Risk Considerations for Combination Drug-Device Products

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Topics

- Examples of Combination Products
- Definitions
- Regulations for Combination Products
- Benefit Risk Considerations
- Risk Management Considerations
- A Case Study
Examples of Combination Products
Examples of Combination Products

• Drug-Device
  – Surgical supplies and alcohol wipes
  – Syringe filled with a drug
  – Drug-eluting coronary stent

• Biologic-Device
  – Syringe filled with a biologic

• Drug-Biologic
  – Chemotherapeutic drug combined with a monoclonal antibody
Definitions
Investigational Products

• IND - Investigational new drug applications – drugs and biologics
• IDE – Investigational drug exemptions - devices
Marketing Approval

- NDA – New Drug Application
- BLA – Biologics License Application
Market Approval - Devices

- Premarket Notification (510K)
  - A premarketing submission to demonstrate that the device is as safe and effective, that is, substantially equivalent (SE), to a legally marketed device that is not subject to premarket approval (PMA).

- Premarket Approval
  - Process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices.
Biological Products

• Include a wide range of products e.g., vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins.

• Can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues.
Biological Products

• Isolated from a variety of natural sources - human, animal, or microorganism - and may be produced by biotechnology methods and other cutting-edge technologies.

• Gene-based and cellular biologics, for example, often are at the forefront of biomedical research, and may be used to treat a variety of medical conditions for which no other treatments are available.
Medical Device

An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article,... which is...intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease..., 
Medical Device

or intended to affect the structure or any function of the body..., and which does not achieve any of its principal intended purposes through chemical action within or on the body...and which is not dependent upon being metabolized for the achievement of any of its principal intended purposes
Device Classification

- Class I –
  - Subject to the least regulatory control.
  - Present minimal potential for harm to the user and are often simpler in design than Class II
  - Subject to "General Controls" as are Class II and Class III devices.
Device Classification

• Class II
  – General controls alone are insufficient to assure safety and effectiveness, and existing methods are available to provide such assurances.
  – In addition to complying with general controls, Class II devices are also subject to special controls.
Device Classification

• Class III
  – Most stringent regulatory category for devices
  – Insufficient information exists to assure safety and effectiveness solely through general or special controls.
  – Usually support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury.
  – Premarket approval is typically required; some may qualify under 510K
Combination Products

• Definition 1: A product comprised of two or more regulated components, i.e., drug/device, biological product/device, drug/biological product, or drug/device/biological product, that are physically, chemically, or otherwise combined or mixed and produced as a single entity.
Combination Products

• Definition 2: Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products.
Combination Products

• Definition 3: A drug, device, or biological product packaged separately that, according to its investigational plan or proposed labeling, is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose.
Combination Products

• Definition 4: Any investigational drug, device or biological product packaged separately that, according to its proposed labeling, is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.
Combination Products

• 21 CFR Parts 3 & 5
  – Designated Agency
    • The FDA agency with primary jurisdiction for the premarketed review and regulation of a combination product.
    • Depends on the primary mode of action of the product.
Final Rule: Primary Mode of Action (PMOA)

• Is the single mode of action of a combination product that provides the most important therapeutic action of the combination product. The most important therapeutic action is the mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product.

• Determines which FDA division will be primary reviewer of the submission
Final Rule: Assignment Algorithm

- FDA or sponsor unable to determine PMOA
  - The agency will assign the combination product to the agency component that regulates other combination products that present similar questions of safety and effectiveness
  - When there are no other combination products that present similar questions of safety and effectiveness, the agency would assign the combination product to the agency component with the most expertise to evaluate the most significant safety and effectiveness questions presented by the combination product.
FDA Agencies involved in Combination Products

• Office of Combination Products – is the designated product jurisdiction officer
• Reviewing Division dependent on the primary mode of action:
  – Biologic = The Center for Biologics Evaluation and Research = CBER
  – Device = The Center for Devices and Radiological Health = CDRH
  – Drug = The Center for Drug Evaluation and Research = CDER
Safety Regulations
Postmarketing

- 314.80 – Adverse Drug Experience (ADE)
- 600.80 – Biologic product adverse experience
- 606.170 – Blood component adverse experience
- 600.81 – Vaccine adverse events
- 803 – Medical Device Reporting (MDR)
Benefit Risk Considerations
“To be alive at all involves some risk.”
-Harold MacMillan
Safe Doesn’t Mean Risk Free!
All Drugs are Associated with Adverse Events

• Which drug causes
  – Gastrointestinal hemorrhage?
  – Decreased platelet adhesion?
  – Asthma in patients with nasal polyps?
Chemotherapy

Benefits > Risks

Kills cancer cells
Improves function of affected organ(s)
Increases survival
Improves quality of life

Nausea & vomiting
Diarrhea
Hair loss
Anemia
Neutropenia
Thrombocytopenia

B

R
Pimple Cream
Risks > Benefits

Diminishes/clears blemishes
Improves appearance

B

Nausea & vomiting
Diarrhea
Hair loss
Anemia
Neutropenia
Thrombocytopenia

R
Thalidomide

- Original indication – “sleeping pill” and treatment for morning sickness
- New indication - treatment of painful, disfiguring skin sores of leprosy
Lotronex™

- Indicated for women with irritable bowel syndrome with severe diarrhea
- Main concern - ischemic colitis leading abdominal pain, gastrointestinal bleeding, fever, vomiting, back pain resulting in:
  - Hospitalizations,
  - Surgery,
  - Blood transfusions, and/or
  - Death
Vioxx

• Benefits
  – Pain relief
  – Decreased risk for GI bleed which can result in hospitalizations/deaths

• Risks
  – Other agents available with same benefit profile
  – Increased risk for cardiovascular death
Guidant Implantable Defibrillators (New Patients)

• Benefits
  – Benefits patients with risk of developing life-threatening ventricular arrhythmias

• Risks
  – Surgery
  – Infection
  – Device malfunction
Guidant Implantable Defibrillators

• 3 models were found to have problems.
• Company knew for 3 years (2002) before informing physicians that these devices were prone to electrical failure because of a design failure
Defective Guidant Implantable Defibrillators

• Benefits
  – May not malfunction

• Risk
  – Surgery
  – Infection
  – Device malfunction
Risk Management Considerations
What are the Objectives of Risk Management?

- Determine risk
- Minimize risk
- Communicate risk
- Determine impact of risk management initiatives
Metrics
Metrics

• Are the Risk Management Initiatives Working?
• How to measure?
Metrics

– Reduced number of:
  • Serious adverse events/deaths/hospitalizations
  • Drug-drug interactions
  • Device malfunctions
  • Medication errors
  • Product complaints/defects
  • “Observations” at audit
Examples of Risk Management Initiatives
Tylenol

- In 1982 7 deaths due cyanide-laced Tylenol – no evidence contamination from manufacturer
- Company Credo – patients first
- Recalled 31 million bottles - $100 million
- Risk Management Plan – “Classic”
- Positive publicity – Company recovered quickly
Perrier

• Traces of benzene found
• Rather than company being accountable for the benzene – claimed it was an isolated finding
• Recalled only a limited number of bottles of water in North America
• Then benzene found in bottled water in Europe
• Worldwide recall ensued; Company “embarrassed” and heavily criticized
Thalidomide

• System for Thalidomide Education and Prescribing Information (S.T.E.P.S,)
• Avoid pregnancy
Lotronex™

- Revisions to the product label including **Black Box Warning**
- Limited access to drug requiring “Physician Attestation”
- Revisions to the Patient’s Medication Guide
Lotronex™

• A “Patient Agreement”
• GSK will:
  – Monitor prescribing patterns to ensure only enrolled physicians prescribe
  – Do additional studies
  – Take other measures to reduce risk
A Case Study
A Case Study

- Investigational combination product
  - Injector device that houses multiple drug doses

- Elderly population
  - Poor eyesight
  - Impaired learning potential
  - Arthritic hands making it difficult to work device properly

- Drug overdoses/device malfunction reported in clinical trials

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Case Study

- Investigation revealed inadequate training of patients.
- Implications for marketed product
  - Increased risk of overdose with everyday use
Case Study

- Risk management plan for marketed product – how would you design?
The Reality of Much of Life
“Common Sense is not Common”