Optimising your Regulatory Strategy to gain FDA and EU Approval

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Outline

- Introductory Comments
- European Regulatory Strategy
  - Medicinal Product or Medicinal Device
  - Interaction with the Notified Body and Competent Authority
- US Regulatory Strategy
  - Interaction with the Office of Combination Products
  - Product Designation
- Future Directions and Conclusions

Simplistic Success Formula

- Know the regulations and guidelines
- Develop quality data using appropriate GMP, GCP, GLP, and QSR requirements
- Have well trained staff at all levels
- Build and maintain strong communication links with the regulatory authority before and during the review process
- Submit a well written dossier
- Plan for all post-approval commitments

European Requirements and Company Strategy

European Union General Principles

- A product is regulated through the Medical Device Directive 93/42/EEC **or** the Medicinal Products Directive 2004/27/EC
- Which directive is applied depends on
  - The intended purpose of the product taking into account the way the product is presented
  - The method by which the principal intended action is achieved
- Be sure which Directive applies – if in doubt look at precedence and discuss.
- Be well aware that products cannot be regulated as both a device and medicinal product

Medical Devices

- Typically **medical devices** function by a physical means which could include
  - Mechanical action
  - Physical barrier
  - Replacement of, or support to, organs or body functions
- The action of a **medicinal product** is generally achieved by pharmacological, immunological, or metabolic means
- The **claims** made for a product also represent an important factor for product classification

Claims

- Claims must be supported by data
- Company should be willing to consider reducing/amending claims if intent on a particular designation or if challenged
- Reducing claims is a company decision and consequences on review and approval need to be weighed

Know the Guidance Documents

- Drug Device MEDDEV 2.1/3 Rev 2
  - Definitions
  - Consultation Process
  - Document requirements
  - Notified Body activities
  - Adverse event reporting
- MEDDEV lists devices, drugs and combinations

General classification

- A device which is intended to deliver a medicinal product is regulated as a device
- The medicinal product in the device must be approved as a medicinal product
- If the device and medicinal product form a single integrated system, and is not reusable, the single product is regulated as a medicinal product (pre-filled syringes, asthma inhalers, transdermal patches)

What do we do if we remain uncertain?

- Borderline products can be discussed with a Notified Body or a Competent Authority
- Getting the classification wrong can be a very costly mistake! (that is, the company develops the product as a medical device but the Review Body has a different view)

Medicinal Product or Device?

- Intrauterine contraceptive containing copper and silver **or** intrauterine contraceptive releasing progestogens
- Wound dressing with antimicrobial agent **or** wound treatment product for delivery of an antimicrobial agent

Assessment Procedure for Medicinal Product/Device Combination where Product is Classified as a Medical Device

- Company identifies appropriate Notified Body (NB)
- NB completes Summary Evaluation Report
- NB provides Evaluation Report to National Competent Authority (CA) who may also link with CAs of other Member States
- CAs should complete their reviews in 9 weeks and respond to Coordinating CA
- Coordinating CA will collate opinions including those of National Authorities and respond to NB
- NB will document final decision on the certification for the product and notify the manufacturer and National Competent Authority. Opinion made available to other CAs on request
- EMEA will likely be consulted if the medicinal product was previously evaluated by them

Key decision – Which Notified Body?

- Previous experience with company
- No language/communication barriers
- Reputation
- Compliance to applicable standards
- Company preferred Competent Authority

Which Notified Body – Notified Bodies per Directive

Directive	Title	Number of NBs
93/42/EEC	Medical Devices	60
98/79/EC	In vitro diagnostic Medical Devices	14
90/385/EEC	Active Implantable Medical Devices	18

Choose an NB that complies with Applicable Standards

- Some Member States nominate NBs without ensuring compliance with
  - EN 45001 (Test laboratories)
  - EN 45011 (Product certification)
  - EN 45012 (Certification quality systems)
- Some Member States audit NBs against EN 45001 and 45011
- Few NBs have been accredited to all three standards

Company can solicit proposals from potential NBs and choose based on responsiveness and quality of proposal

Company and NB responsibilities

- **The company must have followed the declared procedures and those required by the Directive**
- **The company's system for producing the declaration of conformity must be established (the company has ultimate responsibility for product safety and liability through this declaration)**
- **The company's product must conform to relevant provisions of Directive (MEDDEV 2.1/3 Essential Requirements - ERs) with regard to:**
  - Risk analysis
  - Relevant standards
  - Clinical conclusions
- **The Notified Body will:**
  - Ensure conformity with the above
  - Consult with a Drug CA and is unlikely to ignore a negative opinion

Clinical Data Requirements

- NB will work with MEDDEV 2.7.1 “Evaluation of Clinical Data; A guide for Manufacturers and Notified Bodies”
- Represents current state of the art and choices available to companies
- Key decisions for company
  - Literature route
  - Clinical route
  - Combination of the above

Clinical Requirements

- Clinical Studies will be required when
  - Completely new device is proposed for marketing
  - Where a current device is significantly modified in a way that could affect safety and performance
  - For a new indication with an existing device
  - Where new contact materials are used in an existing device
  - Where the device will be used for substantially longer periods

Which CA to use?

- Selected NB will work with its own National CA
- Considerations for the Company with regard to CA:
  - Likely agreement of designation as a drug/device combination under 93/42
  - Knowledge of the drug
    - Access to DMF/reviewed the drug
  - Available resources that understand devices
  - Commitment to timelines
  - Flexibility around claims and openness to discussion

Examples of Competent Authorities

- **MHRA (UK)**
  - Combined agency for drugs and devices
  - Pragmatic but conservative
  - Uncertain timelines
- **MEB (The Netherlands)**
  - Require 2 months notice for submission
  - Structured review and predictable timing
- **MPA (Sweden)**
  - Simple process
  - Open to dialogue
  - Experienced
  - Not accepting new submissions in remainder of 2005
- **IMB (Ireland)**
  - Highly committed but currently some resource limitations

Additional Factors

- Do not approach CA directly without pre-discussion and agreement of NB
- Answer all questions in a timely manner (responses to questions from CA should go via NB)
- Be prepared to adopt CA suggestions to gain approval
- After receiving EC Design Exam Certification generate Declaration of Conformity and apply CE mark
- Enact Post-marketing surveillance plan

EC Declaration of Conformity

- Once the company has obtained full Quality System Registration (QSR), including the applicable EN46000 standard, it is entitled to self-declare
  - Manufacturer quality system must be registered to applicable ISO9000 and EN46000 standards
  - Will be subject to routine surveillance
  - Requires application for assessment of quality system by NB and obligation to notify CA of serious events
  - Any substantial changes to quality system must be notified to NB
  - Manufacturer is required to maintain declaration of conformity for 5 years after last product manufactured

Issues requiring attention

- How should new Medicinal Products in a device be managed – national or EMEA
- Adverse event follow up
- Review of changes after product introduction
- Long term follow up
- Consistency of clinical requirements
- Uncertainty on timing for the review and approval process

USA Requirements and Company Strategy

Definition of a Drug

- Articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man or other animals
- Articles other than food intended to affect the structure or any function of the boy of man or other animals

Definition of a Device

- Instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or similar or related article, including any component, part or accessory which is:
  - Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease….
  - Intended to affect the structure or any function of the body……
  - Which does not accomplish its primary intended purpose through chemical action within the body ….and which is not dependent on being metabolized for achievement of its primary intended purposes

Definition of a Combination Product

- **Until 2002 combination products not defined in CFR**
- **Now defined in 21CFR § 3.2(e)**
  - **A product comprised of two or more regulated components (drug/device, drug/biologic, drug/device/biologic)**
  - **Two or more separate products packaged in a single package and comprised of drug and device products, drug and biological products, or biological and drug products**
  - **A drug, device or biological product packaged separately but where both are required to achieve the intended effect**
  - **Any investigational drug, device, or biological packaged separately but for use only with another specified drug, device or biological**

Paraphrased from CFR

US Regulatory Approaches

Device (CDRH)	Drug (CDER)	Biologic (CBER)
IDE	IND	IND
510(k)	NDA	BLA
PMA		

Office of Combination Products- Useful Contacts

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Office of Combination Products (OCP)

- **Created 2002**
- **Assignment of combination product reviews to a center and coordinating timely premarket reviews involving more than one center**
- **Development of rules and guidance documents**

Primary Mode of Action – an Illustration

- **Drug Eluting Stent**
  - **Primary mode of action – stent opens artery**
  - **Secondary action – drug prevents restenosis and inflammation of artery**
- **Regulated as a device (PMA)**

- **Drug Eluting Disc**
  - **Primary mode of action – cancer chemotherapy**
  - **Secondary action – local drug delivery by device**
- **Regulated as a drug (NDA)**

Adapted from Mark Kramer, Regulation of Combination Products, October 1, 2004

Company and the OCP

- Company Opportunities
  - Early communication with the OCP
  - Meeting to discuss issues and frame strategy
  - Request for designation (but OCP will decide)
- OCP will determine what are the issues that create potential risk to patient and assign primary review
  - To CDER if risk of drug outweighs device
  - To CBER if risk of device outweighs those of drug

Company Responsibilities

- Determine primary mode of action and be able to explain effectively
- Consider most likely regulatory pathway and questions that will need to be addressed
- Understand approaches typically taken by lead center
- Review precedence
- Review guidance documents
- Consult with the Agency

Summary

- Combination Products are an increasingly important sector
- Critical need to understand current guidelines and regulations
- Opportunities for discussion are available
- Guidelines and regulations are continuing to evolve
- Guesses can be expensive mistakes!