Regulatory Updates

IQ Risk-Based Predictive Stability Regulatory Sub-Team

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The RBPS Regulatory Sub-Team

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Mission of the Regulatory Sub-Team

Advocate the use of RBPS in regulatory submissions by sharing member company's experiences and influencing the industry and authorities

Agenda

- Updates on recent RBPS regulatory sub-team publications
  - Publication of the industry survey (PharmTech, March 2017)
  - Publication of the RBPS template (PharmTech, Aug 2018)
- Updates on recent RBPS submission experiences
  - RBPS sub-team case studies (to be published in Q4 2018)
  - Industry case studies from the recent APS book
- Regulatory Trends
  - Regulatory acceptance by country and recent trend
  - Summary

RBPS regulatory sub-team publications

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

Risk-Based Predictive Stability for Pharmaceutical Development–A Proposed Regulatory Template

A published regulatory template sharing best practices for filing RBPS data would benefit the industry and regulatory reviewers by enabling a consistent presentation of predictive data and conclusions.

Aug 02, 2018 By Dennis Stephens, Helen Williams, Megan McMahon, Fenghe Qiu, Cherokee Hoaglund Hyzer, Elke Debie, Yan Wu, Hanlin Li, Jin Wang

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Key learnings from the survey publication

- Of all the companies utilizing RBPS tools, approximately 55% of them were leveraging the data in a regulatory capacity
- RBPS data was used in more than 100 submissions by the working group companies at the time in dozens of countries that covers all major markets
- The majority (85%) of survey respondents would like a published regulatory template sharing the earlier adopters best practices for filing RBPS data

H. Williams, et al, Risk-Based Predictive Stability–An Industry Perspective, PharmaTech, V 41 (2), 2017, pp 52-57

The concept of a regulatory template

- Help companies to standardize on key elements that should be included when filing RBPS data in Module 3 stability sections (i.e., S.7 and P.8) of regulatory submissions
- Intended to be used in setting the retest period/shelf-life for drug substance or drug product that is used to support clinical development

D. Stephens et al, Risk-Based Predictive Stability for Pharmaceutical Development–A Proposed Regulatory Template, PharmTech, Aug 2018

Regulatory Template-high level outline

Table I: Key elements of a risk-based predictive stability (RBPS) filing.
Introduction (Intention of Predictive Study)
Description of the Model Used
Discussion of Experimental Design
Discussion of Results
Confirmatory Stability Program
Conclusion

More details are recommended compared to a typical stability report

D. Stephens et al, Risk-Based Predictive Stability for Pharmaceutical Development–A Proposed Regulatory Template, PharmTech, Aug 2018

Regulatory template-Introduction

- Discussion of stability risk assessment
- Justification of shelf-life limiting attributes (SLLAs) including both physical and chemical attributes

D. Stephens et al, Risk-Based Predictive Stability for Pharmaceutical Development–A Proposed Regulatory Template, PharmTech, Aug 2018

Regulatory template-Model Description

- Provide a description of the model used, along with appropriate literature references, as applicable.
- A description of the software that is used should also be included. Additionally, any assumptions regarding packaging (e.g., material type, moisture permeability, or moisture vapor transmission rate) should be detailed if they are used to support modeling.

D. Stephens et al, Risk-Based Predictive Stability for Pharmaceutical Development–A Proposed Regulatory Template, PharmTech, Aug 2018

Regulatory template-Experimental Design

- Provide the experimental conditions (e.g., temperature/relative humidity and time points) in tabular format
- A discussion may be included on how the storage conditions were selected, especially if they were driven by particular physiochemical properties of the drug substance and/or drug product formulation components
- In some cases, the samples assessed may be not the clinical formulation, but may be deemed as “worst case”. In this case, include a discussion of why the samples used were “worst case” of the clinical formulation
- Also discuss why the studied container closure was selected (e.g., open containers allowing for better correlation with the impact of humidity).
- Provide a summary of what shelf life limiting attributes were evaluated after storage (e.g., degradation product X, appearance). Address any differences in analytical procedures used from those provided in the Analytical Procedures sections of the regulatory filing, if applicable.

D. Stephens et al, Risk-Based Predictive Stability for Pharmaceutical Development–A Proposed Regulatory Template, PharmTech, Aug 2018

Regulatory template-Discussion and results

- Provide a detailed discussion and interpretation of the results. Specifically discuss the shelf-life limiting attribute(s) (e.g., degradation product x) and how this was modeled to set a shelf life for the drug
- A discussion/explanation of any other changes (e.g., appearance) would be appropriate as well

D. Stephens et al, Risk-Based Predictive Stability for Pharmaceutical Development–A Proposed Regulatory Template, PharmTech, Aug 2018

Regulatory template-Long-term stability program

- The planned long-term stability commitment should be discussed
- The study design may be supported by RBPS results. Based on the understanding of the modeling, this could encompass a variety of approaches. These approaches could include ICH-like testing, reduced time points, reduced conditions, and/or contingency storage

D. Stephens et al, Risk-Based Predictive Stability for Pharmaceutical Development–A Proposed Regulatory Template, PharmTech, Aug 2018

Regulatory template-Conclusion

- Provide a conclusion to indicate the shelf-life that is supported by the modeling data. Where applicable, outline how extensions to the initial shelf-life will be assigned

D. Stephens et al, Risk-Based Predictive Stability for Pharmaceutical Development–A Proposed Regulatory Template, PharmTech, Aug 2018

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Accelerated Predictive Stability

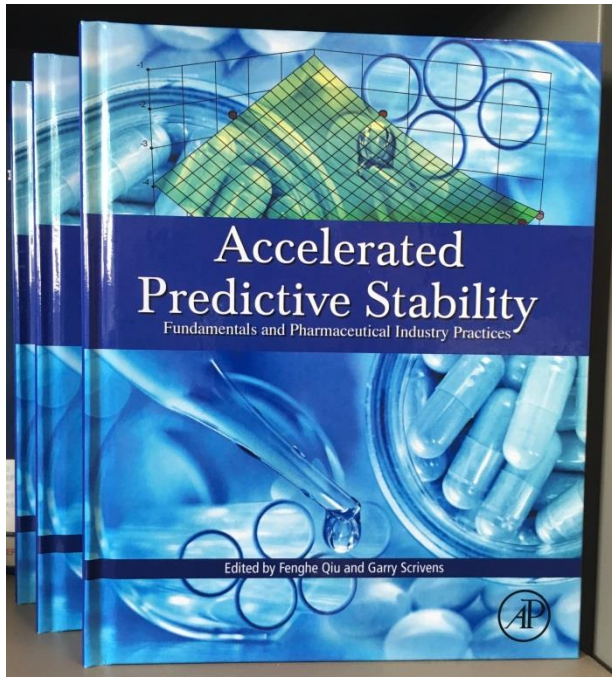
Fundamentals and Pharmaceutical Industry Practices

- Edited and contributed by scientists from IQ member companies
- Covers two mostly used models

$$Lnk = Log\ A - \frac{E_a}{R.T} + B\,(RH) \qquad \text{(ASAP model)}$$

$$\%Deg_t = A\,.\exp\left(\frac{-E_a}{R.T}\right).H^{n_1}.t^{n_2} \qquad \text{(ASM model)}$$

- Currently the most comprehensive resource for theories, experimental design, case studies and regulatory experiences of ASAP/ASM



APS Book Table of Contents

Support regulatory submission in clinical development

- Support initial retest period/shelf life
- Support impact of change assessment
- Support Stability related queries

Support initial shelf life of SOF DP

Situation

- Three strengths of SOF tablets for Phase 2a
- ASAP with 6 T/RH conditions were performed on a development batch with lowest drug loading
- Chemical stability was monitored

Modeling

- ASAPprime
- Shelf life of three strengths

Regulatory submission

- ASAP prediction without long term data but with a commitment
- A 12-month shelf life requested at 5^{o}C
- Both USA and Belgium accepted without queries

Adapted from Risk Based Predictive Stability; Industry's Regulatory Experience, to be published by IQ RBPS working group

Support change of capsule shell

Situation

- Phase 1 capsule reformulated involving change of capsule shell from gelatin to HPMC
- 8 week ASAP with 7 T/RH conditions were performed

Modeling

- ASAPprime
- Shelf life of HPMC capsules based on chemical degradation
- Packaging (bottle type of amount of desiccant)

Regulatory submission

- ASAP prediction and 1 month long term data were submitted
- A 12-month shelf life requested at ambient conditions
- Accepted without queries

Adapted from case study from Risk Based Predictive Stability; Industry's Regulatory Experience, to be published by IQ RBPS working group

Assess Impact of Change in Drug Substance Synthetic Route (Phase III)

Situation

- Initial Phase 3 study; bond formation steps changed compared to stability lot , justifying not performing stability on the DS from the new route

Regulatory submission

- 60M stability data for the prior route, release results of DS from both routes
- ASAP study, results and conclusion for DS from both the original and modified routes, no degradation above LOQ being observed
- No testing commitment made, retained the same retest period (60M)
- Submitted to 33 HAs including Germany, only one query from China (requested DS from new route to be on stability)

Table 3 Summary of the Results From an APS Study

Condition	Duration	Level of Degradant
70°C/10% RH	35 days	NMT 0.05%
70°C/75% RH	35 days	NMT 0.05%
80°C/10% RH	35 days	NMT 0.05%
80°C/40% RH	35 days	NMT 0.05%

RJ Timpano, Accelerated Predictive stability (APS) regulatory
Strategies, in Accelerated Predictive Stability, Edited by F Qiu and G Scrivens, Academic Press, 2018

Support Stability-Related CTA Queries (phase I)

Situation

- A query received for a program in Phase I questioned the strategy of not setting up the drug substance manufactured from the second synthetic route on stability

Response to HA

- Submitted ASAP results for DS from both the original and modified routes, no degradation above LOQ being observed; and from tablets using both drug substances, demonstrating the chemical stability on the tablets using the second synthetic route was similar or better. Thus the original synthetic route drug substance data were considered worst case and supportive of the newer synthetic route.
- The response to this query was accepted .

Table 4 Summary of APS Studies of Drug Product Manufactured With Drug Substance With Original and Modified Synthetic Routes

		Level of Use Period-Limiting Degradant in Tablets	
Condition	**Time interval**	**Original Route**	**Modified Route**
Control (5°C)	14 days	0.04%	0.02%
50°C/75% RH	7 days	0.65%	0.37%
60°C/40% RH	14 days	0.56%	0.08%
70°C/5% RH	14 days	0.06%	0.03%
70°C/75% RH	6 h	0.54%	0.27%
70°C/75% RH	19 h	2.08%	1.71%
80°C/40% RH	2 days	2.59%	0.27%

RJ Timpano, Accelerated Predictive stability (APS) regulatory
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Support Marketing Application Submissions

- Support selection of product formulation
- Support proposed commercial packaging and potential future changes
- Support product manufactured with different API particle size
- Support control strategy

Support the Selection of Drug Product Composition

- ASAP was performed for the selection of dry granulation excipients and a variety of formulation compositions.
- The results and conclusions were filed in the P.2 section of MA to justify the commercial formulation
- The MA was approved
- In this same MA, the stability information including ASAP data allowed the sponsor to justify and propose the subsequent use of ASAP data to assess potential post approval changes

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Support Proposed Commercial Packaging and Potential Future Changes

- ASAP was performed for the selection of the proposed commercial packaging by predicting the shelf life in various packages, the results were filed in the P.2 section of an MA
- Additionally, the average MVTR per tablet ratios of HDPE bottles of varying fill count used in the primary registration study were included in the MA dossier
- The following proposal "the data resulting from packaging modeling and/or accelerated stability studies will support the changes to the bottle configurations (with same materials of construction) without the need for prior stability studies or regulatory approval, provided that the data indicates the change to bottle configuration will not increase the shelf life–limiting degradant above the specification limit over the proposed shelf life." was accepted without queries

Table 5 MVTR/Tablet Ratios for Proposed Bottle Configurations

Strength	Count	Bottle Size (mL)	Closure Size (mm)	Average MVTR/Tablet Ratio
X mg	6	45	28	0.0295 mg/day
	60	60	28	0.0037 mg/day
	180	60	28	0.0012 mg/day
	360	120	38	0.0015 mg/day
Y mg	6	45	28	0.0295 mg/day
	60	60	28	0.0037 mg/day
	180	120	38	0.0031 mg/day
	360	325	38	0.0024 mg/day

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Strategies, in Accelerated Predictive Stability, Edited by F Qiu and G Scrivens, Academic Press, 2018

Assess The Stability of DP Manufactured with DS of Different Particle Sizes

- ASAP was performed to evaluate degradation comparability of an immediate release drug product manufactured with a drug substance of different particle sizes
- The results were filed in the 3.2.P.2 of an initial MA
- ASAP predictions supported the scientific expectation that drug product manufactured from different drug substance particle sizes would generate comparable degradant levels and that these would meet the proposed specification
- The submission was accepted

RJ Timpano, Accelerated Predictive stability (APS) regulatory
Strategies, in Accelerated Predictive Stability, Edited by F Qiu and G Scrivens, Academic Press, 2018

Support control strategy

- An ASAP study on dissolution of an amorphous solid dispersion tablet at conditions ranging from 50°C/60%RH to 60°C/75%RH for up to 2 weeks
- Dissolutions was predicted throughout the product shelf life under long term storage condition with different initial tablet water content, which was consistent with available real time stability data
- ASAP modeling and stability data demonstrated water content is not a CQA and proposed not to controlled it during stability testing
- ASAP study and modeling were submitted in P.2 section of MA to justify the strategy of not controlling water for this immediate release product
- The MA submission was accepted by both FDA and EMA with no related review questions.

Adapted from Risk Based Predictive Stability; Industry's Regulatory Experience, to be published by IQ RBPS working group

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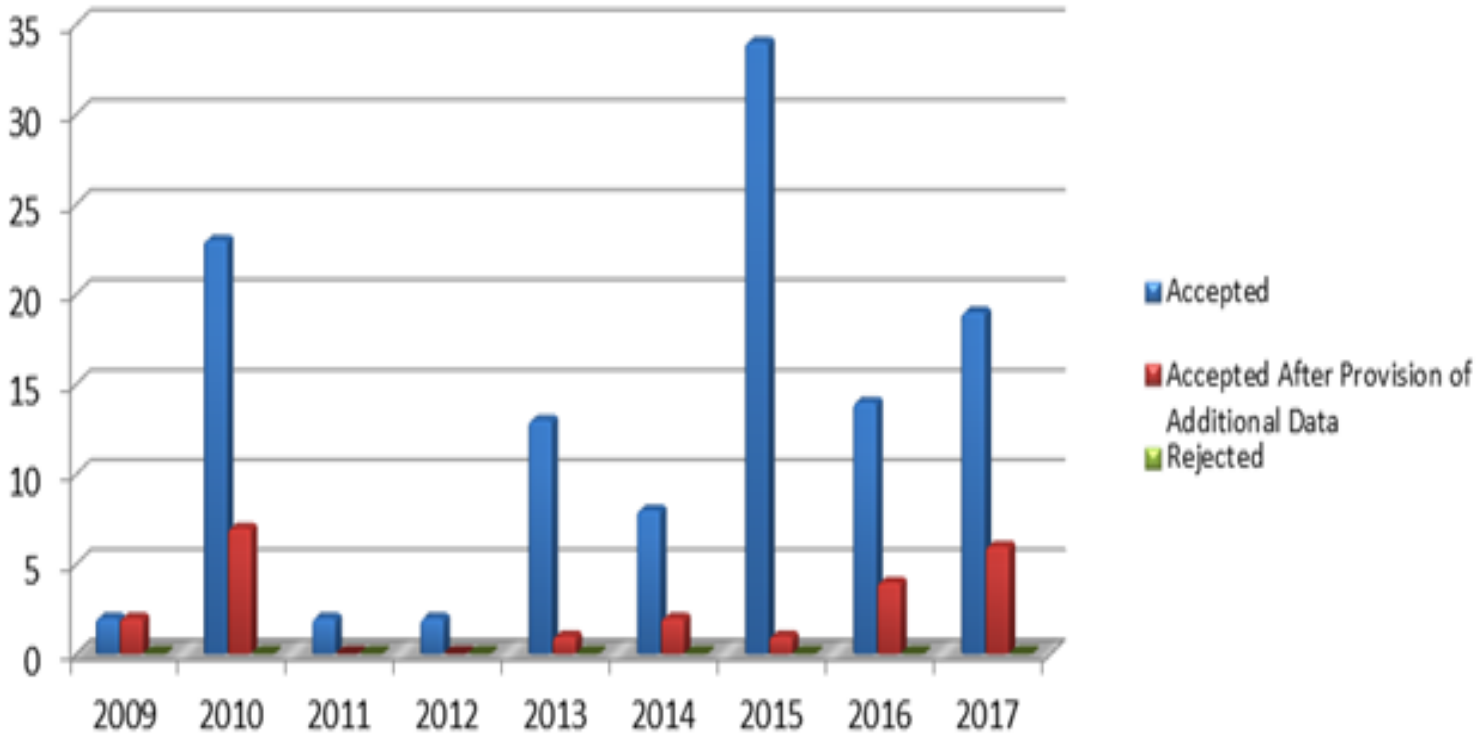
Regulatory experience with RBPS used to set initial shelf-life



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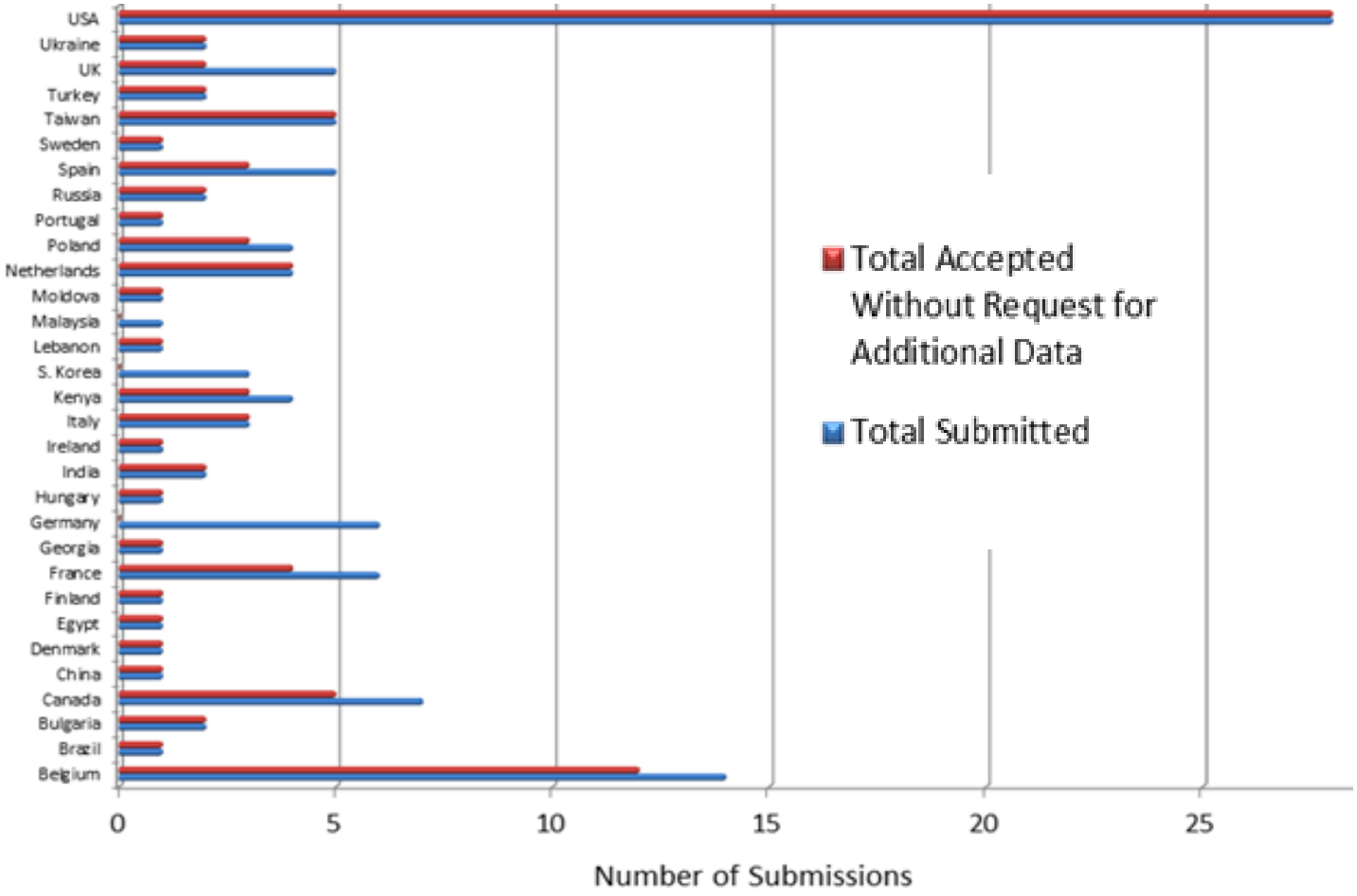
RBPS regulatory experience by country



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Summary

- Some early adopters have been filing RBPS data over a decade, and the regulatory acceptance in general has been high
- RBPS data are mostly used in clinical submissions, and to a less extent in registration and post-approval submissions
- RBPS submission for pharmaceutical development (P.2) (Formulation, packaging, comparability after changes) has been well accepted by authorities in all phase including registration
  - Opportunities exist in extending this strategy for post approval change assessment

Summary (continued)

- Use of only RBPS data in clinical submissions to support initial retest period/shelf life
  - Many authorities have accepted without queries
  - Some countries are known to be reluctant
  - All countries accepted if long term data are provided in the review cycle---this makes the RBPS submission, at least, a time saving strategy
  - Some companies noticed a drop off in direct acceptance since around 2017 in some EU countries (e.g., MHRA), which seems aligned with the 2017 EMA guideline*

* "Guideline on the requirements for the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials" (EMA/CHMP/QWP/545525/2017)

Summary (continued)

- Future perspective
  - Regulatory challenges will continue to exist in some countries, but companies should continue to file RBPS only submissions, maybe with an fall back plan, to continue increasing familiarity of this approach with agencies