The Role of a Notified Body in Defining Risk Assessment for a Recombinant Protein Used in a Medical Device – Case Study

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Update on Medical Device/Combination Products

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Hemodialysis therapy

- Chronic kidney disease (CKD) afflicts around 5% of the Western population.
- Approximately 2 million dialysis patients in OECD countries.
- Designated as a Public Health Threat by the US NIH in 2006 and subject to fast-track approval through the FDAs Innovation Pathway.

Treatment:
Blood is taken from a peripheral vessel and fed by a blood pump through a size-filter
- Molecules small enough to pass the filter escape,
- Larger molecules, irrespective of their toxicity, remain in the blood and are transported back into the bloodstream.

DIANA
- The product is a device composed of a column containing two recombinant proteins linked to a matrix of beads.
- These ligand coated beads are binding proteins (<30kDa) from the blood passing through the column during the routine dialysis.
DIANA is a Medical Device

- What type of product is DIANA?
  - NO pharmacological, immunological, or metabolic action
  - NOT entering the body
  - NOT used for *in vivo* diagnostic
    - **BUT using recombinant human proteins produced in CHO cells**
The manufacturer of a class I medical device, or his relevant authorised representative in the European Union designated by him, must notify their address and a description of the devices concerned to the Competent Authority of the Member State where they have their registered place of business (Article 14, paragraphs 1 and 2 of Directive 93/42/EEC).

For medical devices of classes IIa, IIb and III, Member States may request to be informed of all data allowing for identification of such devices together with the label and the instructions for use when such devices are put into service within their territory (second sub-paragraph of Article 14, paragraph 1, of Directive 93/42/EEC).
Classification of DIANA

Notified body - considered the CHO cells used for manufacturing animal sourced origin for production.

Rule 17 –
Devices utilising animal tissues or derivatives

This rule covers devices that contain or are made of animal tissues that have been rendered non-viable or derivatives from such tissues also being non-viable, i.e. where there is no longer any capacity for cellular metabolic activity. Class III
Rule 17 – Devices utilising animal tissues or derivatives

- The proteins are **not considered as animal sourced**, as they originate from the human genome, while the CHO cells are considered the host for production only, not the origin of the proteins.
- The proteins are also **not considered to be human sourced** as there are several steps taking place modifying the origin, including in vitro nucleotide sequence synthesis and PCR, meaning that the human origin can be considered too far removed from the products to qualify.

Rule 3 – Non-invasive devices that modify biological or chemical composition of blood, body liquids or other liquids intended for infusion into the body

- All non-invasive devices intended for **modifying the biological or chemical composition of blood**, other body liquids or other liquids intended for infusion into the body are in **Class IIb**
Consideration: Does the classification matter?

Notified body considered the CHO cells used for manufacturing of a recombinant protein as derived from animal tissue.

The RISK associated by production of a recombinant protein originating from an animal sourced raw material should be managed by analysis, evaluation and control.
DIANA –
Risk Management of an Animal Derived Medical Devices

Quality System and ISO Compliance
- ISO 13485 Quality System
- **ISO 14971 Risk Management**
- ISO 22442 Animal Tissue
- ISO 13408 Aseptic Processing
- ISO 14155 Clinical Trial
- ISO 10993 Biocompatibility

Medical devices –
Application of risk management to medical devices (ISO 14971:2009)

NOTE 2 A schematic representation of the risk management process is shown in Figure 1. Depending on the specific life-cycle phase, individual elements of risk management can have varying emphasis. Also, risk management activities can be performed iteratively or in multiple steps as appropriate to the medical device. Annex B contains a more detailed overview of the steps in the risk management process.

Compliance is checked by inspection of appropriate documents.
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Medical devices utilizing animal tissues and their derivatives (ISO 22442:2007)

- Part 1: Application of risk management
- Part 2: Controls on sourcing, collection and handling
- Part 3: Validation of the elimination and/or inactivation of viruses and transmissible spongiform encephalopathy (TSE) agents
DIANA – Control and Regulation

• Quality system and ISO compliance
  – Construction and manufacturing of a DIANA as a Medical Device

• The protein preparation must follow the safety requirements for recombinant proteins for human use.
  – The blood is in contact with the proteins, and any contamination can potentially be transferred to the patient. (ICH Q5A and C)
  – The production of the proteins should meet the requirements defined by GMP for the safety of the patient. (ICH Q7A)

• Safety
  – The medical device must be assessed as a unit but also as a total
  – Safety studies in a relevant animal model must be conducted

• Efficacy
  – Clinical evidence must be shown in humans
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