5th Annual Drug Delivery Systems
VISIONGAIN
February 10 – 11, 2010
LONDON

TOXIKON EUROPE NV
Dr. Piet Christiaens
TOXIKON – COMPANY PROFILE

➢ C.R.O.  Headquarters: Bedford, MA

➢ European Lab Facility: Leuven, Belgium

➢ 30 Years of experience in Biocompatibility Testing for the Medical Device and the Pharma Industry

➢ FDA Registered, ISO 17025 and GLP Accredited, GMP-compliant testing

➢ 150 Researchers
TOXIKON – COMPANY PROFILE

- *In-vivo* testing services (US)
- *In-vitro* testing services (US, Europe)
- Analytical chemistry (US, Europe)
  - *Extractables/leachables*
  - *Compendial testing (EP, USP, JP)*
  - *Method development/validation*
TOXIKON EUROPE – COMPANY PROFILE

- Since 2001: fully focussed on Extractable/Leachable Testing
- 800 E/L-Related Projects in 2007-2008
- 30 Employees (8 PhD, 5 Eng, 3 full time QA)
- Dedicated Equipment/Standards For E/L-Testing
- Optimized Procedures/Protocols for E/L-Projects
- Three devisions: 1. Disposables/Single use (in (bio)production)  
  2. Parenterals + Ophthalmics  
  3. Inhalables (OINDP’s)
REGULATORY REQUIREMENTS FOR BIOCOMPATIBILITY TESTING OF DRUG DELIVERY DEVICES
1. Is the product a Drug or a Device: HOW to decide?

2. Consequences for Biocompatibility/Compliance testing
   - For a Medical Device
   - For a Medicinal Product

3. Conclusion
Is the product a Drug or a Device: HOW to decide?

Drug Delivery Devices:

- Often Borderline Products between a Device and Drug
- Case-by-Case: decide which directive is applicable
  - MDD?
  - MPD?
- A very broad scope of applications
- Difficult to “generalize”
Is the product a Drug or a Device: HOW to decide?

Drug Delivery Devices – Broad Scope of Applications

Non-Limitative List:

Drug Eluting Stent, Catheters with Heparin, Bone cement incorporating an antibiotic, Dry Powder Inhaler, Metered Dose Inhaler, Syringes, Pre-filled Syringes, I.V.-Administration Bag, Nebulizers, Drug Delivery Pump, Peritoneal Dialysis Solutions, Eye drops, Desinfectants for Medical devices, Spermicidal Preparations...
Is the product a Drug or a Device: HOW to decide?

Key factors to decide

MEDICAL DEVICE vs MEDICINAL PRODUCT:

- Intended Purpose
- Principal Intended Action

**MEDICAL DEVICE**
- Physical Action
- Physical Barrier
- Physical replacement

**MEDICINAL PRODUCT**
- Pharmacological Action
- Immunological Action
- Metabolic Action
Is the product a Drug or a Device: HOW to decide?

This document is meant purely as a documentation tool and the institutions do not assume any liability for its contents.

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COUNCIL DIRECTIVE 93/42/EEC
of 14 June 1993
concerning medical devices
(OJ L 169, 12.7.1993, p. 1)

Amended by:

Official Journal

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For Borderline Products: what is the MDD telling us?
Is the product a Drug or a Device: HOW to decide?

DEFINITION: WHAT IS A MEDICAL DEVICE

(a) ‘medical device’ means any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

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

Amended by:

Is the product a Drug or a Device: HOW to decide?

MD + MP = SINGLE INTEGRAL PRODUCT

- Exclusively for the use of the given combination
- Not reusable
- Follow the MPD!!

Examples:
Dry Powder Inhaler, Metered Dose Inhaler, Pre-filled Syringe, I.V.-administration solution...
Is the product a Drug or a Device: HOW to decide?

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 M5 2001/83/EC and which is liable to act upon the body with action ancillary to that of the device, M5 that device shall be assessed and authorized in accordance with this Directive.

4 a. Where a device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product constituent or a medicinal product derived from human blood or human plasma within the meaning of Article 1 of Directive M5 2001/83/EC and which is liable to act upon the human body with action ancillary to that of the device, hereinafter referred to as a ‘human blood derivative’, M5 that device shall be assessed and authorised in accordance with this Directive.

IF

- MD incorporates MP / MP derived from blood/plasma
- Action of MP is ANCILLARY to action of MD

Follow the MDD!!

Examples:
Heparin/Antibiotic coated Catheters, Root canal fillers with medicinal substances, Drug Eluting Coronary Stents, Wound Dressing with Antimicrobial Agent...
Is the product a Drug or a Device: HOW to decide?

MEDDEV 2.1/3 rev 3 - December 2009

EUROPEAN COMMISSION
DG ENTERPRISE and INDUSTRY
Directorate F, Unit F3 “Cosmetics and medical devices”

MEDICAL DEVICES: Guidance document

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

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

Foreword

The present Guideline is part of a set of Guidelines relating to questions of application of EC Directives on medical devices. This guideline is not legally binding, since only the European Court of Justice can give an authoritative interpretation of Community law. It has been elaborated by an expert group including experts from Member States’ Competent Authorities, the Commission’s services, as well as industry trade associations. It is therefore intended that the document will provide useful guidance which should assist common positions to be taken throughout the European Union. Due to the participation of the aforementioned interested parties and of experts from Competent Authorities, it is anticipated that these guidelines will be followed within the Member States and, therefore, ensure uniform application of relevant Directive provisions.

The present guideline provides non-exhaustive lists of examples of medical devices, accessories to medical devices and medicinal products. Further examples may be found in the manual on borderline and classification in the Community Regulatory framework for medical devices, published on the European Commission website.1 Particular attention should be paid to borderline cases between medical devices and herbal medicinal products. This issue may be further developed in this guidance in the near future.

Note: This document is a revision of an earlier document published in July 2001 as MEDDEV 2.1/3 rev 2. Some of the examples given in the MEDDEV 2.1/3 rev 2 have not been included in the present Guideline. These examples will be further elaborated in the above mentioned manual on borderline and classification in the Community Regulatory framework for medical devices.

This guidance incorporates the changes introduced by the Directive 2007/47/EC.2 These changes have to be applied as of 21 March 2010.

2 OJ L 247, 21.09.2007
Is the product a Drug or a Device: HOW to decide?

Results of an Expert Working Group
- Drug and Device Competent Authorities
- European Commision
- Trade Associations

It is a Guideline, no “legal” force

Guidelines relating to the demarcation between the
- Directive 90/385/EEC on Active Implantable Devices
- Directive 93/42/EEC on Medical Devices (MDD)
- Directive 65/65/EEC relating to Medicinal products and related directives

Gives Practical Guidance and Examples

Includes as Medicinal Products (even though these do not achieve their PIA by Pharmacological, Immunological or Metabolic Means)
- Water for Injections, I.V.-Fluids (see example)
- Artificial Tears
- Fluoride dental preparations

If it is not clear whether it is a MD or MP: the MPD governs!
Is the product a Drug or a Device: HOW to decide?

Manual on Borderline and Classification in the Community Regulatory Framework for Medical devices (Version 1.5 (09-2009))

This document contains well discussed examples (with a rationale) on the Demarcation line between MD and MP.

e.g.

- Peritoneal dialysis solutions (MP)
- Zinc Oxide Containing Creams
- Eyedrops for soreness, discomfort or irritation
- Products for acute sore throat
- ...
Content

1. Is the product a Drug or a Device: HOW to decide?

2. Consequences for Biocompatibility/Compliance testing
   - For a Medical Device
   - For a Medicinal Product

3. Conclusion
Consequences: Biocompatibility/Compliance testing

EXAMPLE 1: EMPTY STERILE I.V. BAG

Classified as a Medical Device

MEDICAL DEVICE DIRECTIVE
Based upon perceived risk and nature and duration of contact with patient

4 CLASSES

Class 1  Lowest Risk

Class 2A

Class 2B

Class 3  Highest Risk
**Consequences: Biocompatibility/Compliance testing**

Empty sterile (I.V.) administration bag as MEDICAL DEVICE

Considered as an External Communicating Device with indirect blood contact with < 24h contact (ISO/FDA test chart):


<table>
<thead>
<tr>
<th>In-vitro Biocompatibility assays</th>
<th>In-vivo Biocompatibility tests</th>
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<tbody>
<tr>
<td>Cytotoxicity</td>
<td>Sensitization (2 extracts)</td>
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<td>Haemocompatibility</td>
<td>Irritation/intracutaneous reactivity (2 extracts)</td>
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<td>Acute Systemic Toxicity (2 extracts)</td>
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<td></td>
<td>Pyrogenicity</td>
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**NEW APPROACH ISO 10993-1 (2009): RISK BASED ASSESSMENT!**
Consequences: Biocompatibility/Compliance testing

MEDDEV 2.1/3 rev03

Examples of medicinal products:

- Spermicidal preparations,
- Gases intended to be used in anaesthesia and inhalation therapy, (e.g. oxygen, medical air supplied in containers) including their primary containers,
- Topical disinfectants (antisepsics) for use on patients,
- Haemostatic and sealant products interacting with the coagulation cascade through a pharmacological process i.e. where the primary mode of action is not mechanical (such as certain collagens which have a molecular structure capable of surface independent demonstrated interaction with platelet receptors and therefore achieve platelet adhesion through a pharmacological process)
- Water for injections, IV fluids and other fluids for drug injection and plasma volume expanders,
- In vivo diagnostic agents, e.g. x-ray contrast media, NMR enhancing agents, fluorescent ophthalmic strips for diagnostic purposes, carrier solutions to stabilize microbubbles for ultrasound imaging, radioactively labelled compounds for diagnostic use
- Gases for in-vivo diagnostic purposes, e.g. gases used for imaging lung function, tests, e.g. carbon dioxide for vascular diagnostic purposes

- Water for injections, IV fluids and other fluids for drug injection and plasma volume expanders,

2. C(I):147, 16.09.2007

15 See also Directive 75/76/ECC on cosmetic products

action to that of the device.

- Solutions administered in-vivo to the local circulation for the cooling of organs during surgery,
Consequences: Biocompatibility/Compliance testing

FILLED (I.V.) administration bag as PHARMACEUTICAL CONTAINER

It concerns the application of Part 1, Module 3, sections 3.2.1.6, 3.2.2.2 and 3.2.2.7 of Annex I to Directive 2003/63/EC, amending Directive 2001/83/EC for human medicinal products, and Part 2, sections A, C and G of Annex I to Directive 2001/82/EC for veterinary medicinal products, respectively, to plastic immediate packaging materials.

1.3 General Principles

The data to be provided for plastic packaging materials depend on the physical state of the active substance (see decision tree in Appendix I) and the pharmaceutical dosage form and route of application of the medicinal product (see decision tree in Appendix II). The data should be presented according to the standard format described in the Notice to Applicants (Volume 2B of The Rules governing Medicinal Products in the European Union), CTD-Module 3, 3.2.S.6, 3.2.P.2.4 and 3.2.P.7, for human medicinal products or in the Notice to Applicants (Volume 6B of The Rules governing Medicinal Products in the European Union) Part 2 sections A, C and G, for veterinary medicinal products. A correlation table on the location of the EU-CTD dossier versus the previous version for human medicinal products (NTA, Vol. 2B, edition 1998) and the current version for veterinary medicinal products (NTA, Vol. 6B, edition 2004), respectively, is provided in Appendix III.

The guideline should be read in conjunction with the current versions of the guidelines on Development Pharmaceutics (CPMP/QWP/155/96), Stability Testing: Stability Testing of New Drug Substances and Products (CPMP/ICH/2736/99) – Revision of CPMP/ICH/380/95 – and Stability Testing: Stability Testing of Existing Active Substances and Related Finished Products (CPMP/QWP/122/02, corr.) for human medicinal products and the guidelines on Development Pharmaceutics for Veterinary Medicinal Products (CVMP/315/98), Stability Testing of New Veterinary Drug Substances and Medicinal Products (CVMP/VICH/899/99) and Stability Testing of Existing Active Substances and Related Finished Products (CVMP/846/99) for veterinary medicinal products, respectively.
Consequences: Biocompatibility/Compliance testing

FILLED (I.V.) administration bag as PHARMACEUTICAL CONTAINER

9 APPENDIX II: DECISION TREE ON THE PRESENTATION FORM OF MEDICINAL PRODUCTS

- Non-solid dosage forms
  - Material described in Ph.Eur. or in the pharmacopoeia of a Member State
    - yes
      - General information (3.1)
      - Specification (3.2)
      - Interaction studies
    - no
      - General information (3.1)
      - Specification (3.2)
      - Extraction studies (4)
      - Interaction studies (5)
      - Toxicological information (6)

- Solid dosage form
  - for oral and topical other than ophthalmic administration

- Plastic packaging
  - for oral and topical other than ophthalmic administration

Consequences: Biocompatibility/Compliance testing

FILLED (I.V.) administration bag as PHARMACEUTICAL CONTAINER


Parenteral Administrations:

- For Materials, described in the Pharm. Eur.: Compendial tests
- Could limit / avoid extractable tests
- If no Compendial test results available: EXTRACTABLE testing
- Full LEACHABLE Assessment of the IV bag

CONCLUSION:
NO in-vivo/in-vitro biocompatibility tests included!
Complete assessment is based upon chemical/analytical testing
Consequences: Biocompatibility/Compliance testing

Example: Intravenous (I.V.) administration bag

**FINAL CONSIDERATIONS**

I.V.-bag, when used as a medical device: contact with solution is typically limited to < 24 h

- Full in-vivo/in-vitro biocompatibility assessment

I.V.-bag, when used as a pharmaceutical container: contact between bag and solution is determined by the shelf life of the product (up to 3 years!)

- The use of the I.V. **Bag as a pharma container is worst case compared to the use as a medical device**
- **ONLY CHEMICAL/ANALYTICAL EVALUATIONS (in EU)!**
Drug Delivery Devices: broad array of applications

Determine which directive will need to be followed for your application
- Medical Device Directive (MDD)
- Medicinal Product Directive (MPD)

Determine which action is PRIMARY/ANCILLARY (physical vs pharmacological/immunological/metabolic)

If not clear which action is Primary/Ancillary:
- follow the Medicinal product Directive (MPD)

If not clear: consult
- MEDDEV 2.1/3 rev 03
- Manual on Borderline and Classification in Community Regulatory Framework for Medical Devices
- Notified Bodies / Competent Authorities
ANY QUESTIONS?

Visit our booth!

For further questions, please contact: piet.christiaens@toxikon.be
OR, visit our website at: www.toxikon.be