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Achieving Simultaneous New Drug Document Submission for the FDA and EMA

International Conference on Harmonization (ICH) guidance makes it feasible to construct a new drug submission dossier that can be used for applications to multiple countries. Two of the largest markets with the most evolved regulatory landscapes, the U.S. and Europe, have similar documentation requirements, but with important considerations to recognise that need special attention.

By planning for simultaneous document submissions, drug developers can minimise rework, maximise efficiencies, compile optimal data packages, and create the most direct path to U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval. Many other countries follow FDA or EMA approvals, further extending the benefits of a combined approach.

While Module 1 of the ICH Common Technical Document contains regional information and will therefore present significant differences between FDA and EMA submissions, Modules 2, 3, 4, and 5 are similar in comparison. However, terminology and seemingly small grammatical distinctions can loom large if overlooked. Careful planning is crucial if not pivotal. A submission team can greatly accelerate global document submission by first creating and reviewing a checklist of differences, agreeing on the best approach to address each difference, planning the summary documents based on these decisions, and collaborating closely in pursuit of a successful outcome.

With any submission dossier, some aspects are under the developer's control, and some are not. Timing, authoring differences, and regulatory requirements can be accounted for in the planning phase, whereas the standard of care and unmet need, regulatory interactions and agreements, and marketing and product regional differences may have to be addressed on the fly. Regardless, the first step is to consider simultaneous document submission up front.

Most drug developers seek new drug approvals in both the U.S. and Europe. They are two of the largest markets, with the most evolved regulatory landscapes and highest uptake of new medicines. Approvals in the U.S. and Europe also provide a gateway to other countries that follow FDA or EMA guidelines.

Historically, submission teams have viewed and managed the two document submissions separately. After all, the U.S. and Europe are an ocean apart, with different policies and their own regulatory bodies in the FDA and EMA, respectively. Meanwhile, the number of people involved in any submission dossier can create complexities and – let's face it – inefficiencies in the crucial phases of document preparation. Add in comparing, contrasting, and completing FDA and EMA submissions, and those inefficiencies become doubled and magnified.

Is there a better way? The question always breeds critical thinking and often leads to new solutions. In this discussion, it can entirely rewrite the approach to, and relieve many of, the common pitfalls experienced during dossier development for the U.S. and Europe. Before plunging headlong into submission preparation, consider your whole global submission plan and the feasibility of simultaneous document submission to optimise the process. It takes more planning and deliberation up front but streamlines each step thereafter.

Why It's Possible

The traditional two-lane mindset served its purpose when the U.S. and Europe truly represented two completely different regulatory environments with little to no crossover. That changed in 2000 with the finalisation and adoption of ICH guidance facilitating mutual acceptance of clinical data between the regulatory bodies of the U.S., European Union (EU), and Japan to make new drug registration less resource intensive.

"ICH's mission is to achieve greater harmonisation worldwide to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner," ICH says on its website. "Harmonisation is achieved through the development of ICH Guidelines via a process of scientific consensus with regulatory and industry experts working side-by-side."

ICH's leading Article of Association hinges on "the interpretation and application of technical guidelines and requirements for pharmaceutical product registration and the maintenance of such registrations." While licensing, joint ventures, and globalisation were previously softening the borders of clinical data, ICH was the turning point enabling simultaneous document submission particularly to the FDA and EMA.

All drug developers are familiar with ICH guidance from a regulatory perspective, and most have been pursuing simultaneous submissions for the past 15 to 20 years. However, that harmonisation has been drifting apart the past several years. Dossiers for the FDA and EMA can still be merged to start and managed as one for the bulk of the work before later being adjusted as necessary to suit the final submissions, but few address up front what is required from a tactical standpoint to do so efficiently.

Main Differences

The FDA and EMA dossiers have their differences, giving simultaneous document submission its limitations. The most notable difference is Module 1 of the ICH Common Technical Document. This consists of regional information that will need to be compiled separately. Module 1 is best set aside so it doesn't hinder the rest of the information that can be compiled simultaneously.

The significant differences in Module 1 may be the reason submission teams assume FDA and EMA submissions are different

undertakings altogether. However, there are some very specific differences in requirements across other Modules, including:

- Clin Pharm Highlights checklist (FDA only, submitted outside of eCTD)
- TQT checklist (FDA only, submitted outside of eCTD)
- eSub package (FDA only. Clinical CDISC and BIMO placed in Module 5, SEND datasets in Module 4 and ECG wave forms submitted outside of eCTD to the ECG warehouse.)
- EMA Module 5.3.5 (Overview of Clinical Efficacy (tabular format))
- Justification document (May be needed for EU to justify missing or excluded components of an eCTD. Can be appended to summaries in Module 2 for Nonclinical or Clinical.)

It can also be helpful to understand how the FDA and EMA review submissions through different lenses. The FDA is very data-driven, with robust requirements for data sets and programs used to generate statistical analyses. They first look at individual listings, case report forms for patients with adverse effects, and other deep documentation, working from the bottom up to arrive at a decision.

EMA reviewers, on the other hand, tend to take a more top-down approach. They prioritise key messages and information in the clinical overview to develop their interpretation of what a drug is doing for patients and modern medicine. The EMA does not require data sets or case report forms like those required by the FDA. In general, the EMA is more qualitative while the FDA is more quantitative.

More Similarities

Aside from Module 1, submission teams should be happy to hear that Modules 2, 3, 4, and 5 are similar between FDA and EMA submissions. The U.S. and Europe are two of the most similar regions in the world when it comes to their submission requirements, again thanks to ICH guidance on summary documents and submission format.

The main differences discussed above are really the exceptions, so we can (and should!) reframe our approach to assume that 75% or more of the compilation can be conducted simultaneously. But don't dive in just yet! Remember that small details can become big headaches in these large and technical documents. Careful planning is pivotal to gain an understanding of where the risks and opportunities lie.

Biggest Risks

With any submission dossier, some aspects are under your control, and some are not. Those that are not in your control are effectively the risks, or things you will have to roll with as they arise. During simultaneous document submission, the key risks are:

Regulatory Interactions and Agreements

Your team may be well into the process of creating shell documents alongside pre-submission meetings when the FDA and/or EMA might ask for additional information or analyses. This is more common from the FDA due to its detail-oriented approach.

It's a good idea to review the regulatory interaction history for each agency and note any commitments that were not addressed. Cite specific agreements, such as endpoints, time points to be analysed, pooling of data, relevance of patient subsets, and studies considered supportive of efficacy or safety. Plan when all pre-submission meetings will occur relative to your final data availability, document preparations, and submissions. Even when taking these measures, regulatory interactions are ultimately out of your control.

Standard of Care and Unmet Medical Need

Other product approvals can cause untimely changes in the Standard of Care and Unmet Need. Are the standard of care, disease definition, and affected patient population the same across both submissions? To what extent can the wording of the proposed indication be identical across all planned countries? Can you write one unmet medical need section for Module 2.5 that will work in all submissions? These are important and productive questions to ask to mitigate – though not fully eliminate – the impact of any unexpected changes along the way.

Marketing and Product Regional Differences

The marketing of your product can potentially be similar in both the U.S. and Europe, but oftentimes, there are standout differences that impact the two submission documents. These differences include indication wording, brand name, and dosage form or even dose. Brand name is perhaps the key piece in this area, with the question for marketing and product purposes being whether you were or will be able to get adoption of a single brand name globally.

Awareness of these factors folds into the proactive planning that follows and can help buffer against unwanted surprises so they can at least be taken in stride en route to on-time and ultimately successful submissions.

Examples of Missteps

It's a lot less painful to learn from others' mistakes than your own. Here are a few simplified examples of real-life teams running into submission roadblocks that could have been avoided:

- The Afterthought: A sponsor completed a full regulatory history review, accounting for all agreements and resolutions for successful NDA submission. However, they completed the NDA without considering the MAA planned 3 to 6 months after NDA submission. This resulted in extensive rework of approved NDA versions to create MAA versions. (To make matters worse, they had outsourced preparation of the NDA and MAA submissions to different vendors.)

- The Comment Carousel: With the goal of writing documents in a way that one version would work or at least require minor revisions for all countries, the team took off running…and spinning…and sputtering. They were unable to stop commenting on standardised global introductory text, derailing a well-intended plan when version control between submissions finally caught up with them and caused delays.

- The Caveat: Starting with the assumption of no differences in Module 2.7 documents and identifying differences in Module 2.5, a submission team built a combined BLA/MAA version up to point of first draft, including specific MAA sections highlighted. For BLA Draft 1, they removed the MAA sections. Once BLA Module 2.5 was approved, they used that approved version as the initial draft for MAA and replaced BLA-specific content with MAA-specific content. But by the time of MAA creation, data presentation agreements with EMA and team agreement to include a label Adverse Reactions table in Module 2.7.4, that Module required tedious EU-specific modifications as well.

How can you avoid missteps like these? Quite simply, with planning.

Planning You Can Control

The key takeaway to this point has been that the FDA and EMA submission dossiers are more similar than they are different. Now,

the important message is that more of the documentation process is in your control than not. You can plan for:

Timing
You don't necessarily control your deadlines per se, but you know what they are and can plan accordingly. How soon after the first submission do you want (or need) to make the second submission? How long is the duration between submissions, and will that lead to additional study data being available or the need for a new cut-off date for safety data? What are the plans for supplements if filing for multiple indications? These are just a few of the many questions to ask early regarding timing of final submissions.

Authoring
If there is one component that is undeniably in your control, it's your process for authoring your dossiers. Possible strategies include generating one version that can be re-used mostly unchanged, generating a full version for one with the goal of minimising any revisions needed for the other, or generating a core version followed by country-specific versions from that core for global simultaneous submissions beyond the U.S. and Europe.

There are four immediate considerations for authoring FDA and EMA dossiers simultaneously. Three of them are almost laughably simple but can cause significant rework if overlooked.

- First, deciding whether to use British or American English is much easier before starting submissions than it is to address after the documents are underway.
- Second, note the name of the submission, e.g., BLA vs MAA and use of "application" or "submission" as a generic identifier.
- Third, consider cross-referencing, e.g., sNDA & Type II variation cross-referencing.
- Fourth, and more involved is whether you will account for reviewer tendencies noting the differences in the FDA's and EMA's respective approaches discussed in the "Main Differences" section of this article.

Throughout the submissions, writers know how to find workarounds to be as universal as possible with language; they just need the instruction and guidelines in advance to minimise the work and uncertainty for editors later.

Regulatory Requirements
Over the years since ICH introduction, regulatory requirements in the U.S. and EU have slowly drifted apart. Still, the requirements are known, clearly stated, and can thus be planned for in the submission process.

For example, in considering the inclusion of integrated summary of efficacy (ISE) and integrated summary of safety (ISS), it's easier if the ISE and ISS are just the outputs. However, there are no issues with including ISS and ISE in an EMA submission after these pieces were developed for an FDA submission.

Separately, for the Benefit-Risk sections, you can convert the content of an FDA table into subsections with the exact same text to fulfil the comparable EMA description.

These are just a few glimpses of efficiency with simultaneous document submission, knowing and accounting for the regulatory requirements.

Identifying and Managing Differences
The goals of simultaneous document submission are to minimise rework, maximise efficiencies, compile optimal data packages, and create the most direct path to FDA and EMA approval. It starts with assessing and identifying all possible country and regional differences while also keeping in mind timing. Develop a checklist and discuss it in detail with the entire submission team, followed by a timeline. Review the full regulatory history and highlight any gaps that may need to be filled or could potentially present obstacles to successful submission and approval.

Given the similarities between FDA and EMA submissions, it's quite feasible to write one global version excluding Module 1, and then make specific edits for the key differences in the two final submissions – or it can be equally effective to write one version first and then edit that version into another. It's a significant undertaking by any measure and means, but the first step is one that any team can implement off the bat – consider simultaneous document submission up front to help ensure on time and successful submissions.

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