Breakout Session Summary

COMBINATION PRODUCTS

FY 2020 Generic Drug Regulatory Science Initiatives Public Workshop

Drug-Device Combination Products Breakout Session – May 4, 2020

Elizabeth Bielski, PhD
Chemist, Division of Therapeutic Performance, ORS, OGD, CDER

Expert Discussants

- ***Markham Luke, MD PhD*** – FDA, Division of Therapeutic Performance (DTP) - moderator
- ***Róisín Wallace, PhD*** – Mylan Global Device Development
- ***Molly Story, PhD*** – Sanofi Medical Device Development Unit
- ***Ravi Harapanhalli, PhD*** – Amneal
- ***Elizabeth Bielski, PhD*** – FDA, Inhaled Products Team, DTP – our rapporteur
- ***Priyanka Ghosh, PhD*** – FDA, Topical Products Team, DTP
- ***Bin Qin, PhD*** – FDA, Complex Injectables & API Team, DTP
- ***Kimberly Witzmann, MD*** – FDA, Office of Bioequivalence
- ***Maryam Mokhtarzadeh, MD*** – FDA, Office of Combination Products
- ***Bing Cai, PhD*** – FDA, Office of Pharmaceutical Quality (OPQ), Lifecycle Drug Products
- ***Dhaval Gaglani, PhD –*** FDA, OPQ, Lifecycle Drug Products

Main Speakers

- ***Speaker: Markham Luke, MD PhD – FDA, Division of Therapeutic Performance (DTP) – moderator***
  - **Role of OGD and Identifying Research Gaps and Priorities**

- ***Speaker: Róisín Wallace, PhD – Global Device Development, Mylan***
  - **Risk Management Considerations for Drug-Device Combination Products**

- ***Speaker: Molly Story, PhD – Medical Device Development Unit, Sanofi***
  - **Comparative Human Factors Studies**

Drug-Device Combination Products Overview

- ***Speaker: Markham Luke, MD PhD – FDA, Division of Therapeutic Performance (DTP) – moderator***
- **Main Topics**
  - **What Makes Drug-Device Combination Product Complex?**
    - Complex API, formulations, dosage forms, route of delivery, device design
  - **Role of OGD**
    - Bioequivalence (BE) – comparison of T and R
    - Comparative Analysis
  - **Identifying Research Gaps**
    - Devices constituents and relation to BE
    - User interface considerations
    - External operating principles – labeled "steps"
    - Material and device design considerations
    - Future considerations
  - **FY2020 GDUFA Research Science Priorities**
    - Evaluation of user-interface from RLD on the therapeutic equivalence
    - Develop criteria for device performance that would support a BE via in vitro methods to eliminate need for in vivo BE
  - **Questions for the experts**
    - Key knowledge gaps?
    - How can research facilitate generic drug development?
    - Priorities?

Risk Management for Drug-Device Combination Products

- ***Speaker*: Roisin Wallace, PhD – Global Device Development, Mylan**
- **Main Topic: Risk Management Considerations for Drug-Device Combination Products**
  - **Case for Risk Management**
    - Integrated approach to increase product understanding, incorporate early on
    - Reduce design/manufacturing changes later in development, potential costly changes due to non-integrated approach, complaints/adverse events of product performance
  - **Risk Management for Combination Products: What & Why**
    - Evaluation of risk profile continuously from concept to lifecycle management
    - Ensure device meets intended user needs, intended uses and specified design requirement (21 CFR 820.30)
    - to estimate and evaluate the associated risks, to control these risks, and to monitor the effectiveness of the controls (ISO 14971)
  - **Risk Management Process – Design, User, Process**
    - Identify potential hazards, understand severity of potential harms, estimate risk, eliminate hazards through design changes (focus on generics vs RLD), be considered in all aspects of development
    - New risks introduced from generic vs. RLD for combination products
  - **Risk Management: Confirmation of Effective Risk Controls**
    - Confirm device robustness and reliability for intended use
  - **Risk Management Input to Control Strategy**
    - Control Strategy an output to Risk management

Could scientific research into risk analysis methodologies and approaches be conducted to drive engineering and scientific understanding, consistency in approach and ultimately lead to increase in accessibility of robust generic drug-device combination products?

Comparative Human Factors Studies

- ***Speaker*: Molly Story, PhD – Sanofi, Medical Device Development Unit**
- ***Main Topic: Human Factors Engineering for Medical Devices***
  - **Goal: Safe and Effective**
  - **Methods: Observe, Interview, Analyze**
  - **505(j) [of the FD&C Act]**
    - Drug product similarity, not necessarily the "device"
  - ***Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (Jan 2017)**
    - Minimize use error rate, same rates of error
    - No mention of "severity" or "harm"
  - **Guidance from IEC 62366-1:2015**
    - Hazard-related use scenarios, based on severity of potential harm
    - Not all use-errors cause hazardous situations
  - **Aspects of Agreement**
    - Compare user interactions, identify possible use errors, determine potential hazardous situations, perform human factors evaluation
  - **Aspects of Disagreement**
    - Use errors are equal
    - Number of errors is meaningful - Focus on qualitative not quantitative use error rates (not all use errors are equal)
    - What about intellectual property/patent infringement, post-approval changes in devices, labeling similarity of "old instructions"?

Discussion

- **What does FDA consider complex vs simple combination products?**
  - **Combination product definition in CFR 3.2 -** drug and or device and or biologic put together in a single, co-packaged, or cross-labeled
  - **Complexity based on API/dosage form, site of action, device**
    - Ex: autoinjectors, inhalation products, nasal products, transdermal systems
  - **Potential grey areas in terms of complexity**
    - Ex: prefilled syringe – simple, but with complex dosage form can become complex
    - If not sure about complexity, can reach out to FDA and send question (CCs)

Discussion

- How many lots of reference should be examined for a non-complex combination product, and how many lots of reference should be examined for a complex combination product?
- When a device is made to be used by the health care provider, and not by a ordinary consumer, how does FDA expectation change for risk assessment and management?
- If the threshold analysis shows no major differences between RLD and generic product, FDA typically grant waiver for comparative HF study, do we still need to conduct HF studies on the generic device?

Discussion

- Reliability study is required for emergency use product such as EpiPen, it's not required for regular drug-device combination products. Is it correct?
- We cannot fix patients how to use the combination products. For instance, for inhalation, we cannot control how patient inhale the product/medicine. In this aspect, we can train patient but we cannot control the outcome. Is an in vitro study like ACI and NGI with fixed flow rate would be the way to go for BE to evaluate the product? It does not seem accurate or detailed guidance. Is there any discussion ongoing research in these aspects?
- What do “critical errors” mean for various drug-device combination products? Can “critical errors” be further defined specified for clarity?

Discussion

- What are the key gaps in knowledge that could be addressed with targeted research in the context of developing generic drug-device combination products?
- What review issues or questions have you encountered that you believe can be addressed in the context of FDA's generic drug research program?
- Drug-device combination products (DDCPs), variety have been discussed (device, indication, users). We have listed 9 types of combination products. Would it help to categorize further for these DDCPs? Good use of resources?

Conclusions

- ***Lots of unknowns still warranted surrounding drug-device combination products***
  - CQAs
  - How formulation and device interact
  - Devices constituents and relation to BE
  - User interface considerations
  - External operating principles – labeled “steps”
  - Material and device design considerations
- **Over 160 participants within this session**
  - Thanks to all participants for great discussion!

Thank you!