4th FDA/PQRI Conference on Advancing Product Quality Breakout Summaries

April 10, 2019

Hilton Rockville

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Product Quality Research Institute

FDA U.S. FOOD & DRUG ADMINISTRATION

TRACK 2: EMERGING TECHNOLOGIES AND PATIENT CENTRICITY IN EARLY DRUG DEVELOPMENT

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Session 1: Early Drug Development: A Vision for the Future

Moderator: Geoffrey Wu, FDA

Speakers: Ramesh Sood, FDA

Gregory Troup, Merck

Matthew Burke, GlaxoSmithKline

Presentations

1. Early Drug Development: Regulatory Perspective

   Ramesh Sood, FDA

2. Accelerating Drug Product Development Using Small Scale, Data Intensive, Iterative Design Approaches

   Gregory Troup, Merck & Co., Inc.

3. Challenges and Opportunities with Patient-Centric Drug Product Design: Industry Perspectives

   Matthew Burke, GlaxoSmithKline

Session Background/Premise/Challenges

- Each phase of the drug development process has unique challenges.
- The early stage of drug development provides the foundation for lifecycle management.
- It offers opportunities for innovative technical and patient-centric approaches that can yield safe and effective drugs for patients.

Key Points from Talk #1

Early Drug Development: Regulatory Perspective

- In all phases of investigation, FDA's primary objectives in reviewing an IND are to assure:
  - The safety and rights of subjects
  - That the quality and scientific evaluation of drugs is adequate to evaluate the drug's effectiveness and safety.
- Treatment INDs can be submitted for drugs intended to treat serious or life threatening disease; however, the sponsor of the controlled clinical trial should actively pursue the marketing approval.
- Sufficient quality information (drug substance and product) is needed to ensure safety of the subjects in INDs.
- Quality expectations are not based on the approval process (expedited vs standard).
- Breakthrough, fast frack, accelerated approval, and priority review are part of the FDA's expedited programs. Innovative approaches needed to strike a balance between risk and benefit.

Key Points from Talk #2 *Accelerating Drug Product Development Using Small Scale, Data Intensive, Iterative Design Approaches*

- Iterative design approaches can be deployed throughout the development lifecycle, but goals and aims may change in each phase.
- Formulation development is a multivariable, multi objective function optimization problem.
- Smart Throughput experimentation is a data-rich materials-sparing approach to developing products and optimizing performance.
  - A small amount of drug substance can be used to generate enough drug product material to run a meaningful analysis and test formulations.
- Extending this approach with modeling and simulation (e.g., Finite Element Modeling) allows us to create a suite of data-driven analytic tools for formulation design and risk evaluation, and ultimately improve product robustness.
- Model-based product design approach = *f* (formulation, characterization, data modeling)

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Key Points from Talk #3

Challenges and Opportunities with Patient-Centric Drug Product Design: Industry Perspectives

- Working *with* patients during drug development is increasingly critical to designing successful treatments.
  - We must seek patient feedback in a way that is actionable. A challenge to this is the collection of meaningful patient feedback.
  - Input from external stakeholders (e.g., patients, regulators), internal departments (e.g., clinical, manufacturing), and other scientific disciplines (e.g., epidemiology, industrial design) can be translated into the TPP.
- Patient opinions and needs will vary; consider more than one product design when appropriate.
- Call for action: Patient centric drug development could be enhanced by a centralized public database, standardized data collection methods, and data contributions from independent patient advocacy groups.

Panel Discussion and Q&As

- There is often a discrepancy between patient feedback (what they tell you) and patient experience (how they use the drug)
  - Tracking the patient journey helps to pick up different attributes and informs later stages of drug development
- Modeling and simulation involve a lot of variation
  - Need to educate stakeholders on the appropriate use of the model
  - Build in safeguards for outliers and extrapolations
- Iterative design approaches can be used to simulate high shear on a small scale
  - The physics won't be the same, but it can answer questions (e.g., sticking and picking) with broad brushstrokes
- FDA is involved in patient-centric approaches
  - The Voice of the Patient release by FDA
  - FDA has draft guidance, and two more on the way

Overall Conclusions

- Quality is a shared effort between regulators and industry.
- Small scale, data intensive, iterative design approaches provide value throughout the development cycle.
- Patient centricity should be a fundamental part of the early drug product design process.

Session 2: Designing for Delivery: Drug Discovery and the Early Development Interface

Moderator: Diane Paskiet, West

Speakers: Christopher Breder, FDA

Mike Hageman, University of Kansas

Ron Iacocca, Eli Lilly and Company

Presentations

1. Value-Driven Drug Development

   Christopher Breder, FDA

2. Discovering and Developing Non-Traditional Drug Modality Molecules with Optimal Pharmaceutical Properties

   Mike Hageman, University of Kansas

3. Designing for Delivery: The Use of Mathematical Modeling

   Ronald Iacocca, Eli Lilly and Company

Session Background/Premise/Challenges

- There are opportunities to optimize drug delivery during the early stages of drug development.
  - Planning and testing for trial and program design
  - Computational and mathematical modeling
- Complex chemical entities have great potential for commercial success, but moving from preclinical to clinical and CMC manufacturing and delivery is a challenge.

Key Points from Talk #1

Value-Driven Drug Development

- The current standard in Quality aspects of drug development incorporates proactive optimized development features.
  - Clinical trial and program design will benefit from this methodology.
  - Target product profiles (TPP) has multiple facets; plan for multiple-attribute optimization.
- Sponsors, CROs, and Regulators need to familiarize with the 'language of planning' and recognize the needs of other stakeholders
  - Regulatory TPPs are under- and misused.
- Once you have TPP, attributes and optimize modeling processes add value to the clinical development program.
- Planning and testing for trial and program design should begin before the candidate is nominated.

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Key Points from Talk #2 *Discovering and Developing Non-Traditional Drug Modality Molecules with Optimal Pharmaceutical Properties*

- Increased Chemical Diversity Requires More Integrated Role of Drug Delivery During Lead Optimization
  - Challenges for oligonucleotides and peptides include moving from preclinical to clinical and CMC manufacturing and delivery
- Generate a **Preliminary** Target Product Profile (PTPP)
  - Provides basis on which developability hinges
  - Initiated with target identification & based on business needs
- Drug Delivery and Line-of-Sight Strategies are critical to de-risk progressability and developability
  - Obtain appropriate marriage of delivery technology and molecular entity selected

Key Points from Talk #3

Designing for Delivery: The Use of Mathematical Modeling

- There are three basic kinds of mathematical models in drug development:
  - Analytical
  - Finite Elemental Analysis
  - Statistical modeling
- These models can be used effectively for designing drug delivery.
- A useful application of models is to determine range of variability; get a proven acceptable range for what you are assessing and factor it into product design.
  - Saves time in proof of concept stage
- Consider context of use, model risk, and model credibility.
- When validating a model, know requirements and margins of safety.

Panel Discussion and Q&As

- Sometimes the relationship between a parameter and an outcome is unknown. Insight may be gleaned from examples outside of industry (e.g., dissolution strategies learned from aquifers and oil industry)
- Modeling has been used to promote change management and get industry to think differently about integrating device development into early stages.
- Modeling forces you to rank order attributes earlier. This can be used to address important questions early in the development process.
  - However, there may be down sides to making decision early

Overall Conclusions

- Sponsors, CROs, and Regulators need to recognize the needs of other stakeholders and begin planning and testing for trial and program design before the candidate is nominated.
- Increased chemical diversity will require more integration between the molecular entity and delivery technology.
- Mathematical models can be used effectively in early stages of drug delivery design.

Session 3: Drug Device Combination Products – Emerging Technologies & the Evolving Regulatory Landscape

Moderator: Ajit Narang, Genentech

Speakers: Susan Neadle, Johnson & Johnson

Kristina Lauritsen, FDA

Alan Watts, Savara Pharmaceuticals

Presentations

1. Drug Device Combination Products: Evolving Global Regulatory Landscape

   Susan Neadle, Johnson & Johnson

2. Emerging Drug-Device Combinations: A Digitally Enhanced Patient Experience

   Kristina Lauritsen, FDA

3. Inhaled Product Advances for Aerosolization, Breath Coordination and Patient Monitoring

   Alan Watts, Savara Pharmaceuticals

Session Background/Premise/Challenges

- Combination products growth weaves together the life sciences, pharmaceutical sciences, and engineering and technology.
  - Major industry growth is anticipated in upcoming years.
- The growth of combination products has led to greater focus on safety and more guidance from health authorities to provide a structure to bring combination products to market.
- The evolving global regulatory landscape creates challenges for the industry in the development of combination products.
- The underlying theme of regulatory expectation is aligned. To safeguard patients, we must implement integrated development of the combination product and risk management control strategies. However, differences exist in how the information is expected in regulatory submissions.

Key Points from Talk #1 (Susan Neadle)

- Combination products are subject to multiple regulations.
  - Control strategies focus on **safe** and **effective use** for the proper functioning of the device, the drug, and the combination product.
  - The cornerstones of control strategies are combination product integrated development and risk management.
- Evolving global regulations focus on **patient safety and consistent performance through robust development and implementation of control strategies** throughout the product lifecycle to assure public health and ensure that risk is commensurate with product complexity and patient needs.
  - Opportunities for harmonization exist.
  - Primary mode of action and type of combination product drive regulations, submissions procedures, pathway to market, and post marketing safety reporting.
- Engage with a notified body (in Europe filings) early on because the requirements can differ based on the country.

Key Points from Talk #2 (Kristina Lauritsen)

- The digital health market is growing rapidly. Devices are used with drugs in a variety of ways, but not all "software" is a device.
- 21st Century Cures act definition of "device" excludes certain software functions (e.g., general wellness product).
  - FDA oversight focuses only on device function related to the diagnosis, cure, mitigation, prevention or treatment of a disease or condition.
- FDA has proposed Prescription Drug Use Related Software (PDURS) Framework to give sponsors the flexibility to develop and disseminate innovative software while the FDA maintains appropriate oversight.
  - Open for comments until April 29 (Docket No. FDA-2018-N-3017).
  - Under PDURS, only the output of the software disseminated by or on behalf of a drug sponsor for use with one or more of the sponsor's prescription drugs would be treated as drug labeling.
- PDURS is required in labeling if sponsor demonstrates clinically meaningful outcome, or PDURS is essential constituent of combination product.

Key Points from Talk #3 (Alan Watts)

- Inhaled product advances with a focus on patient adherence.
  - $213B avoidable medical cost (IMS Institute, 2013)
  - $105B of this is due to nonadherence
- Tools to mitigate nonadherence: regulatory guidance, technological advances, and user-focused design
  - Designing out potential misuse is the best way to improve a device
- Product advances are emerging to reduce misuse and nonadherence:
  - Patient monitoring (add-on devices, smart devices, monitoring adherence and efficacy in clinical studies).
  - Patient coordination (breath coordination with DPIs and nebulizers).
  - Aerosol technology (aerosolization of liquid and powder).
- As these technologies advance and demonstrate patient benefit, payers will begin to cover more smart devices and regulators will begin to require such smart features..

Panel Discussion and Q&As

- Software used solely for research purposes (e.g., collect data for clinical trial) could potentially be a device.
  - Such technology would have to be validated, but that would fall under the Center for Devices instead of CDER.
- The 21st Century Cures Act defines device vs non-device
  - Does not apply to clinical decision software (separate guidance for that)
- Harmonization of regulatory guidances is possible, but consistent definitions and processes are needed.
  - Engage with a notified body (in Europe filings) early on.
- FDA is trying to be more proactive with regard to digital health.
  - Defining terms remains a challenge. Regulators define terms for their purposes, but not necessarily for the world at large.

Overall Conclusions

- Combination product regulations are evolving, and opportunities for harmonization exist.
  - The regulations focus on **patient safety and consistent performance through robust development and implementation of control strategies** throughout the product lifecycle to assure public health and ensure that risk is commensurate with product complexity and patient needs.
  - However, which data must be generated and how it must be submitted might differ and evolve.

- The focus of evolving global regulations is on successful practices and control strategies.

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Overall Conclusions

- Regulatory Framework gives sponsors the flexibility to develop innovative software. However, whether it is classified as a device or not depends on how the output informs the patient and how it might impact clinical outcome.
- Developers of software and combination products should:
  - Consider relevant regulatory approaches early.
  - Use pre-submission meeting opportunities to gain agency input.
- Emerging technological advances in inhalers can reduce misuse and nonadherence.
  - Design elements to overcome user errors and compliance monitoring is increasingly being emphasized.
  - As these technologies develop further, regulators could start to require such smart features.