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

April 11, 2019

Hilton Rockville

PQRI
Product Quality Research Institute

FDA U.S. FOOD & DRUG ADMINISTRATION

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

Session 4: Development Considerations for Evolving Non-Traditional Drug Modalities

Moderator: Allen Templeton, Merck

Speakers: Rubi Burlage, Merck

Serge Beaucage, FDA

Kelvin Lee, NIIMBL, University of Delaware

Presentations

1. Unlocking the Promise of Immunoncology and Combination Therapies

   Rubi Burlage, Merck & Co., Inc.

2. Delivery of Nucleic Acid Sequences in Mammalian Cells Mediated by Phosphorothioate DNA or RNA Transporter Elements

   Serge Beaucage, FDA

3. Developing Next Generation Technologies in the Context of a Public Private Partnership

   Kelvin Lee, NIIMBL/University of Delaware

Session Background/Premise/Challenges

- Advancing different paradigms to get best medicines to the patient
- Advancing innovative therapies through novel scientific, industry, and regulatory approaches that consider patient need
- Advancing efforts for cellular penetration by nucleic acids
- Leveraging public private partnerships to advance technologies to get medicines to patients faster.

Key Points from Talk #1 (Rubi Burlage)

- Immuno-oncology area is leading to a number of effective, novel medicines.
- FDA regulatory framework assists in development, e.g., breakthrough therapy designation can decrease delivery time of medicines to patients although CMC timeframes are stacked and shortened. Expansion cohorts guidance is another useful tool to expedite development and provide flexibility
- Biology of disease is complex so treatment will also be complex. Variety of treatments will provide a differentiated benefit. Combination therapies provide a way to augment checkpoint inhibitors (e.g., bispecifics)
- There are opportunities to develop patient-centered formulations that can serve patient and caregiver needs.
- Complex therapies and combinations may also require an array of analytical techniques to be used to understand the formulation and the process
- Is the current stacked development requirements the best way to develop immuno-oncology therapies?

Key Points from Talk #2 (Serge Beaucage)

- Investigated Peptide Nucleic Acid (PNA) and Phosphorodiamidate Morpholino (PMO) Sequences as Potential Nucleic Acid-Based Drugs
- Key challenge is delivery of negatively charged PNA and PMO to cells (which have negatively charged membranes). Modified peptides can also have toxicity concerns
- Variations on cationic charge inclusion is possible, e.g., via poly-A tails which allows DNA and RNA as agents to mediate delivery into the cell.
- Effectiveness of DNA and RNA mediated delivery for promoting excision in inducing the excision of exon 23 from the *mdx*mouse dystrophin pre-mRNA.
- Indications are that cytotoxicity low (in vitro, HeLa cells)

Key Points from Talk #3 (Kelvin Lee)

- Public-private partnerships allow for sharing of knowledge efficiently, de-risk technology adoption, leverage risk and investments for development.
- NIIMBL is a platform for bringing together industry, academia and regulatory (BARDA, NIST, FDA, others). Provides funding for projects.
- Given new modalities and needs of the market, new and flexible technologies for manufacturing are needed and in some situations a need to scale to smaller manufacturing platforms.
- Seeking to develop flexible and adaptive manufacturing technologies/processes.
- Current NIIMBL focus areas include mAbs, proteins, vaccines, ADCs, bispecifics. Developed technology roadmaps including for cell and gene therapy. Established workforce training programs applicable to national and regional needs

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NIIMBL The National Institute for Innovation in Manufacturing Biopharmaceuticals

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Panel Discussion and Q&As

- How does NIIMBL deal with IP? How are FDA and industry interactions managed?
  - Teams that execute the work own the IP. NIMBLE does not own the IP but requires that licensing terms be available to members on projects. When project is contracted, team members negotiate terms and must be compliant with overall NIIMBL paradigm. Proprietary issues and NDAs are not discussed. Focus is on cross-industry issues. Established high level agreement between NIMBL and FDA that allows interactions with CDER, CBER. Set expectations with Centers regarding how to interact.
- High concentration biologics – has industry achieved maximum concentrations possible, or can we go beyond with new methods?
  - Not at limits, but there are risks with higher concentrations -- need ability to have predictive tools in place to detect failure modes early in development to know if process/product is robust.

Overall Conclusions

- Non-traditional drug modalities will require creative and flexible approaches to development and regulatory review processes – both on part of industry and regulators
- A variety of analytical approaches (existing and new) are and will continue to be needed
- Different manufacturing and information sharing paradigms such as through public-private partnerships with diverse collaborators can aid in advancing science and speeding the availability of medicines to patients

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Session 5: New Visualization and Analysis Techniques in Drug Development

Moderator: Bob Meyer, Merck

Speakers: Douglas Kiehl, Eli Lilly and Company

Eric Munson, Purdue University

Marcus Adams, Merck

Presentations

1. What do Petroleomics, Jet Fuel and Pharmaceuticals Have In Common? Visualization and Characterization of Complex Mixtures of Extractables/Leachables and Other Pharmaceutically Relevant Compounds using High Resolution 2-D and 3-D Mass Mapping

   Douglas Kiehl, Eli Lilly and Company

2. Advanced Analytical Techniques for Characterizing Amorphous Solid Dispersions

   Eric Munson, Purdue University

3. Beyond the Big Crunch of Excel: The Big Bang of Digital Visualizations

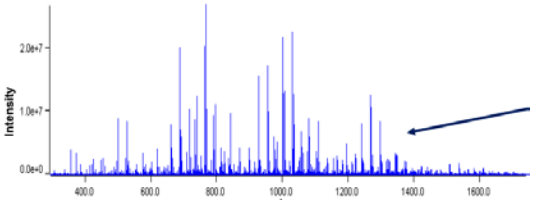
   Marcus Adams, Merck & Co., Inc.

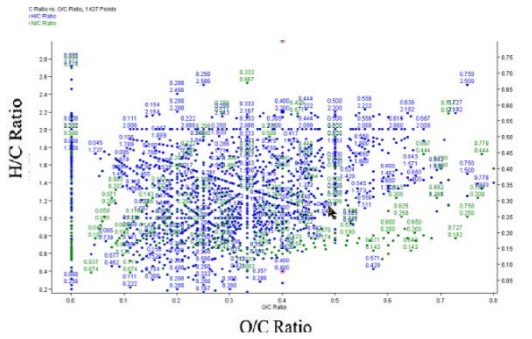
Session Background/Premise/Challenges

- New analytical approaches are emerging constantly to look closer and in more ways than ever before
- New methods are required to efficiently assess large amounts of diverse data collected in across the product lifecycle
- Data *Transformations* and *Visualizations* data can more effectively communicate key information

Key Points from Talk #1 (Doug Kiehl)

- Pharmaceutical development and lifecycle management require separation of compounds having structural, isomeric and compositional diversity (e.g., extractables, leachables assessments).
- Borrowing techniques from petroleomics, transformations of mass spectra of complex mixtures allow patterns to emerge
  - Van Krevelen diagrams and Kendrick mass transformations are two useful tools
- Mass mapping provides
  - intuitive and visualized information
  - graphic sorting of complex mixtures by series or class based on structural and compositional features
  - confident assignment of elemental composition
  - assembly of N-dimensional mass maps based on mass differences
  - ability to rapidly compare mixtures for similarity according to custom indices



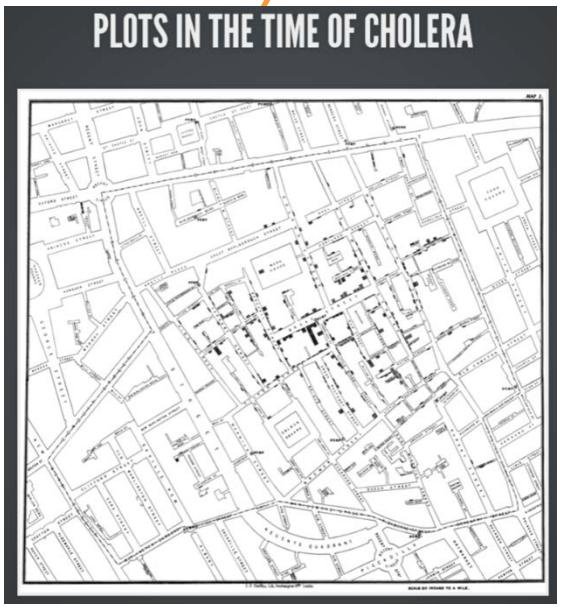


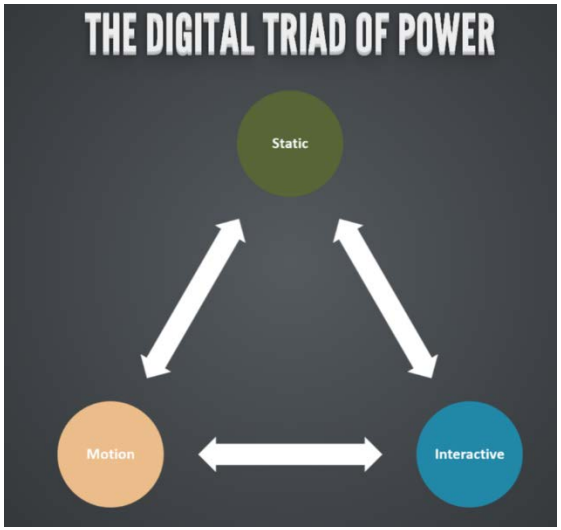
Key Points from Talk #2 (Eric Munson)

- Work in this area is motivated by the story of Norvir, where an amorphous solid dispersion (ASD) was pulled from the market following recrystallization over time
- ASDs must find a balanced polymer loading, which increases physical stability but also increases pill size
- Deeper understanding of ASDs can be achieved by analysis of chemical interactions and advanced characterization techniques
  - Advanced techniques for crystal detection and molecular interactions include Raman, Synchrotron XRD, Second Harmonic Generation, and ssNMR
- Drug stability in polymeric systems depends extensively on water content, drug loading, and drug/polymer interactions
- Similar approaches can be used to evaluate protein stability

Key Points from Talk #3 (Marcus Adams)

- Reminder of John Snow's powerful visualization of cholera cases
- Data visualization requires author to be
  - Purposeful – what are you trying to show?
  - Deliberate – how does the eye perceive?
  - Consistent – standardization helps viewers
- There is a big world beyond excel
  - Open source software provides opportunities
- Data visualizations lose some power when printed – consider electronic presentation!
- Excellent references provided to learn more
- Improved visualization will lead to better insights, which will lead to better drugs for patients





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Panel Discussion and Q&As

- Regarding 3D mass mapping -- can you identify unknowns? Can you quantitate them?
  - No right now software is qualitative.
- How quick is turn around for analytical workflow?
  - One example -- less than a day versus three weeks with traditional methods.
- Mass mapping conversion of data to QR codes and conducting similarity check -- what is reception at supplier end?
  - Receptiveness is high within the company but will need more diversity and more data to deploy into commercial space.
- In a global company how to introduce new concepts into large organizations?
  - We automate and develop web applications, and provide means to make things more efficient, and clarify the benefits.

Overall Conclusions

- Improved and innovative analytical and visualization approaches can streamline and speed evaluation of highly complex processes and data compilations
- Thoughtful consideration of how to present, visualize and interact with information can simplify, clarify, and provide important insights from the data

SESSION 6: EMERGING TECHNOLOGIES FOR IMPROVING PATIENT ADHERENCE

Moderator: Dave Schoneker, Colorcon

Speakers: Douglas Throckmorton, FDA

Stephanie Barrett, Merck

Ali Rajabi-Siahboomi, Colorcon

Presentations

1. Challenges in the Opioid Epidemic Crisis

   Douglas Throckmorton, FDA

2. The Expanding Universe of Patient Adherence Solutions: Long-acting Implantables, Micro-Chip, Smart Packaging, Apps, and Social Robotics

   Stephanie Barrett, Merck & Co., Inc.

3. New Formulation Technologies for Patient Adherence: Solid Oral Dosage Forms

   Ali Rajabi-Siahboomi, Colorcon

Session Background/Premise/Challenges

- Basic questions – Why don't patients take their medicine? What can we do to change this behavior?
- Can emerging technologies improve patient adherence?
- Improving patient adherence and demonstrating patient benefit is difficult
- There are a large number of approved and emerging technologies available from formulations, packaging, software applications, devices with use in real-world situations and clinical studies
- Patient involvement, considerations and needs must be central to future drug development

Key Points from Talk #1 (Douglas Throckmorton)

- Non-adherence carries a high cost - ~125,000 deaths per year and at least 10% of hospitalizations. Promise of new drug development is only realized when the drugs are used as directed
- A number of reasons for non-adherence, including human (don't want dependence on a medicine, complex dosing regimens), structural (limited time during appointments, reminder fatigue).
- Need to improve adherence and detect non-adherence.
- The future of innovative drug development is in the adherence area; important for industry and FDA to work together; FDA approved a number of products in this area (smart inhaler, tablet with sensor) and implemented PDURS to streamline use of software in applications
- Guidance on development of drug products addressing adherence – not yet developed. Current guidance on patient centric approaches, e.g., safety consderations for product design to minimize medication errors, can be used
- Opioid crisis -- FDA developing ways to encourage development of packaging to better ensure appropriate number of tablets for given patient pain/situation

Key Points from Talk #2 (Stephanie Barrett)

- Not if, but when will we use emerging technologies in clinical trials and beyond. In trials, the technology can improve the validity of data and information, and could speed development of improved medicines designed for patient adherence
- Impact of non adherence is significant in population and also in clinical studies (adherence in clinical studies is a challenge)
- Patient engagement is at the core of adherence improvement
- Simplified dosing regimens offer opportunities to improve adherence
- Smart dosing and digital technologies provide opportunities to get more and better data from clinical trials.
- No single intervention strategy will work for every patient. Packaging and IT solutions and simplified dosing regimens are only two of many options.

Key Points from Talk #3 (Ali Rajabi-Siahboomi)

- Formulation approaches are important in increasing adherence, e.g., reduce frequency and number of doses (once daily, fixed dose); improve taste and swallowability; improve trust around anti-counterfeiting; reduce dosage size. More innovation is required
- Critical to consider patients acceptance for taking meds at early stage of development (safety by design). Patient/clinical volunteer testing and response is key (ease of swallowing, mouthfeel)
- Conducting research in coating to increase/improve swallowability – important to understand the key issues involved, e.g., sight, oral feel/tongue, ability to swallow with water, texture.
- Approaches to enhance film coating which includes unique taggants such as DNA, etc. to authenticate products

Panel Discussion and Q&As

- No questions were asked

Overall Conclusions

- Patient benefit of emerging technologies is still to be demonstrated – large challenge
- Patient adherence will remain an ongoing challenge and significant concern
  - High detrimental impact of non-adherence
  - Variety of potential behaviors, contexts and situations that must be considered and addressed
- A variety of diverse approaches are needed and are being developed. FDA regulatory frameworks and tools are supporting these innovations
- Involvement of patient and volunteers is key