

# Global Regulatory Requirements for Stability: It's Not Such a Small World After All

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CASSS CMC Strategy Forum

Amy St. Charles, January 27, 2020



**BioTherapeutics Pharmaceutical Sciences**

 **Pfizer** WORLDWIDE RESEARCH, DEVELOPMENT AND MEDICAL



# Presentation Outline



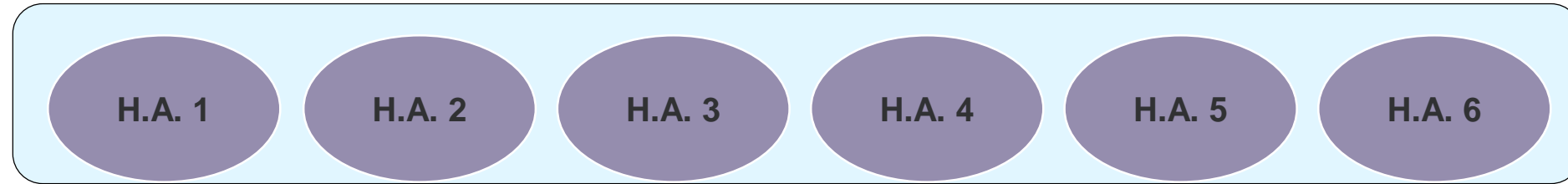
- Abstract:

The ICH gives guidelines on how to set-up and perform stability testing in order to support commercial expiry, however, the recommendations are more suitable for Zone 1 & 2 countries. Therefore, it can be challenging designing and implementing stability studies that satisfy all country application requirements while still adhering to a lean stability approach. This presentation will highlight two examples of stability challenges related to global filing applications

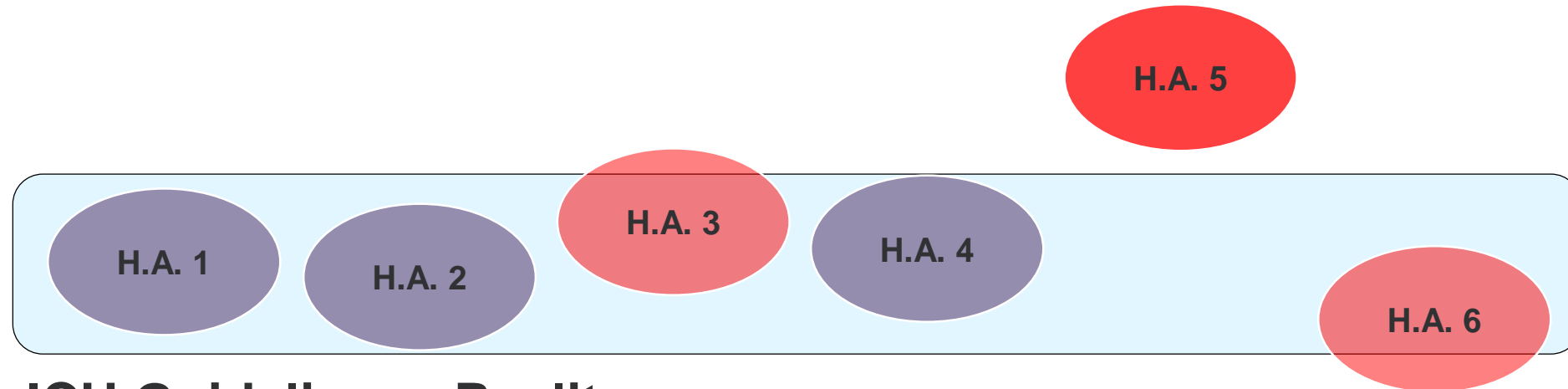
- Temperature Excursion Stability IQ Working Group
- General Global Filing Challenges
- Conclusion



# Not All Health Authorities Are Aligned With ICH

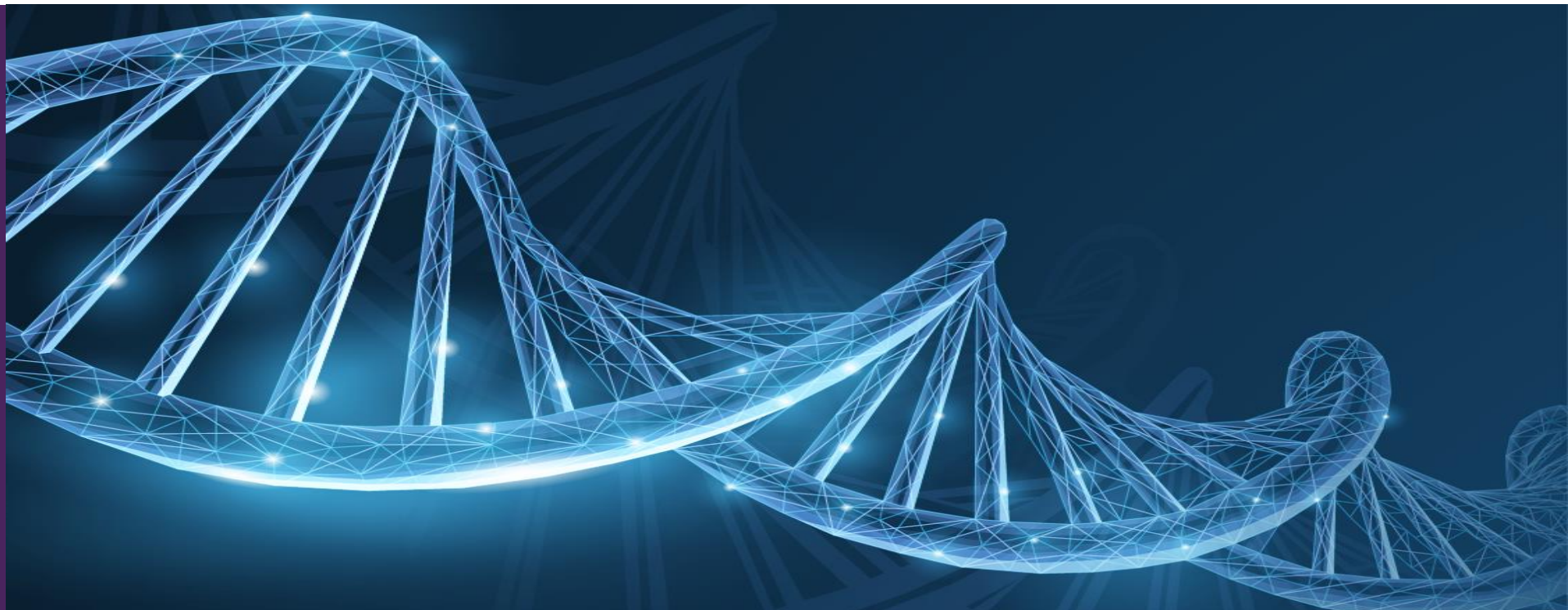


## ICH Guidelines - Ideal



## ICH Guidelines - Reality

# Temperature Excursion Stability Working Group



# Shipping & Temperature Excursions



**Challenge:** Countries are requesting stability studies to support shipping excursions beyond what is required by ICH

- TGA (Australia) and ANVISA (Brazil) guidelines want stability studies to reflect real-life conditions for shipping and temperature excursions.
- How best to incorporate these studies with requirements for other markets (US/EU/J/Asia) and translate into real-life experiments and stability test plans
- Is there a possibility to achieve all/most agency expectations with a more standardized and efficient platform approach



# ANVISA Regulations



**Background: ANVISA (Brazil's Regulatory Authority) has enacted regulations requiring additional temperature excursion data for refrigerated biologics (RDC Resolution No. 50, September 20, 2011 DOU Sept/22/2011).**

- Evaluate what excursions may occur during distribution
- Simulate excursions to evaluate the impact to the quality of the finished drug product
- Establish the freezing point of the drug product
- Conduct a simulation study with at least one lot of finished biological product (New guidelines are now proposing at least three lots)
- Test/monitor the exposed drug product until the end of shelf life via stability studies with at least annual timepoints



# TGA Regulations



## Background: Regulations from Australia's Department of Health Therapeutic Goods Administration (TGA)

(Stability testing for prescription medicines V1.1 March 2017)

- Justify you are using worst-case shipping conditions and container
- Data for justifying any temperature excursion includes real time studies of the proposed excursion, followed by return to normal conditions, for the entire shelf-life of product
- Temp cycling of 3 DP lots at commercial scale (Below and above condition, multiple cycles)
- Duration of cycles should mimic or exceed likely duration of shipping excursion
- End to End: Cycle at the beginning and assess at end of shelf



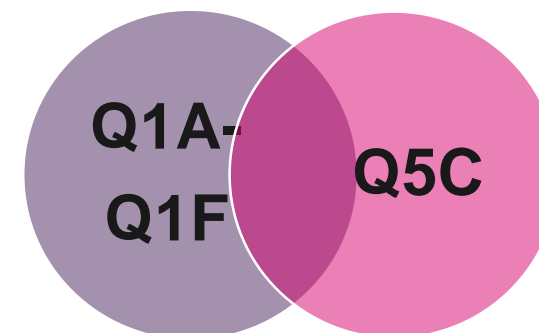
# Comparison Against ICH Guidelines



## ICH Guidelines General Stability requirements)

Condition	# Batches (DS) or # Lots (DP)
Intended Storage (Long Term)	3
Accelerated	3
Thermal Stress	1
Photostability	1
Thermal Cycling*	1

\* NOTE: Thermal Cycling is not required by ICH guidance, however these studies should be carefully considered to support filed claims and are highly recommended



Cannot be utilized to justify shipping excursions

Recommended that 3 Batches/Lots Be Used Per Study

Cycles to represent worst case scenario and then return to intended storage





INTERNATIONAL CONSORTIUM *for*  
**INNOVATION & QUALITY**  
*in* PHARMACEUTICAL DEVELOPMENT

This presentation was developed with the support of the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ, [www.iqconsortium.org](http://www.iqconsortium.org)).

IQ is a not-for-profit organization of pharmaceutical and biotechnology companies with a mission of advancing science and technology to augment the capability of member companies to develop transformational solutions that benefit patients, regulators and the broader research and development community.

# Biologics CMC Leadership Group Mission

To identify challenges that are impeding the progress of biologic development, including mAbs, other protein therapeutics and vaccines, and share information on cross-industry best practices to proactively advance innovative, science and risk-based phase-appropriate strategies for process and testing controls, and justify approaches to enable alignment with regulatory bodies.

# IQ Temperature Excursion Working Group:

## Membership:

Frank Wiegeshoff (AbbVie): Co-chair

Amy St. Charles (Pfizer): Co-chair

Claudia Arana (BMS)

Giovanna Camanella (GSK)

Bryan Castle (Eli Lilly)

JunYan (Andrea) Ji (Genentech)

Ranjini Kaushik (Amgen)

Elisabeth Krug (Eli Lilly)

Malte Meppen (GSK)

Bob Rozaieski (Merck)

LG Sponsor Martin Gastens (AbbVie)



# IQ Working Group: Mission

## Establishment

- IQ Exploratory Group Kick Off: Early 2018
- Approved IQ Working Group: Mid 2018

## WG Mission:

The Temperature Excursion Stability Working Group aims to provide industry with a common understanding on how to interpret and translate the current temperature excursion (TE) regulatory requirements from Brazil and Australia into real-life experiments and stability test plans.

# IQ Working Group: Outline of Activities

Review available literature for guidance  
(TGA, Brazil, ICH, EBE etc.)



Define draft questionnaire and  
select optimal audience



Gather test input from  
working group team



Revise/adapt based on dry  
run results

Conduct "real" survey with  
broader internal teams



**Analyze data**

**Outputs:**

Publish results via IQ  
site / results only

Written consensus  
paper for members

Interact with  
Regulatory Agencies

Phase 1

Phase 2

# IQ Working Group: White Paper Deliverables

- Common understanding & interpretation of the Brazil and Australian guidelines
- Combine EU/US/ROW requirements with Brazil and Australia
- Experimental setup for TE studies for respective phase (e.g. clinical or market application purpose)
- Strategy on study design (e.g. number of lots, representativity of used lots, sample size, test plan)
- Utilization of survey tool to get insights from participating companies
- Second phase alternative strategies: What could be a future proposal for TE studies to fulfil agency expectations (e.g. Arrhenius approach or use of historic data).

# Learn more about IQ

For more information about the IQ Consortium's past work and current activities, we invite you to review the following resources.

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IQ Website

<https://iqconsortium.org>

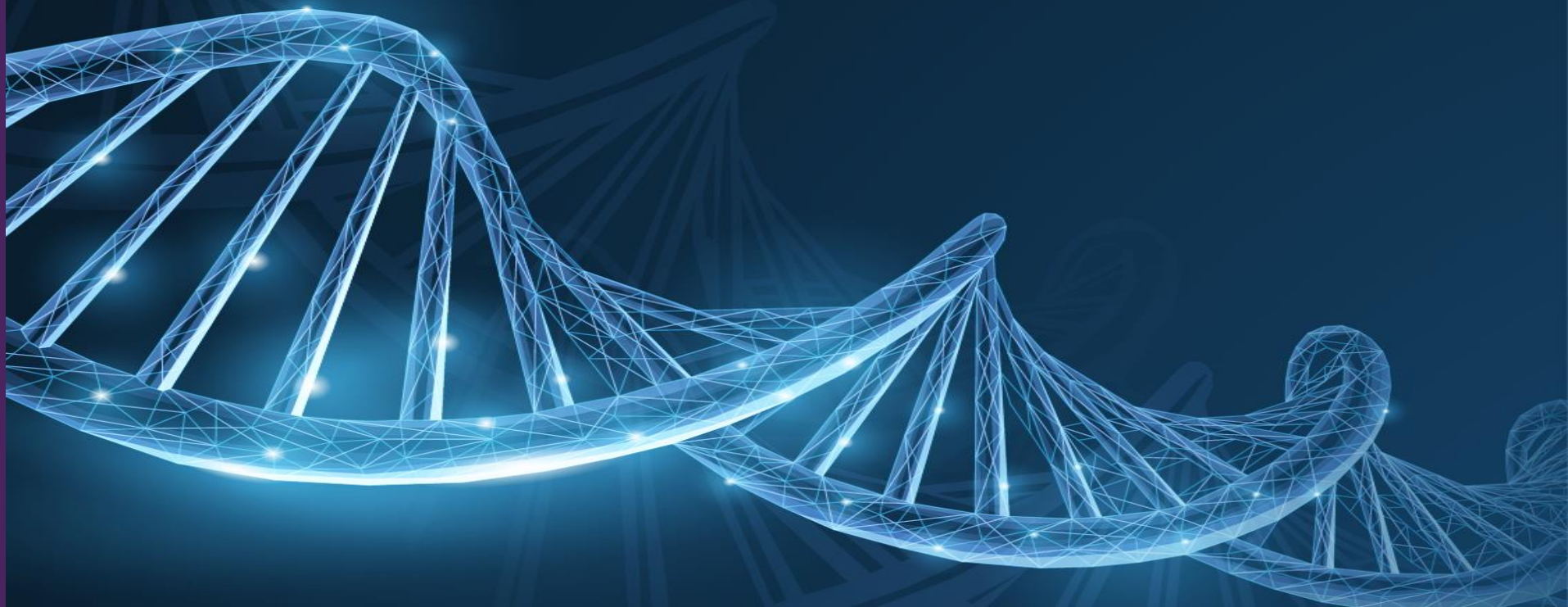
IQ Annual Report 2018

<https://iqconsortium.org/annual-report-2018>

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To find out how your company can join the IQ Consortium or if your company is already a member and you would like to get involved, please email us at [info@iqconsortium.org](mailto:info@iqconsortium.org).

# General Global Filing Challenges



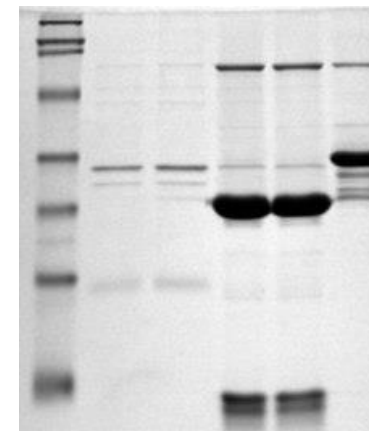
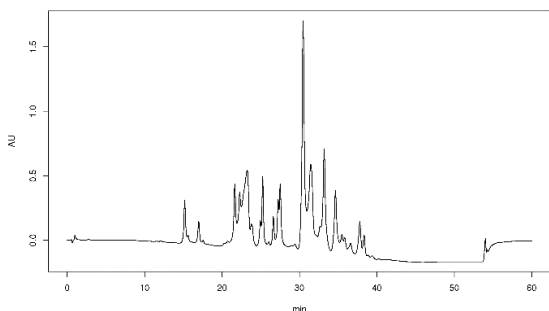


# Global Filings



## Challenge: How to best manage the Rest of World submissions

- Various countries have requirements for submission that may be different than or in addition to what was provided in original submission (e.g. BLA)
- The additional requirements may include requests such as raw data (chromatograms, electropherograms, gel stains, etc.) that spans the lifetime of the product
  - This can be applied to pre-commercial filings as well as commercial
- These requests can be very resource intensive



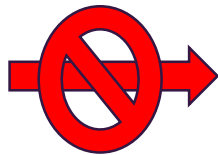
# Global Filings



Critical to consider timing of the ROW submissions

- Additional risks, expanded timelines and increased resources are to be expected
- Communication of these risks and additional requirements need to be factored into business strategies

Global harmonization is the dream, but for now, each filing will be unique and present its own challenges



# Conclusions



## Stability is a continued focus for regulatory agencies:

- Regulations are changing and evolving (not necessarily aligning)
- Requirements for submissions can be country specific
- Further regulatory discussions will facilitate a harmonized approach





# Questions

