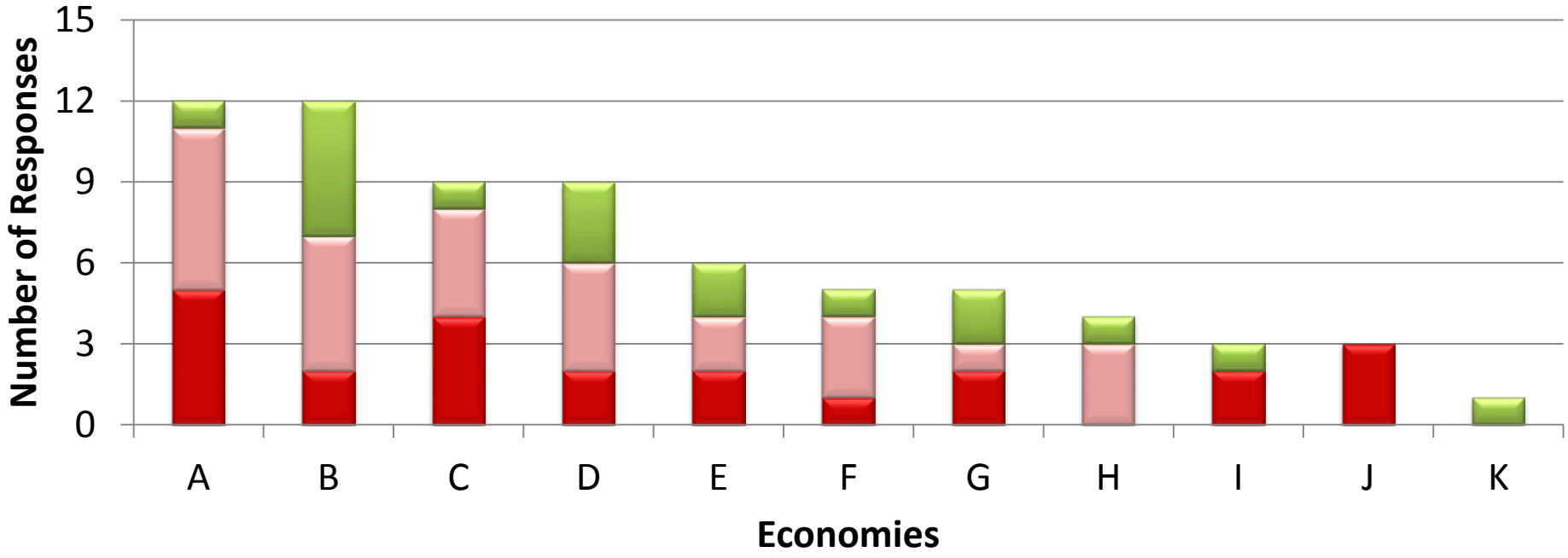
Topics Raised In Change Control Submission in Asia

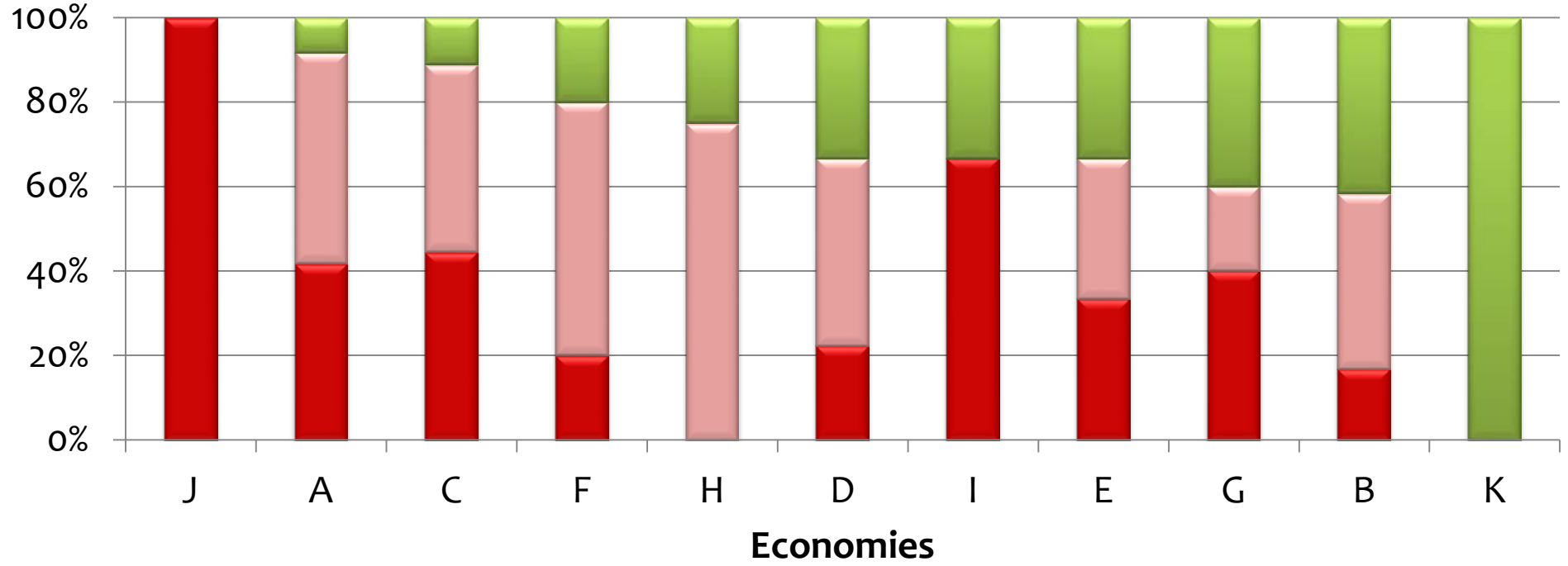
- **Purpose:** For the convergence of change control management in Asia, JPMA conducted a survey for the topics that were encountered for the quality / CMC related topics
- **Response:** Members of Asian Committee, International Affairs in JPMA (36 companies)
- **Questions:**
  1. Regarding additional 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
- **Countries / Region covered:** China, Korea, Taiwan, Thailand, Indonesia, Malaysia, Viet Nam, Singapore, Philippines, India, Hong Kong (11 countries / regions)
- **Responded companies:** 30

APAC

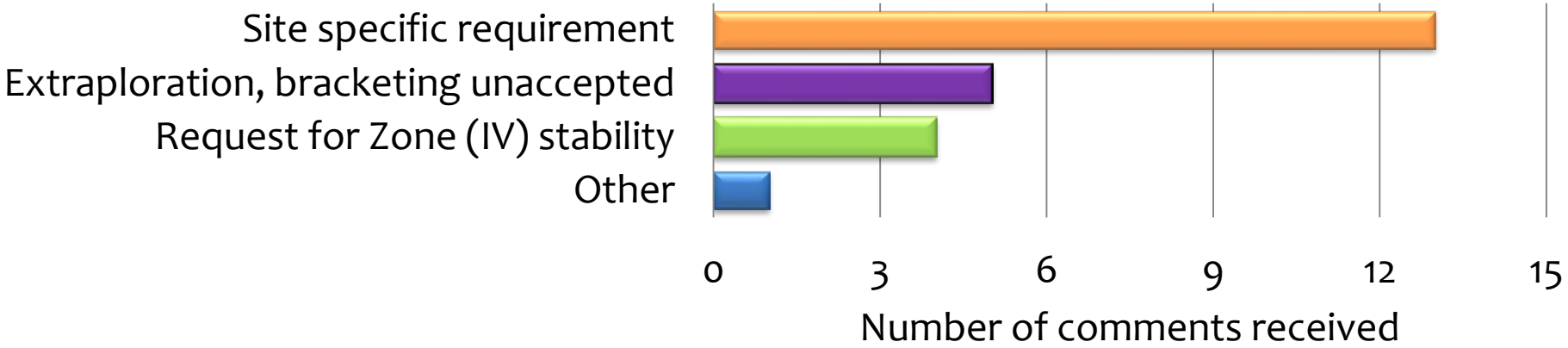
Number of Responses for Each Topic



Ratio of Responded Topics for Each Country



Topics Related To Stability Study Data Submission At The Time Of New Submission

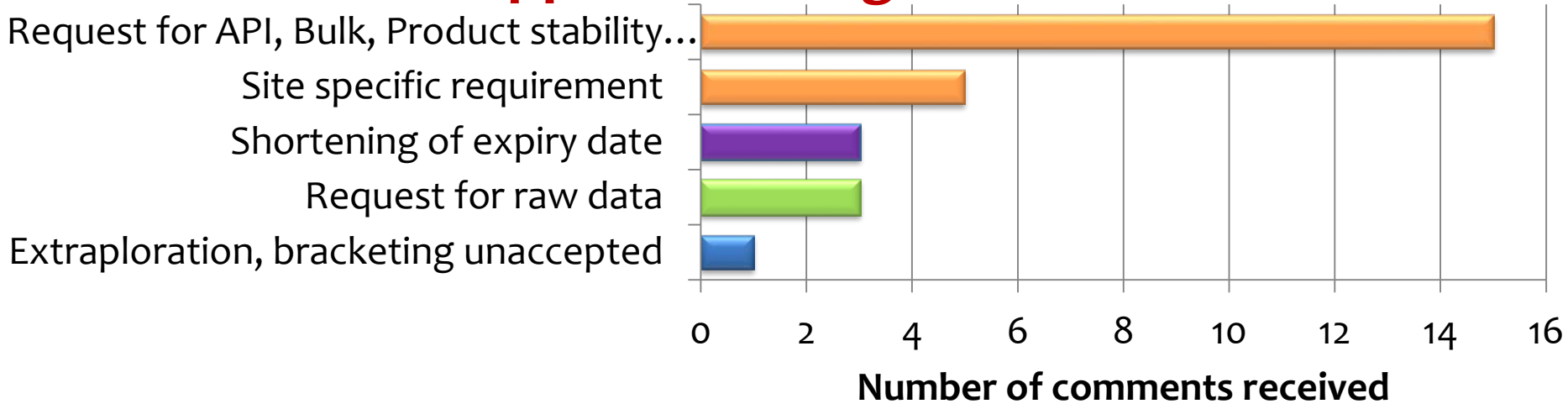


- ✓Stability data using the API and the Product at commercial scale in the newly registering site" were requested
- ✓Site specific stability (SSS) was requested but requirement was not clear
- ✓Site specific open stress stability test was requested

- ✓Bracketing stability study approach was not accepted
- ✓Real time stability study was requested; extrapolation data was not accepted
- ✓Commercial scale 12 month stability data was requested at the time of new submission

- ✓Zone IV(b) study was requested even if the temperature control was committed
- ✓Three lots of stability data was requested, even the if bulk tablet was coming outside of Zone IV (b)
- ✓ Final package stability was requested, which was not stipulated in ASEAN Guideline

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.

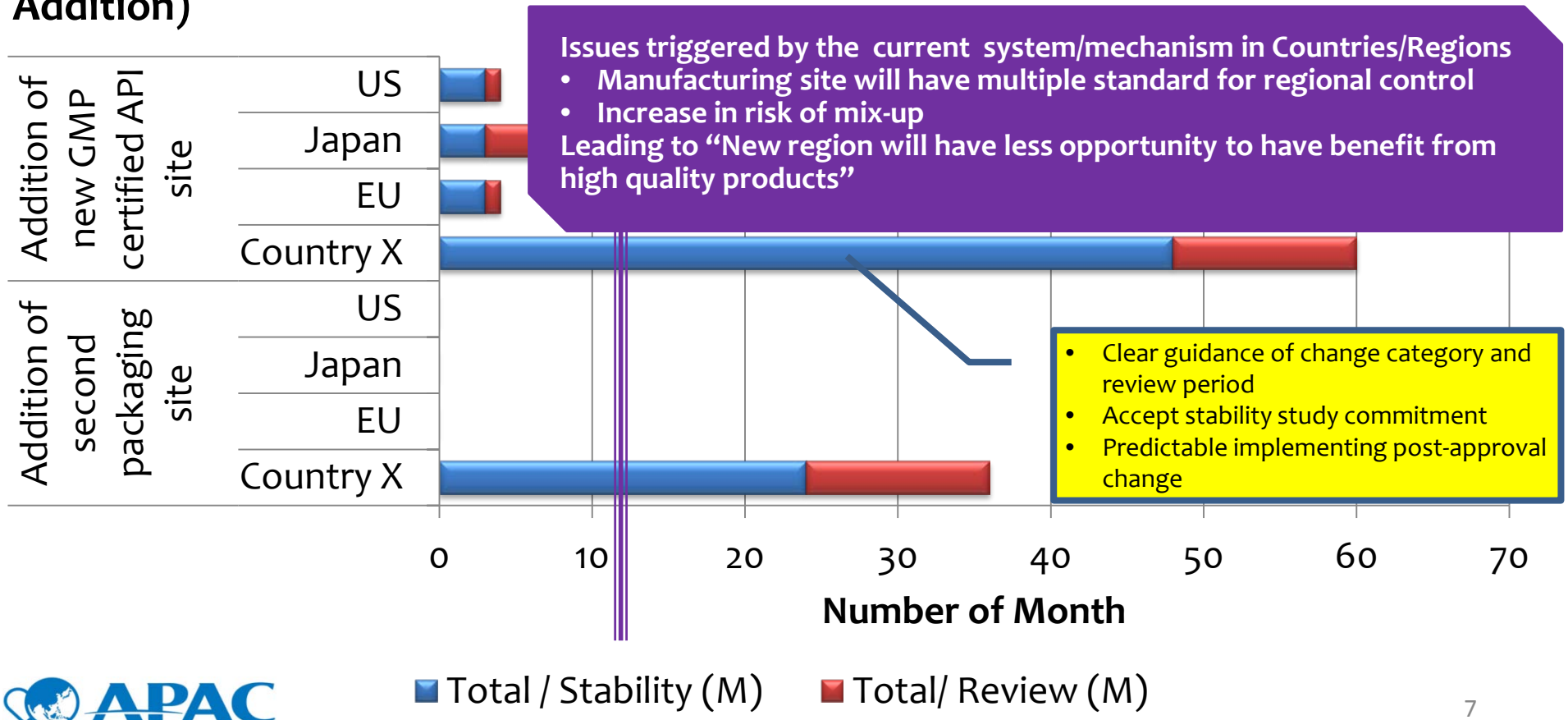
- ✓Raw data for chromatogram was requested
- ✓Raw data for all stability study was requested

(Tool)

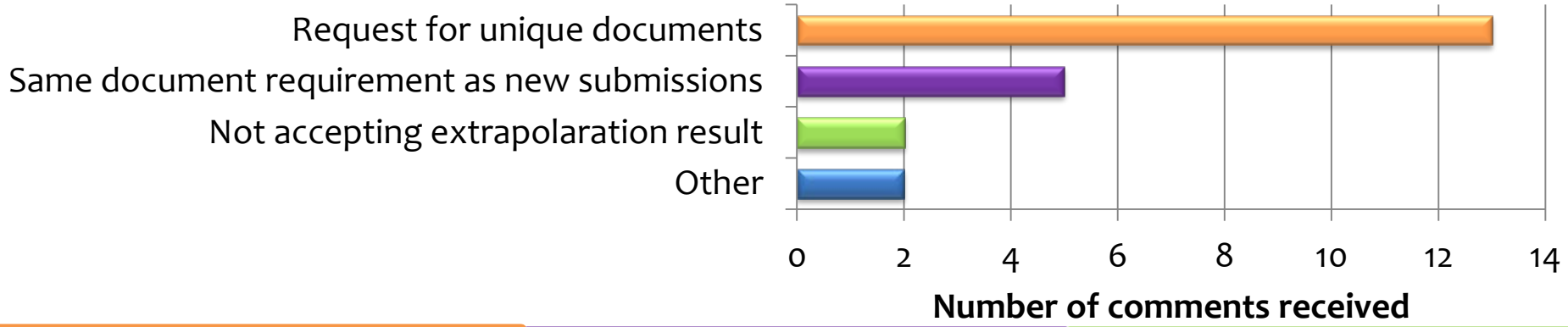
Post-approval CMC change Reporting Categories

Impact product quality	Japan	US	EU
High	Prior approval for changes	Major change (Prior approval supplement)	Type II variation (Application for approval of variation)
Moderate	Notification within 30 days after implementation or shipping	Moderate change 1)Supplement-changes being effected (CBE) in 30 days	Type IB variation (Notification before implementation and MAHs must wait a period of 30 days)
		2)Supplement-changes being effected (CBE)	Type IA_{IN} variation (Immediate notification)
Low	**SOP** (Under GMP change control)	Minor change (Annual report)	Type IA variation (Notification within 12 months after implementation)

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



Topic Related To Changing Manufacturing Site And Formulation



- ✓Requested to submit 6M valid GMP certificate
- ✓Submit report based on specific HPLC format
- ✓Requested to submit BE data
- ✓Requested to submit drug product validation report and batch record using changed API
- ✓Asked to include NDA equivalent information in API QOS section

- ✓At the time of submitting Drug Product site addition, full CTD format document was requested for API site, which was not a part of initial submission
- ✓When switching from in-house site to outsource site, site change document needed to follow new submission review process

- ✓API "retest date" was not considered, and handled as "expiry date"
- ✓Since stability extrapolation was not considered, when API expiry date was established, the shelf-life with less than 1 year API was not allowed for importation

Industry Perspective For Convergence Of Post-Approval Change Procedure

- Introduce scientific 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