Expedite Development While Ensuring Successful Commercial Outcomes

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WHITE PAPER

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Pharmaceutical and biotechnology companies reap the most benefit from their strategic collaborations by working with CRMOs whose strategic and operational practices aim to combine and apply the comprehensive knowledge gained during the entire development process. The best strategies include a greater focus on process knowledge compared to a conventional milestone driven and three-batch validation strategy. This focus should be coupled with a design space framework that focuses on a true technical understanding of operations, as well as an establishment of critical process parameters, quality attributes and controls.

Service providers whose solutions are strategically positioned to execute across the entire development process provide the robustness needed to meet and exceed evolving regulatory expectations. CRMOs that coordinate a broad range of solutions – from sourcing, through process development and analytical to regulatory documentation – will ensure a broader development strategy that balances progress with caution on the path toward pharmaceutical registration and ultimate commercialization.

Requirements for Commercialization

The basis of achieving pharmaceutical registration is the ability to demonstrate safety and efficacy of the drug. The clinical requirements of Phase I through Phase III range from animal toxicology studies through dose tolerability and dose ranging studies in Phase II to multicenter efficacy studies in Phase III. The pharmaceutical development process, from a CMC perspective, is defined by “The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use” (ICH) guidelines, which establish the particular requirements expected to achieve product registration and commercialization. The U.S. Food and Drug Administration’s (FDA) current cGMP regulations, as written in the Code of Federal Regulations lists these tenets, as well as specific requirements, for a firm to uphold and follow in order to manufacture products in accordance with current GMP.[1] The “c” stands for “current” because it is understood that good manufacturing practices are not a static concept; instead, they must be defined in relation to current insight and regulatory expectation brought on by technological advancements and collective lessons learned, and best practices developed, within the industry.[2]

The key to being able to operate within the boundaries of ICH is the adaptation of cGMP. GMP is the standard and backbone of the pharmaceutical industry pertaining to the mechanism of operation that a facility must base its entire pharmaceutical operation upon. The cGMP guidance is law at an individual country level, so application to the specific laws of the given territory of manufacture, testing, and/or drug sale should be adopted. That being said, conforming to the regulations of key territories – United States, Europe and Japan – is generally considered appropriate for most other countries as regulations are predominately similar in their desire to ensure product quality and product consumer safety. The U.S. Food and Drug Administration’s (FDA’s) current cGMP regulations as written in the Code of Federal Regulations – for example, 21 CFR parts 210 and 211 – contain explicit requirements for the manufacture of finished pharmaceuticals. APIs and drug products must be manufactured in accordance with cGMP.[3]

The corresponding EU guidance is the EudraLex Volume 4 Guidelines for GMP Practices for Medicinal Products for Human and Veterinary Use.[3] The relevant guidelines for Japan are those specified by the Japanese Pharmaceutical and Medical Devices Agency (PMDA).[4]

Enhancing Commercial Viability

The current industry focus can be to somewhat compartmentalize pharmaceutical development and move from milestone to milestone, without a broader vision on the end goal, and with a fixed view on what should occur at each stage. It is important that CRO/CMOs be aware of customer requirements, to realize milestones and achieve defined clinical endpoints. This is especially important when working with venture capital backed entities, since their access to capital may be limited and by design they have to operate on tight and restricted budgets. In doing this, it is beneficial to take a much more holistic approach to development consisting of two key points.

Firstly, a CRO/CMO should apply high-level scientific diligence to work within the boundaries of the evolving regulatory framework. For example, one significant change in Process Validation is described in the January 2011 FDA Guidance for Industry.[5] The core of this update is to advise industry to focus more on process knowledge and less so on a conventional three-batch validation strategy; thus minimizing the potential for surprises and reducing the risk of issues arising during commercialization. This framework should be used and coupled with the design space philosophies described in ICH Q8 and the recently effective ICH Q11.[6,7] This will create a development philosophy focused on true technical understanding of the operations and the establishment of critical process parameters and their control through the determination of critical quality attributes.
Furthermore, the adoption of a more progressive validation strategy based on process knowledge also takes considerable risk and potential cost away from achieving commercialization and then ongoing commercial supply. This is because not only can process development occur on a smaller scale and at an earlier time – with potentially a reduced batch validation strategy being performed – but also process knowledge within the design space is increased such that validation becomes a more true definition of the process, and risks from non-robust processing, associated deviation management and disruption to commercial supply are reduced.

Secondly, operations should be undertaken with consideration of the equilibrium between achieving the current goal and building a robust and efficient product for the future. For example, in developing a first-in-man formulation, a CRO/CMO should consider the potential impact of the physical properties of a molecule through a preformulation study, relying on additional scientific capability. This allows for optimal understanding of compound properties and reduces the chance for bioavailability anomalies during clinical phases. Enhanced formulation optimization studies could be used to develop a lead formulation pertaining towards the final formulation at an early stage, hence making continued use of the analytical methods development and validation information and also enabling the stability data and ‘formulation-like’ supporting data to be obtained.

This approach of scientific diligence coupled with an end-game focus may also lead to enhanced commercial viability. This may include a positive contribution to the remaining molecule/process patent life and establishing a novel scientific process to enable an IP position to be achieved – either in finite portions or across the development process. This offering brings benefit to either the potential license holder or the endpoint driven investor.

How AMRI Optimizes the Design Space

Design Space is recognized as the area of knowledge in and around the defined process where technical and operational parameters have been evaluated and are understood. This enables the defining of both critical process parameters and critical quality attributes. The design space philosophy is sometimes misinterpreted and under-used throughout the industry.

AMRI has developed three tiers of process knowledge that the company seeks to identify, understand and document during development. In effect the three stages correspond to IND, Phase III/Registration and Commercialization. AMRI is focused on the CMC (Chemistry, Manufacture and Control) elements of achieving these clinical endpoints to enable the clinical operations and ultimately to provide a robust process affording safe commercial product.

Within the aforementioned framework, AMRI has identified the supply chain, processing, analysis and logistical standards that will be achieved at each stage, which together form an integrated process knowledge platform (See Diagram 1). The goal of this effort is to continue to decrease manufacturing risk as a compound progresses through the clinical phases, leading to a de-risked and robust process for ultimate commercialization.

Outside of this, AMRI has also developed and enacts a robust, efficient and compliant development strategy, related to another key point. Since AMRI works on more than 50 projects at any given time and is continually reevaluating best practice, this number of projects means the company’s learning and implementation cycle can be much quicker than other CRO/CMOs. This not only ensures benefit within development, but an enhanced position related to the application of that knowledge to regulatory filings. We are continually engaging with, and have a constant view of, global agencies’ views and evolving requirements. For example, four products that have been developed by AMRI and submitted for market authorization are currently under regulatory review as this is written. As a result of AMRI’s process knowledge framework, the company is well-equipped to advise customers on how to position their file and what the areas of focus are likely to be with the regulators.

AMRI also understands and adopts a global perspective; the company is not just focused on specific regulations, but rather has developed a global enhanced standard that meets and achieves success in all major markets.

There’s No Need to Compromise Because of Cost Pressures

All too often in the recent past, the drive for lower costs resulted in compromises in decision-making, putting price before quality, service, scientific excellence and even manufacturing capability.

Cost pressures have caused leaders in many companies to seek the (purportedly) cheaper option, even at the expense of quality, or the risk of working with a new, unproven provider. These decisions were made in a sometimes false belief that close management of the CRO/CMO could overcome any shortcomings. History has proven this to be very difficult – and these efforts add to a true cost anyway. Such a short-sighted approach is proving to be a false economy. Cost and value are two different things!
Working with a well-known supplier with a strong regulatory track record aids partnerships and success. For example, investing a little more upfront – e.g. on preformulation for better understanding and facilitating optimized process and analytics – has the potential to significantly increase the opportunity for first-time success as a molecule is developed. This is important for customers who intend to take the molecule to market as it may save time and, therefore, increase the patent lifetime. For customers looking to achieve a clinical endpoint, such as proof of concept, and considering partnership for a molecule, the process and analytical work will be evaluated during due diligence. The quality of the data package is crucial so that no surprises or backward steps will occur.

Time and return on investment are intrinsically linked in the drug development process, which is extremely important from both the customer, as well as the patient perspective. This is highly applicable with orphan molecules and molecules in regulatory fast-track programs. Here, delivering a product to market quickly is of major commercial and patient importance.

In the area of market growth, and using the EMA mutual recognition approach, AMRI has played a key role in assisting with the supply of technical information for submissions and supports questions from the reference country. AMRI works closely with the customer to ensure a technically robust solution while also keeping a firm eye on commercial value and regulatory risk mitigation. AMRI, with exceptional global regulatory experience and a track record of achieving multiple commercializations, is uniquely positioned to play a partnership role during these activities. This is an excellent example of being part of the lifecycle management of a drug and a multiyear collaboration/partnership through development, initial commercialization and ongoing territory management of a drug.

Supporting customers means understanding their needs and quickly finding solutions to problems. Pharmaceutical and biotechnology companies will improve their success rates and outcomes at all stages of their development pipeline by working with CRO/CMO suppliers whose practices aim to optimize the design space by combining and applying the comprehensive process knowledge gained during development.

Simply working with a partner that conducts development work, handles testing and offers project management services is not enough to ensure that processes and ultimately drug commercialization will be successfully completed. Very few CRO/CMOs have a proven track record of success and the technical capabilities to support the discovery, development and manufacture of new compounds commercially and subsequently throughout their lifecycle. Partnering with a high quality CRO/CMO at the early stages can be very important – it allows the CRO/CMO to understand project complexities in real time and offer more considerations at an early stage, before inefficient processes become locked in or key early experiments get overlooked. This can be vital to setting a project up for success and protecting financial investment, or even saving the project itself in the long term.

Diagram 1: AMRI has identified the supply chain, processing, analysis and logistical standards that will be achieved at each stage, which together form an integrated process knowledge platform.

References:
1. FDA Title 21 CFR Parts 210, 211 Current Good Manufacturing Practice for Finished Pharmaceuticals, April 2012.
6. ICH, Q8 (R2) Pharmaceutical Development (2009).

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