Mind The Gap: The Importance Of Gap Analysis In Securing Regulatory Approval

Biopharma companies may have conducted successful research and put in the work to warrant approval and market access, but to an uninitiated sponsor bridging the gap between good science and regulatory expectations is not always intuitive. A significant quantity of information must be compiled to constitute a successful marketing application. Sponsors have submerged themselves in their drug's development for many years by the time a new drug application (NDA) or biologic licensing application (BLA) is submitted, but a lack of understanding of the regulatory requirements and expectations could mean critical details are missed. Before initiating the process to prepare an NDA or BLA, conducting a thorough gap analysis can avoid delays, or even a refusal to file, and ensure products reach the market and patients quicker.

Make An Early Start

Biopharma companies often focus their attention and limited funds on completing their last Phase III clinical study before turning to the task of writing the NDA or BLA, only to learn that documentation needed to support Chemistry, Manufacturing and Controls (CMC) or nonclinical areas has been overlooked. Successful sponsors begin to plan their marketing applications in early drug development Optimally, they re-evaluate each program in parallel with initiating Phase 3 studies to avoid potential late-stage delays.

The plan for the NDA or BLA should include an assessment of the regulatory, CMC, nonclinical and clinical arms, as each has its own criteria and presents its own unique challenges. During a gap analysis, CATO SMS, a trusted provider of specialized regulatory and clinical research solutions,

has reviewers with specific expertise in each area populate the common technical document table of contents with available data, and then make recommendations on any additional information needed to ensure the fileability of the application.

Your submission will be delayed if you learn that additional work is needed after Phase III has been completed, so it is critical that you conduct as thorough a review as possible early on. A lower anxiety approach is collating submission documents during Phase III studies, as this gives sponsors time to ensure every necessary element is in place, avoiding burdensome setbacks and facilitating a successful application.

Regulatory Meeting Commitments

Along the drug development process, interactions with FDA can provide valuable cornerstones for a successful marketing application. Too many sponsors fail to implement FDA advice fully, or to respond to FDA concerns that may not be addressable.

Be mindful that FDA will review past official meeting minutes to confirm that NDA and BLA sponsors have addressed commitments that were made earlier in the drug development process. Advice that was offered, even if not tied to a formal sponsor commitment, may resurface at a pre-NDA meeting or in a "refusal to file" letter. A gap analysis reviews commitments made and advice offered and creates a list of open actions to address discrepancies.

Interpretation can also cause issues. CATO SMS has observed this: the sponsor responded to FDA and believed they met a commitment, but did not follow up to confirm their actions met FDA's expectations. The actions often are correct, but incomplete, and failing to confirm FDA acknowledgement may leave unresolved commitments. In either instance, a gap analysis can identify issues in sufficient time to reach agreement with FDA, ensuring criteria have been satisfied.

Managing Data

The analytical control strategy and development data comparability are key aspects often overlooked during NDA/BLA preparation. For the former, Greg Hileman, vice president, regulatory strategy at CATO SMS, notes, "It's very common to have focused on things like discrete analytical or process validation methodologies, but we need to take a step back and ask: Do you have a solid rationale, and a solid quality data plan to ensure a comprehensive control strategy has been executed?"[1]

Creating specifications that will ensure product success is a common error, because to establish a meaningful control strategy these need to be justified by the data generated. If the limited available data support a narrow percentage range for an assay, and you have included, for example, compendial ranges such as 90–110% of claim limits in your application, often FDA will ask you to revise this. As a result, your application may be delayed, or post-approval commitments may be incurred for reasons that are easily avoidable.

Development data comparability can pose difficulties due to the amount of time it takes to develop a drug prior to filing the NDA or BLA. The average drug development process takes at least 10 years,[2] and in that time, inevitable stepwise manufacturing and analytical changes occur. These stepwise changes are validated as they happen, but may ignore the overall change from initial studies to final commercial product, which can require bridging studies. Some bridging studies can be avoided by having early and honest discussions with FDA, but you need to ensure you have this clarity. If a bridging study does need to be executed, a gap analysis can avoid discovering at the pre-NDA or BLA meeting that the damaging outcome of a long delay to complete it must occur.

Institutional Memory

The need to compile and submit all final, signed reports is another challenge the length of the drug development process poses to your marketing application. Changes in personnel, electronic storage media, even company ownership for small companies, can create institutional memory loss, for example, missing links in data or report storage and retrieval. Incredible amounts of time may be required to find complete records, as this can involve identifying third parties such as contract research organizations (CROs), former employees or

predecessor companies.

Sheila Plant, senior director, regulatory at CATO SMS, states that where biopharma sponsors have in-licensed their products, a particular complexity is presented: "This is where reviewing the totality of all the nonclinical documents is important, because not everyone may know what was done in the distant past and where all those reports are."[1] Collating all this documentation without first-hand experience of the prior undertakings can be a very difficult task, and so starting this as early as possible is critically important to tackle any unexpected findings that could impact your NDA's or BLA's prospects.

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Much of the early work, particularly nonclinical development, may be obscured by time and forgotten as the later stage increasingly focuses on clinical development. In CATO SMS's experience authoring nonclinical summaries for the electronic Common Technical Document (eCTD), as many as three times the number of nonclinical reports initially identified by a sponsor emerge from the start of the NDA working period to completion. This makes the process of preparing nonclinical summaries unpredictable, cyclical and inevitably much longer, costing sponsors unplanned time and money.

The Bigger Picture

Ultimately, a quality gap analysis prepared by an experienced NDA/BLA submission team ensures sponsors have complete oversight and understanding of where they are with regards to the progress of their application. This knowledge not only enables proper assessment of the time and cost of the marketing application, but also results in fewer unwelcome surprises when it comes time to submit.

Significant pressure to achieve regulatory approval to start generating return on investment can affect any sponsor, but it is of greatest magnitude to small biopharma companies without existing marketed products. Given the complexity of the submission process and requirements, sponsors can benefit from added expertise, especially if approaching the NDA or BLA process for the first time. Greg Hileman states, "The NDA comes at the end of a multi-year, multimillion-dollar development program when everyone in the company – and your investors – are anxious to get this NDA/BLA under review. This is not the time to learn of painful delays that other people have already experienced. What you don't know is what's going to surprise and delay you."[1]

Like any audit, a quality gap analysis takes significant investment and personnel, and may best be conducted by a third party. At a time when biopharma companies are focusing their resources on the science behind their marketing applications, building the in-house capacity to conduct an independent gap analysis is not on the forefront. Instead, utilizing an experienced partner to carry out a gap analysis is the optimum way to gain complete clarity and achieve success with regulators as quickly as possible.

References

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Dr. Hileman has more than 35 years of research and industrial experience, including 25 years in strategic regulatory affairs. He has led drug development meetings with most FDA divisions and contributed to submission of multiple fast track designation requests, breakthrough therapy designation requests, FDA meeting packages, INDs, NDAs, and BLAs. Dr. Hileman currently leads CATO SMS' regulatory strategy group and serves as primary FDA contact for multiple sponsors. Dr. Hileman has clinical and product development experience in neurology, psychiatry, oncology, gastroenterology, cardiology and women's health.

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Dr. DiMichele has more than 19 years of clinical and translational research experience. She has led many projects including writing and reviewing regulatory, clinical, and scientific documents; providing clinical trial management, pharmaceutical development, and project management; assisting with Clinical Trial Operations; and preparing for and attending FDA meetings and providing scientific consulting. She has experience in therapeutic areas such as infectious disease, oncology, nephrology, neurology, psychiatry, dermatology, and hematology. Her product experience includes monoclonal antibodies and other biologics, small molecules, and vaccines. Dr. DiMichele also leads the CATO SMS Clinical Strategy Department and Fellows Department.

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