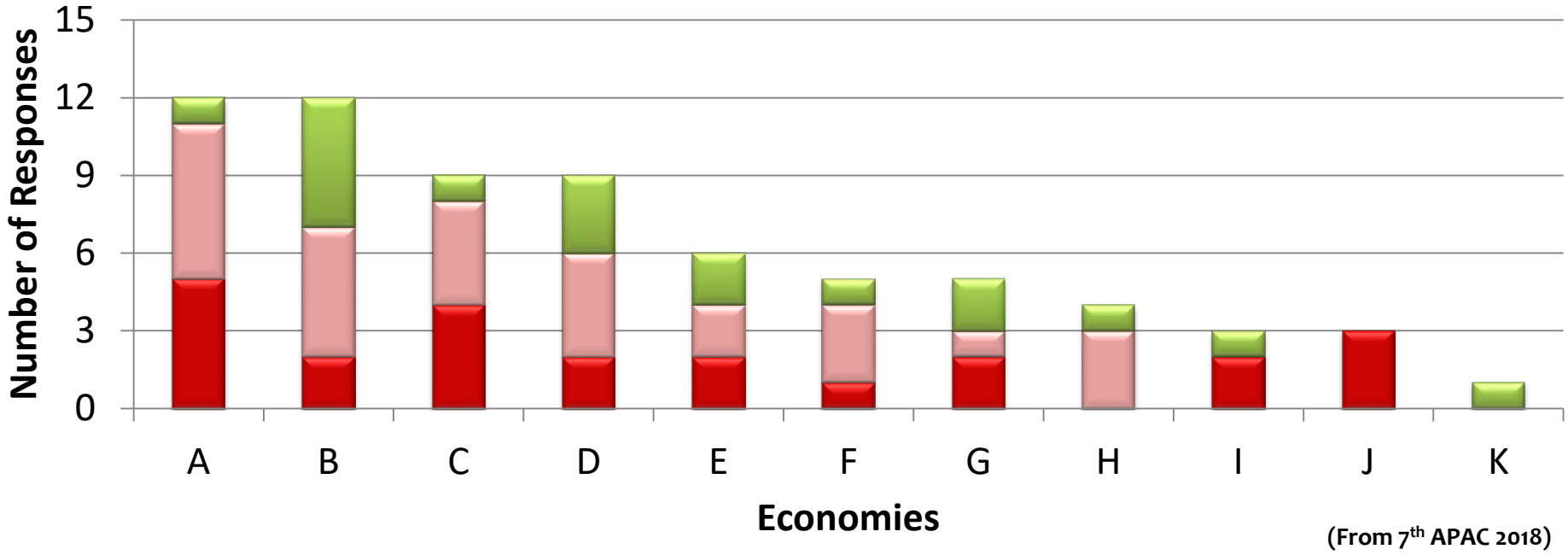
ATIM Session:
Stability Data Requirement for Post-Approval Changes

- To achieve the APAC mission, in the last ATIM TF picked up a topic on the change control systems in Asia and shared current situation of each region
- After analyzing provided information, the ATIM TF picked a topic on post-approval change procedure focusing on the stability data requirements
- JPMA ATIM TF made an approach to accomplish APAC mission by proposing "Position paper on efficient CMC/GMP for Access to Innovative Medicine" and invites leading ASEAN regulatory agencies to discuss on the Stability data requirements through the Panel discussion
- ATIM TF believes if the stability data requirements would be handled by science-base and risk based approaches, it will bring efficient use of time and resource to review the change proposals and reduce the stock out risk in the patients in Asia.

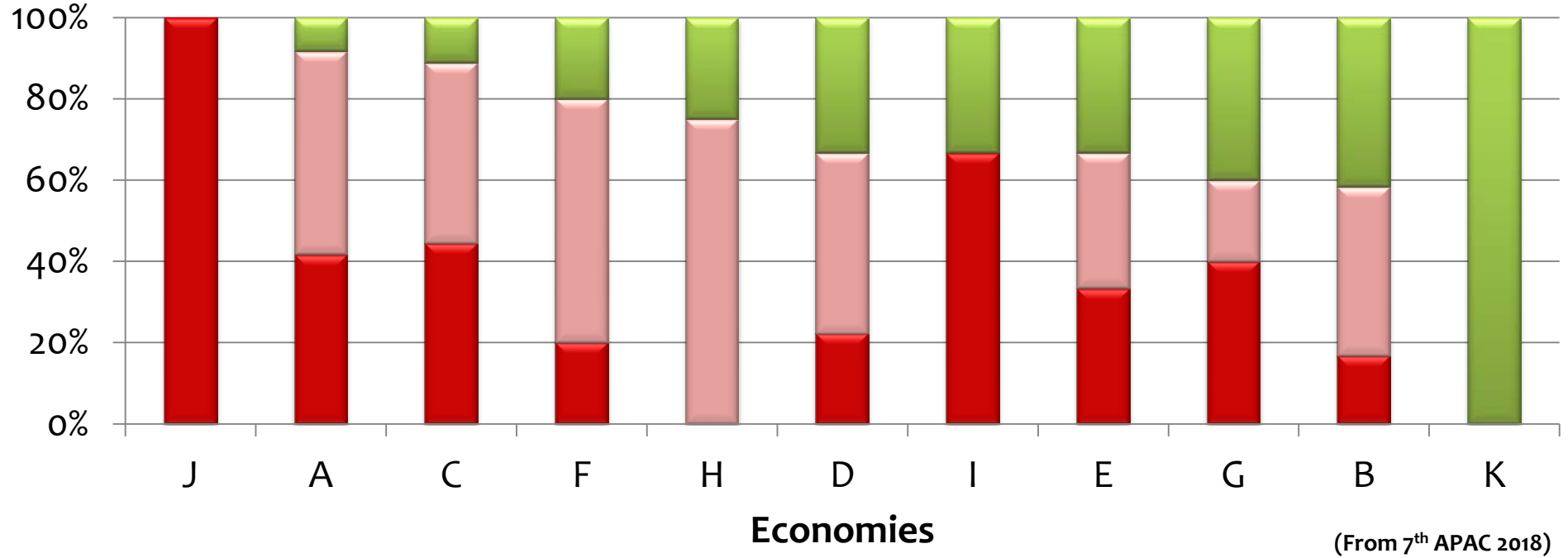
Topic In Change Control Submission in Asia (From 7th APAC 2018)

- **Purpose:** For the convergence of change control management in Asia, JPMA conducted a survey for the topics that were encountered for the quality / CMC related topics
- **Response:** Members of Asian Committee, International Affairs in JPMA (36 companies)
- **Questions:**
  1. Regarding additional request and document for Stability Study (At the time of new submission or post-approval change)
  2. Regarding site addition or formulation change
- **Scope of Time Range Covered:** Examples between 2014-2018

Number of Responses for Each Topic



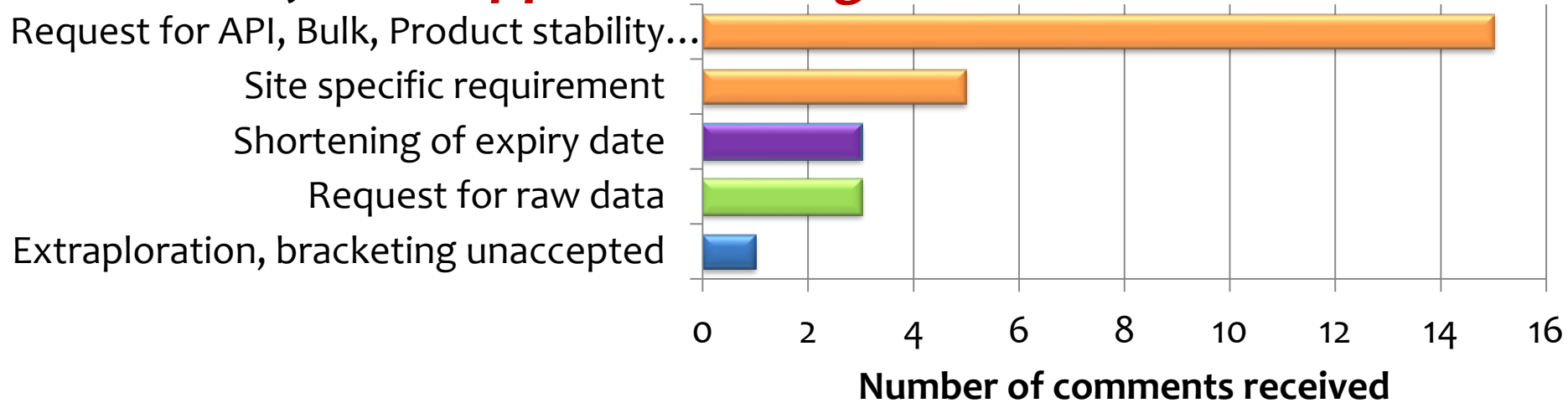
Ratio of Responded Topics for Each Country



(From 7th APAC 2018)

- Total / Specific request at the time of post-approval change of site or formulation
- Total / Additional stability data at post-approval change
- Total / Additional stability data at the time of new submissionNDA

Topics Related To Stability Study Data At The Time Of Post-Approval Change Submission



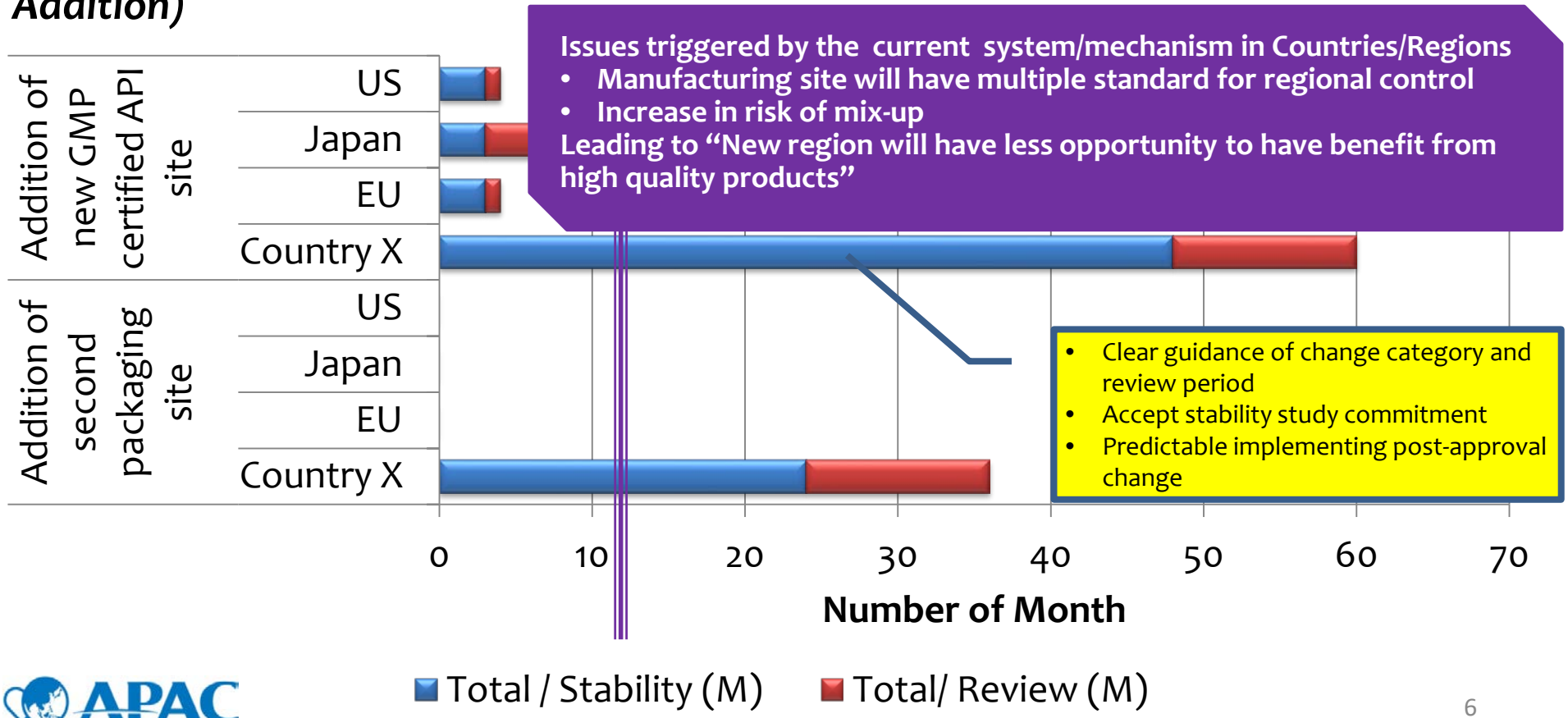
- ✓Drug product stability data using changed API was requested
- ✓Request for certificate of analysis for "upright stored" product and "near expiry date" in-use test result
- ✓Bracketing stability was not accepted, and stability data for all packaging configuration was requested

- ✓Expiry date was shortened because there was no 3 lots of long-term stability data
- ✓Content of stability data report according to ASEAN stability study GL was not fully endorsed. As a result, expiry date was shortened.

- ✓Raw data for chromatogram was requested
- ✓Raw data for all stability study was requested

(From 7th APAC 2018)

Case Study On Timeline To Implement Post-Approval Change by Region (For Secondary Packaging Site & API manufacturing Site Addition)



Industry Perspective For Convergence Of Post-Approval Change Procedure

- Introduce **science-base and risk-base approach** for change review process for efficient use of resources such in WHO guideline
- Seek an opportunity to **adopt ICH Q1A stability approach** to enhance and promote continuous improvement of the product and lower the level of introducing new innovative medicine to the patient
- Consider to implement **mutual understanding and commitment approach**, to conduct efficient stability and change management, using the tools such as Post-Approval Change Management Protocol (PACMP)
- Examine Support Biopharmaceutics Classification System (BCS) of medicinal products and provide recommendation to **support waiver of bioequivalence studies**

Presentations From Last APAC Meeting

Overall Impression from last year;

- **Participating countries shared the conditions required for change management** (cases for API process change, API site change, DP formulation change, DP primary packaging change)
- In all, for those countries belong to **ASEAN followed the contents in the ASEAN variation guidelines**, however, there are some regional requirement that have **slight gaps in the requirement**

- For the intend of this APAC, the ATIM task force have asked the participants to give their country's practice weather **Post-Approval Change stability commitment is accepted or not**.

ASEAN VARIATION GUIDELINE FOR PHARMACEUTICAL PRODUCTS

2. Purpose

- Provide **recommendations on the core stability study package required for drug products**, but leaves sufficient flexibility to encompass the variety of different practical situations…specific scientific considerations and characteristics of the products...

3. Scope

- This guideline addresses the information to be submitted during application…in ASEAN Member States including examples of a protocol of stability study, a report format, reduced design and extrapolation of data…
- The drug products covered in this guideline include **NCE, Generics and Variations (MaV and MiV) but exclude biologicals and drug products containing vitamin and mineral preparations.**

ASEAN GUIDELINE ON STABILITY STUDY OF DRUG PRODUCT

4.6 Testing Frequency

- **Reduced designs**, i.e., matrixing or bracketing, where the testing frequency is reduced or certain factor combinations are not tested at all **can be applied, if justified**

4.7.9 Variations

- Minimum Time Period Covered by Data at Submission - 6 months

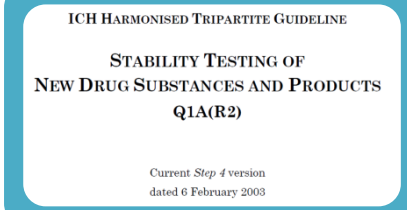
4.11 Stability Commitment

- When available long term stability data on primary batches do not cover the proposed shelf-life granted at the time of approval, a **commitment should be made to continue the stability studies post approval** in order to firmly establish the shelf-life. 5.3 Reduced design (Bracketing and Matrixing)

ASEAN GUIDELINE ON STABILITY STUDY OF DRUG PRODUCT In General

- ASEAN Variation Guideline and ASEAN Stability Guideline both reserves conditions considering each countries' regulation
  - Determine change control categories
  - Authorize to have additional requirement, if needed
  - **Recommendations not mandatory/agreed requirement**
- If ASEAN participating **countries can commit the stability study condition at the time of variation as given in the guidelines**, not referencing to as recommendation, it will bring harmonized understanding of the conditions and data submitted for the stability study data
- In addition, if the countries have agreed to **accept matrixing and bracketing based on the similar science- and risk-base approach condition**, this will bring larger benefit for the regulatory review process efficiency and stable supply from the industry

Tools for Convergence of Post-approval Change Control Stability Study

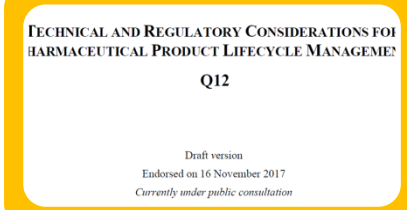

ICH HARMONISED TRIPARTITE GUIDELINE

STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS Q1A(R2)

Current *Step 4* version dated 6 February 2003

ICH Q1 series

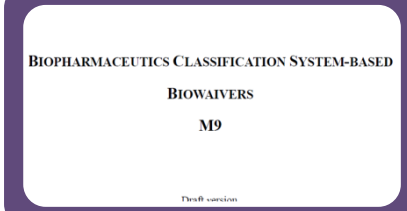
- Stability study program for new DS/DP
- Matrixing and Bracketing for Stability study


TECHNICAL AND REGULATORY CONSIDERATIONS FOR PHARMACEUTICAL PRODUCT LIFECYCLE MANAGEMENT Q12

Draft version
Endorsed on 16 November 2017
Currently under public consultation

ICH Q12 (under development)

- Product Lifecycle Management – Established Condition, PACMP
- Stability Data Approaches to Support the Evaluation of CMC Change


BIOPHARMACEUTICS CLASSIFICATION SYSTEM-BASED BIOWAIVERS M9

Draft version

ICH M9 (under development)

- Recommendations biopharmaceutics classification of medicinal products
- Support the waiver of bioequivalence studies

Position paper on efficient CMC/GMP for Access To Innovative Medicine

GOAL and ACHIVEMENT

APAC proposes the following recommendations for the post approval change procedure and **reduce burden for conducting most time limiting stability studies while keeping regulatory science justification**. Innovative medicines of comparable or improved quality can be supplied in a more efficient manner by:

- Introduce *similar* science- and risk-base approach for post approval change process.
- Implement mutual understanding and commitment approach for change management using the tools such as Post-Approval Change Management Protocol (PACMP) and Biopharmaceutics Classification System (BCS).
- Increase opportunities for dialogue and collaboration between industry and regulators to discuss integrated science- and risk-based approaches to stability.

Position paper on efficient CMC/GMP from ATIM

About GMP Qualification

- Asia Training Center
- SMF Template

Pharmaceutical Quality System

- Promote ICH Q10

CMC Registration

- Science-base and Risk-base approach
- Established Condition

Change Mgmt (CM)

- PACMP / BCS
- Use of Existing Data (ie Stability data)