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Regulatory Roadmap & Key Considerations for Executives Building a Clinical-Stage Company

Scendea Authors:

Dr Asha Kattige
Principal Consultant

Cadoret Global Authors:

Enith Morillo, M.S.
Founder & Principal Consultant

Introduction

The pathway for transitioning into a clinical-stage company is a crucial step in the development lifecycle of a product, as a favorable safety profile needs to be demonstrated and regulatory approval received before embarking on first in human clinical studies. There are multiple technical and non-technical aspects that must be considered to secure a path into the clinic that is compliant and destined for success.

Some of the key considerations to ensure a smooth transition into the clinic are the topic of discussion in this paper.

Quality Target Product Profile (QTPP)

A starting point for a successful drug development program involves creating a blueprint of the relevant attributes required for a marketed product. The attributes which should be considered essential are usually driven by a QTPP. The QTPP describes the design criteria for the product and forms the basis for development of the critical quality attributes (CQAs), critical process parameters (CPPs), and control strategy.

Establishment of a QTPP helps focus the drug development activities in working towards a clear goal and provides an understanding of the specific attributes that will ensure the quality, safety, and efficacy of a specific product for the patient. Furthermore, during early phases, as we navigate from pre-clinical into clinical, compilation of these attributes will also enable educated decisions to be made at critical junctures pertaining to investment, candidate selection and progression towards market approval.

The QTPP typically includes:

- Characteristics of the active molecule (conformation, molecular weight, etc) and characterisation of its impurity profile
- Physiochemical properties of the active molecule (pH, melting point, solubility, polymorphism)
- Information on possible mechanism of action
- Intended use in a clinical setting, including route of administration, dosage form, dose strength, and delivery system
- Characteristics of the Drug Product (DP) that would facilitate efficacy and safety
- Therapeutic moiety release or delivery and attributes affecting PK characteristics (e.g., dissolution, aerodynamic performance) appropriate to the DP dosage form under development

Drug Development Plan (DDP)

Preparation of a drug development plan that includes the first major milestone, a First in Human (FIH) clinical study, should take a holistic view of the separate disciplines (CMC, nonclinical, clinical, and regulatory) to ensure a unified approach to development. A strategic, streamlined, and clearly defined drug development plan ensures reduced costs and faster timelines towards enabling successful approval. Early discussions with key opinion leaders in the management of the disease under investigation will be helpful to define the DDP.

CMC

In any early drug development program for a novel therapeutic entity, developers are required to provide adequate assurance that the product will be safe for use in human subjects. In the context of development of chemical entities (in comparison to complex products containing biological active substance) the purity of the drug substance (DS, active pharmaceutical ingredient [API]) is a key consideration. The impurity profiles of early-stage pharmaceutical candidates attract particular interest of regulatory authorities when they are considering the approval of clinical trial applications (CTAs) and investigational new drug (IND) applications. It is worth bearing in mind that in this context, relevant ICH guidelines are taken into account when determining the purity and impurity profile of a candidate.

In addition to the considerations given to the purity/impurity profiles of a drug candidate, regulatory authorities such as the US Food and Drug Administration (FDA), MHRA and European Union Member States mandate in legislation that investigational drugs are manufactured in accordance with current Good Manufacturing Practices (cGMP). This ensures the quality of the product and is employed to assure against adulteration of investigational products. Furthermore, establishment of a suitable manufacturing process and controls that are development stage specific to meet the QTPP, manufacture of representative non-GMP and GMP material for use in pivotal nonclinical studies and clinical studies, respectively, are also essential.

NON-CLINICAL

To support the initiation of a FIH clinical trial, the non-clinical studies required to be completed prior to that need to be identified and executed. These include pharmacology, safety pharmacology and toxicology studies, either *in vitro* or *in vivo*. Pharmacology studies are particularly necessary to obtain insight in the mode of action of the drug candidate and at what levels of exposure the intended activity is achieved, to inform the levels needed in humans. Careful selection of relevant *in vitro* and animal models is therefore essential, though not always possible (e.g., if the drug target does not exist in animals).

Safety pharmacology studies (effects on respiratory, cardiac, neurological functioning), together with the toxicology studies (including toxicokinetics) are required to assess whether and which potential safety issues are associated with the drug candidate. Dose and exposure at which these toxicities occur determine the maximum recommended starting dose (MRSD) for the FIH study, also taking into account certain safety margins, experience with drugs in the same class and manageability of the identified potential adverse reactions.

Non-clinical studies, and particularly pivotal GLP non-clinical studies, should be conducted using the intended clinical route of administration. The batches of drug used in the GLP toxicology studies should be representative of the material that will be used in the clinical trial. In the EU and US, safety pharmacology and pivotal toxicity studies (including toxicokinetic studies) should be compliant with the OECD Principles on GLP (Series on Principles of Good Laboratory Practice and Compliance Monitoring). Selecting a CMO that is in an OECD country or regularly inspected by an OECD country is important to take into account in this respect.

CLINICAL

Development of a FIH clinical study outline is one of the early activities required, as it will determine for a large part the nonclinical study design. Route of administration, dosing frequency and duration all affect the CMC and non-clinical strategy. In the DDP such outline is usually already described. Closer to the actual start of the FIH trial, a synopsis and protocol have to be written.
Whether healthy volunteers or patients with the disease of interest will be enrolled in the FIH is determined by the drug candidate. Cytotoxic agents, e.g., may only be tested in cancer patients. The non-clinical toxicology results will also determine whether initially only a single administration of increasing dose can be tested, or multiple administrations are allowed. Alternatively, this could be done after evaluation of the safety with the single administration. To get the most out of your first study in humans, one could look for pharmacological effects. Another important document to start creating when CMC and non-clinical data become available is the Investigator's Brochure (IB). This is a document that compiles a summary of all data available for the drug candidate and needs to be updated at least annually to inform regulatory authorities, ethics committees and investigators conducting clinical trials. It also forms the basis for reporting of drug safety information during development and contains a start of what later becomes the Prescribing Information/Summary of Product Characteristics in the US and Europe, respectively.

REGULATORY

Planning regulatory actions is of extreme importance. Checking the plans for CMC, non-clinical and clinical with authorities is usually very helpful. Following the advice is recommended as well, with higher chances of development success. These interactions can be at local level (individual European countries, including UK MHRA), European Medicines Agency (EMA) and FDA level. An experienced regulatory affairs person will be able to devise a strategy for interactions like pre-IND meetings, Scientific Advice/Protocol Assistance, and others. Programs to help small to medium enterprises (SMEs) exist. Programs such as orphan drug designation, Innovative Licensing and Access Pathway (ILAP), Priority Medicines scheme (PRIME), INitial Targeted Engagement for Regulatory Advice (INTERACT) are some of the programs helping with the interactions and providing incentives. The choice of the country to conduct the FIH also has strategic aspects to be considered such as cost, speed of approval and e.g., patent restoration time in the US from the moment an IND is open. An early, strategic regulatory plan is therefore important.

Although the technical aspects of drug development are directly tied to the clinical and regulatory strategy and enable the progression of a drug candidate into the clinic, there are also non-technical aspects that need to be considered and indirectly enable a startup transitioning into a clinical-stage company.

Phase Appropriateness

The recent wave of layoffs in the industry is a strong reminder of the importance of phase appropriateness. Oftentimes, clinical-stage companies get ahead of themselves by making unreasonable projections for commercialization without clinical data to substantiate considerably large investments. Inspection readiness, launch planning including commercial CMO selection and tech transfer, and adoption of validated computer systems, are a few of the "too-much, too-soon practices" encountered when working with early-stage pharmaceuticals.

Although it is understood drug development requires long-term planning, the statistics are hard to beat:

- Globally, more than 80% of clinical trials fail to enroll on time resulting in considerable delays and/or the need to add new study sites[1]
- The overall success rate of drugs entering clinical development is estimated at about 10%[2]
- Of the 90% clinical failures of drug development, 40-50% are due to lack of clinical efficacy, 30% unmanageable toxicity, 10-15% poor drug-like properties, and 10% lack of commercial needs and poor strategic planning[2]
- For every 5,000 to 10,000 compounds that enter the R&D pipeline, ultimately only one receives approval for commercialization.

Against all odds, it is imperative for companies to put their focus on what matters most: ensuring the clinical study design and conduct will yield data that is conducive to advancing the drug candidate through the clinical phases, ultimately resulting in a successful NDA/BLA submission and approval.

1. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7342339/
2. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9293739/

An experienced clinical development leader who is supported by knowledgeable, collaborative, and transparent clinical operations are non-negotiable to pave the way for success.

On the CMC front, the US FDA Guidance for Industry on CGMP for Phase 1 Investigational Drugs[3] along with ICH Q7 Guidance for Industry on Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (API)[4] specifically the section on APIs for use in clinical trials, provide a reliable framework for evaluating what are the must-haves and what can wait.

A phase-appropriate, scalable quality system lays the foundation for a company culture of compliance. A handful of value-added procedures that can inform the organization of their responsibilities help to set the stage for either a successful IPO, due diligence, and/or transition to becoming a clinical-stage company.

Plan Ahead

In order to initiate clinical trials in either the EU, UK or the US, both the DS and the DP need to be manufactured under applicable GMP. One of the key considerations in selecting a suitable contract manufacturing organization is to ensure it has the right expertise in the range of services required for the clinical trial material. When moving from the non-GMP to GMP manufacture, the resulting clinical product needs to be of equivalent or better quality to the batches used in non-GMP toxicology studies.

Furthermore, it is important to consider scalability in selection of the contract facilities to allow for the increase in material or resource requirements as development progresses. Testing and further optimization or refinement of transferred synthesis at the selected contract facility may be needed to provide a scalable process for manufacture within their facility. Unless there have been profound manufacturing changes, a formal comparability study is unnecessary.

Project Management & Communication

To facilitate effective decision making and collaboration, it is important to establish a project team at the outset of the drug candidate designation and set clear project expectations. Routine communications are essential to ensure the team is informed and aligned to meet the same targets and any issues are openly discussed and risks mitigated as a team. In this respect, a well thought out project plan serves an as effective tool for communicating and tracking important milestones and ensures clear visibility across the entire team.

When developing project timelines and forecasts it is paramount to allow for additional buffer time for unexpected issues (e.g., shipment failures, deviations) and endeavour to define actual costs (including costs of raw material that are often high yet excluded from cost estimates). This will allow for realistic planning.

Relevant Expertise

Virtual, emerging, and early phase pharmaceuticals and biotechnology companies often rely heavily on expert consultants to support their core team of qualified employees. Often, these consultants join based on referrals or relationships built through prior work experience, and can provide valuable foundational, strategic, and operational guidance while being tactical.

A common pitfall, however, is when their presence and expertise is siloed, with a lack of visibility across the organization. This is most evident during the time of compilation of regulatory filings, given the complexity and cross-functional nature of this effort, with large teams of writers and subject matter experts, and technical, quality, and regulatory reviewers. Without clear roles and responsibilities and commonly overlap in expertise, companies face challenges in figuring out who is who, and how they fit in the organization.

In addition to a current organizational chart that includes consultants, a helpful tool companies can utilize to foster transparency is a profile slide deck containing a few words on the core expertise of each team member, their location/time zone, and their key role in the company. Sharing this information proactively creates stronger bonds across departments leading to high functioning, cohesive teams.

Likewise, it is crucial for companies to invest in a knowledgeable and experienced project manager. Their role goes beyond creating attractive presentations with pipelines and milestones and time-consuming Gnatt charts to illustrate dependencies, by creating visibility across the organization on the resources available, their unique expertise, and pave the way for effective collaboration. The project manager is essential in ensuring a running roster of experts accessible across the organization is available, fostering teamwork and camaraderie, and proposing strategic meetings with the correct players to create the necessary visibility for maximum efficiencies.

3. https://www.fda.gov/media/70975/download
4. https://database.ich.org/sites/default/files/Q7%20Guideline.pdf

Clear Vision

One of the first questions asked of prospective clients seeking GxP compliance and Quality Assurance support is: **What is your vision for the organization?**

The aim is to understand if a light aircraft or the next Boeing 777X is being built.

When organizations can articulate with clarity their vision, employees, consultants, and partner vendors are able to embrace it and align their respective teams with the set strategy to ensure they are all working towards the same goal. An organization pursuing a drug candidate with the intent to capitalize on the asset before it even enters the clinic will innately have different milestones from an organization that intends to enter the clinic and stick with the program long term. By sharing the vision and communicating with the organization as the vision takes shape, evolves, and/or changes, organizations can maintain engagement and solicit feedback from their expert teams on ensuring the organization is putting its time and resources on the right considerations.

Compliance & Culture

Compliance and culture start at the top. This is why management's responsibility is a key part of ICH Guideline Q10 on Pharmaceutical Quality Systems. Senior Management is responsible for demonstrating "strong and visible support for the pharmaceutical quality system and ensuring its implementation throughout the organization".

While compliance can be black or white, quality is more of a spectrum, with management setting a point of reference for how the organization will adopt and endorse it. Thus, it is imperative for senior management to understand the role they play in creating a compliant organization that is quality-oriented, and where a positive culture of respect, collaboration, and excellence is fostered.

In early-stage companies, founders and the founding team generally hold a significant stake. As the company culture emerges, management must be prepared for tough conversations as it relates to organizational direction, and to make the necessary adjustment to maintain a culture of collaboration, transparency, and teamwork, which in turn lead to compliance and quality.

Having an experienced HR professional on board becomes a must for organizations that are in it for the long term. Their expertise is required not only to stay in compliance, but to drive the growth of the organization and maintain the balance between strategic and tactical hires.

A common pitfall of early-stage companies is to hire high level executives as a strategic front for fundraising purposes, overlooking the more tactical, value-added hires that are needed during development. Further, executive hires who only have big pharma experience can be detrimental to the fast-paced, nimble, phase-appropriate mindset needed in an early-stage company. Working with an experienced HR professional, companies will be better equipped to discern what candidates are able to bring to the table, and "hire fast, fire faster" when the candidates turn out not to be a good fit for the organization.

Conclusion

In conclusion, transitioning into a clinical-stage company even though challenging can be successfully navigated by creating a blueprint of the relevant attributes required for a marketed product, focusing on key factors such as Quality target product profile, phase appropriateness, a Drug Development Plan, sound knowledge of the regulatory landscape and strategy, relevant expertise in conjunction with softer skills such as efficient project management, open and clear communication across the team, appropriate compliance & culture across the organization and a clear vision for success.

SCENDEA

www.Scendea.com
info@Scendea.com

About Scendea.

Scendea is a leading product development and regulatory consulting practice serving the pharmaceutical and biotechnology industry. We are committed problem solvers, redefining the meaning of customer service, with a focus on reducing time-to-market and minimising development costs.

A combination of scientific excellence, industry experience and a collaborative approach enable us to deliver high-quality innovative solutions, which allow our clients to succeed.

Our international team offers strategic and operational support in the fields of quality/CMC, non-clinical/toxicology, clinical/medical and regulatory, which guide products efficiently from early development to marketing approval.

Head Office

Scendea Ltd
20 The Causeway
Bishop's Stortford, Hertfordshire,
CM23 2EJ
United Kingdom

+44 (0)1279 656 305

EU Office

Scendea (NL) B.V.
De Cuserstraat 93
1081 CN Amsterdam
The Netherlands
Tel: +31 (0)208 949 169

AUS Office

Corporate House
Office 40, Level 2
52 McDougall Street
Milton QLD 4064
Tel: +61 721 398 527

US Office

Scendea USA inc.
4079 Governor Drive #5082
San Diego
CA 92122
Tel: +1 619 793 4511

Cadoret Global

www.CadoretGlobal.com
Solutions@CadoretGlobal.com

About Cadoret Global.

Cadoret Global was established on the premise that consultants are partners invested in the success of their Clients.

We specialize in supporting start-up, virtual, early-stage, and small-size pharmaceutical companies in taking their investigational drug through development and clinical trials.

Our aim is to provide high-caliber and phase-appropriate Quality Assurance consulting services tailored to our clients' budget and timelines.

We are here to support our Clients with:

The progressively complex and time-sensitive requirements of getting investigational drugs through development and clinical trials.

The pressing need for a phase-appropriate Quality Management System that runs in parallel with the development lifecycle and is tailored to support both on-site and virtual teams.

The risk-based and relationship-driven qualification and oversight of outsourced manufacturing, testing, storage and distribution of clinical trial materials.

Head Office

Cadoret Global Inc.
2178 Mendon Road
Cumberland, RI 02864
USA

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