

Workshop Summaries

Discussions of the Global Stability Workshop are summarized for the following topics:

- QbD and Stability Program – Dr. Alasandro
- Setting Specifications – Dr. Gentry
- Challenges of Different Products – Dr. Choudhury
- Impurities & Physicochemical Stability – Dr. Baertschi
- Emerging Stability Guidance – Dr. Zahn

Quality by Design *Session Highlights*



Presented by
Dr. Mark Alasandro, Merck

Stability

- Stability critical quality attribute to ensure safety and efficacy through out the product shelf life.
- Stability integral part of product development

QbD in General

- General Audience supports QbD
- Encouraged by the FDA
- When to start QbD?
 - Staged approach
 - Level of QbD studies based on phase of development
 - Phase 1, 2, 3, NDA or post approval
 - Decided by the company
 - Dependent on type of drug product

QbD and Generics

- If the Innovator files under QbD, what is the impact on Generics?
 - Innovator QbD filing information is proprietary and confidential
- Generics going to QbR (Question based review)
 - QbD type questions
- More QbD post approval for generics

QbD and NCE

- QbD allows focus on quality attributes rather than all product attributes
- QbD provides potential to file with reduced stability package –if drug product development based on QbD.
 - Examples of predictive stability tools given
 - Stability will not go away
- QbD is recognized by other countries; but, limited to ICH regions

QbD and Stability Testing

- Examples given on how to present the knowledge gain in QbD
 - Stability data typically submitted in tables and tables of data
 - Wouldn't the graphic presentations of correlations (degradation rate and moisture) be better?
 - Graphical presentation would facilitate review
 - Data tables should be available when requested.

QbD and Stability Testing

- QbD and Analytical Methods
 - Examples given on the use of DOE for Robustness testing
 - Not a significant resource drain
 - Industry has always been validating methods based on QbD

QbD and Analytical Methods

- Applying QbD to analytical methods allows one to use multifactor to assist in method development.
 - Reduced effort in method development.
 - No need to file minor changes with there is movement within the design space.
 - Suggest the sponsor to present the range (from QbD study) to the reviewers for intelligent data review.
 - Pharmacopeia style methods are acceptable
 - Good to have ranges and target set points for QC methods
 - QbD method design are not time consuming

Specifications

Session Highlights

Presented by
Dr. Abbie Gentry, McNeil

Summary of Specifications Session

- Focus on quality attributes that impact fitness for use.
- Some quality attributes may be evaluated only at release.
 - Only those quality attributes that can change over time should be evaluated on stability.
 - It is appropriate to have in-house release criteria that are tighter than shelf-life criteria

Summary of Specifications Session

- The vision of Qbd will be lost if the specifications are set to control limits based on process capability ranges observed during development studies.
 - The design space should reflect the specifications, and should be larger than the process capability space.
- Generally, stability specifications are established on the basis of batch means, however, decisions pertaining to acceptability of batches are based on individual data points

Summary of Specifications Session

- As a product moves from Phase I – III, perceived safety risk increases as patient population increases
 - Increase patients & increase dosing duration
 - Impurity levels and specifications need to be supported by pre-clinical safety data
- Don't set overall product specifications prematurely
 - Justification of impurity specifications for finished product depends on clinical exposure to impurities

Summary of Specifications Session

- Signal-to-noise calculations of many pharmacopeias are not harmonized with current industry practice.
- FDA issued final OOS Guidance in 2007.
 - Applicable to all testing except PAT
 - Quality Control Units need to consider all results of lots manufactured in a campaign – both OOS and within-spec.

**Biologics, Generics, OTC, Drug-
device Combinations and
Nutraceuticals**
Session Highlights

Presented by
Dr. Dilip Choudhury, Scios Inc.

Biologics, Generics, OTC, Drug-device Combinations and Nutraceuticals

Biologics

- Stability evaluation of protein and other biologic drugs present unique challenges because of their structural complexity
- Intensive stability evaluation at early development stage is recommended to develop knowledge of product, performance of analytical methods, and develop science-based process (**QbD**)
- Complementary suites of analytical methods are essential to determine purity and degradant profile

Biologics, Generics, OTC, Drug-device Combinations and Nutraceuticals

Biologics

- Accurate and specific determination of aggregates is critical because of potential immunogenic concerns
- Clinically relevant bioassay methods to ensure desired potency during the shelf life are essential. Bioassay methods typically have high variability and are not sensitive to small degradative changes
- Well characterized reference standard is critical for accurate measurement of stability attributes and to relate the final product analytical data to the data from clinical and toxicological batches

Biologics, Generics, OTC, Drug-device Combinations and Neutraceuticals

Generics

- Question based review (QbR) is more relevant for ANDA submission than QbD based development
- ANDA requires less stability data for submission . Typically data from 1 batch required; for complex dosage forms data from more than 1 batch required. API stability can be obtained from vendors (DMF).
- Stability requirements are different for US, EU and Canada

Biologics, Generics, OTC, Drug-device Combinations and Nutraceuticals

OTC Products

- CHPA has developed two guidelines for stability requirement for OTC drug products and nutraceuticals. The guidelines have been provided to FDA

Nutraceuticals

- Adequate guidelines for stability and shelf life determination are desired. CHPA guidelines may be helpful. USP chapter on stability is also helpful.

Biologics, Generics, OTC, Drug-device Combinations and Neutraceuticals

Drug-device combinations

- Stability study design following current ICH guidelines require a large portion of typical batches at a significant cost
- Product approval may require review by multiple groups within FDA based on the nature of the combination product

Impurities, Degradation
and Physicochemical
Characteristics
Session Highlights

Presented by
Dr. Steve Baertschi, Eli Lilly

Impurities & Degradation

- Our ability to detect and measure impurities exceeds our ability to interpret the meaning. The Detection level should move from ALARA (As Low As Reasonably Achievable) to ALARP (As Low As Reasonably Practicable)
- Stage-based TTC (Threshold of Toxicological Concern) approach for genotoxic impurities approach) was proposed to FDA by PhRMA. This approach is based on the length of time that patients are exposed to the impurity.
- Genotoxic impurities are generally from synthetic processes and are therefore controlled in API. In contrast, degradants are controlled in both the DS and DP.
- For low levels of impurities (e.g. 1-10 ppm), typically would need to develop special “tailored” methods.
- Residual metals can cause significant problems for conducting tox studies. Trace metals may cause positive tox results which could be false positive.
- It is not uncommon to detect new, unknown impurities during development. Don't panic if you have an unknown impurity until further testing/knowledge is available.

Impurities & Degradation

- Well designed stressed testing is a good example of QbD.
- Stress Testing studies should be designed to produce all “likely” or “potential” degradation products. Real time stability will likely be a subset.
- Good Degradation Knowledge Space should be the foundation of QbD for Analytical Methods Development and Stability. “Holes” in knowledge space can lead to serious problems later.
- Oxidative/photolytic degradation is complex. Studies need scientific design based on known oxidative mechanisms.
- Stress testing is a research tool, while accelerated testing is part of stability requirement. This should be kept in mind when designing studies.
- Confirmatory photostability studies are analogous to accelerated testing for stability (i.e., part of formal stability requirements)



Physicochemical Stability

- Molecules from research often have poor solubility and physicochemical characteristics and are not readily “druggable”. Thus, physical characterization, salt selection, polymorphic choice, are bigger issues than used to be.
- Vast knowledge is available in the literature, but not well used. Reinventing-wheel phenomenon is common.
- Molecular “loosening” within crystalline materials (i.e., increased mobility) is the key to predicting stability of solids.
- Solid state technology NMR, XRD, DSC, etc. data are techniques that can provide knowledge to be used to predict stability.
- Predicting stability using energy temperature diagrams was discussed.

- Excipients compatibility is part of the QbD effort. There are many different philosophies for conducting such studies.
- Microenvironmental pH created by excipients can be a critical variable in stability of formulations.
- Formulation stress testing is necessary.



Emerging Stability
Guidance
Session Highlights

Presented by
Dr. Manuel Zahn, Astra Zeneca

Draft WHO Stab Guideline

- New version will be published any day;
- On the agenda of the WHO Expert meeting in Geneva in October;
- Still working document; send comments to Sabine Kopp, please.

Long-Term Photostability Testing?

- Gap in current guidance → hot and humid countries
 - Temperature / humidity / light
- More realistic evaluation of shipment and distribution practice required;
- WHO Good Storage Practice / Good Distribution Practice not implemented.

Long-Term Testing at 30°C/70% RH?

- ASEAN & Brazil require testing at 30°C/75% RH
 - More protective packaging;
 - Shorter shelf-life;
 - Labelled storage recommendations
“Store below 25°C”?
- 30°C/75% RH data cover India and all other markets in Climatic Zone III & IV.

Accelerated Testing for 9 or 12 Months?

- 6 months are sufficient to cover excursions;
- Acc testing (e.g. at 40°C/75% RH) for 9 or 12 months could be of benefit for products that are stable for 6 months;
- Could expand knowledge space (QbD);
- Should not be required routinely.

Excursions during Shipment

- We should monitor (and control) shipment and storage to mitigate risks;
- We should know more about the impact of high or low temperatures on the quality of our products;
- Product stress testing at 50°C/ambient humidity could complete data package.