Roundtable Session 2 – Table 5 – The Road to One Global CMC Dossier

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Abstract:

On the journey towards harmonization and the ultimate goal of one submission and one approval for all patients worldwide, striving towards one global CMC dossier is imperative and also an enabler for reliance. Although there are many benefits (i.e. reliance), managing varying expectations (i.e. internal and external stakeholders including affiliates and Health Authorities, intellectual property risks and country specific requirements) across global regulators can often be challenging. The aim of this roundtable is to explore and share experiences in navigating the registration and maintenance of one global CMC dossier across both initial registration and throughout lifecycle management including opportunities, challenges and lessons learned.

Discussion Questions:

1. What is your experience with implementing one CMC dossier regionally or globally?
2. If none, what are the major concerns preventing such a pilot?
3. If so, what metrics or key performance indicators (KPIs) are being used to track success for initial registrations and post-approval changes?
4. Have you seen any impact on:
    - enabling reliance
    - the reduction in the number of HA Q&As
    - expedited filing and approval timelines
    - reduction in the number of dossier versions (more convergence) or country specific requirements

Notes:

When preparing dossiers for global submissions, a company took the following approach:

- Core (full) dossiers were prepared for major markets.
- Reduced dossier for rest of world submissions based on the EU dossier (some identical sections to the major markets but some sections had much less information).
- EU-following markets received the full EU dossier.

When determining if a single CMC dossier could be implemented, the company assessed:

- For countries where there are IP infringement risks, these countries would always receive a reduced dossier.
- All other countries receive the core dossier and this enables leveraging formal and informal Reliance pathways.

Where there is no formal Reliance pathway, can still aim to leverage an informal pathway:

- Have a presubmission meeting with the agency to discuss the process and the possibilities. This could include requesting a pilot for a Reliance submission.
- Include EMA assessment report for transparency.
- Health Authorities may still have additional questions during review.
- However, this pathway still enables a quicker review of the submission.

A core dossier is the single biggest requirement for Reliance:

- This could have an impact on the number of post-approval changes for submissions in the participating countries.
    - There could be more submissions but if these also use the Reliance pathway, the approval times could still be faster.
- Reliance pathways resulted in:
    - 78% acceleration in approval timelines.
    - 49% less questions from the Health Authorities.
        - The Health Authorities are getting the full content so would not be asking clarification questions where there is missing information.

For the discussed submission, the product is approved in 85 countries.

- Many countries did not have a mature regulatory framework.
    - Additional support may be needed during review for these countries to help them understand the submission package.
- Need to build in a risk-based approach to managing these post-approval submissions.
    - Where there were minor changes with no impact, used the EU variation framework in these countries with less mature regulatory framework.

The aim is to reduce country-specific requirements to enable a Reliance procedure:

- Include legislated requirements in the dossier.
- Include major regional requirements into one core dossier.
- Discussed other typical but not legislated requirements with the countries prior to submission to ensure they would not be required on submission.

Egypt example:

- Worked closely with the Health Authority throughout the procedure.
- Pushed back on the sample testing requirements to enable the Reliance procedure.
    - Pushed back on the sample testing requirements and received a waiver.
- The Health Authority in Egypt has now issued a guidance for Reliance procedures.

The aim is to set up an approach and then ensure that it is implemented in the policy landscape. Help by supporting the regulators through providing workshops. Topics could include implementation of ICH Q12, use of established conditions, sample testing requirements, etc.

The company tried to reduce sample testing for the submissions by providing all testing results. However, some countries did still require testing so could not be part of the Reliance procedure.

The company applied Reliance across all post-approval submissions. The largest pilot involved 49countries and approval was received within 6 months.

The recommendation if to manage minor changes within the Product Quality System (PQS). The agency should be notified and all these minor updates can be bundled into the next major submissions.

A core practice should be to leverage unilateral Reliance procedures wherever and whenever possible. This would therefore include influencing internation countries to take part in these procedures.

There could be some country specific differences, e.g., stability requirements, shipping validation requirements. There may be some divergence. However, where possible, keep to ICH requirements and bush back in the responses to Health Authority questions:

- For example, for bracketing and / or matrixing approaches to stability design, some countries may have inconsistent requirements or may ask for additional supportive information (letters, justifications, scientific literature) to support the approach and this should be pushed back on, with justification, in the responses to questions.
- For example, for stability, may always want to include 3 batches on stability rather than using an abbreviated approach.
- It might ultimately be necessary to include the additional information in the responses to questions.

If you can provide the EMA or Swissmedic dossier and the assessment report from that Health Authority, it will give confidence to other agencies to provide an appropriate.

Use regulatory intelligence to see what the regional requirements are in all participating countries:

- Provide this regional information where it is an absolute requirement.
- If this is a request seen in the occasional question, do not automatically provide this information and push back on Health Authority requests for this information in the responses to questions.

This approach was taken for submissions in the LATAM region:

- Provided the core dossier and the EMA assessment reports.
- The approval timeline was reduced from 12-18 months down to 4 months.

Outside of a formal Reliance procedure, where the core dossier and the assessment reports were provided, a 25-35% reduction in the review timelines was observed.

The company did have presubmission meetings with other countries to start these Reliance procedures. However, even when there was no presubmission meeting, there was still a faster approval timeline.

When preparing the submission. Build in a rationale for the approach into the cover letter. Clearly explain what the change is, include a justification and provide links to the relevant sections. This helps build trust with the Health Authority. During the process, help the Health Authority navigate the dossier so that they do not require the country-specific documents.

Most countries will accept the EU dossier and EMA assessment reports:

- This may however depend on which agency (FDA vs. EMA) approves the submission first.
    - Need to be strategic about the submission sequencing.
        - The EU dossier may have less source reports included and this could be preferential for ROW submissions.
    - Some countries may still request the US dossier, e.g., if they are joining Project ORBIS.
        - However, FDA does not have assessment reports in the same way that EMA does.
    - Can also provide CPPs from countries where there are approvals.

For countries where there are IP risks:

- This is not a fixed list and the landscape does change.
- Keep up-to-date and leverage expertise in these regions.

Push back on GMP inspection risks:

- Aim to rely on FDA or EMA inspections for these submissions.
- This can be a tough argument.

Encourage Health Authorities to join the WHO program:

- Using the WHO assessment tool:
    - Determine the maturity level of the Health Authority.
    - Assess where additional support is needed.
    - WHO will provide trainings, where needed.

Another way to support the Reliance procedure if to invite all Health Authorities into virtual meetings where industry and the regulators can discuss requirements and concerns.

There is work on-going with industry associations to develop position papers on a proposal for the contents of the core dossier.

We are not there yet with one common dossier – this is a dream for the future:

- But we are trying to minimize how many variant dossiers there are.