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Device/Drug Combinations BSI's Expectations & Experience

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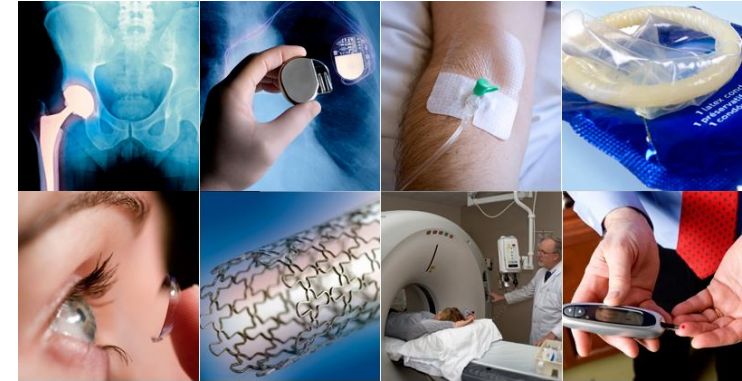
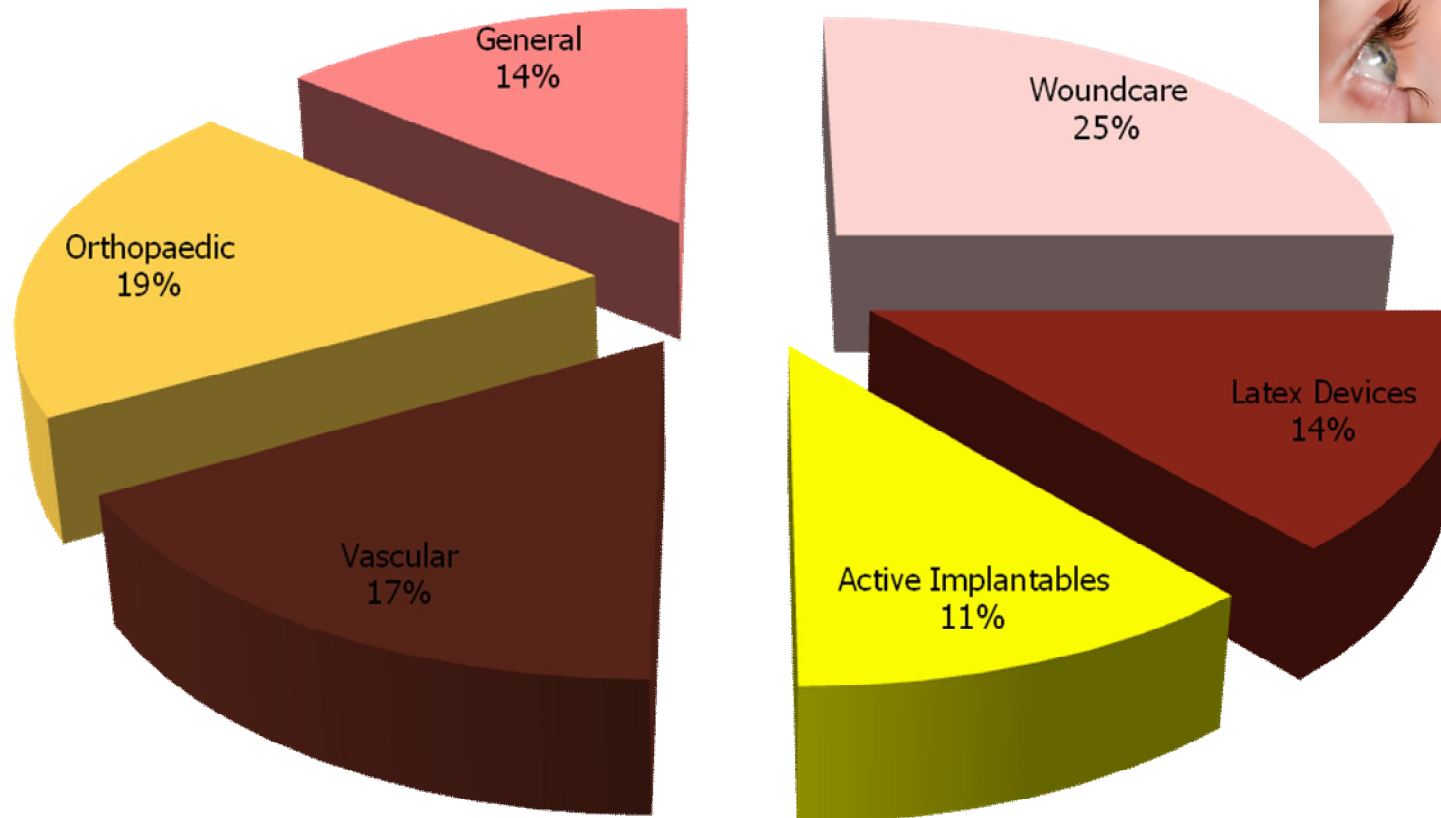
Agenda

- BSI Experience
- Classification of Device Drug Combination Products
 - Factors to Consider
 - Classification Issues
 - Available Guidance
- Device/Drug Combination - Route to CE Certification & NB Expectations
 - NB Design Dossier Review
 - Common Gaps in Submissions
- Post CE Marking
 - Strategies for handling changes
 - Transfer of Device Drug Combinations between NBs
- Factors to consider when selecting the Competent Authority

The BSI Experience

The Medtech Team and Device Drug Combinations Experience

BSI consultations expertise teams



Device Drug Combinations Classification

Key Considerations and Common Misconceptions

Classification Considerations & Misconceptions

- What claims are being made for the product?
- Primary Mode of action?
- Only contains a small amount of
 - No concept of “amount” of a medicinal substance in the medical device regulations
 - Inclusion must be justified and scientific data provided to support any claims that they are not liable to act to avoid a Class III, Rule 13 classification
- Drug is not intended to act
 - This does not preclude them from being liable to act on the body
- Countries may have differing opinions
- Important to communicate with Notified Body early in the development process

Classification Watch Outs – Natural Ingredients

- “Natural” Ingredients = Safe and Healthy ????
- Herbals, Chinese and Homeopathic Medicines
 - Clove oil – antiseptic, analgesic and sedative properties
 - Tea Tree Oil – antibacterial & antifungal properties
 - Aristolochia – Used in TCM as a slimming aid - contains toxic and carcinogenic aristolochic acids associated with kidney failure and cancer.
 - Belladonna contained in comfort eye drops
- Perceived gap between Medicinal Product and MDD regulation
- Does the therapeutic benefit outweigh the risk ?

Classification Watch Outs – Orally Administered ?

- Examples of products administered orally?
 - Simethicone
 - Products for acid reflux
 - Slimming aids
 - Products for constipation
- Generally considered medicinal products
- Potential secondary pharmacological action through absorption into systemic circulation
- Never intended to be classified as a Medical Device
- Rule in MDD

.....Yet

Classification Watch Outs – Biotech Products ?

- Examples of products produced using Biotechnology
 - Extracellular matrices (ECM) in wound healing
 - Growth Factors – Orthopaedic and wound healing applications
 - Recombinant DNA / Proteins
- Regulation (EC) No 726/2004 requires approval via centralised procedure (EMA)
- Manufacturers perceive biotech derived materials safe
 - Safer alternative to use of animal tissue such as collagen
 - Do not contain tissues / cells of human origin
 - Caution: May utilise animal tissue in manufacture – Rule 17
- Potent compounds – can be difficult to determine primary mode of action
- Seeing a huge increase in applications

Available Guidance on Classification

- Speak to NBs with experience of Device Drug Combinations
- MEDDEV 2.1/3 Rev 3
- MHRA Bulletin No. 17 – Medical devices and Medicinal Products
- MHRA Guidance Note No 8 – A Guide to what is a Medicinal Product
- Manual on borderline and Classification in the Community Regulatory Framework for medical devices

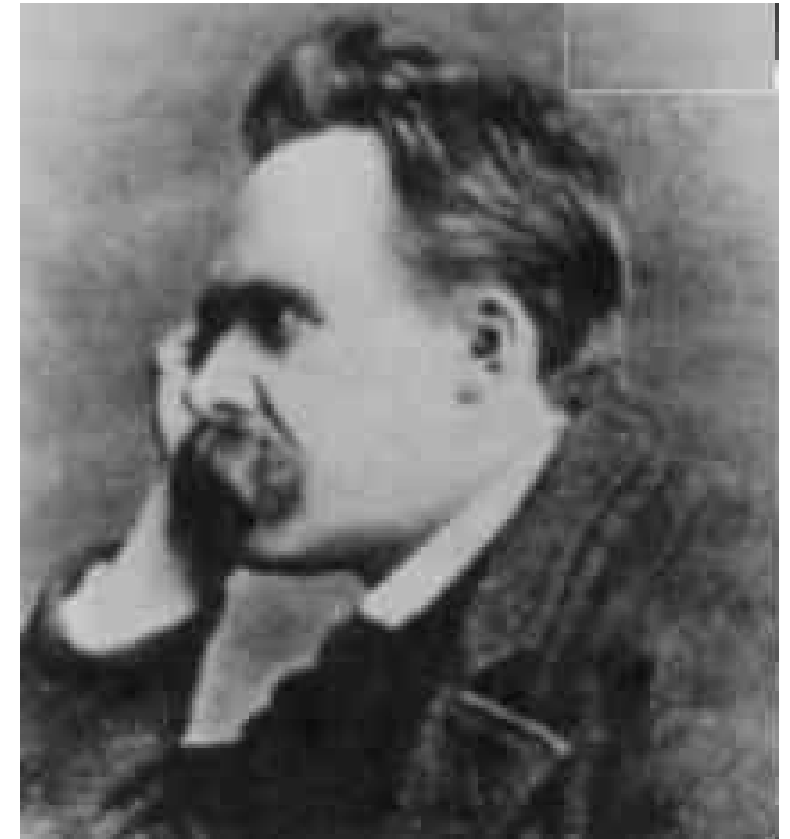
http://ec.europa.eu/health/medical-devices/documents/borderline/index_en.htm

Classification

Conclusion:

There are no facts, only interpretations
(Friedrich Nietzsche 1844 to 1900)

- Case by Case Basis
- NB and Drug Competent Authority interpretations may differ



Notified Body Responsibilities & Expectations

Notified Bodies Responsibilities

- To check that the manufacturer has followed his declared procedures and those required by the Directive
- To monitor the manufacturer's system for producing his Declaration of Conformity
- The manufacturer through his Declaration of Conformity takes ultimate responsibility for device safety and product liability

Notified Bodies Assessment

- To confirm product conforms to relevant provisions of Directive (ERs) by verifying:
 - conclusions of risk analysis
 - applicable ERs addressed
 - devices must not compromise the clinical condition of patients
 - risks are acceptable when weighed against the benefits to the patient
 - relevant standards applied or other solutions adopted to meet ERs
 - conclusions of clinical data
 - NB may require further tests to be conducted or other data

Notified Bodies Assessment

Annex II.3 EC full quality assurance

- QMS Assessment conducted to assess capability of Quality System for device drug combinations
- Assessors must have some Industrial experience with Pharmaceutical products
- Key Areas assessed
 - Incoming controls and warehousing
 - Manufacturing controls & procedures
 - Test Laboratories & procedures
 - Controls to minimise cross-contamination
 - Customer Complaints
 - Vigilance and PMS

Notified Bodies Assessment

Annex II.4 EC design examination

- NBs responsibility is to confirm product conforms to the relevant provisions of the Directive Essential Requirements by verifying
 - Conclusion of risk analysis
 - Applicable ERs addressed
 - Relevant standards applied or other solutions adopted to meet ERs
 - Conclusions of clinical data
- Must be the same NB for the Annex II.4 and the QA certification under Annex II.3

Notified Bodies Assessment

Key Essential Requirements

- ER 1
 - Devices must not compromise the clinical condition of patients
 - Risks are acceptable when weighed against the benefits to the patient
- ER 7.4
 - Verification of safety, quality and usefulness of the substance ... by analogy with Directive 2001/83/EC
 - NB must consult a Drug CA before taking its decision
 - NB shall only consult drug CA having verified the usefulness of the substance taking into account the intended purpose of the device
 - NB will give due consideration to the views of the Drug CA when making its decision
 - **NB will almost certainly not go against a negative Drug CA opinion**

Notified Bodies Assessment

Expectations for drug-device combinations

- Properties of medicinal substance considered in manufacturing controls, processing parameters and storage conditions
- Appropriate controls on the medicinal substance to assure quality in the device is maintained
- Stability should be conducted in accordance with ICH
- Quality Management System considers the importance of the medicinal substance as well as the device aspects
- Controls taken to minimise risk of harm to end user
- Use relevant guidance documents from EMA where relevant

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000043.jsp&mid=WC0b01ac05800240cb

- Dossier in line with MEDDEV 2.1.3 or CTD format

Notified Bodies Assessment

Certification and CE-mark

CA/EMA provide a scientific opinion report to NB

- **Positive Outcome:** NB issues EC Design Exam Cert and informs CA/EMA of its decision. Manufacturer generates Declaration of Conformity and applies CE mark
- **EMA Negative Outcome:** The NB may not issue the Certificate

Common Issues with Device Drug Combination CE Certification

- **Unrealistic Project Plans**

- Used to fast CE Certification process
- 210 Day procedure following validation of submission
- Clock stops for questions
- **Solution:** Work with NB who has experience of process and discuss plans early on
- **Solution:** Set realistic expectations internally - allow 9 – 12 months for CE Certification

- **Quality of Medicinal Dossier Submission**

- Technical File / Design Dossier STED Format
- No consideration given to the ancillary medicinal substance
- **Solution:** Use extensive medicinal product guidance
- **Solution:** Use Common Technical Format (CTD) will provide detail on CA expectations

Common Issues with Device Drug Combination CE Certification

- **Medicinal Substance Supply**

- Manufacturer may not consider regulatory requirements when selecting a supplier
- Medical device manufacturers usually only require small quantities on an annual basis
- Issues obtaining necessary information and access to information
- Does the medicinal substance manufacturer have a European DMF or Certificate of Suitability
- For Human Blood Derivatives – Can the Device Manufacturer obtain access to PMF
- **Solution:** Make medicinal substance sourcing a early and critical decision

Common Issues with Device Drug Combination CE Certification

- **Technical Gaps**

- No controls on the medicinal substance to assure quality in the device is maintained
- No data available on the incorporation of the medicinal substance within the device
- No consideration given to medicinal substance in process validation studies
- No data available on potential impurities formed during processing
- No consideration of medicinal substance in stability evaluation
- No data on local tolerance in area indicated for use
- Limited/no clinical evaluation available
- Risk/benefit profile not evident
- **Solution:** Use medicinal product guidance – ICH / EMA / CA Guidance

Notified Bodies Assessment

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Don't forget Post Market Surveillance

Changes made post CE Certification

Impact on original CA Consultation

Post assessment

Essential Requirement 7.4, Paragraph 4

- Where changes are made to an ancillary substance in particular related to its manufacturing process, NB shall be informed of the changes and shall consult the relevant medicines competent authority (i.e. the one involved in the initial consultation), in order to confirm that the quality and safety of the ancillary substance are maintained.
- Competent Authority shall take into account the data related to the usefulness of the substance in the device as determined by the notified body to ensure that the changes have no negative impact on the established benefit/risk profile of the addition of the substance to in the medical device.
- Generally case by case basis but useful to discuss requirements with NB

Post assessment

Impact of changes and review required

- Significant Changes relating to the medicinal substance or indications
 - New Consultation
- Minor change which could impact on the quality, safety or usefulness of the medicinal substance
 - Supplemental Consultation
 - Timeline for review much shorter than New Consultation
 - Supplemental conducted with CA who performed the Original Consultation
 - Documentation needs to be provided to justify and support changes proposed

Post assessment

Guidance for changes

- Manufacturers Change Control procedures
- MHRA Guidance Note 31
- Analogy with variation guidance for medicinal products
 - Reference Commission Regulation (EC) No 1234/2008
 - Type 1A, 1B (Supplemental type changes) and Type II (Significant) variations
 - http://ec.europa.eu/health/files/betterreg/pharmacos/classification_guideline_adopted.pdf
 - http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000104.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac0580025b88

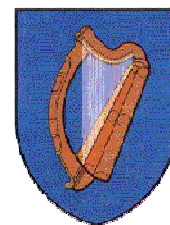
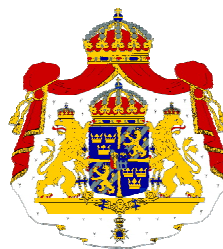
Transfers

- Manufacturer should know which CA conducted the original consultation and the original consultation reference number
- The new NB will check classification is correct
 - like for like transfer will be conducted
 - correction may be conducted following the transfer

Factors to consider when selecting a competent authority

Factors to consider when selecting the competent authority

- Knowledge/expertise relevant drug access to Drug Master File (DMF)
- Availability of resources and knowledge of medical device regulation
- Does the CA have a process for consultation
- Availability for contact/discussion of any questions raised with the NB
- Language Requirements for consultation documents and considerations
- Will the CA agree the product is a device/drug combination under 93/42/EEC?



Consultation fees

- Each CA has their own pricing structure
- Published on CA websites
- Fees are based on level of review required
 - Categories are
 - A known medicinal substance from a known source
 - A known medicinal substance from a new source / New indication
 - New Active Substances

Conclusion

Summary of key points

- EU system is utilising all available qualified resources
- Joint assessments Notified Bodies and Drug Agencies
- Classification of devices is on a case by case basis
- Be cautious of using traditional herbal and homeopathic ingredients in your device
- Have realistic expectations for the timescales involved
- Applications for Device/Drug combination products continue to show good growth
- Don't forget to consider the impact changes may have post CE Certification
- Talk to your Notified Body at early stages and over the lifetime of your device

The END



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