Newest Regulatory experiences- IQ risk-based predictive stability update

Regulatory Sub-Team

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Goals and accomplishments

Regulatory Sub-Team Goals

(defined in Sept 2015)

Current Focus

Conduct industry survey to get a sense of to what extent Risk Based Predictive Stability (RBPS) are being utilized in regulatory filings along with the regulatory experience. Publish the results

Additional Short Term Goal

Publish regulatory experience around multiple cases studies. In conjunction with webinar/workshop.

Long Term Goal

Harmonize the level of detail and publish a formatted template that could be used for regulatory filings.

Lobby ICH to update Q1A of publish a Q1A Q&A document regarding RBPS.

Leverage findings with regional policy groups via company regulatory policy groups.

RBPS Reg Sub-Team 2016 Accomplishments

- Written, executed and evaluated benchmarking survey
- Survey results presented at IQ June 2016 Webinar
- Survey results presented at SOS, September 2016
- Poster presented at IQ Meeting, October 2016
- Paper submitted to Pharmaceutical Technology in November 2016

RBPS Reg Sub-Team 2017 Goals

- FDA meeting – learnings from survey
- Request case study examples from companies who contributed to survey
  - Pull together sub-group examples, covering several scenarios and phases of development and models
- Define the structure of an investigational template
- Publish case studies along with template strategy/strategies

Survey

Survey Details

- 56 Questions
- Survey Distributed to IQ Analytical Leadership Group (33 Companies)
- 19 companies responded
  - 58% Response Rate
    - 100% NME's, 11% Generics

Modeling in RBPS

- Types of Models
  - At least 9 of the companies who responded are using “typical” ASAP studies and at least 2 are using in house predictive statistical approaches
- MVTR
  - 12 companies reported sometimes utilizing MVTRs in predictions, with the source of the MVTR data split fairly evenly between experimentally derived, default values in software and from supplier information.
  - 5 of these companies also utilized MVTR data and the resulting predictions in regulatory submissions
- What types of things are modelled
  - The majority of responders utilized RBPS approaches to model assay/potency or impurities. Physical attributes such as dissolution, formation of crystalline in amorphous, hardness and color were also modelled.

Regulatory Experience using RBPS

- Clinical
  - Clinical submissions containing RBPS approaches have been successfully approved in over 23 countries. Countries who did not accepted some of these approaches were named as Spain, Czech, France and Italy
- Marketing Application
  - Only 3 companies gave further details of using RBPS approaches in Marketing applications but successful applications "worldwide" were achieved.
- Post Approval
  - One company gave further details of using RBPS approaches Post Approval, to support a packaging change in the USA

Conclusions

- RBPS is being used by several companies
  - Primarily small molecule
  - Focus on clinical development
- Regulatory experience suggest data has been accepted by many countries
- Limited experience in New Market Applications and post approval changes

Opportunities

- Ground has been set for broader utilization of RBPS approaches
  - However, based on response, still many companies not working in this space

- More opportunities to utilize in new marketing application/post approval scenarios
  - Tool to understand stability as opposed to simply demonstrating stability

- Some regulators from certain countries refused to accept RBPS approaches
  - Education opportunity

- Several companies still performing full ICH stability to verify RBPS
  - Could this testing be reduced

Article in Pharmaceutical Technology

http://www.pharmtech.com/risk-based-predictive-stability-industry-perspective

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Risk-Based Predictive Stability–An Industry Perspective

A survey on risk-based predictive stability tools reveals how pharma companies are leveraging advanced stability approaches throughout the drug development process.

Mar 02, 2017 By Helen Williams, Dennis Stephens, Megan McMahon, Elke Debie, Fenghe Qiu, Cherokee Hoaglund Hyzer, Lois Sechler, Rachel Orr, Debra Webb, Yan Wu, David Hahn

Pharmaceutical Technology

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Template

RPBS template

- Scope:
  - CTA submissions
  - Use of RBPS data to support Retest date for DS and SL (Shelf life) for DP
- Recommendations based on industry early adopter experience
- Content:
  - Introduction
  - Description of the model used
  - Discussion of experimental conditions
  - Discussion of results
  - Confirmatory stability program
  - Conclusion
- 2 docs: high level outline + specific example

RPBS template high level guideline

- Introduction
  - Potential shelf – life limiting attributes (pSLLA's): Chemical and physical attributes
  - Rationale for choice attributes that were modeled as SLLA's
  - Sponsor should note the limitations of its modeling approach and assess the potential impact on study results and interpretations
  - Planned long –term stability commitment
- Description of model used
  - Introduction to model + appropriate literature references
  - Software used
  - Explanation on additional assumptions on packaging if applicable
- Discussion on experimental conditions
  - Experimental conditions in tabular format
  - Justification of choice of these conditions
  - Justification on container selection
  - Summary of SLLA's that were evaluated
  - Description of analytical procedures if different from those provided in P.5.2. Analytical procedures

RPBS template high level guideline

- Discussion of results
  - Detailed discussion and interpretation of the results
  - Discussion of results obtained for SLLA and how they were modeled to set SL/retest
  - Discussion of any other change (e.g. appearance)

- Confirmatory stability program
  - Discussion on plans to generate confirmatory data to further support the model as applicable (full ICH, lean stability with reduced timepoints, reduced conditions, contingency storage, or reduced storage time,….)

- Conclusion:
  - Provide a conclusion to indicate the SL/retest supported by the modeling data

Case Studies

Example case study

Background

- Phase 1, new clinical study
- three existing common granule tablet strengths on market (commercial)
- stable product, high product knowledge
- 5 year shelf life at 25°C/60% RH for commercial product
- Clinical trial proposed using a new low strength tablet (common granule) with only 3 months real time stability data available at time of submission
- performed ASAP study using crushed tablet – worst case, increased surface area

Model (not software) or Summary of RBPS Approach Used

- ASAP incorporating multiple temperature and humidity conditions
- Degradation was modeled
- No packaging prediction included

Outcome/Conclusions

- This ASAP study data was used to support a 3 year shelf life claim based on just 3 months real time stability data for this new low strength formulation.
- The ASAP data was submitted to the USA, UK, France, Italy, Turkey, Egypt, Lebanon and Kenya
- Accepted with no questions
- Good agreement between predictions and real-time data

16 Case studies

- From 8 different companies
- 12 were used in a regulatory filing
- 8 were validated against real time data
- 3 were about API - 9 oral solid cases – 1 oral solution – 1 parenteral – 1 lyophilized prod
- Purpose:
  - Packaging selection (2)
  - SL predication during clinical development (9)
  - Demonstrate equivalency (1)
  - ASAP validation (3)

Influencing HA’s

Workshop with FDA: RBPS + lean stability

- 2 days
- Objective: socialize the principles of RBPS and Lean stability with FDA reviewers, auditors, and management
- Content RBPS part:
  - Models (modeling sub team)
  - Use of modeling in regulatory filings (Reg sub team)
  - Case studies
  - Template
  - Q&A
  - Discussion with FDA on
  - Review of industry standard RBPS tools + discussion for future use
  - Use of RBPS tools in regulatory filings

- Waiting for formal FDA acceptance

- Looking for an opportunity to also meet with MHRA on this topic (Nov 2017, TBC)