Risk-Based Predictive Stability

Feedback from IQ Working Group Regulatory Sub-Team

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Janssen Pharmaceutica NV

SOS stability, Amsterdam, 14th October 2019

Agenda

- IQ and Risk Based Predictive Stability Working Group
- RBPS IQ Working Group Regulatory Sub-Team Activities
  - Survey Responses
  - Overview of Proposed Regulatory Template
  - Case Studies
  - Regulatory Experience to Date

IQ Consortium: vision and working groups

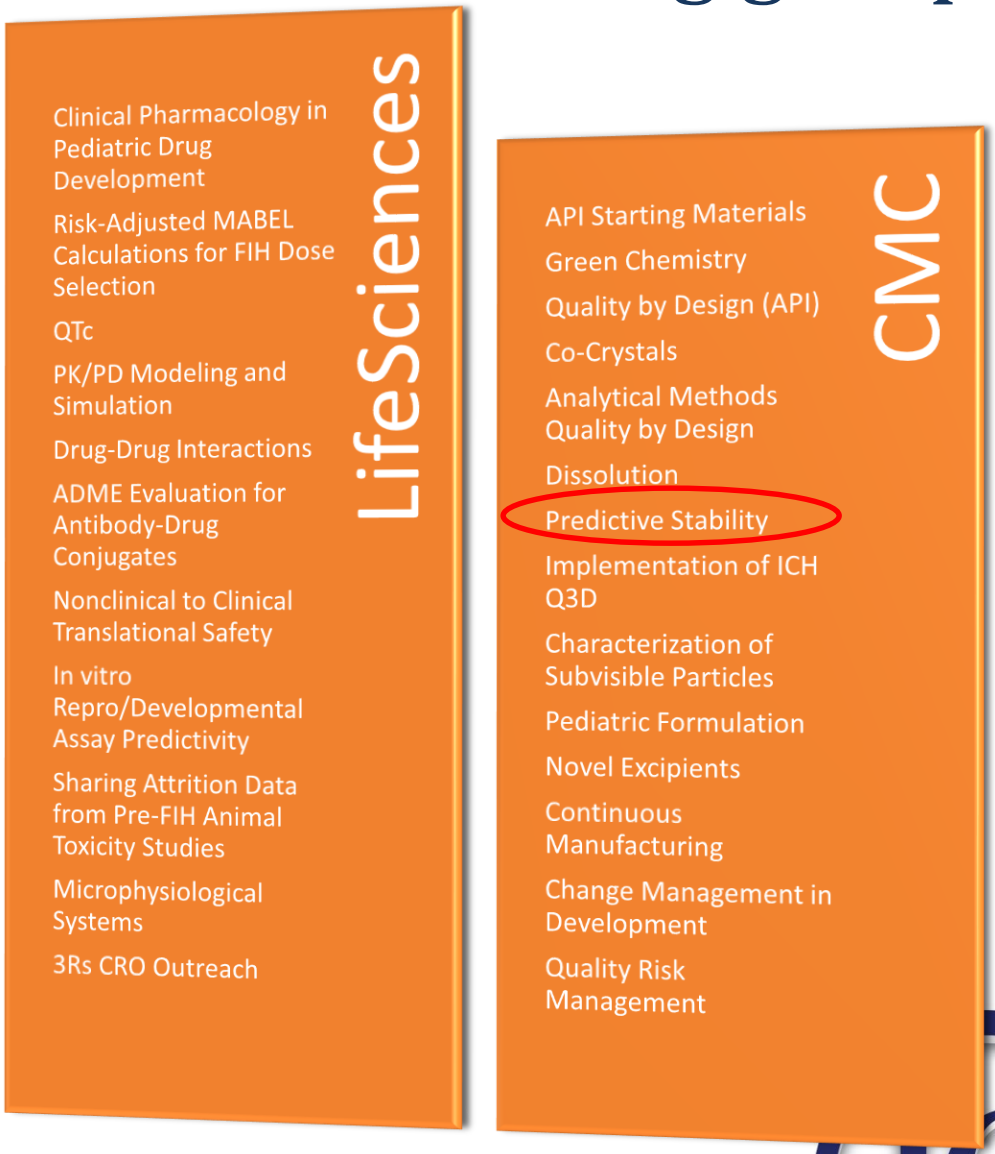
International Consortium for Innovation and Quality in Pharmaceutical Development ("IQ Consortium" or "IQ")

Vision

To be the leading science-based organization advancing innovative solutions to biomedical problems and enabling pharmaceutical companies to bring quality medicines to patients.

Selected working groups:

- # Total WGs > 50
- # CMC WGs > 20
- # LifeSciences WGs > 30



RBPS IQ Working Group - Background

- RBPS IQ Working Group set up in October 2015
- Originally 28 members representing 17 different pharma companies
- Now approximately 50 members from 18 companies
- 4 sub teams
  - Modelling
  - Shelf Life Setting
  - Statistics
  - Regulatory

- Encompasses all predictive stability techniques
  - Accelerated Stability Assessment Program (ASAP)
  - Packaging Predictions
  - Predictive models used by individual companies.

RBPS IQ Working Group - Background

Initial Focus Areas

- Assess how the Industry is leveraging RBPS
- Reaching a consensus on what to include in regulatory filings
- Building a community with a common purpose – all pulling in the same direction. Industry alignment on “next steps”
- Broadening the focus to all aspects of lean stability
- Using modelling to predict dissolution
- Greater acceptance of modeling
- Evaluating the different models and to determine what model works where (or when)
- Influencing HA’s

RBPS Regulatory Subgroup Members

Megan McMahon (lead)	Pfizer
Dennis Stephens/ Preeti Sejwal	Abbvie
Helen Williams	Astra Zeneca
Cherokee Hoaglund Hyzer	Eli Lilly
Fenghe Qiu	Boehringer Ingelheim
Elke Debie	J&J
Andie Dahl/ Yan Wu	Merck
Hanlin Li	Vertex
Donnie Pulliam	Biogen
Murakami Tomonori	Daiichi Sankyo
Jin Wang	Genentech
Patrick Forenzo/Stefano Carenini	Novartis

Mission of the RBPS Regulatory Sub-Team

Advocate the use of RBPS in regulatory submissions by sharing member company's experiences and engaging with the wider industry and health authorities

RBPS Industry Drivers

- Develop robust early products
- Shorter time to clinic/patient
- Clinical supply chain management (match supply to demand, avoid CTA driven relabelling)
- Increased understanding of degradation mechanisms compared to traditional stability studies, which primarily seek to confirm stability
- Support accelerated development, especially for breakthrough indications
- 'Stability by design' : commercial product/ packaging that maximises eventual shelf life
- Facilitate post approval change management

In short: the aim is to maximise quality and minimise wasted time and resource

RBPS submissions

- Support Initial retest period/shelf life (S7/P8)
- Support a longer retest period/shelf life (S7/P8)
- Assess impact of change (S7/P8)
- Support formulation development (P2)
- Support stability related CTA queries (S7/P8)
- Justification of Specifications (S45/P56)

Summary of Activities of RBPS IQ Working Group Regulatory Sub Team

RBPS regulatory sub-team publications

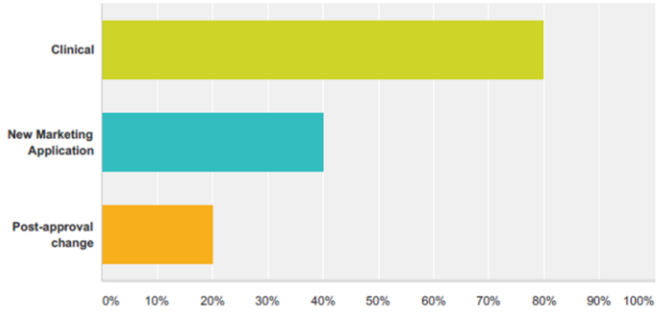
Risk-Based Predictive Stability–An Industry Perspective
Mar 02, 2017

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, Volume 41, Issue 3, pg 52–57

Risk-Based Predictive Stability for Pharmaceutical Development
A Proposed Regulatory Template
Aug 02, 2018

By Dennis Stephens, Helen Williams, Megan McMahon, Fenghe Qiu, Cherokee Hoaglund Hyzer, Elke Debie, Yan Wu, Hanlin Li, Jin Wang
Pharmaceutical Technology, Volume 42, Issue 8, pg 42–4

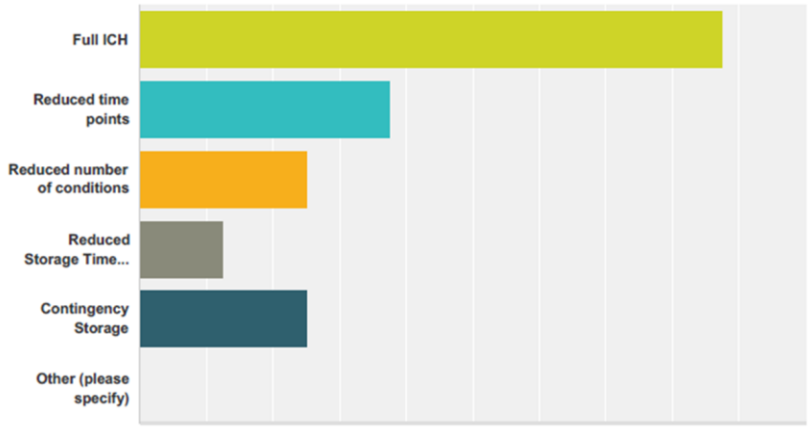
Conclusions From Survey



- RBPS is being used by several companies
  - Primarily small molecule
  - Focus on clinical development
- Regulatory experience suggest data has been accepted by many countries
  - successfully approved in over **23 countries**. Countries who did not accept some of these approaches: Spain, Czech Republic, France and Italy.
- Limited experience in New Market Applications and post approval changes
  - Only 3 companies gave further details of using RBPS approaches in Marketing applications but successful applications “worldwide” were reported.
  - Only one company reported using RBPS approaches Post Approval to support a packaging change in the USA.

Opportunities from Survey

- 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 and post approval scenarios
- Some regulators from certain countries currently not accepting RBPS approaches
- Several companies still performing full standard stability to verify RBPS



RBPS - Need for a Regulatory Template

- Only about 55% of companies leveraging RBPS data in a regulatory capacity.
- Over the course of IQ working group discussions, it was determined that utilization of RBPS data were used in excess of 100 submissions by the working group companies.
- The majority (85%) of survey respondents confirmed that a template would benefit the industry.

RBPS Regulatory Template

Risk-Based Predictive Stability for Pharmaceutical Development
A Proposed Regulatory Template
Aug 02, 2018

By Dennis Stephens, Helen Williams, Megan McMahon, Fenghe Qiu, Cherokee Hoaglund Hyzer, Elke Debie, Yan Wu, Hanlin Li, Jin Wang
Pharmaceutical Technology, Volume 42, Issue 8, pg 42–4

Advantage of a Published Regulatory Template

- Shares best practices for filing RBPS data which would benefit the industry and regulatory reviewers
- Template could help companies standardize on key elements that should be included when filing RBPS data in Module 3 stability sections (i.e. S.7 and P.8)

Key Elements of Regulatory Template

- Introduction
- Description of the Model Used
- Discussion of Experimental Design
- Discussion of Results
- Confirmatory Stability Program
- Conclusion

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

Regulatory Template - Introduction

- A discussion of the stability risk assessment
- Justification of the chosen potential Shelf-Life Limiting Attributes (pSLLAs)
  - Includes chemical and physical attributes

Regulatory Template - Description on Model Used

- Describe model used
  - Appropriate literature reference (as applicable)
- Description of software used
- Assumptions regarding packaging (e.g., material type, MVTR) should be detailed if they are used to support modeling.

Regulatory Template - Experimental Design

- Provide the experimental conditions (e.g. temperature/ relative humidity and time points) that were used for the study in tabular format
- Discussion on how the storage conditions were selected
  - Especially if driven by particular physiochemical properties of the DS and/or DP formulation components
- Discussion of samples used in the study
  - Rationale as to why the samples are considered representative and/or worst case
- Discuss why the studied container closure was selected
- Provide a summary of what shelf life limiting attributes were evaluated after storage
- Address any differences in analytical procedures

Regulatory Template - 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 an initial retest period / shelf life.
- A discussion/explanation of any other changes (e.g. appearance) would be appropriate as well.

Regulatory Template - Long Term Stability Program

- The planned long-term and accelerated stability commitment should be discussed.
- The study design may be supported by Risk Based Predictive Stability results.
- Based on the understanding of the modeling this could encompass a variety of approaches.
  - Full long term and accelerated testing
  - Reduced time points
  - Reduced conditions
  - Contingency storage

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.

Case Studies of RBPS submissions

RBPS Regulatory Sub Team are planning to publish a group of case studies, demonstrating the use of RBPS in regulatory submissions and to summarise the global acceptance, in late 2019 in AAPS (American Association of Pharmaceutical Scientists) Open.

Case Studies of RBPS submissions

- 16 case studies:
  - Different phases in development: Ph I (8) – ph II (5) – ph III (2) – registration (2)
  - Different purposes: initial SL setting – SL setting of formulation/DS synthesis variant– justification of testing strategy – product characterization
- Setup of each case study:
  - Background
  - Modeling information
  - Outcome/conclusion

Case Study 1 (2015)

Background

- Phase 1, alternate low strength of existing tablet formulation
- 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
- Only 3 months real time stability data for low strength tablet available at time of submission
- Performed ASAP study using crushed tablet – worst case, increased surface area

Modeling

- 4-week ASAP study incorporating five temperature and humidity conditions
- Chemical degradation was modeled
- Predictions did not consider the packaging

Case Study 1

Outcome/Conclusions

- The ASAP predictions were used to support a 3-year shelf life claim, supported by 3 months real time stability data for the existing higher strength formulation.
- The ASAP data was submitted to the USA, UK, France, Italy, Turkey, Egypt, Lebanon and Kenya
- Accepted with no questions
- Subsequently good agreement between predictions and real-time data observed

Case Study 2 (2017)

Background

- FIH Phase 1 submission for an IV solution
- 12-week ASAP study for drug substance and 6-week ASAP study for drug product, with 6 temperature and humidity conditions performed
- Chemical stability was monitored

Modeling

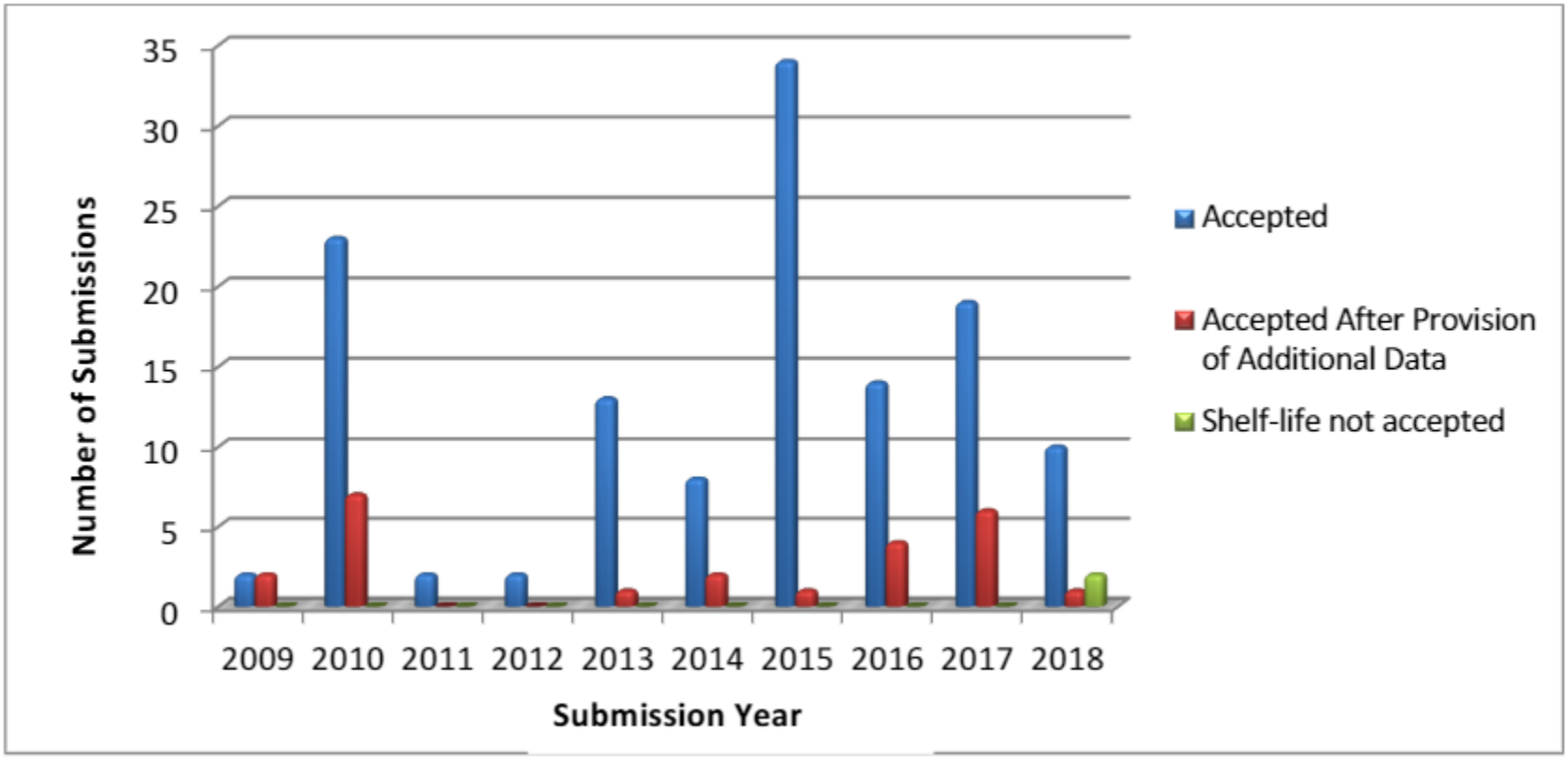
- Drug substance: no degradation, modeling was not possible
- Drug product: ASAP for shelf life

Case Study 2

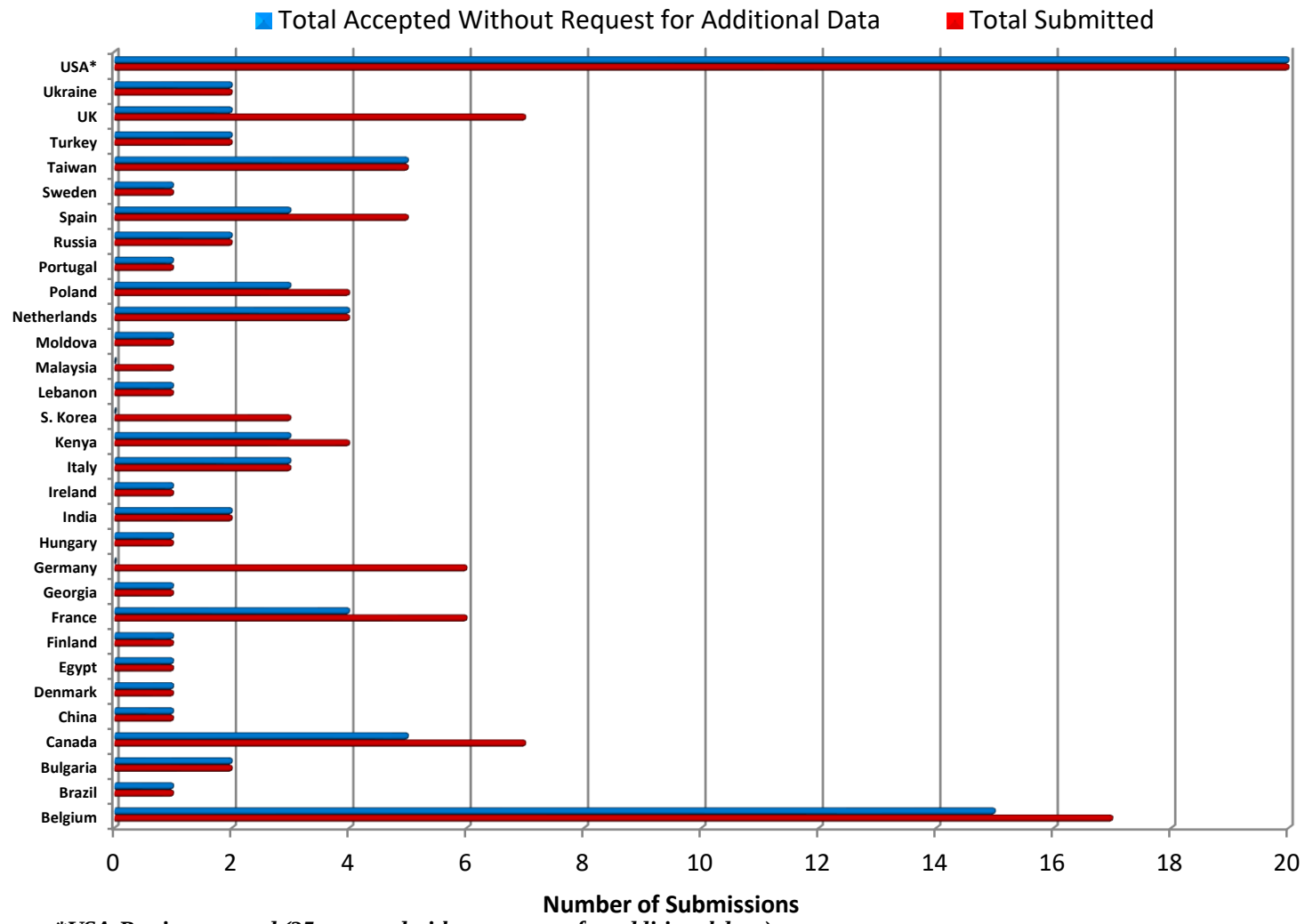
Outcome/Conclusions

- ASAP predictions submitted without long term or accelerated data but with a commitment to set down
- A 12-month retest period at ambient conditions for drug substance
- 12-month shelf life at 5°C for drug product proposed
- Netherlands: accepted both without queries
- Germany: retest period accepted; 6 month shelf life suggested
- UK: long term data were requested for drug substance and product
- Response to Germany and UK: 1 and 3 month stability data provided to support 12 month claims and compared to ASAP prediction; accuracy of ASAP prediction demonstrated.

Global acceptance of RBPS used to set initial shelf-life



Regulatory experience with RBPS by country



**USA Bar is truncated (35 accepted without requests for additional data)*

Summary: use of RBPS data in submissions

- Some early adopters have been filing RBPS data for over a decade, and the regulatory acceptance has been high
- More companies started to use RBPS and to file the data in submissions
- Support pharmaceutical development (P.2) (Formulation, packaging, comparability after changes) : usually no queries
- Support initial retest period/shelf life with RBPS only and a commitment for long term and accelerated stability
    - Acceptable by FDA and several other authorities
    - Often challenged by some countries, e.g., Germany and UK, but acceptable if standard stability data is provided during the review cycle
    - There has been a noticeable drop off in direct acceptance since 2017 in some EU countries, which seems align with the 2017 EMA "Guideline on the requirements for the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials" (EMA/CHMP/QWP/545525/2017).

Other activities

- Through AstraZeneca: engaged with MHRA in Oct 2018 and communicated our working group goals, learnings and initiatives
- Through AstraZeneca: proposal to create a ‘Europe focused predictive stability group’ in Efpia (Issue sheet)
- IQ regulatory subteam is working on a white paper around use of RBPS in post-approval life cycle applications

Acknowledgements

Megan McMahon (lead)	Pfizer
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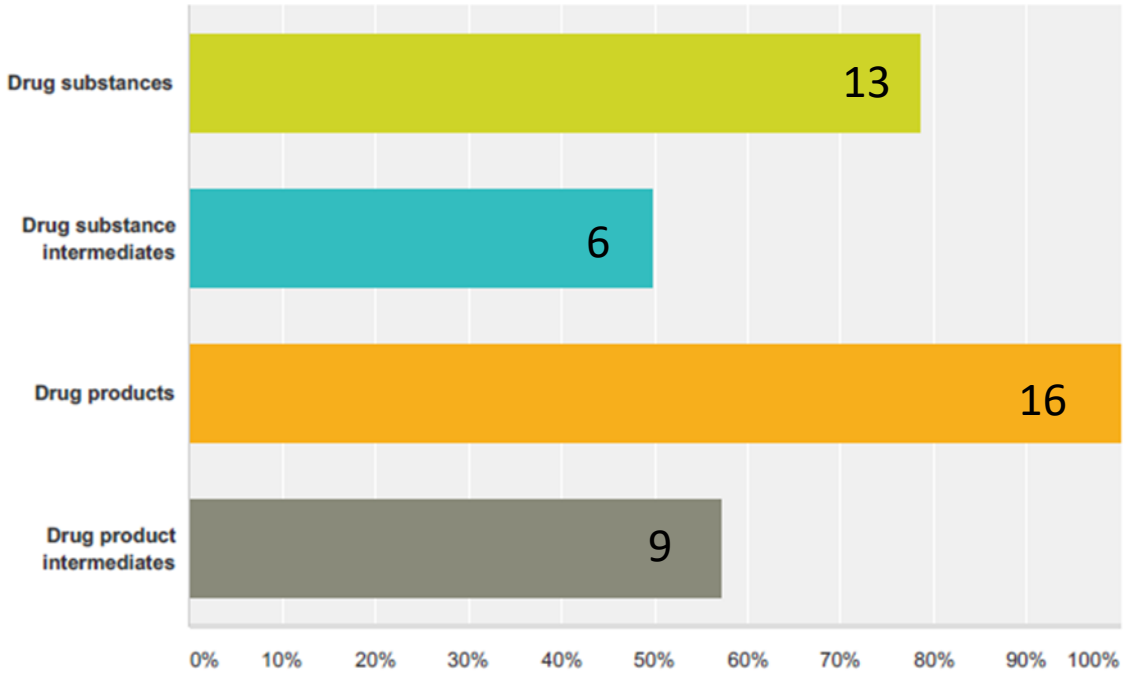
Cherokee Hoaglund Hyzer	Eli Lilly
Fenghe Qiu	Boehringer Ingelheim
Andie Dahl	Merck
Hanlin Li	Vertex
Donnie Pulliam	Biogen
Murakami Tomonori	Daiichi Sankyo
Jin Wang	Genentech
Patrick Forenzo	Novartis
Yan Wu	Merck
Preeti Sejwal	Abbvie
Stefano Carenini	Novartis

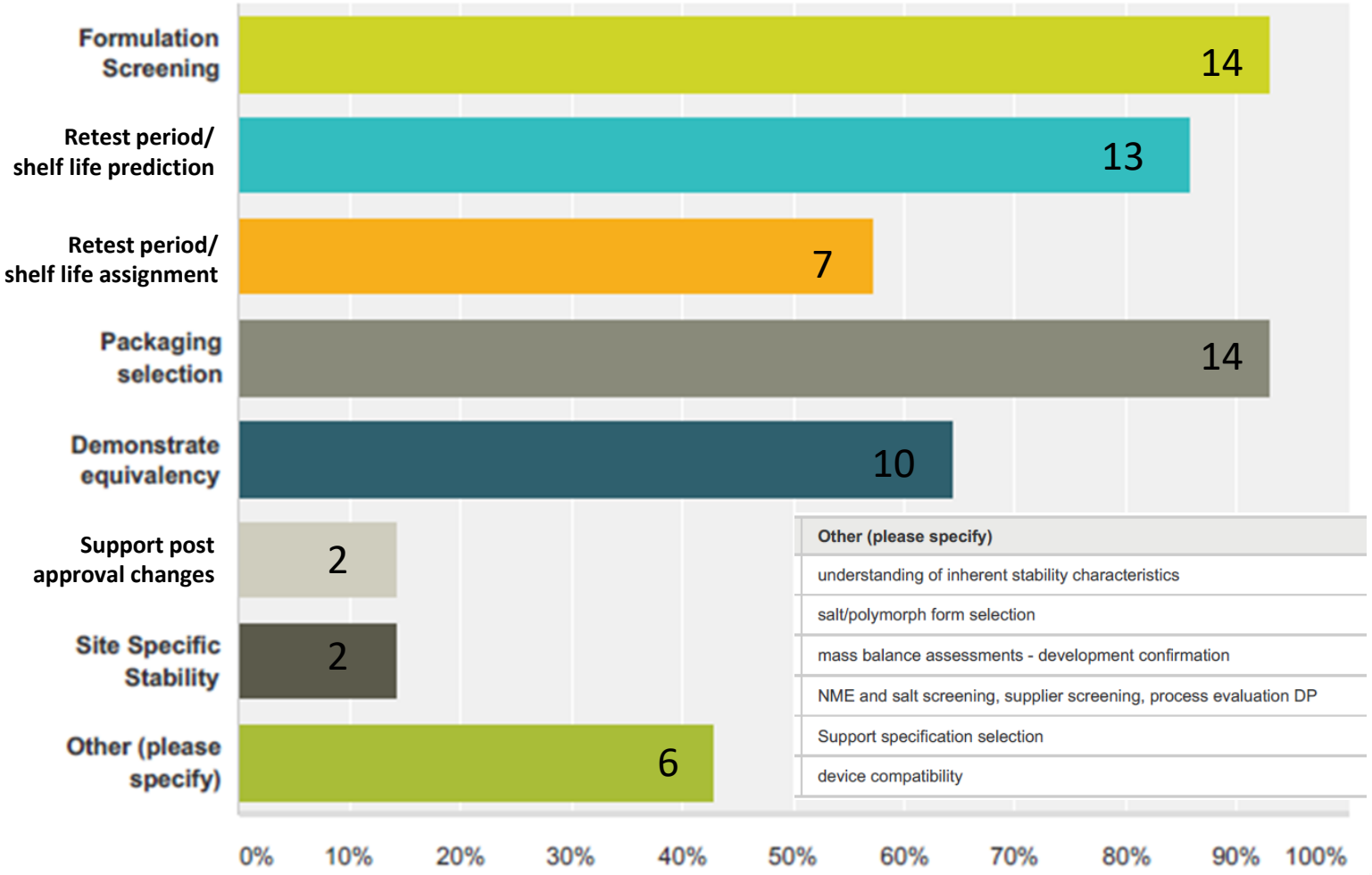
Back-up

RBPS Survey Details

- 82% (14/17) have used risk based predictive stability designs
  - 93% Small Molecules
  - 21% Large Molecules
- Types of materials studied



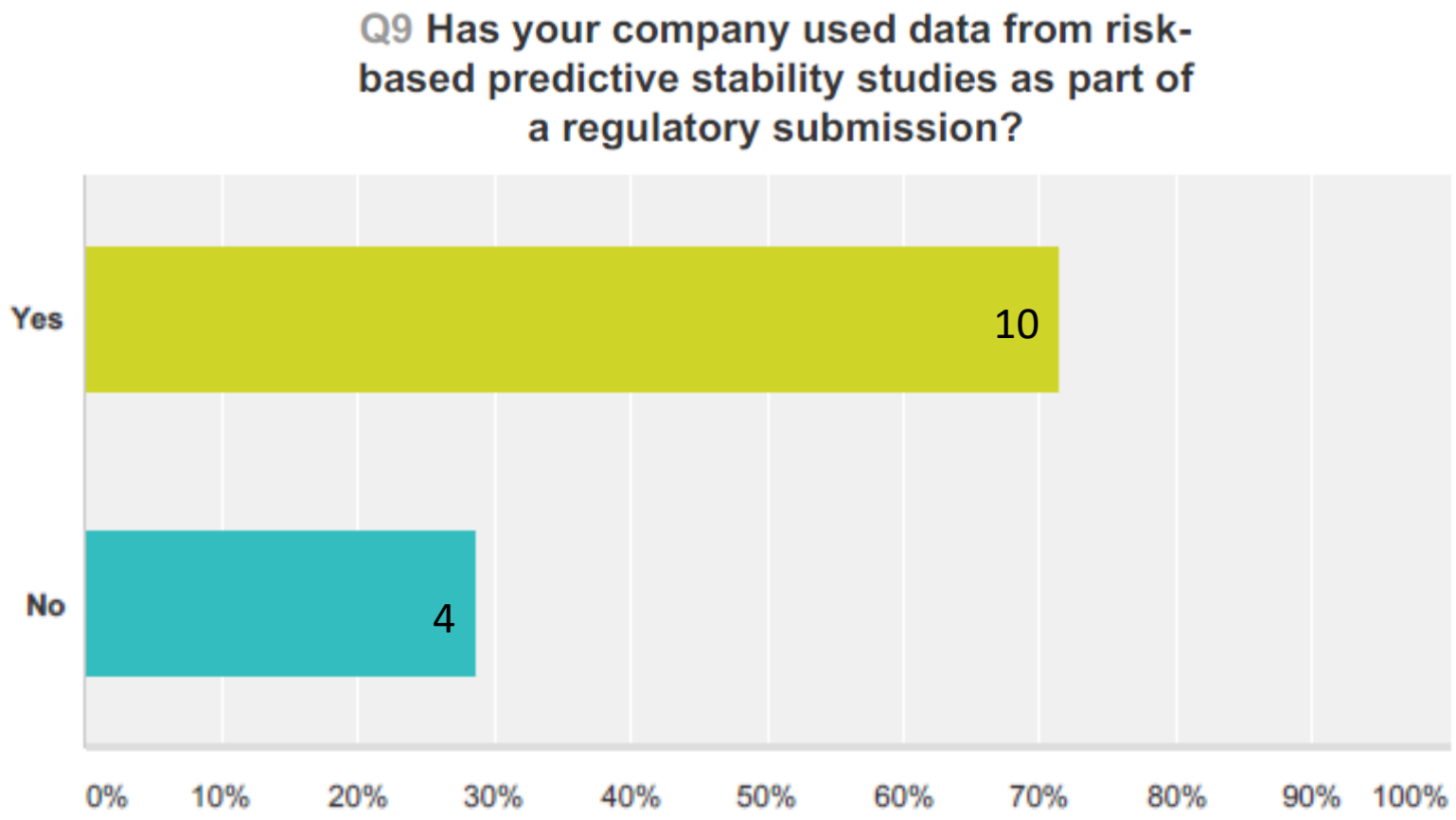
RBPS used in a variety of applications



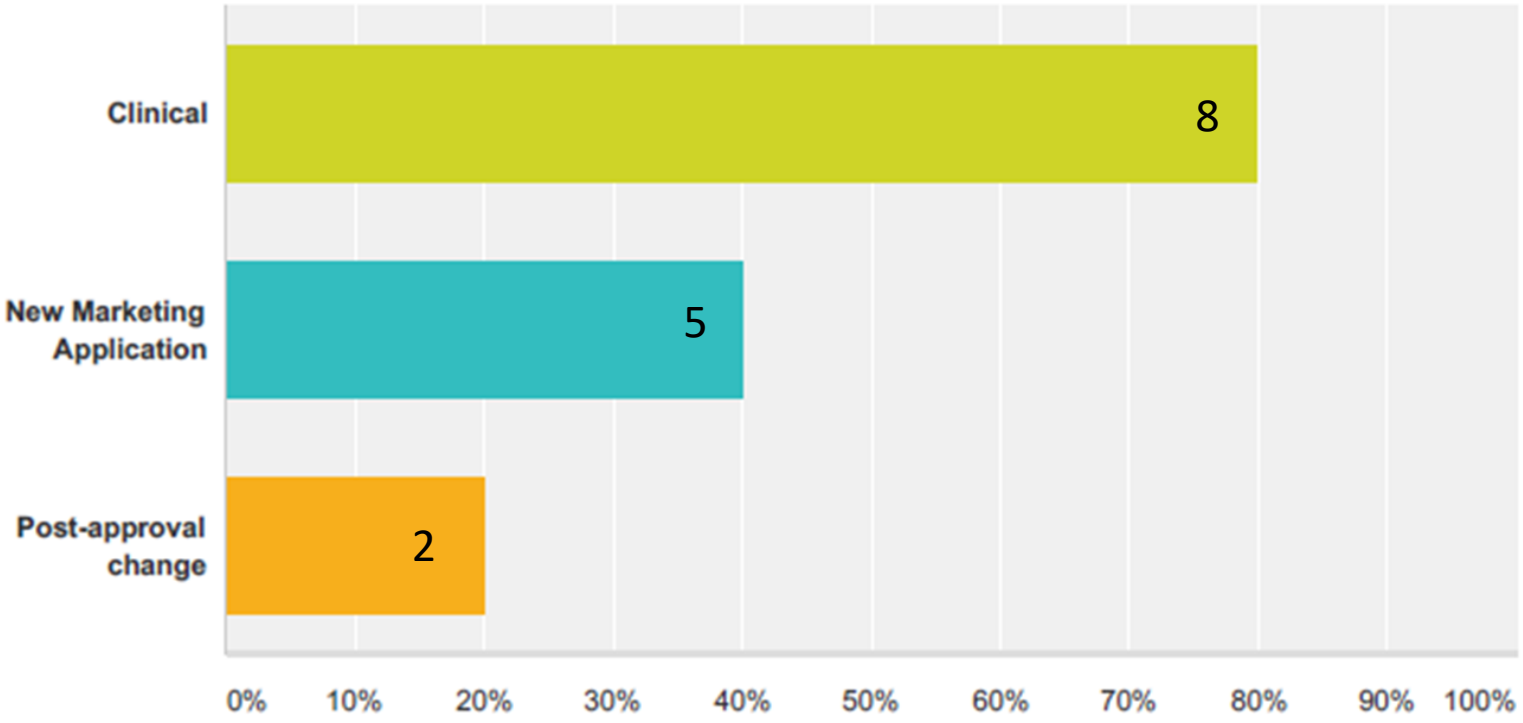
RBPS Modeling

- Types of Models
  - At least 8 of the companies :“typical” ASAP studies
  - at least 2 of the companies: in house predictive statistical approaches
- Moisture Vapor Transmission Rate
  - 11 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.
  - 4 (or 5) of these companies also utilized MVTR data and the resulting predictions in regulatory submissions
- What types of things are modeled
  - 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 modeled.

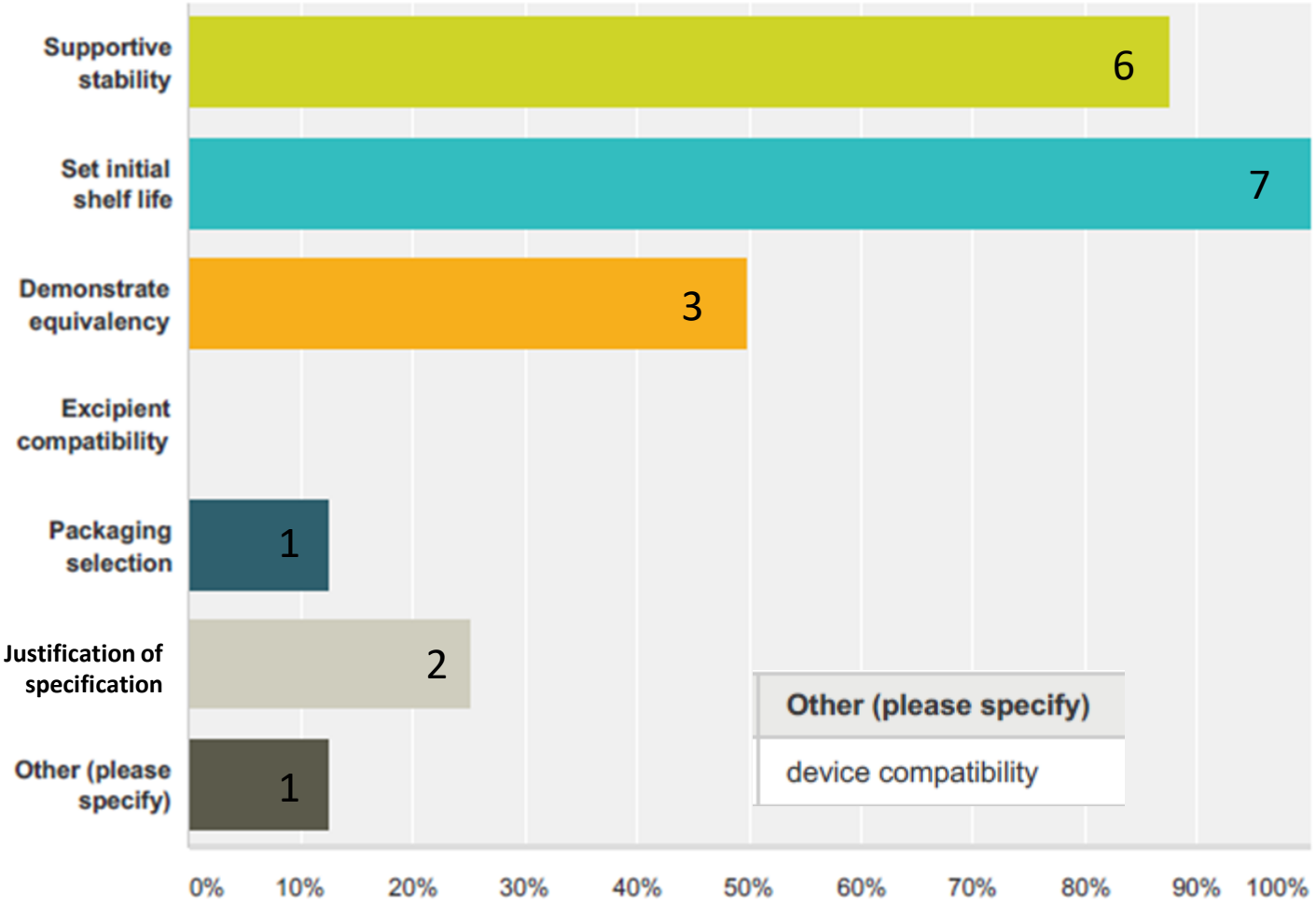
RBPS in Regulatory Filings



Regulatory focus of RBPS in Filings



Regulatory purpose of RBPS in IND/IMPD filing



Verifying Results of RBPS in Clinical Development