2nd FDA/PQRI Conference on Advancing Product Quality

Breakout Summaries

October 7, 2015

North Bethesda Marriott

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FDA

Track 1:
Emerging Regulatory Initiatives

Biopharmaceutics – BCS Biowaivers

Moderators: Vinod Shah, PQRI and Mehul Mehta, FDA

BCS Related Guidance

BCS Guidance: Waiver of in vivo bioavailability and bioequivalence studies for immediate release solid oral dosage forms based on a biopharmaceutics classification system - August 2000 – Waiver for Class 1.

Draft Guidance: Update on the (above) BCS biowaiver guidance - May 2015 – Waiver for Class 1 + Class 3

Draft Guidance: Dissolution Testing and Specification Criteria for Immediate-Release Solid Oral Dosage Forms Containing Biopharmaceutics Classification System Class 1 and Class 3 Drugs - August 2015 – Dissolution Specification for BCS Class 1 and 3 drug products

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Biopharmaceutics - BCS Biowaivers

Biowaivers – welcome as long as Generic manufacturers are not overburdened

BCS is also used in risk based approach in drug development

BCS Class 3 biowaiver – a big step forward towards harmonization. BUT is not complete, there are some differences – there should be one rule

In vivo Predictive dissolution / PBPK model is a good approach for all classes of drugs

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Does dissolution method predict in vivo performance?

Improve in vitro methods to better predict in vivo behavior

IPD/PBPK model -

Overall found to be very useful – can help in predicting particle size function, rate controlling steps; can be utilized to improve physiochemical aspects of API.

Challenge PBPK/in-silico methods and models to be more informative of changes in formulation or physicochemical properties.

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Some concerns:

Class 1 requirements – at times expensive, not money saving

Solubility: Highest therapeutic dose vs. highest dose strength

Dissolution Test: 900 ml → 500 ml; 50 rpm→75 rpm

Class 3: Q1 and Q2 requirements – difficult, expensive, may not be feasible because of patent restrictions

Biowaiver for class 3 may have less impact compared to biowaiver for class 1

Class 4: No biowaiver consideration. SUPAC IR can be used for class 4.

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Pharmaceutical Product Lifecycle Management – Q12

Moderators: Moheb Nasr, GlaxoSmithKline and Robert Iser, FDA

Lifecycle Management – ICH Q12 (1)

- How can FDA gain confidence in sponsors' change management systems
  - Sponsor should demonstrate a robust change management system
  - Improving inspector/reviewer communication -- appropriate information from inspectors should be shared with reviewers.
- Better utilization of of regulatory tools, e.g., consistent information on PQS, NIPP protocols, FDASIA records requests, knowledge management, risk-based inspections can help FDA (and other agencies) address increased number of global sites and ECs

Lifecycle Management – ICH Q12 (2)

- Changes to an EC need not always require a prior approval supplement; need for specific types of notification will be based on risk and level of product and process knowledge.
- Q12 can provide examples related to ECs, e.g., less information/knowledge versus information with enhanced product development and robust PQS. Former may result in more ECs (or different ECs), latter may have fewer ECs
- Q12 will need to address legacy products and ECs, e.g., should there be a default set of ECs and what should they be? Incentivize companies to update ECs as gain knowledge – need further perspectives from industry on this
- Need input on level of granularity for Q12. For example, can Q12 provide a high level guidance or template for change protocol; with inspections done via global, harmonized standards

Lifecycle Management – ICH Q12 (3)

- Consider need for clarifying data requirements to provide confidence in manufacturing changes, stability and BE requirements . Is it possible to do it at high level and still make it useful for industry and regulators (within and outside ICH)?
- Consider a concept of a change management "Master File" that is applicable globally and can be referred to by sponsor.
- Consider application of Knowledge Management up through the supply chain – many lifecycle changes are initiated via supplier or supply chain issues

Dissolution Testing and Specification for BCS I and III Drugs in Immediate Release Products

Moderators:

Rik Lostritto, FDA and Gregory Amidon, University of Michigan

Dissolution Testing & Specs IR BCS I & III (1)

- Draft Guidance another example of FDA implementing risk/science based regulatory approaches; draft generally supported by industry
- FDA supporting research within FDA and in academic centers to developed improved in-vitro methods to support development of clinically relevant specifications
- Dissolution testing and specifications considerations would ideally address both
  - Predicting impact of changes on clinical outcomes; trends, rank-ordering, etc
  - Predicting in-vivo profiles/behavior generally
- FDA has continued interested in validated, verified, reproducible alternative in-vitro methods that are relevant for the given product

Dissolution Testing & Specs IR BCS I & III (2)

- Dissolution testing serves both development and QC purposes. More complex methods, e.g., multi-compartment, partitioning, other, can provide valuable development information, which could also be of interest to regulators
- Depending on the nature of the drug, sponsor may choose to use particular methods that increase ability to provide in vivo correlations, e.g., simulated stomachs. For other drug types, e.g., obvious Class I, then bucket/paddle may be most clinically predictive

Dissolution Testing and Specification for Extended Release Products

Moderators:

Paul Seo, FDA and James Polli, University of Maryland

Dissolution Testing & Specs – ER (1)

- Much on-going research within industry to advance in-vitro methods predictive of in-vivo outcomes (develop clinically relevant specs), e.g.,
  - Use of osmotic systems to rapidly assess in vivo viability and confirm biopharm models
  - Coupling Biopharm models with digital dosage form design to select the ER formulation composition
  - Radio labelling and scintigraphy to identify lead formulations and obtain useful in vivo information
  - Chemical analysis to assess matrix effects on dissolution
- Disintegration throughout GI regions is typical; effects not clear – may not be important clinically for ER generally. Depending on matrix and individual drug, other aspects may be of more importance, e.g., diffusion rate.
- Fed or fasted states as well as release rate/nature of matrix may influence transit and location of spread, eg., stomach versus colon.

Dissolution Testing & Specs – ER (2)

- Scintigraphy/radiolabelling can provide additional information along with in-vitro dissolution methods (which are needed for QC purposes); use of radiolabelling should be tailored to drug and formulation type, e.g., erosion mechanism, other
- Use of extemporaneous formulations can assist in efficiently getting to clinical studies to confirm Biopharm models, and e.g., can be made in dose units for individual study subjects without need for long term shelf-life in early development
- For ER drug product, erosion can be more important than API particle size which is usually controlled to ensure content uniformity
- Matrix products -- rate controlling polymers (e.g., HPMC) grades as well as natural variations can have effect on release

Quality Metrics

Moderators:

Tara Gooen Bizjak, FDA and Louis Yu, Perrigo

Quality Metrics (FDA)

- FDA encourages on-going dialogue – draft guidance a way to continue this dialogue
- Important aspect of quality metrics effort is visibility of the supply chain
- Context will be important for all metrics/numbers collected via QM efforts (common across all presentations)
- FDA would welcome comments on data points that could be "gamed"
- Product complaints by lot and optional CAPA effectiveness/retraining rate
  - Using "lots" because units difficult to define, however recognize that lots creates challenges with variable lot size
  - Units can also be challenging, for example multiple size packs in OTC – statistically challenging; open to better way to address denominator issue
  - CAPA effectiveness – a challenging metric. Goals is to address robustness of root cause evaluation

Quality Metrics (Industry/ISPE)

- Think big, but start small, move forward with experience based learnings
- Industry is supportive of FDA addressing quality metrics; standardization across industry is difficult, be wary of unintended consequences
- ISPE has started Wave 2 study to generate specific data to expand learnings
- APR on time metric – questions remain on this:
  - ISPE Wave 1 data showed that this APR on time metric did not correlate to other metrics, e.g., culture, deviations.
  - Could result in focus on time rather than on content of the report
  - Consider survey approach for initial information collection on this

Quality Metrics (Industry/ISPE)

- Free text field for reporting metrics is appreciated
- Initial focus on collecting site by product data, except for complaint data
- Still question on how CMOs will be part of reporting requirement. Identifiers for sites so that FDA can combine information from a particular site
- NDC numbers may not be unique to manufacturer in the OTC industry

Botanical Drug Development and Quality Standards

Moderators:

Sau Larry Lee, FDA and Steven Hoag, University of Maryland

Session Summary

- Three Speakers
  - Botanical Drug Development and Quality Standards
    - Sau (Larry) Lee, Ph.D. / FDA
  - Aspects of the Discovery and Development of Plant-Derived Drugs
    - A. Douglas Kinghorn / College of Pharmacy The Ohio State University
  - Challenges in Botanical Supplements Product Development and Quality Testing
    - Vikas Moolchandani, Ph.D. / Nutrilite Institute of Health (Amway)

Challenges

- Botanical complexity
  - Multiple chemical components
  - Active components are not well-defined/characterized
  - Large natural variations
    - Harvesting conditions, processing conditions, plant parts, etc.
- CDER considers entire botanical mixture as the active ingredient (API) for botanical drugs
- Botanicals products should meet same standards as non-botanical drugs for quality, safety and efficacy
  - Usual small-molecule techniques are insufficient for quality control of botanical products
  - Prior human use can provide information on safety profile
  - Level of clinical efficacy and safety requirements are the same for botanical and non-botanical drugs
- Need to better define how “totality of evidence philosophy/approach” applies to botanicals
- Today development of plant based medicines not mainstream in pharma, but is important need to find ways FDA can work with companies, NIH/NCI and academics (where much of plant discover occurs) to promote new medicines for patients

Research Needs API (extract) Level

- Better methods for quantitating complexity
  - Analytical methods for characterizing phytochemical profile
  - Analytical guidelines for characterizing API when not all peaks can be characterized with reasonable effort
    - Single leaf can contain > 30,000 distinct chemicals
- Characterization of API variability
  - Harvesting techniques
  - Extraction procedures
- Plant species identification
  - Need fast and easy methods, and fit for purpose methods
- Assessment of API stability
  - With out knowledge of which components affect efficacy what is an acceptable level of degradation
- Cataloging possible environmental contaminates, relative to plant source
  - Pesticide and herbicide profile, heavy metals, etc.

Research Needs Product & cGMP Level

- Definitions of product quality
  - Product quality is a real issue as pointed out by Dr. Moolchandani in their studies many botanical products had poor quality
  - Need standards that account for unique nature of plant.
- Tests for product quality
  - Similar issues to API level but with the product
    - Need reasonable product performance standards
- Test for product stability
  - Difficult when dose is hard to define
  - Are all changes significant and import to patient outcomes
- Effect of processing methods affect on dose, product stability, etc.
  - Eg., wet granulation alter phytochemical profile in a manner affects efficacy and safety
  - Standardization of extraction procedure and its effect on phytochemical profile

How to Interact and Communicate with FDA on Quality Issues

Moderators:

Giuseppe Randazzo, FDA

Communicating with FDA (1)

- The Integrated Quality Assessment (IQA) will incorporate inspections as a part of the review team (ORA has representation) – all stakeholders are included. Throughout the review process communication will exist between field investigators and review team
- Sponsors can have informal clarification teleconferences.
- RBPM and ATL will make sure right people are on calls
- Review teams will collaborate with ORA when appropriate, e.g., join an inspection

Communicating with FDA (1)

- FDA CDER quality related offices have undergone major restructuring to achieve “one quality voice” integrating NDA, ANDA experts, inspectors, reviewers, etc along with project managers
- ATL role is application based; for ANDAs the same ATL can be assigned to the same type of product; for NDAs and BLAs ATLs are aligned with clinical division or expertise respectively; the ATL is generally the Branch Chief or designee
- Currently PMs facilitate specific applications; expertise is being expanded with cross training so that PMs may eventually facilitate all application types
- Challenge – large size of review teams

Communicating with FDA (1)

- RBPMs: centralized POC in OPQ for information regarding the quality portion of applications; continue to use the OGD/OND RPM as POC for general inquiries.
- Provides a focal point for communication external to the review team
- Contact the RBPM for all questions related to Quality-only correspondences received (IR).
- Be aware of your information request response deadline.

Communicating with FDA (1)

- Correctly code all submissions and amendments to ensure accurate triage
- Clearly identify all facility changes for all submissions
- Ensure all facilities and their responsibilities are clearly listed on the 356h
- Reach out to your assigned RBPM for any quality specific areas of uncertainty when submitting information