Drug Device Combination Regulations

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Outline

- Device-Drug Combination: The European perspective
- GHTF Background
- GHTF Combination Products working definition
- GHTF Combination Products regulatory principles
- Comparison of GHTF members' regulatory approaches for combination products
- Examples of Drug Device combination

‘Medical device’ definitions

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

• diagnosis, prevention, monitoring, treatment or alleviation of disease;

• diagnosis, monitoring, treatment, alleviation or compensation for an injury or handicap;

• investigation, replacement or modification of the anatomy or of a physiological process;

• control of conception

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

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Device-Drug Combination: The European perspective

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More definitions

‘– *Pharmacological means*

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

– *Immunological means*

... an action which involves an action in or on the body by stimulation and/or mobilisation of cells and/or products involved in a specific immune reaction.

– *Metabolic means*

... an action which involves an alteration, including stopping, starting or changing

the speed of the normal chemical processes participating in, and available for, normal body function. The fact that a product is itself metabolised does not imply that it achieves its principle intended action by metabolic means.

‘Pharmaceutical’ definitions

- ***Directive 2001/83/EC as amended by Directive 2004/27/EC (OJ L 136 pp 34-57)***

- ***Medicinal product (Art 1(2)):***

(a) Any substance or combination of substances *presented as having properties* for treating or preventing disease in human beings
(b) Any substance or combination of substances which may be *used in or* administered to human beings *either* with a view to restoring, correcting or modifying physiological functions *by exerting a pharmacological, immunological or metabolic action, or to* making a medical diagnosis

Pharmaceutical' definitions

'***Directive 2001/83/EC as amended by Directive 2004/27/EC***
Art 2:

1. This Directive shall apply to medicinal products for human use intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process
2. 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 provision of **this Directive shall apply**
3. Notwithstanding paragraph 1 and Article 3(4), Title IV of this Directive shall apply to medicinal products intended only for export and to intermediate products

‘Pharmaceutical’ definitions

Substance:

– Any matter irrespective of origin which may be:

- human, *e.g. human blood or blood products*;
- animal, *e.g. micro-organisms, whole animals, parts of organs, animal secretions, toxins, extracts, blood products, etc*;
- vegetable, *e.g. micro-organisms, plants, parts of plants, vegetable excretions, extracts, etc*;
- chemical, *e.g. elements, naturally-occurring chemical materials and chemical products obtained by chemical change or synthesis*.

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Drug-device combinations Examples

Drug delivery device + drug = Pharmaceutical

– e.g. prefilled syringe

– e.g. trans-dermal drug delivery system

Intended for use only as a complete product

• Medical device + drug (secondary action) = Medical device(?)

– e.g. pacemaker lead impregnated with steroid to prevent local tissue reaction and thus extend life of lead

– e.g. IV catheter coated internally with heparin to help prevent occlusion

Drug or device? Questions to ask yourself ...

- What is the manufacturer's intended purpose for the product, taking into account the way in which it is presented?
- What is the mechanism by which the product achieves its principal intended action?
  - Medical devices typically achieve this through *physical means*
  - Pharmaceutical products typically achieve this through *pharmacological means, immunological means, or through metabolism*
  - *Impact of new pharmaceutical directive scope?*

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Experience in Europe

- A number of dossiers have been submitted since 1995 …
- At least one positive approval from EMEA (published on web site)
- MHRA - around 180 submissions, 82 positive Opinions, 32 negative Opinions (no information published on web site)
  - Processing time around 240 days in 2007
- BfArM – around 80 submissions

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Experience

- Comments received from those who have used the system:
  - – Ability to choose the CA for consultation welcomed
  - – No clear time lines may be provided from the CA
  - – FDA processing faster and with a different focus for the same product; in-house processing of all aspects seems to be advantageous
  - – Requests for supplementary information common
  - – Applications made to a number of different authorities by different manufacturers/NBs
  - – Some Agencies more flexible about format than others
  - – Lack of direct contact between manufacturer and CA a disadvantage – the NB is usually required to reflect the manufacturer's position
  - – CAs appear to give priority to pharmaceutical product licence applications – can result in delays for device-drug assessments

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GHTF Background

- Established Ad Hoc Working Group in 2007
- Reviewed existing GHTF documents to see what changes needed
- Established a working harmonized definition
- Developed general principles for regulation of combination products
- Considered establishing liaison with appropriate medicines and biological organizations

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GHTF Combination Products Working Definition

"Products that meet the GHTF harmonized definition of a medical device and that are assisted in achieving their intended function by an incorporated medicinal substance or material of biological origin"

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GHTF Combination Products Regulatory Principles

- Predictable, transparent, efficient, and least burdensome harmonized regulatory framework
- Flexible guidance documents easily adaptable to existing regulatory systems
- Consideration of appropriate elements of medical device, medicines and biologics regulatory models

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GHTF Combination Products Regulatory Principles

- Determination of regulatory requirements
  - Based on one of traditional regulatory frameworks—not adding 2 together
  - Based on principal intended mode of action of product
  - Take into account secondary mode of action
  - Consider entire product life cycle
  - Include documented risk assessment
  - Application of appropriate international standards

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Comparison of GHTF Members' Regulatory Approaches

	Definition of Combination Products (CP)
AUS	Not defined as a separate product. CPs regulated according to main function/purpose of the CP.
Canada	A therapeutic product that combines a drug component and a device component (which by themselves would be classified as a drug or a device), such that the distinctive nature of the drug component and device component is integrated in a singular product.
Japan	No specific definition. CPs are regulated according to main function/purpose of the CP.
US	Product comprised of 2 or more regulated components that are physically, chemically or otherwise combined or mixed and produced as a single entity or co-package product, or as cross-labeled products.
EU	No general definition of combination product. A 'combined advanced therapy product' is defined as one that incorporates as an integral part one or more medical devices, or active implantable medical devices, and viable cells or tissues, or non-viable cells or tissues where the action on the human body of these cells or tissues is primary to the device.

Comparison of GHTF Members' Regulatory Approaches

	Agency Review Determinations – Who is the lead?
AUS	Consider primary intended purpose and mode of action. May be referred to an internal committee consisting of staff from relevant regulatory areas of TGA.
Canada	Medical Devices Bureau – when classified as a Device.
Japan	PMDA leads review – Offices under PMDA will lead depending on how the CP is regarded.
US	Assignment by Office of CP to Agency Center based on "primary mode of action" of CP. If PMOA cannot otherwise be determined, assignment will be based on the following algorithm: If there is an Agency Center that regulates other CPs presenting similar questions of safety & efficacy with regard to the CP as a whole then the CP should be assigned to that Agency Center. If not, the CP will be assigned to the Agency Center that has the most expertise related to the most significant safety & efficacy question presented by the combination product.
EU	Consider primary mode of action. Opinions must be sought from relevant expert committees for certain CPs.

	GMPS/QS Requirements
AUS	Same as for other Medical Devices or Medicines.
Canada	Required to meet acceptable standards of safety, efficacy and quality.
Japan	According to main function (drug, device) requirements.
US	Draft guidance published 2004. Proposed regulation is under development.
EU	Same as for other Medical Devices or Medicinal Products.

	Adverse Event/Vigilance Reporting Requirements
AUS	Same as for other Medical Devices or Medicines.
Canada	Same as for other Medical Devices or Medicines.
Japan	According to main function (drug, device) requirements.
US	Draft concept paper published 2004. Proposed regulation is under development.
EU	Same as for other Medical Devices or Medicinal Products.

	Registration and Listing
AUS	Entry into Australian Register of Therapeutic Goods.
Canada	Product licensing scheme.
Japan	According to main function (drug, device) requirements.
US	Most of manufacturers R & L according to type of pre-marketing application.
EU	No central register for devices.

Example: Combination Device Review via Device Approval Process

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Combination Device Example

- CYPHER™Sirolimus-eluting Stent is:

Bx Velocity™ Balloon expandable Stent

coated with Sirolimus

... a device incorporating a drug component with the combination product having the primary intended purpose of fulfilling a device function

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Combination Device Example

The sirolimus is intended to serve as a secondary purpose of retarding formation of intimal hyperplasia. If the acute gain is coronary luminal diameter and prevention of remodeling is not achieved as a result of stent scaffolding, the sirolimus serves no useful purpose. Thus, the stent must achieve its device function for the drug to be of any benefit. In accordance with the guidance, CDRH would have market approval authority with an intercenter consultation from CDER.

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Combination Device determination in the EU

- BSI consulted with several National drug Competent Authorities within EU regarding: Conducting a medicinal substance consultation on behalf of BSI

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Combination Device in the EU

- The Cordis CYPHER Sirolimus-eluting Stent has been reviewed and approved by BSI as a device with a consulting drug review by the Competent Authority.

- None of the Competent Authorities raised any objection to CYPHER Sirolimus-eluting Stent being reviewed as a device.

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U.S. FDA Determination

- The U.S. FDA responded:

  ... “We note the primary purpose of the combination product is to physically buttress the vessel wall -- a device function -- and that sirolimus is present to augment the product’s safety and efficacy. Therefore, we conclude that the primary mode of action of the product is that of a device component and CDRH should be assigned principal review responsibility.”

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U.S. FDA

- FDA's decision was based on:

  - The primary mode of action is to physically support the vessel wall -- a device function.

  - Sirolimus serves a secondary function to enhance the product's safety and efficacy.

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Example A Combination Product Via Drug Approval Process

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Inhaled Insulin

- Primary Mode of Action (PMOA) is the systemic effect of insulin.

- Rationale of inhaled route of administration of Insulin
  - Large absorptive area in the lung alveoli
  - Fast absorption of insulin into the bloodstream as rapid as subcutaneous injection of rapid-acting insulin
  - Peak plasma level (Tmax) comparable to subcutaneous

Inhaled Insulin (Cont)

- Injection c (~ 40-90 min after inhaled)
- Rapid onset of action after inhalation
- Drug particle size and density are important attributes for optimal pulmonary delivery. Smaller particle sizes are important to deliver to distal lung for systemic absorption
- Insulin power is used in conjunction with a special inhaler
- Clinical pharmacology and biopharmaceutics (Phase 1) studies used early drug formulations device prototypes
- Device design and drug formulations optimized during early phase clinical trials
- “Final” (P3 version) configuration of inhaler used in phase 3 trial.

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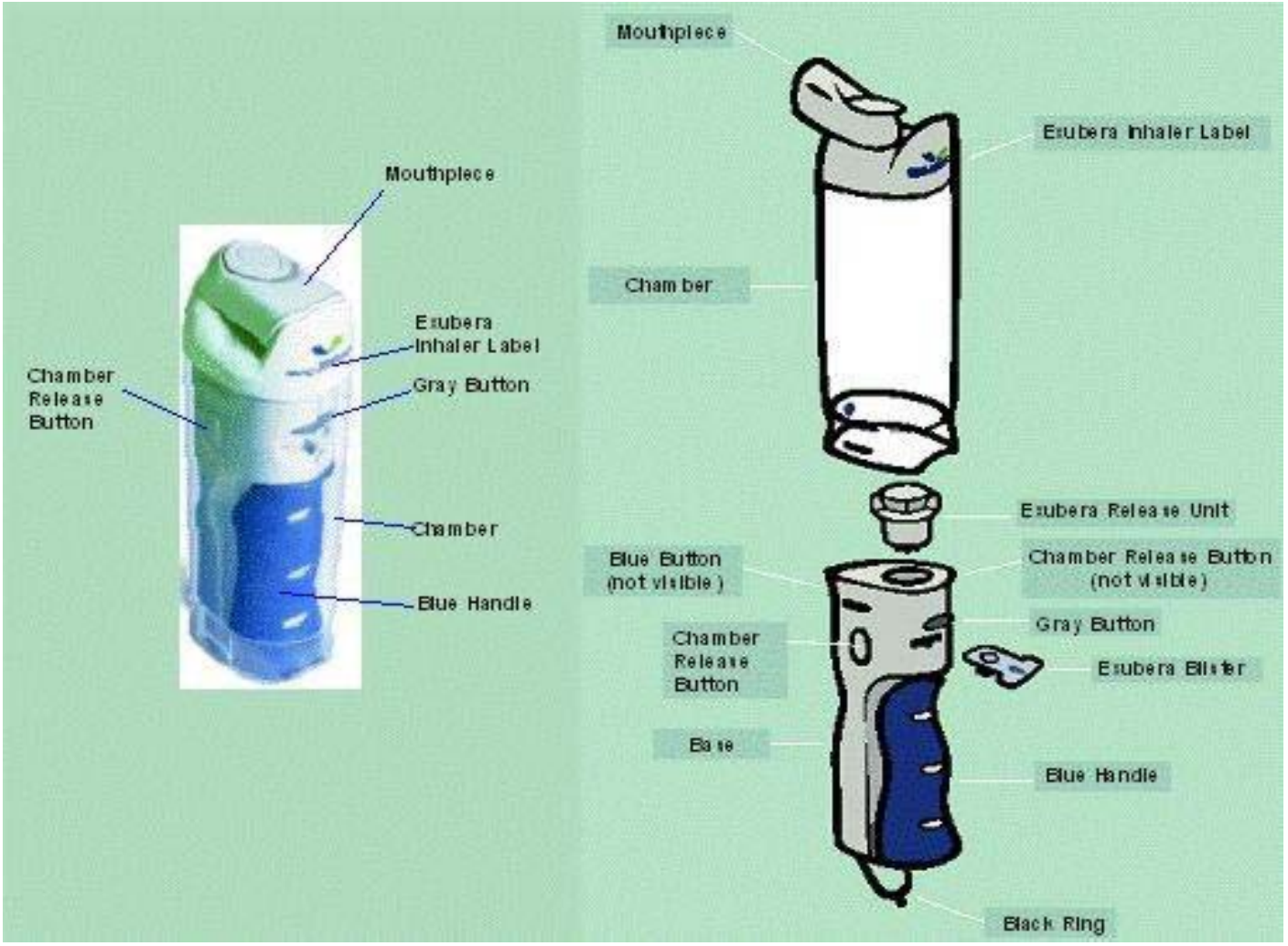
Inhaler and Dry Powder [drug] Blisters



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Regulatory Information

- FDA considers this a “drug-device” combination
- Primary Mode of Action (PMOA) – drug action (insulin)
  - Indication: For the treatment of adult patients with diabetes mellitus for the control of hyperglycemia.
- Regulatory Approval Path – NDA (New Drug Application)
- Lead Review Center FDA CDER (Center for Drug Evaluation and Research)
- CDRH (Center for Device and Radiological Health) as consult review (as part of a large review team)

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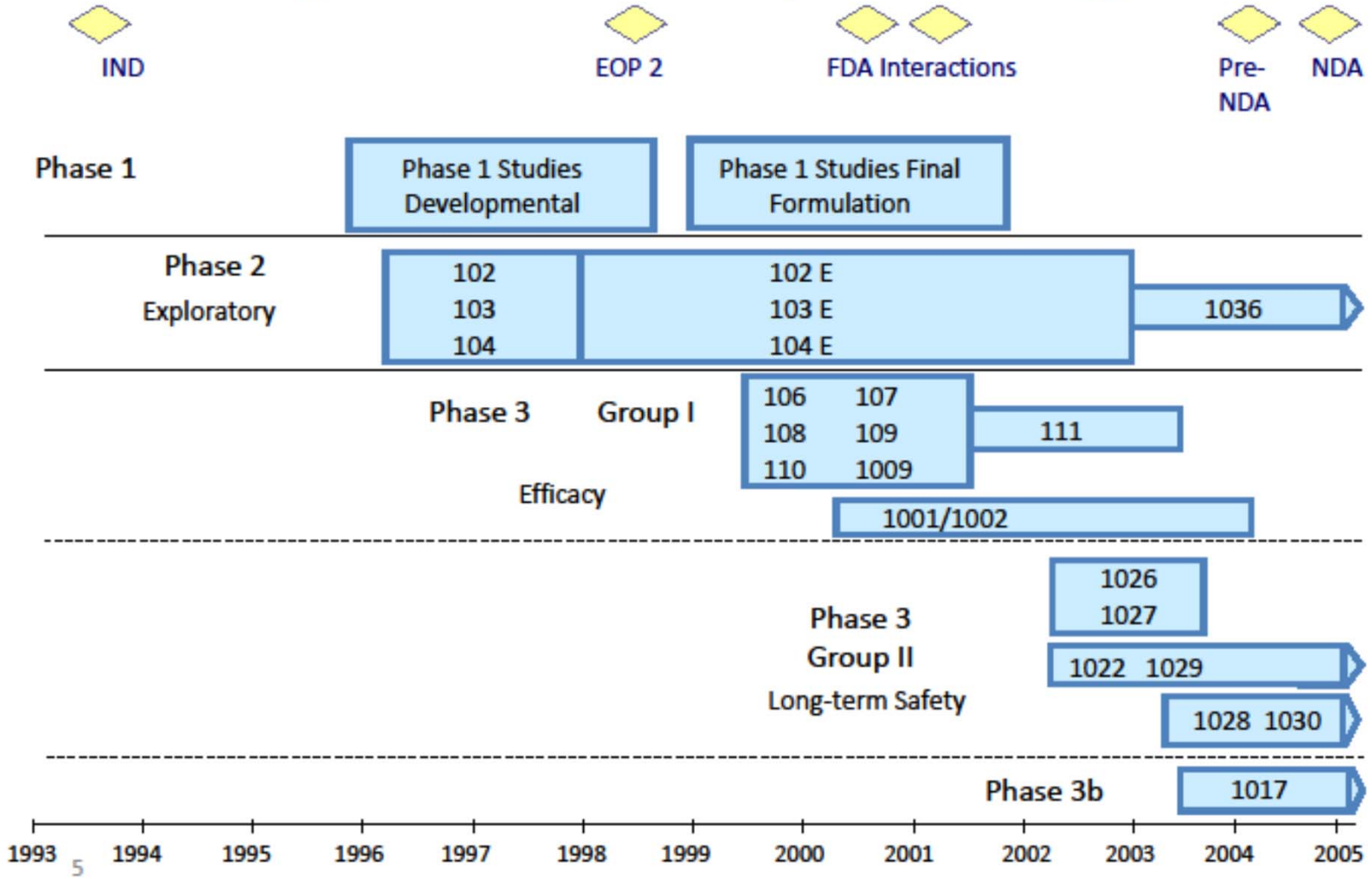
Drug Clinical Development Program



Participation of Device Reviewers

- During IND (Investigational Drug) phase at one of the “guidance” meetings with company
- Final device design “locked” before phase 3 (i.e. pivotal trials). Commercial device essentially the same as version used in Phase 3 trials.
- CDER Project Manager has overall responsibilities to coordinate review and response (with CDRH reviewers).
- NDA contains data on device in CMC (Chemistry, manufacturing and controls) Section
- Device information can also be in a MAF (Device Master File) to protect proprietary information. Note – not in this case.
- Device reviewers part of the review team – present at NDA Filing meeting.

General Comments on Inhalers – Current Trend For Inhalers

- ICH* Guidance Q8 (R2) – Pharmaceutical Development, Nov 2009 – dry powder inhaler identified as a “dosing device” and set requirements. Recognized the inhaler contribute to accurate and reproducible dosing of the drug.
- CDRH reviewers serve as consult, as part of review team
- CDER defers to CDRH Human Factor Engineers for device use testing
- Human Factor studies help optimize device designs as drug progress through clinical program from Phase 1 (feasibility) to Phase 3 (pivotal) trials
- CDRH reviewers participate in mid-review meetings/conferences with company during NDA review

* International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, Quality Expert Working Group

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