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 1:
NOVEL APPROACHES TO IMPROVE TREATMENT OUTCOME AND PATIENT SAFETY

Session 4: Predictive Approaches to Gain Insight into the Clinical Performance of Inhaled Medicines

Moderator: Mehran Yazdanian, Teva

Speakers: Jayne Hastedt, JDP Pharma Consulting

Per Bäckman, Emmace Consulting

Bing Li, FDA

Presentations

1. Biopharmaceutical Classification of Inhaled Medicines: Development of an iBCS

   Jayne E. Hastedt, JDP Pharma Consulting

2. Modeling Aspects Related to Inhaled Medicines

   Per Bäckman, Emmace Consulting

3. Regulatory and Scientific Challenges in Establishing Bioequivalence for Orally Inhaled Drug Products

   Bing Li, FDA

Session Background/Premise/Challenges

- Orally inhaled and nasal drug products (OINDPs) are complex dosage forms.
- In vitro tools are in general helpful to streamline development.
- Develop a physiologically-based pulmonary drug product classification system based on biorelevant drug and product attributes

Key Points from Talk #1 (Jayne E. Hastedt) 1/2

- PQRI WG developing a classification system for inhaled medicines (iBCS)
  - Classification based on solubility, permeability, and lung regional dose.
- Challenges:
  - Lack of harmonized measurement tools
  - Limited number of compounds and lack of relevant published data
  - Simulation approaches are still being developed
- Opportunities:
  - A common set of tools to aide pulmonary drug product development.
  - Impact of phys chem properties on the fate of inhaled medicines
  - Determine approaches to assess bioequivalence
  - De-risk pulmonary drug development programs

Key Points from Talk #1 (Jayne E. Hastedt) 2/2

Next steps for the PQRI iBCS WG

1. **Sensitivity analyses** to understand the impact of dose, solubility, and permeability on the proposed regional classification grids and boundaries will be conducted using PBPK simulations.

2. **Validation studies** will be conducted using various software platforms to assess the ability of the software to simulate exposure using parameters of solubility, permeability, and regional dose.

Key Points from Talk #2 (Per Bäckman)

- Computer based models
  - Are capable of clinically meaningful simulations of systemic exposure in response to changes in critical product attributes
  - May provide insights into the rate limiting steps as a function of critical product attributes and phys chem properties.
  - May enable definition of drug and/or product classes with distinct development risks
  - Combined with compound classifiers, could support development of inhaled drugs
  - Could help with lung targeting, drug retention, and therapeutic equivalence while minimizing clinical studies
- Question for future regulations:
  - Role of computer models for approval of inhaled products?

Key Points from Talk #3 (Bing Li) *slide 1/4*

Regulatory and scientific challenges in establishing bioequivalence for generic orally inhaled drug products (OINDP)

- Have a number of complex regulatory and scientific challenges
- FDA recommendations for therapeutic equivalence of OINDPs takes into account

Formulation similarity:

- The formulation of T and R be Qualitatively (Q1) and quantitatively (Q2) the same
- FDA product specific guidance also indicates that Q2 differences may be justified

Key Points from Talk #3 (Bing Li) *slide 2/4*

Equivalent in vitro drug product performance

- Is achieved through a battery of in vitro tests, designed to provide sensitive measures to identify differences associated to product- and process-related factors between T and R

Equivalent Systemic Exposure

- Is achieved through PK BE study measuring AUC and Cmax parameters
- PK BE study is considered as a high challenging task due to:
  - Low drug level in the systemic circulation
  - Early onset of PK profile
  - RLD batch -to-batch PK variability
- Validated analytical method with adequate sensitivity, robust study design, adequate user training should be considered when conducting PK BE study

Key Points from Talk #3 (Bing Li) *slide 3/4*

Device similarity:

- FDA does not expect that the design of a generic drug-device combination product be identical to the design of its RLD
- FDA recommends that potential applicants minimize design differences between a proposed generic drug-device combination product and its RLD
- FDA expects that the end-users of generic combination products can use the generic combination product when it is substituted for the RLD without intervention of the health care provider and/or without additional training prior to the use of the generic combination product

Key Points from Talk #3 (Bing Li) *slide 4/4*

Equivalent Local Delivery

- Is achieved through PD endpoint study or comparative clinical endpoint study
- Bronchoprovocation may provide more sensitive means of demonstrating BE between a test and reference albuterol MDI product
- FDA recommends to use the to-be-marketed drug product in the comparative clinical endpoint study

Panel Discussion and Q&As

- How do you model deposition – impactor data vs clinical deposition data?
- Models used for sensitivity analysis? Parameters? Gut absorption
- Is the transition from sink to non-sink conditions validated for a given compound?.
- How about other compounds (non BCS2)?
- Dissolution rate is key – how is t`at piece of information integrated into the model?
- Macrophage clearance?
- Cascade impactor data seems to underlie the presented iBCS grid, yet there is so much more to a product's performance in the lung than CI. What is the minimum set of data between two products that would be predictive of deposition and clinical?
- potential for in vitro only?

Panel Discussion and Q&As, *slide 1*

Questions right after the talks on iBCS

- Q: There were several parameters mentioned in the talk (solubility//dissolution rate and permeability // retention time) – are these the ones that are likely to be used/confirmed/validated for iBCS
  - A: It's too early to say. These are critical parameters but the validation and confirmation work is still ongoing.
- Q: How do you account for gut absorption in these models?
  - A: The mechanistic simulates both oral and pulmonary absorption

Panel Discussion and Q&As *slide 2*

Panel discussion after all three talks – all relate to iBCS

Q1: How do you model deposition – impactor data vs clinical deposition data?

- A: Deposition is mechanistically modeled based on 3 sets of data: (i) subject specific-specific factors (e.g. lung geometry, size); (ii) product specific (e.g., inhalation profile, flow through the device, breath hold) and (iii) batch specific data, (e.g., APSD, GSD, coarse fraction). All three datasets inform the 1-dimensional deposition model.

Q2: Models used for sensitivity analysis?

- A: Initially, sensitivity analysis is based on the Preludium model available to all in the working group since no distinct model bias was observed. This assumption will be tested by remodeling some sinsitivities using other models.

Panel Discussion and Q&As *slide 3*

Q3: Is the transition from sink to non-sink conditions validated for a given compound?

- A: No since this would require access to e.g. SAD data where Do for a given poorly soluble compound is varied significantly in a single study. Data of this type is proprietary and not available to the team today but would be very valuable if it could be made available.

Q4: How about other compounds (non BCS2)?

- A:General experience that simulations of clinical exposure following dosing of BCS2 compounds works well based on first principles provided that data on aerosol performance (deposition) and dissolution (VMD, solubility) is of decent quality. This is not always true for BCS3 compounds (limited by tissue interactions, mainly due to the quality of the input data on parameters such as Kp and Peff, and also due to specific deep tissue binding in e.g. lysosomes.

Panel Discussion and Q&As *slide 4*

Q5: Dissolution rate is key – how is that piece of information integrated into the model?

- A: The current model approach is based on first principles (Nernst-Brunner type approach informed by e.g. VMD and solubility). Models are being refined to account for non-idealities observed in dissolution experiments .

Q6: Macrophage clearance?

- A: Less important for small molecules compared to large.

Panel Discussion and Q&As *slide 5*

Q7: Cascade impactor data seems to underlie the presented iBCS grid, yet there is so much more to a product's performance in the lung than CI. What is the minimum set of data between two products that would be predictive of deposition and clinical?

- A: we are just at the beginning of the journey. Clinical impact of variations in lung deposition will be investigated as part of the sensitivity analysis and could be related back directly to variations in CI data
- An iBCS could be based on drug properties such as solubility and permeability or on product performance data such as dose deposition and dissolution – or a combination thereof.

Panel Discussion and Q&As *slide 6*

Q 8: potential for in vitro only?

- Using in vitro study as surrogate for in vivo, for budesonide inhalation suspension, is possible because API is the only insoluble particle in that formulation.
- Recently, had a nasal spray where API is mixed with an insoluble excipient. There, a MDRS approach was used to differentiate API from excipient particles.

Overall Conclusions

- PQRI WG developing a classification system for inhaled medicines (iBCS)
- Computer based models are being developed for simulations of systemic exposure in response to changes in critical product attributes
- Therapeutic equivalence of OINDPs takes into account
  - Device and formulation similarity
  - Equivalent in vitro drug product performance
  - Equivalent systemic exposure
  - Equivalent local delivery

Session 5: Enabling Patient-Focused Quality Standards via Modeling and Simulation for Oral Products

Moderator: Sandra Suarez Sharp, FDA

Speakers: David Good, Bristol-Myers Squibb

Yang Zhao, FDA

Christophe Tistaert, Janssen Research & Development

Presentations

1. PBPK-based and Traditional IVIVC as Complementary Tools to Quality by Design in the Biopharmaceutics Space

   David Good, Bristol-Myers Squibb

2. The US Food and Drug Administration Perspective on Physiologically-Based Absorption Modeling in Biopharmaceutics

   Yang Zhao, FDA

3. Mechanistic Absorption Modeling and Clinically Relevant Specifications for Enabling Formulations Technologies

   Christophe Tistaert, Janssen Research & Development

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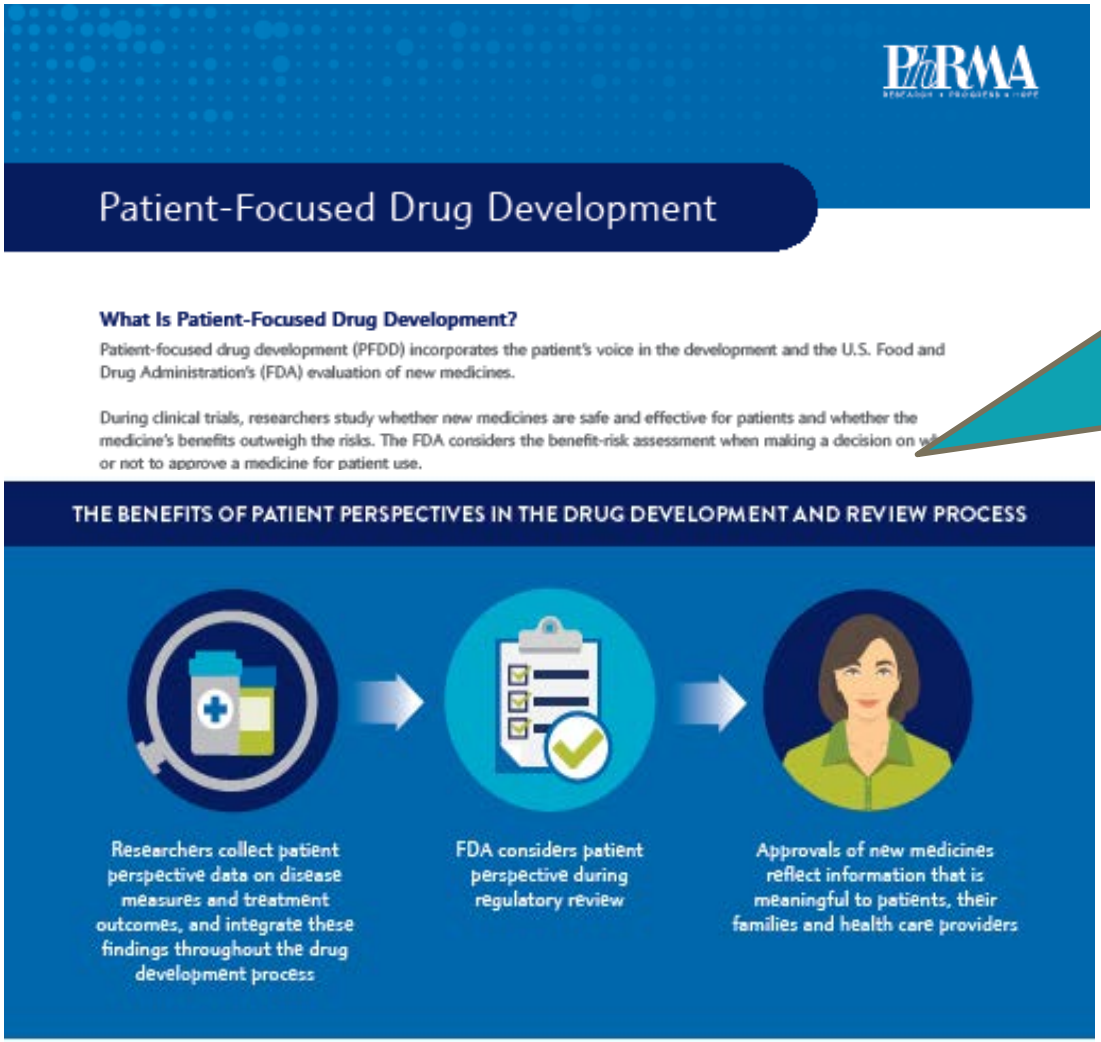
Session Background Premise Challenges

Patient-Centric Drug Product Development (PCDPD)



PCDPD incorporates the patient's voice in the development and the FDA's evaluation of new medicines. Drug product approvals reflect information that is meaningful to patients…

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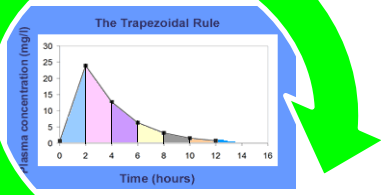
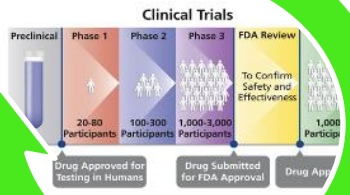
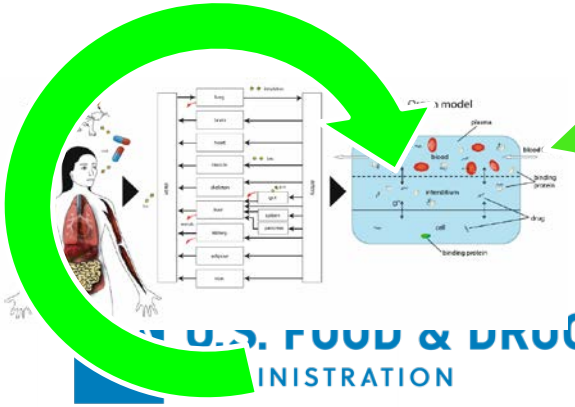
Patient-Centric Drug Product Development, cont.







From product Quality perspective, what is our role towards Patient-Centric Drug Product Development?

The Role of Product Quality in PCDPD

Patient-Centric Drug Product Development (PCDPD)

From a drug product quality perspective, PCDPD is the development of science- and risk-based drug products based on the **implementation of drug product specifications**, in-process controls and control strategy **that are clinically relevant (CR).**

How does modeling and simulation help us in achieving this goal?

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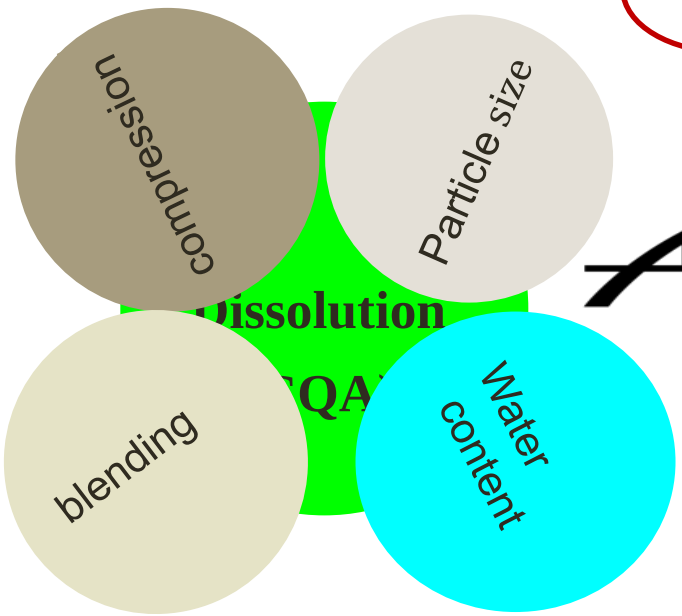
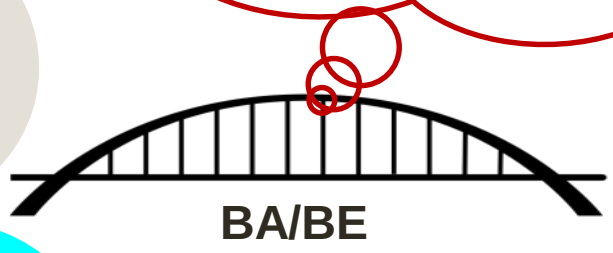
CR Implies the Establishment of a Bridge

Modeling and simulation can provide the means for predicting/determining the clinical impact of CMC changes without the need for additional in vivo studies





In Vivo Performance

Clinically Relevant Drug Product Specifications/Safe Space

Patient-Centric Drug Product Development

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Dr. Gottlieb's speech tohte Regulatory Affairs Professionals Society (RASP) 2017 Regulatory Conference

"We're on an unsustainable path, where the cost of drug development is growing enormously, as well as the costs of the new medicines. We need to do something now, to make the entire *process less costly and more efficient*. Otherwise, we won't continue to realize the practical benefits of advances in science, in the form of new and better medicines"

- ……we're also taking new steps to modernize how sponsors can evaluate clinical information, and how FDA reviews this data as part of our regulatory process.
  - ……This includes more widespread use of modeling and simulation, and high performance computing clusters inside FDA.

Key Points from Talk #1 (David Good)

PBPK, IVIVC and QBD

- Mechanistic modeling
  - strengthens IVIVC models
  - helps with compounds with complex PK
- Full ADME knowledge extends possible applications and success
- IVIVC is achievable, with more mechanistic possibilities, for both modified release and immediate release drugs
- PK absorption modeling is important for product development (e.g., biorelevant dissolution)
- Expanding the regulatory use of PBPK modeling will establish greater precedent and guidance for mechanistic IVIVCs

Key Points from Talk #2 (Yang Zhao)

- Common deficiencies noticed by FDA for Physiologically-Based Biopharmaceutics Modeling (PBBM)
  - Model is not mechanistically sound,
  - Verification data is insufficient,
  - Model structure information is insufficient,
  - Reliability of simulation results is questionable
- Recommendations based on the presented case study
  - First, “Learn and confirm” the mechanism and the model
  - Input determines your output!
  - Conduct Parameter Sensitivity Analysis (PSA) for your parameters of uncertainty!
  - Conduct virtual BE to take into consideration variability of individual parameters!

Key Points from Talk #2 (Yang Zhao) *cont'd*

More General Advice

- Questions to ask yourself
  - What is the proposed model purpose or intended regulatory use? • Are there sufficient data for model development and verification to justify the intended purpose? • Are the data robust? • What is the appropriate model strategy?
- Document checklist
  - Model report (stating model objective and your "thought" process) • Modeling workflow • Drug product/formulation information and process understanding • Solubility data • Relevant dissolution information and dissolution profile data • PK data and study design • Sources of parameters • Coding or mathematical equations • Hypothesis • Datasets (allowing executing independent analysis)

Key Points from Talk #3 (Christophe Tistaert)

- Biopharmaceutics / MAM to understand in vivo behavior
  - Absorption rate limiting steps
  - Guidance in the formulation development process
  - Derisk BA/BE trials
  - Criticallity assessment of CQA's / CPP's / CMA's
  - Polymorphic purity
  - Quality Control Dissolution specification
- Major progress in the last years
  - Science (OrBiTo, UNGAP, User groups, publications, algorithm qualification...)
  - Regulators (Guidelines, acceptability...)
- Room for improvement
  - In vitro / in silico tools
  - In vivo characterization
  - Complexity...

Panel Discussion and Q&As *slide 1/2*

- IVIVC vs IVIVR – what's the difference?
  - A correlation (…C) is stronger than a relationship (…R). Both have value in development, but IVIVR may not allow a biowaiver unless a safe space is developed (data defining a region where all the batches are bioequivalent)
  - Safe space can be built via conventional IVIVR or mechanistic IVIVR/ IVIVC
- Q: regulators often ask about clinical relevance of dissolution method, and how dissolution could pick up non-equivalent batches. Any recommendations on how to do that?
  - A: dissolution can be a surrogate for BE relying on a safe space established via IVIVR or IVIVC. Mechanistic models in particular could be helpful with that. They leverage data generated in clinical trials to possibly expand safe space region.

Panel Discussion and Q&As *slide 2/2*

- Q: is it necessary to always use modeling and simulations to establish clinical relevance?
  - Not necessarily. Modeling and simulations have advantage in reducing the number of in vivo studies to show clinical relevance. Currently, all the paths are acceptable to reach this goal.
  - Scientists from academia, industry and regulatory agencies (FDA, EMA, Japan, Canada) published a paper (https://www.ncbi.nlm.nih.gov/pubmed/30151612) that describes a decision tree showing in which cases to implement a particular simulation. Decision depends on product type, solubility, etc. If only have clinical data to set specifications, those boundaries are reduced compared to what simulations can give you.
- Clinically relevant specifications are challenging. How to get there? Takes efforts by each company and by FDA.
- Harmonization across countries is also a challenge.

Overall Conclusions

Simulations based tools are finding its way into regulatory approaches

Industry should lead the way, investigate and publish

Some of the session participants suggested that modeling and simulations should not be required for submissions, but the implementation of clinical relevant drug product specifications (using simulations or other approaches) should be a requirement as part of NDA and ANDA submissions to FDA

Session 6: Oral Biopharmaceutics: Challenges, Opportunities, and Advancements

Moderator: Andreas Abend, Merck

Speakers: Greg Amidon, University of Michigan

Adam Procopio, Merck

Gilbert Burckart, FDA

Presentations

1. Advancing the Dissolution Toolbox in Drug Development: Novel Bio-predictive Dissolution Methodologies for Oral Products

   Greg Amidon, University of Michigan

2. Use of 3D-printed Tablets as a Biopharmaceutics Investigation Tool

   Adam Procopio, Merck & Co., Inc.

3. Advancing Biopharmaceutics Knowledge and Toolkit to Improve the Quality of Pediatrics Medicines

   Gilbert Burckart, FDA

Session Background/Premise/Challenges

Oral medicines provide a convenient, reliable and safe route of drug administration to patients of all ages

The in vitro and in silico toolkit to support solid oral drug product development has evolved significantly over the past decade and continues to provide pharmaceutical scientists with new and enhanced understanding of the *in vivo* performance of new drug candidates.

3-DP of tablets (and other formulations) holds the premise to deliver an array of formulation protypes for early clinical trials to identify optimal formulations for the patient and can support the development of novel or traditional in vitro methods to reliably assess drug product in vivo performance.

Developing patient centric oral products for pediatric patients is challenging due to a highly diverse patient population and lack of certain clinical data in pediatric patients. Model-informed Drug Development holds the premise to increase the success of pediatric formulation development and enables children access to much needed medicines already available to adults.

Key Points from Talk #1 (Greg Amidon)

- Different dissolution tests are needed for different purposes
  - Quality control
  - In-vivo predictive
- QC tests need to be sensitive to change, fast and easy to implement
- In-vivo predictive tests need to be
  - Physiologically relevant
  - Appropriate for drug properties (acid, base, neutral)
  - From several methodology options (no less, no more)
    - • Current compendial methods (eg: Apparatus 1, 2, 3, 4)
    - • Multicompartment systems: Gastrointestinal Simulators (eg: ASD, GIS, TIM)
    - • Multiphase systems to simulate absorption: (eg: Biphasic, polymer membrane systems)
    - • pH – Dilution methods
    - • Other?

Key Points from Talk #2 (Adam Procopio)

3D printing (3DP)

- is a new tool to improve quality and timeliness of drug development
- can create complex geometries and customized material properties
- is gaining acceptance in industry and academia
- may enhance understanding of PK (via dose and dissolution customization)

Clinical 3D Printer

- can create novel shell dosage forms with various fill options
- studied the impact of in-vitro and in vivo release with various combinations
- controlled and delayed release

Case-study issues identified (and addressed)

- dissolution variability
- anisotropic nature of both the dosage form and the dissolution media flow field

Key Points from Talk #2 (Adam Procopio)

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- Our Team has worked towards designing novel shell dosage forms with various fill options and studied the impact of in-vitro and in vivo release with various combinations • Controlled and delayed release concept oral dosage forms have been demonstrated successfully with Metformin and other proprietary Merck compounds

Issues: • Dissolution variability root cause has been identified as the anisotropic nature of both the dosage form and the dissolution media flow field

Clinical 3D Printer

- 3D printing (3DP), offers R&D a new tool in the biopharmaceutical toolbox to improve the quality and timeliness of oral drug product development • This technology is gaining significant academic acceptance as well as industrial interest and commercial implementation due to its ability to create complex geometries along with customizable material properties. • We believe there is a potential to enhance our understanding of PK through both dose and dissolution flexibility in early clinical programs through the creation of complex and custom drug products.

Key Points from Talk #3 (Gilbert Burckart)

- Pediatrics is an area of special medical need, special ethical necessity, and special regulatory science questions, in particular:
  - Bioequivalence (BE)
  - Drug Drug Interactions (DDIs)
  - Physiologically-Based Pharmacokinetics (PBPK) modeling
- Advances over the past 11 years include
  - Failure rate from 42% down to 20% for drug development studies
  - MIDD find new applications in pediatrics
- Remaining challenges
  - Optimizing pediatric study designs is still a challenge in the face of such diverse clinical problems
- Parting advice
  - Pediatric MIDD works best in the context of a multidisciplinary team of clinicians, clinical pharmacologists, biostatisticians and pharmacometricians.

Panel Discussion and Q&As: 3D printing, *slide 1/2*

Q1: how do you translate the presented 3D printing technology to commercial manufacturing?

- A: with this particular tool, we are not planning to do that now. It's too slow for that. The tool is still valuable, for development (both early and clinical).
- Technology evolves rapidly. In ten years, 3DP could become standard and wide-spread. Today, we are learning.

Q2: 3DP strategies are improving. Have you tried to integrate API into the printing material itself (rather than filling a pre-printed 3D shell)?

- A; Yes. There still remain some technical challenges, as well as regulatory challenges (e.g., when changing from liquid to solid form).

Panel Discussion and Q&As: 3D printing, *slide 2/2*

Q3: 3DP materials – is the range expanding? Polymers with different sets of properties.

- A: have used mixes of polymers, but it is challenging. Some academic tech centers have been able to expedite printing or accommodate various needs for critical product/quality attributes. Today, are leveraging the already-approved ingredients list. It's a limited list but with a known safety record. CDRH is further along, compared to CDER. Academic research is going forward, and many small tech companies are pushing ahead.

Q4: Does the drug release rate differentiate by shell thickness or other shell factors?

- A: we are still investigating. Still discussing, how to verify the dose that will go into the patient.

Panel Discussion and Q&As: Pediatrics

Ethical considerations of pediatric testing vs ethical need for pediatric drugs

- For pediatrics, FDA only requires small studies, use weight banding, rely on mg/kg (weight-based dosing) for dose finding etc. FDA has a number of well trained experts ready to help, as well as academic collaborators.

Pediatrics risk assessment. DDIs cannot be done as easily as in adults, and PBPK is challenging.

- There is no requirement for pediatric testing for bioequivalence assessments. If appropriate modeling tools could be developed, that would address this concern.

Pediatrics is not just a smaller dose. Children go through changes in size and maturity.

- Simulating and in-vitro devices are still helpful. Absorption is difficult to simulate but still could learn something that would be useful in product development.

Overall Conclusions

- The *in vitro* tool box to develop *in vivo* predictive dissolution methods continuous to evolve.
  - In vivo-predictive dissolution is a key enabler of QbD

- 3D printing is an exciting technology but not a mature technology yet.
  - Close collaboration between industry and regulatory agencies are needed to overcome both the technical and regulatory challenges

- Pediatric drug product development remains to be challenging and could benefit from novel *in vitro* and *in silico* approaches that are more adequate to simulate drug product in vivo performance