Table 26: Harmonization of Global Regulatory Submission Writing to Enable Acceleration

Facilitators –

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Scope:

There has been a recent shift in submission practices where the timeline gaps between regulatory submissions to major regions (e.g., FDA/EMA/PMDA) vs. other regions have narrowed. This has been enabled by accelerated regulatory pathways and a recognition of the need to get potential access to life-saving therapies globally. While faster, broader access is a positive benefit, there are practical implications in trying to gain approval in multiple countries as the same time. This roundtable will discuss and share best practices on how to author global Module 3 submission content to enable accelerated submissions to multiple regions. Topics to be discussed include: development of "core" dossiers, balancing customization to various HA requirements vs. minimizing differences in submissions, reacting to developing/changing regulations, lifecycle management approaches, and experiences using reliance pathways. Also, we may discuss how ICH Q12 and KASA (Knowledge-aided Assessment and Structured Applications) may facilitate or complicate the preparation of global dossiers for accelerated programs.

Questions for Discussion:

1. Are companies creating one global dossier or multiple versions that can be tailored to most major regions?
    a. Are templates prepared and agreed upon ahead of time?
    b. Does parallel authoring occur between regions?
2. What core manufacturing and testing content can be authored to meet most regional expectations (e.g., critical parameters only, key manufacturing steps, etc.)?
3. What Q12 aspects might be binding in different regions?
4. What challenges have companies faced in different regions (e.g., chromatogram requirements, compendia differences, development data expectations, registering information typically provided during inspection, protocol challenges [e.g., reference standard/WCB regional expectations])?
5. Do companies develop a strategy beforehand regarding which details to omit in anticipation of a query vs. what to include in anticipation of having to push back on other items? Is a risk assessment/risk register used for making these strategic decisions?

Discussion Notes:

January 26 and 28, February 1 and 3, *combined* –

Companies/Agencies/Industry Forums Represented:

NovoNordisk
Amgen
DSI
CGEN
Abbvie
Biogen
Seattle Genetics
BMS
Biomarin
Genentech Roche
BioPhorum
BI
Novartis
GSK
Pfizer
Merck
Ministry of Health Peru
IPQ

In general, most companies are challenged in preparing global dossiers. Acceleration of global submission timelines have pushed companies to reduce the degree of customization and increase the speed to submission. Below is a summary of the current state and the various approaches industry has taken in the area of harmonization of global regulatory submission authoring and preparation.

- General approach to authoring and maintaining global submissions:
    - Most companies are authoring the US or EU dossier (major markets) first and then other markets receive a redacted version of the EU dossier to help with lifecycle management; Japan is a special consideration, and Canada generally gets a dossier aligned with the US. There was agreement that the global dossier approach (e.g., one dossier for all markets) has challenges and is rarely done, although templates could be adapted to be more global-reaching. Some companies have a global dossier but only update specific sections (e.g., specifications and manufacturing sections). Some companies author dossiers for all major markets at the same time using one master template, highlighting areas where specific redaction/revision will be needed post-authoring for certain markets; this approach requires planning with

commercial to know ahead of time where commercial intends to market the product.

- Many companies use pre-defined templates or model documents based off ICH guidelines with specific instructions for authors to follow when writing their assigned sections. The templates offer guidance to teams about what to include (e.g., instructions for authoring rabbit pyrogen testing as required by FDA). Some companies also use templates with different requirements for INDs, MAAs, and post-approval submissions (especially stability sections and Annual Reports).
- It was noted that CMOs generally have their own templates, which can cause confusion when a company has their own template to follow.
- Several companies use their Subject Matter Experts (SMEs) to author their Module 3 content while some use Regulatory Affairs to author Module 3 based off of very well-written source reports.
- The timeline for putting together a marketing application (including planning) seems to be around 18 months; line extensions could be done as fast as 9 months. A few companies mentioned exploring the use of digital tools to accelerate timelines and the process, i.e., batch analyses, stability tables.
- Most companies use a central repository to store their dossiers. Different approaches seem to be taken for storage of dossiers which require translation for different markets. Some companies back-translate their dossiers from key markets into English and stores this version in a central repository along with all other global dossiers. For Japan and Russia, they may back-translate and store the Approved Matters and Normative Document, respectively, rather than the full Module 3.

- Approaches to redaction of information for certain markets:
  - Depending on the specific product and commercial plan, a proactive approach can be taken to streamline the dossier for particular markets. Some companies are asked to submit to other countries as an after-thought by commercial and have limited time to pull together a streamlined dossier for countries outside the major markets.
  - Redaction is a common practice and key areas of redaction for certain markets includes manufacturing details/process descriptions, analytical method information, process validation, non-critical parameters/controls, CQA information, details around diagrams, etc. Some companies have experience with submitting more information than required in certain markets and having this lead to delays and more questions, especially around emerging technologies and QC topics where there may be less experienced reviewers in certain markets. A general

driver for redaction was perceived to be ease of lifecycle maintenance, e.g., fewer future regulatory reporting requirements.

  - Most companies strategize around speed of submission vs. lifecycle management when it comes to redacting enough information vs. accepting a certain level of questions. Some companies choose to put a lot of development data and details into Section 3.2.S.2.6 rather than receive queries. This section is generally considered not to contain registered details (Established Conditions [ECs]) that require lifecycle maintenance so these companies do not feel there is a risk to omit details.
  - One company has experience (for biologics) of not submitting a lot of process validation information to emerging markets (e.g., no shipping studies, no characterization information, heavily redacted validation sections).
  - One regulatory assessor from Peru noted that they have an expectation that dossiers submitted to them meet ICH requirements; however, they are seeing initial dossiers with minimal information and are issuing requests which result in a more complete dossier. Sometimes they are receiving post-approval submissions with more detail than the original dossier, leading to many questions. This may be the experience of other similar countries.

- Experience with individual country approaches and expectations:
  - It was generally acknowledged that some countries ask for more details around methods and development (e.g., Japan).
  - Switzerland and Canada:
    - SwissMedic generally requests RTQs from EMA to facilitate the review. Likewise, Health Canada generally requests RTQs from FDA.
  - Brazil:
    - One company has experience with Brazil requesting specific validation studies beyond ICH requirements.
    - Overall, companies have challenges with Brazil accepting common ICH stability studies (e.g., extrapolation and matrix approaches). Additionally, Brazil has required DP stability data for DS changes that aren't expected to impact DP. It was acknowledged that there has been some improvement in these requirements being harmonized with ICH since Brazil joined the ICH.
  - US:

        - Several companies have experience being requested to provide a lot of inspectional/GMP information in Module 3 for FDA such as facilities details and microbial controls (e.g., isolator and autoclave validation reports) and shipping qualification details. Many companies felt these requests highlight a trust issue with the Quality Management System, as these items should be viewed on inspection only rather than incorporated into Module 3. These examples highlighted the fact that it is not just the countries with less mature regulations that ask for more information.
    - Russia:
        - Russia has unique testing requirements and specific documents which require a lot of detail around analytical methods (e.g., Normative Document). Russia also requires stability on finished goods, which poses multiple challenges for companies but also adds little value compared to the data obtained from bulk DP.
    - Mexico:
        - Mexico requires raw data from labs (e.g., chromatograms), and it was felt that this adds little value to the overall review of the dossier and takes a lot of resources and effort for industry to compile.
    - China:
        - China has numerous changing requirements and requires more detail in the dossier than in EU. There was a feeling that China has tried to absorb all the different requirements from different regions into one set of regulations, and that many of the requirements don't seem to have logical scientific basis. Additionally, it seems that sampling and pre-launch requirements require more effort than the Module 3 assessment.
    - Requirements for device/combination product information in the dossiers is not harmonized globally – either in definitions or amount of detail required, and this poses additional challenges for companies.
    - Several industry groups have been trying to influence harmonization of these unique requirements for many years and some with success (e.g., Brazil expectations have improved and aligned better with ICH guidelines), but the trend does continue in several markets.

- Knowledge management:

- Most companies are capturing queries for knowledge management and recycling responses where possible. Some companies are exploring the use of artificial intelligence to pull previous queries/responses without a manual search.
- Multiple companies use a country requirement database (sourced from internal and external intelligence). They also use a system which houses updated templates per each country's requirement.

- PACMPs and other protocols:
  - Many companies have successfully utilized the PACMP pathway where it is currently applicable (FDA and EMA). Japan does have a PACMP pilot program, but not many companies have experience with that yet.
  - Many countries still do not have an official procedure for PACMPs, but sometimes companies try to include proposals into Module 3 (e.g., WCB and reference standard qualification protocols); however, it was noted that sometimes this can lead to a "grey" compliance situation if a product is approved with these proposals as part of Module 3, but there is not a conceptual framework for the follow-on post-approval submissions in those countries.
  - Biophorum has feedback from companies that LATAM countries have provided negative feedback recently around attempts to use PACMPs as their regulations don't allow it.
  - A regulatory assessor from Canada noted that they will accept protocols embedded into Module 3.
- Specifications setting and comparability approaches:
  - Many companies are using statistical approaches for setting specifications. Many companies also use a +/- 3 standard deviations approach for setting comparability criteria. Some companies have received feedback that for biosimilars in particular, this approach is not acceptable as it is too simplified and applied too broadly.
  - Many companies are applying one set of global specifications per product, but not every test might be registered in all markets. Some companies generate country-specific CoAs.
  - Many companies only revise specifications if requested by a health authority.
- ICH Q12 considerations:
  - Many companies felt that some regulatory agencies are expecting industry to submit the same content everywhere; however, different information is being expected and companies are trying to streamline the dossiers for lifecycle

management post-approval. It was also felt that agency requests/needs are not aligned even among areas of ICH Q12 (e.g., ECs).

- Not many companies have submitted a dossier per ICH Q12 to date. Covid may have stalled some of these efforts. Some companies did participate in the FDA pilot, which has stopped. One company has "informally" submitted ECs without actually calling them ECs in the submissions (e.g., submitting statements in Module 3 that new reference standards and WCBs would be submitted as Annual Reportable). Other companies also have taken this approach, including with reprocessing protocols.
- There was a feeling that Q12 may not significantly help harmonization of Module 3 as lot of the elements of Q12 are not uniformly supported in all markets or regulations. Agencies are struggling to implement this guidance. Likewise, there was a general feeling that divergent approaches will be present for quite some time, especially for emerging markets that seem to require so many different details. Most companies felt that there is a lot of room for improvement on agreement of ECs among regulatory agencies. It was also noted that during the current Covid pandemic, both industry and agencies have shown that it is possible to align quickly when needed; however, it is yet to be seen if this trend would continue post-Covid.
- Many companies did acknowledge that PACMPs may now get more recognition globally. Additionally, Covid may precipitate the need for bringing on additional manufacturing sites quickly by using PACMPs globally.

- Breakthrough/accelerated development and emergency use considerations:
  - It was generally noted that data needed to support Emergency Use Authorizations was far less than a traditional dossier; however, these types of submissions are also a lot of work. Every stability data point and batch test has to be reported, and monthly updates of statistics, etc. are required.
  - General advice for managing breakthrough products and/or accelerated development resulting in numerous post-approval changes is to have early and often engagement with regulators and proactive planning across all impacted lines. The number of changes can quickly become overwhelming without appropriate resourcing or prioritization.
  - In order to shorten timelines, streamlined documents are generated by some Regulatory CMC in some companies. Full reports are provided in some cases to shorten timelines. Some review timelines get shorted too and or streamlined to limited reviewers or just Regulatory, or even the use of courtesy reviews for SMEs in order to prepare for potential queries.