Use of ASAP*prime*® in Regulatory Filings

FreeThink Technologies, Inc.

Outline

- Overview
- Pre-Clinical
- Early clinical trials (IND)
- API, reference standards
- ASAP and QbD
- ASAP in NDA (sNDA) submissions
- ASAP in ANDA submissions
- Post-approval change

Overview

- ASAP*prime*® has been successfully used as part of regulatory documents
- ASAP replaces/supplements standard methods for meeting regulatory obligations
- **FreeThink can help**
  - **Key references**
  - **“Talking points”**
  - **Responses to queries**
  - **Meetings with regulatory authorities**

Agency Awareness

- Presentations made to many country agencies
- Specific countries we are aware that presentations have been made:
  - US
  - Canada
  - UK
  - Brazil
  - China
  - Czech Republic

Pre-Clinical

- ASAP estimation of degradant level at end of shelf-life used to guide what specification limit to request with authorities
  - Allows regulatory groups to determine what to request
  - Supports requested levels

API and Reference Standards

- **ASAP-only used to set 1-year retest period**
  - No reported regulatory issues in US
  - Expect acceptance world-wide
  - Note that patient safety is not at risk since the drug product will get tested—stability testing is part of product control and understanding

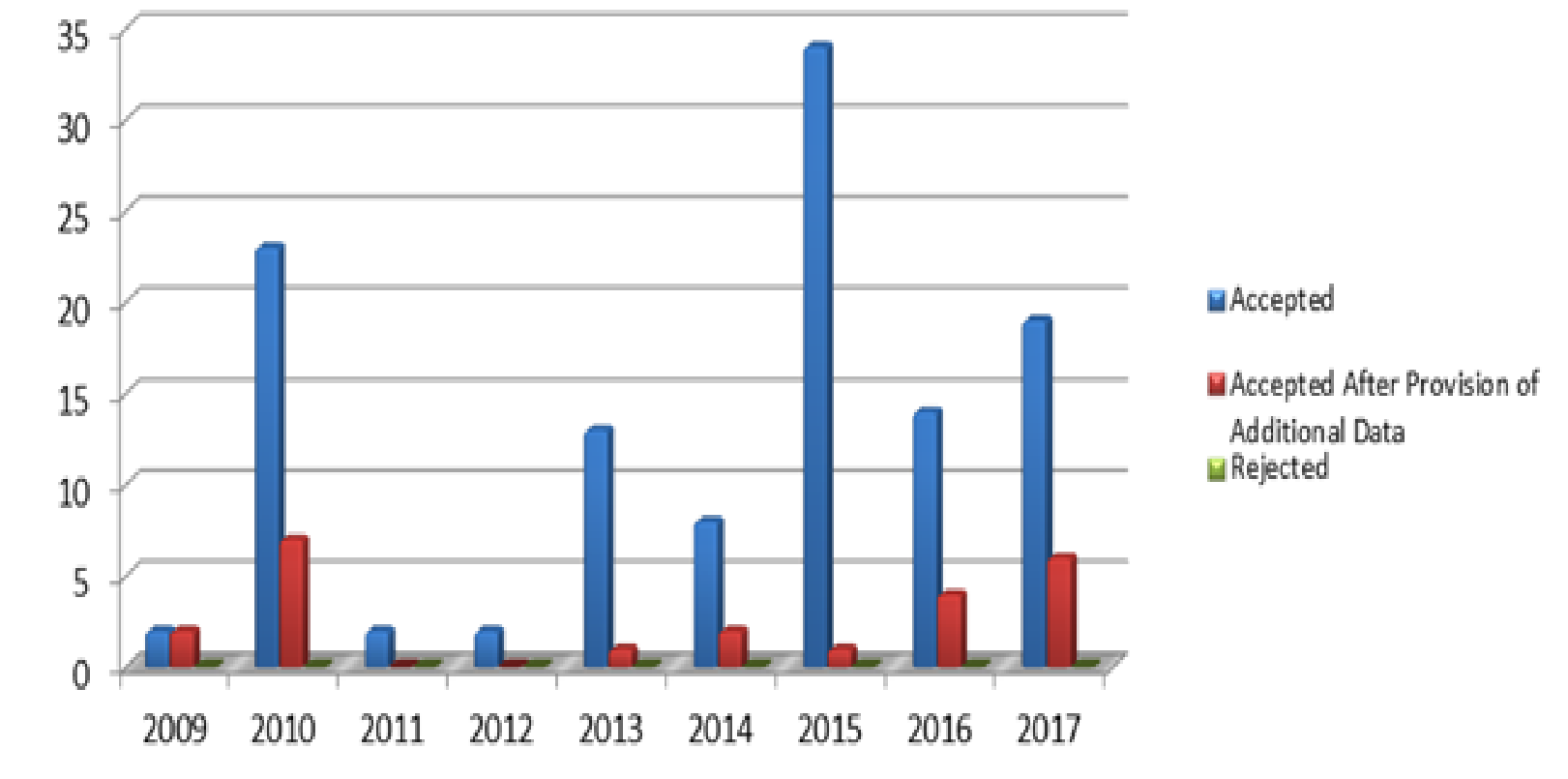
Early Clinical Trials—IND's, Generics

- **ASAP only** using prototype formulations to justify 12-month use-period
- Date clinical supplies for 12-months (if >95% probability of passing under storage conditions)
- Place clinical material on standard ICH stability protocol
  - Only analyze if queried

Early Clinical Trials—IND's, generics

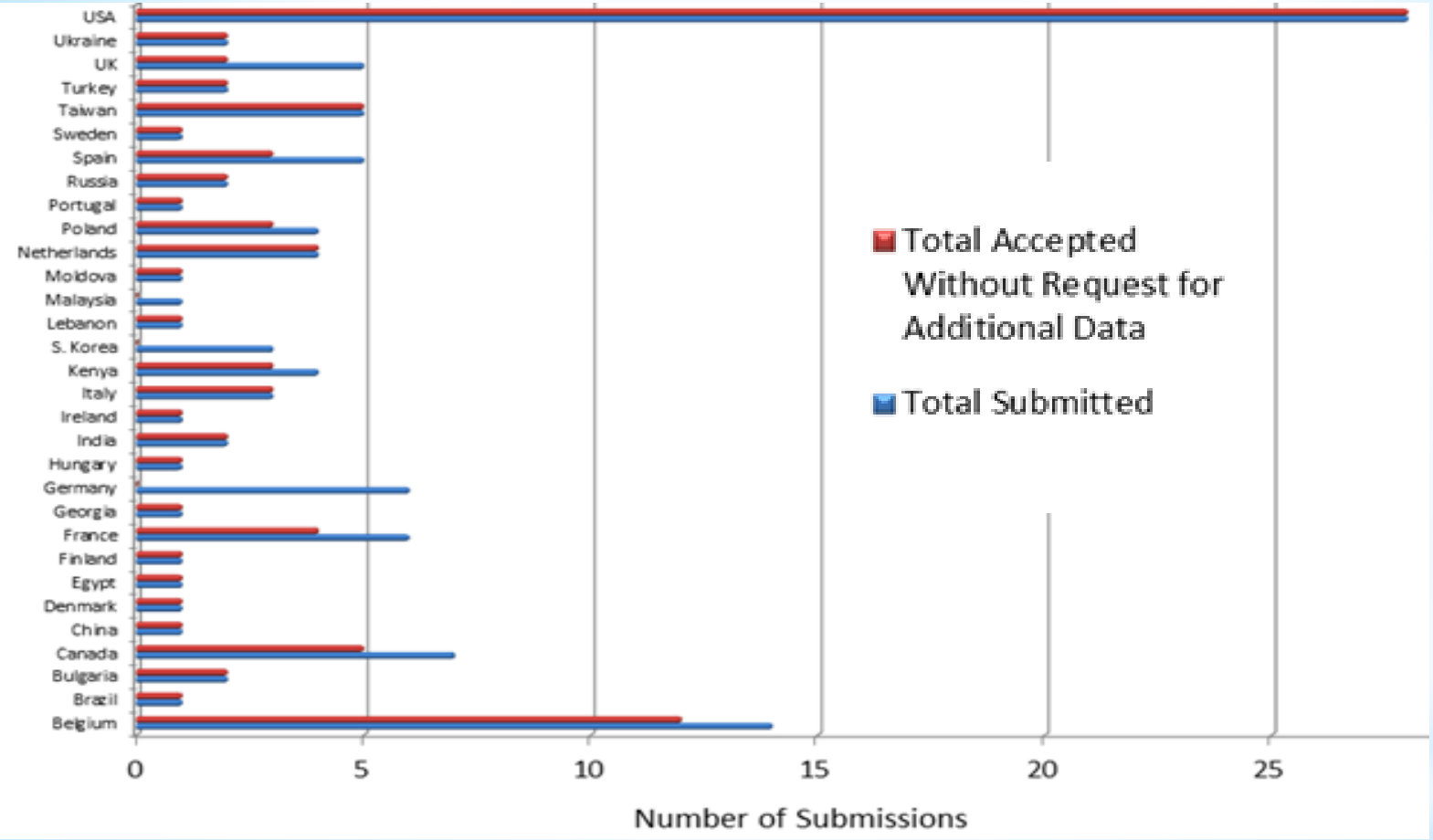
- >10 Companies have employed this strategy
  - Pfizer, AZ and Janssen (Johnson & Johnson) have discussed this publically
- Regulatory authorities in each case have the following options:
  - Make no comment—no further data required
  - Query the approach—need an explanation, more data
  - Reject and request traditional

ASAP Regulatory Experience (Clinical)



From F. Qiu presentation "Science of Stability Conference" Boston 2018

ASAP Regulatory Experience (Clinical) by Country



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ASAP under Quality Systems

- **FreeThink SOP's/practice**
  - Set-up of ASAP study including
    - Chambers
    - Salt solutions
    - Use of monitors
    - Sample handling pre and post stressing until testing
  - Calibration of monitors
  - Chambers
  - Analytical methods
  - Data handling
    - Empower III output as input to ASAP*prime*®
    - Algorithmic point/condition removal

ASAP under Quality Systems

- **GMP and use of ASAP**
  - Most companies do not conduct ASAP studies under GMP for IND's
  - Many companies use some part GMP for NDAs/post approval applications
    - Most only have GMP for analytical
    - Some outsource to FreeThink for regulatory filings

- ASAP*prime*® Validation
  - ASAP*prime*® fully validated and CFR11 compliant
  - Validation documentation available on request (no charge)
  - Starting 2019, IQ/OQ service will be available

ASAP and QbD

- Quality by Design (QbD) for stability requires understanding factors that influence stability
  - T, RH impact
  - Packaging impact
  - Lot-to-lot consistency
    - API lots
    - Excipient variability
    - Process variability

ASAP and QbD

- Can use ASAP to examine range of factors
- May not be able to scope all variables
- Quality by Testing (QbT) using ASAP may de-risk future changes
  - Run ASAP on product after changes to test impact
  - Establish change as minor change and therefore not needing full stability program

ASAP in NDA Submissions

- **ASAP used in registration packages world-wide**
- No ASAP-only NDAs
- ASAP used to bridge clinical to commercial changes

ASAP demonstrating validity of model against ICH data for clinical

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ASAP in NDA Submissions

- **ASAP plus 3 month ICH data successfully used to justify 3-year shelf-life at launch (EU)!**
  - **Note: commitment to ongoing monitoring of commercial material**

- **ASAP used to justify specification limit change successful in EU**

ASAP in ANDA Submissions

- Show generic product in its packaging is at least as stable as originator in its packaging
  - Easier to show statistical equivalence with ASAP
  - Especially helpful when specification limits not known

Post-Approval

- Companies have **successfully** used ASAP-only submissions for reduced-protection packaging without other (new) data
  - US only (so far)
- Justification for acceptance after shipping excursions

Summary

- ASAP can play a significant role in meeting regulatory obligations
- ASAP provides understanding which improves filings
- In some cases, ASAP can replace ICH stability studies
- When ICH stability studies needed, they can be minimized (confirmation only)