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Writing at Lightspeed: Optimizing Submission Dossiers in Today's Environment Through Better Planning

A New Drug Application (NDA), Biologics License Application (BLA), Marketing Authorization Application (MAA), or other marketing application submission is a significant undertaking for any drug development program. A large, diverse team, numerous tools, planning, and processes must work together in harmony for a successful outcome. Complexity, risk, time, and costs typify every regulatory submission. Without careful planning, execution, and the ability to navigate unexpected challenges, your submission may fall off track.

With every submission dossier, some aspects are under your control, and some are not. This table presents some of the major considerations when planning for submission to both the FDA and EMA and provides our recommendations on how to optimize your dossier for submissions to multiple countries.

THINGS YOU CONTROL AND DECIDE

Category / Topic	Insights/Details
Timing	
• How soon after the first submission do you want (or need) to make your next (or subsequent) submission(s)? • How long is the duration between submissions, as well as from first submission to last submission? • What are the plans for supplements if filing for multiple indications?	• Will additional studies have started and now need to be added as "ongoing?" • Are any data cutoffs you used for safety now too long in the past? This is especially important for serious adverse event (SAE) reporting from ongoing studies or any post marketing safety if the product is on the market elsewhere. • Do any studies ongoing for the first submission now have final reports, locked data, or an additional interim or final readout? • Have you considered the calendar of activities for regulatory defense responses to the first country in your plans for subsequent submission completion? • Will regulatory defense responses have already occurred on the first submission that might impact the presentations needed for the subsequent submissions? • For multiple indications, note that a Type 9 submission in the US allows for submission of a second indication while the first is still under review • NOTE: You may have to roll with some of these depending on health authority feedback or shifts in planned data cutoffs, and study start and stop dates.
Authoring Differences	

• What strategy will you select for developing the Module 2 summary documents for your submission?	• Possible Strategies
	  • Generate one version that can be re-used unchanged in multiple countries
	  • Generate a full version for one country, with goal of minimizing any revisions needed for simultaneous/subsequent submissions to other countries
	  • Generate a core version, then country-specific versions from that core
	• Specific considerations
	  • English spelling – British vs. American
	  • Name of submission (e.g., BLA vs MAA; use "application" or "submission" as a generic identifier)
	  • Cross-referencing (e.g., sNDA & Type II variation cross-referencing. No active links, but any need to mention prior submission number or name would be country-specific.)

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THINGS YOU CONTROL AND DECIDE (cont.)

Category / Topic	Insights/Details
Authoring Differences	
• Will you take reviewer tendencies into account?	• More bottom-up, data-focused FDA review vs EU top-down more qualitative review (shows up especially in Benefit-Risk)
Regulatory Requirements - *Note that over the years since ICH introduction, these have been drifting further apart*	
Risk Management	• Varying levels of inclusion/mention within modules 2.5 and 2.7.4; can limit to just a cross-reference or two. Preference for limiting risk management plan (RMP) mention/inclusion as much as possible.
Inclusion of integrated summary of efficacy (ISE) and integrated summary of safety (ISS) in EU submissions	• Easier to deal with if ISE and ISS are just the outputs; however, no issues with including ISS and ISE in MAA submissions if they were needed and created for US FDA submission
Benefit-Risk	• FDA framework table versus EMA description of benefit-risk. Can just convert content of FDA table into subsections with exact same text.
CMC (biologics)	• EMA much more stringent in review and acceptance of raw/starting materials and drug substance than FDA and has not yet allowed active substance master files (ASMFs) for biologics. • For EU, must also comply with and complete an environmental risk assessment for genetically modified organisms (or a statement that the product is not recombinant) for all biologics.
Integrated Summary of Immunogenicity (ISI)	• [Biologics, and gene and cell therapies] Often required by FDA. Otherwise, can be addressed as part of 2.7.2 (with appendices if needed)
Module 2.7.1 appendix tables for methods	• FDA-driven but no need to remove or change for other countries
White papers, expert reports (in Module 5 Other)	Multiple circumstances for FDA and EU that might require or warrant these
Differences in Requirements (Excluding Module 1)	
Clin Pharm Highlights checklist (FDA only)	Submitted outside of eCTD
TQT checklist (FDA only)	Submitted outside of eCTD
eSub package (CDISC, BIMO, SEND datasets, ECG wave forms)	FDA only. Clinical CDISC and BIMO placed in Module 5, SEND 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)
Oncology Assessment Aid	FDA only
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.

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THINGS YOU WILL HAVE TO ROLL WITH

Category / Topic	Insights/Details
Standard of Care and Unmet Need	
• Are the standard of care (approved/used treatments), disease definition, and affected patient population the same across all countries to which submissions are planned?	• Are you submitting to countries that were not represented in your clinical trial program? If so, how are you addressing generalizability, and will you present that in the submissions to all countries? • 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?
Regulatory Interactions/Agreements	
• What regulatory interactions have occurred? • Have agreements been made that differ across countries? • Pediatric development agreements	• Review entire regulatory interaction history for each country and create a table of all reg interactions, with key agreements – and especially note any commitments that were not addressed • Cite specific agreements: Can include only those interactions with the health authority for that submission, or include all health authority interactions, noting common agreements and any differences. • Examples: Endpoints, time points to be analyzed, pooling of data, relevance of patient subsets, studies considered supportive of efficacy or safety • Have you planned out when all pre-submission meetings (FDA, EMA Scientific Advice, UK, Switzerland, Canada, etc.) will occur relative to your final data availability, document preparations, and submissions? • Have you considered all the possible regulatory pathways (especially for the EU)? • PIP and PSP waivers or agreements, including agreed plans for any pediatric studies and proposed indicated age range. Confirm that PIP and PSP agreements will be in place prior to submissions.
Marketing/Product Regional Differences	
• Will the marketing of the product be similar globally and, if not, will those differences impact any of the submission documents?	• Indication wording • BRAND name. Were you (or will you be) able to get adoption of a single BRAND name globally? • Dosage form or even dose

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