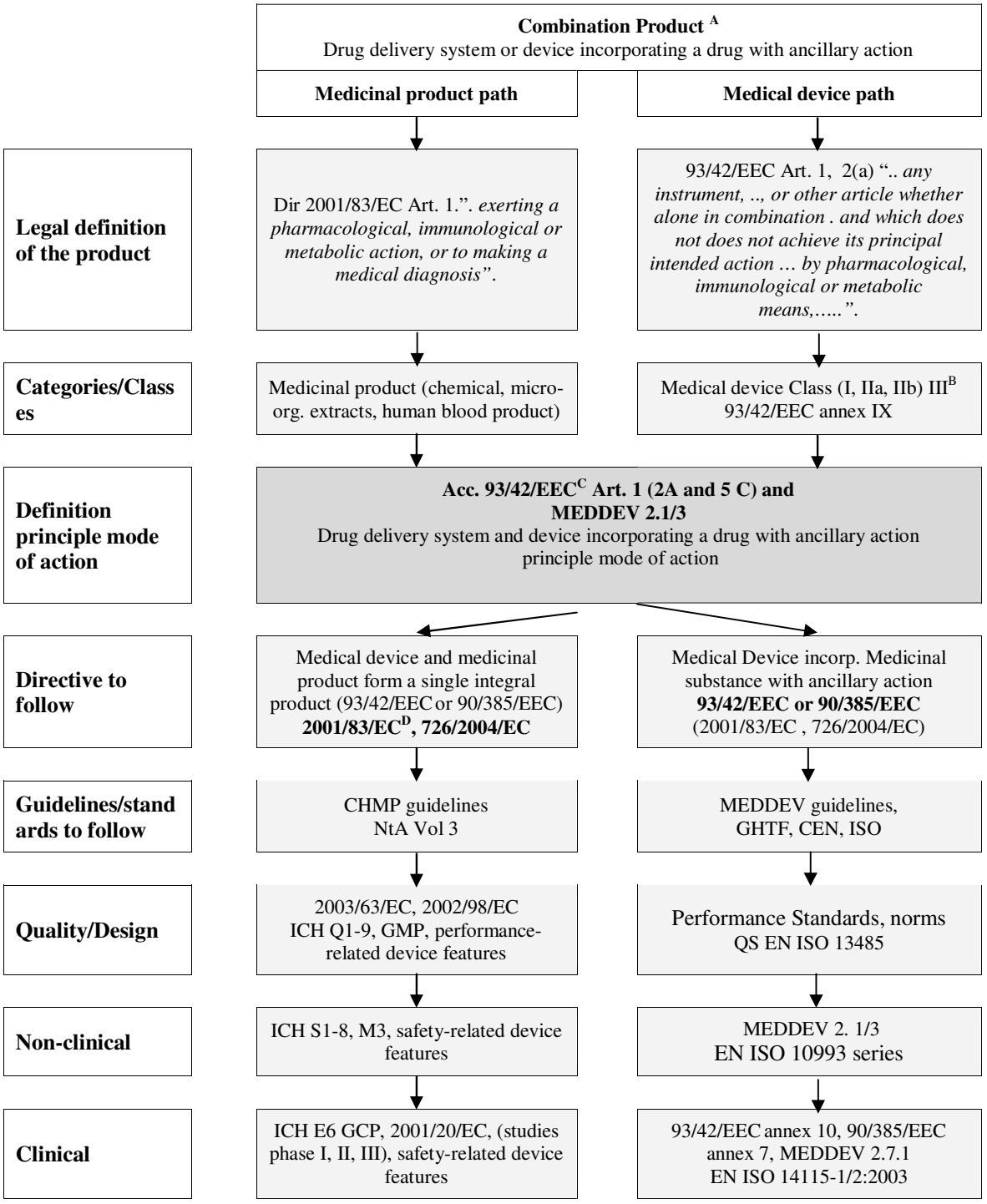
7.1 Overview Authorisation of Combination Products in the US



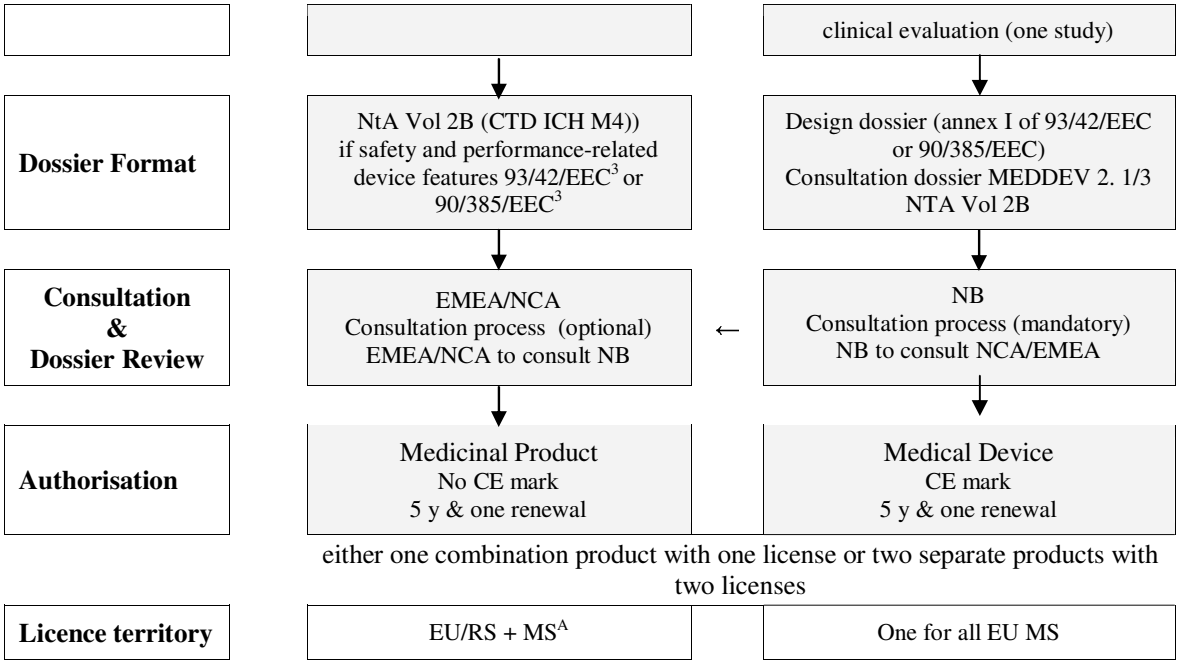
[A] The overview does not claim to be exhaustive


combination prod.
21CFR210/211, 21CFR600-680
GMP & QS 21CFR820
Performance Standards, norms
Non-clinical
Guidance Combination Products
ICH S1-S8, M3
Guidance Combination Products
EN ISO 10993 series
Clinical
IND (21 CFR Part 312/601),
ICH E6 GCP phase I, II, III
(2 pivotal studies)
IDE (21CFR812),
ISO 14115-1/2:2003
(1 pivotal study)
Dossier Format
21CFR314 NDA, 21CFR601
BLA; CTD ICH M4
21CFR807.81ff, 510(k)
21CFR814 PMA
Consultation &
Premarket
Review
Consultation process between concerned parties
NDA/BLA
CDER
↔
BLA
CBER
↔
PMA, 510(K)
CDRH
Authorisation
Drug or Biologic
Device
registration and listing
(21CFR807)
either one combination product with one license or two separate products with two licenses (cross-labeling)
Licence territory
US
US

7.2 Overview Authorisation of Combination Products in the EU



[A] The overview does not claim to be exhaustive
[B] Combination products are classified as Class III device (93/42/EEC rule 13)
[C] amended by 2007/47/EC 5 September 2007
[D] as amended 30 April 2004



[A] depends on the product and chosen authorisation procedure

7.3 Content of the European Design Dossier (Class III Devices)

Design Dossiers[106]

1. Product documentation
• Most important technical data, reports, attachments, photographs, blueprints, flowcharts, sample of product
• According to MDD article 11 section 12 the file shall be in an official language of the EC member state where the chosen Notified Body is located and/or in another Community language the Notified Body agrees to
• Once completed, the Design Dossier needs to be a controlled document. It does not need to be under document control, but it still needs to be controlled in some manner. Therefore a complete pagination of the design dossier is indicated

2. Description of the medical device
• General description (design, characteristics, mechanism of the device)
• Summary of manufacturing method (moulding, extrusion, chemical process, assembly, etc.)
• Final product release criteria
• Universal Medical Device Nomenclature System (UMDNS)

3. Variants
Model no(s) where appropriate

4. Accessories (integral part of package)
List of accessories or equipment intended to be used in combination with the device system

5. Tissue of animal origin (Annex I.8)
• Viral, bacterial, prion-inactivation/reduction
• Directive 2003/32/EC, EN 12442-1-3, MEDDEV 2.5-8

6. Drug/medical device combination (Annex I.7.4)
• Medicinal substances that have an ancillary action to that of the device
• Consultation of one of the competent authorities established by the member states.
• Consultation Dossier according to MEDDEV 2.1/3

7. Measuring function (Annex I.10)
• Sufficient accuracy and stability within appropriate limits of accuracy
• Council Directive 80/181/EEC

8. Emission of radiation (Annex I.11)
• Exposure of patients, users and other persons to be reduced as far as possible
• Compatible with intended purpose

9. Combination with other medical devices (Annex I.9.1)
Whole combination must be safe and must not impair specified performances of the devices.

10. Biological requirements/chemical requirements (Annex I.7)
• Categorization of the device according to nature and duration of body contact
• Tests performed (qualification of the test laboratory; accreditation) ISO 10993-1:2003
• Justification for tests not performed
• Final statement of the manufacturer

11. Compatibility with drugs
Devices must be compatible with the medicinal products concerned according to the provisions and restrictions governing these products.

12. Mechanical safety (Annex I.2, I.12)
• Pre-defined protocol: test method, applicable standards, parameters, equipment, calibration arrangements, acceptance criteria, and statistics
• Test report: deviations from the protocols and justification, raw data, statistical analysis, interpretation of data, and conclusion(s), approval signature(s)

13. Clinical data (Annex I.1, I.6, I.14)
• Data from market experience of the same or similar devices, clinical investigations and information from scientific literature
• MDD Annex X, ISO EN 14155-1+2, MEDDEV 2.7.1

14. Packaging and shelf life (Annex I.4, I.5, I.8.5, I.8.6, I.8.7)
• Detailed description of the packaging and packaging materials, supplier certificates

• Physical package qualification, performance of the product after real time and/or accelerated aging, shelf life (expiration date), EN 868-1 ff, ISO 11607

15. Sterility (Annex I.8)

• Installation qualification and validation summary (SAL of 10^{-6})
• Process validation report with physical and microbiological performance qualification
• Sterilization plant certified by a Notified Body (ISO 9001/2, ISO 13485/8, EN 550 ff, ISO 11130 ff)

16. Labeling (Annex I.13)

Requirements of the MDD (Annex I.13), EN 980, ISO 15223, EN1041.

17. Instructions for use (Annex I.13)

Description/indication for use/contraindications/ warnings/precautions/adverse events/ operation

18. Risk analysis (Annex I.1 to I.6)

• All hazards known or reasonably foreseeable in both normal and fault condition, together with the likelihood and consequences of occurrence and measures taken to reduce the resulting risks to acceptable levels
• Demonstration of appropriate risk analysis.

Conclusion that the remaining risks are acceptable when weighed against the benefits. Results to be reviewed and approved

• EN ISO 14971, EN 12442-1/2/3, MEDDEV 2.5-8

19. Essential requirements checklist

Table format: essential requirement/applicability of requirement/standards or methods utilized to show compliance/location of supporting documentation/rationale or comments.

20. History of the device

Market release, items sold, history of the materials used, techniques applied, including existing regulatory approvals (i.e. FDA 510(k) or PMA clearance)

21. Conclusion

Summary of the design dossier data including a risk vs. benefit statement.

22. Declaration of conformity (draft only!)

7.4 Questionnaire on Drug-device Combination Products

Question 1

Did you perform any evaluation on medical devices containing a medicinal product as a constituent part with ancillary action to that of the medical device (acc. article 1 (4) of directive 93/42/EEC; e.g. drug-eluting stent) in context of a consultation by a Notified Body.

1a) If yes, could you please indicate exact annual numbers, if available.

Year	**2004**	**2005**	**2006**	**2007**
Number				

1b) What types of product have been evaluated? Please categorise according to indicated types.

Product type	**2004**	**2005**	**2006**	**2007**
drug-eluting stents				
Antibiotic-containing bone cement				
Antibiotic-containing wound patch				
Antibiotic-coated catheter				
[others please indicate]				

Question 2

Did you authorise any medicinal product in which a medical device and medicinal product form a single integral product (acc. article 1 (3) of directive 93/42/EEC) and contacted a Notified Body for evalution of the medical device part.

2a) If yes, could you please indicate exact annual numbers, if available.

Year	**2004**	**2005**	**2006**	**2007**
Number				

2b) What types of product have been evaluated? Please categorise according to indicated types

Product type	**2004**	**2005**	**2006**	**2007**
Coated intrauterine pessar				
Single use insulin pen				
Single use inhalor				
[others please indicate]				

Question 3

What information has been evaluated and supported the decision on quality, safety and efficacy/effectiveness of the product. Would it be possible to obtain anonymously information (confidential parts could be shown in black) relevant for the decision and marketing as e.g. the label, summary of information and data related to the device for two from each category of indicated product types, if applicable. Please provide the documentation as separate electronic files.

Category A:
Devices containing a medicinal product as a constituent part with ancillary action
1. [please indicate]

2.

Category B:
Medical device and medicinal product form a single integral product
1. [please indicate]

2.

Question 4

Do you know of any current activities in your CA to implement the obligation laid down in the Directive 93/42/EEC as amended by 2007/47 Article 20 to ensure compliance after the transfer into national law.

[please indicate]

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