Leverage the power of CMC in early drug development

Introduction

The drug development process, from drug discovery to the clinical proof of concept (PoC) is costly and high-risk. The high rewards of a successful development, both ethical and commercial, excites scientists, researchers, and investors . Starting from scientific endeavors, drug discovery is mainly driven by the pre-clinical pharmacology and toxicity as well as the fast entry into the clinical phase to establish the clinical PoC.
Once a pharmacological target is identified and lead chemical compounds emerge from the drug screening process, many activities around drug development take place in parallel, while at the same time depending on each other. Drug development is a multidisciplinary process by which data are generated in various scientific fields: the chemical synthesis of the drug candidate, its characterization, purity, stability, formulation into a finished drug product, the drug product performance, and biopharmaceutics in animal models. These data represent the critical learning curve for a drug and are essential for entry into clinical trials, risk mitigation, and ultimately, development into a marketable product. The systematic processing and documentation of these Chemistry Manufacturing and Control (CMC) data pose a major challenge, especially in expedited drug development and approval procedures, and for smaller companies [1].

Challenges in CMC and CMC regulations

The European Medicines Agency (EMA) CMC guidelines provide general guidance on the expected information to be presented in the Investigational Medicinal Product Dossier (IMPD). For investigational medicinal products (IMPs), the information required in the quality dossier should be phase-appropriate and focus on the risks, thereby taking into account the nature of the product, the patient population, and the underlying disease of the population being studied. [2]. Similar guidelines have been put forward for Investigational New Drug (IND) filings by the United States Food and Drug Administration (FDA) [3] and the Pharmaceutical and Medical Device Agency (PMDA) in Japan [4]. With the CMC guidelines, Health Authorities make clear that a minimum level of information and data is expected to ensure the safety of patients in the clinical trial. At the same time, they offer advance consultations to bring innovative drugs to patients quickly.
Recently, the FDA performed a survey on the success of IND submissions of oncology drugs. IND filings that were not successful primarily affected First in Human trials and were put on hold. Over 40% of these unsuccessful IND filings were due to CMC problems and were submitted predominantly by

sponsors with limited regulatory experience. Resolving the quality issues took on average 114 days but, in some cases, up to more than two years. The review also demonstrated that sponsors with regulatory experience benefited most from the FDA consultations in the pre-IND meetings [5]. CMC is therefore a critical building block for product quality throughout the process, from product development to marketing, and will continue to progress dynamically in the future as also regulatory guidelines evolve. [6; 7].

Building up the right level of CMC at each stage

In the early development phase, the non-clinical studies (e.g., pharmacology, toxicology), have to take place in parallel with the manufacturing and characterization of the drug substance and its formulation development. Since both are interdependent, it is paramount to build a comprehensive and well-coordinated project plan, which successively combines the most important data from both in order to obtain valid evidence on the efficacy, safety, and druggability of the compound. From a CMC perspective, the drug must be characterized in terms of solid state properties, impurities, stability, and solubility, and appropriate analytical methods must be validated. Thus, it is recommended to sufficiently investigate the solid state properties of the drug substance during lead compound selection in order to secure the non-clinical data and to determine the Critical Quality Attributes (CQA) [8; 9]. In addition, impurities have always been an area of major concern, even more so since the revelation of high nitrosamine concentrations in blood pressure medicines known as 'sartans'. It was shown how increased formation of nitrosamines occurred in the course of synthesis optimization, and GMP non-compliance resulting in stricter regulatory guidelines [10]. A multidisciplinary team can avoid such issues by building on the quality by design (QbD) principles for active pharmaceutical ingredient (API) [11] and drug product [12] manufacturing as well as the early establishment of quality systems [13; 14]. This will ensure the generation of a stage-appropriate product, process understanding, and adequate CMC documentation.

Risk mitigation by utilizing external expertise

Ardena ensures the goal of moving from scientific conception to clinical PoC as quickly as possible through coordinated action among its Centers of Excellence (Figure 1).

Figure 1: Ardena's Center of Excellence

Starting from chemical structure, synthesis, and physicochemical analysis, a "druggable" drug substance is developed followed by a scalable formulation based on the defined target product profile (TPP) . From the beginning, process parameters and control are evaluated and CMC documentation is prepared. Problems that occur in the course of development are therefore immediately

identified and resolved. A common issue encountered during development is the solubility profile of a new compound resulting in low or highly variable bioavailability.

A very typical case that Ardena solved was a project with a drug substance with insufficient solubility. The analysis of the solid state properties showed that the cause was a low dissolution rate. Therefore, as a solution approach, the multiple enlargement of the crystal surface area by particle reduction to the nanoscale was developed. Different size reduction methods and stabilization of the nanoparticles were evaluated. During the nano-milling, the particle size change was monitored by laser diffraction allowing the selection of the best milling technology. As depicted in Table 2, the nano-milling led to a 20-fold decrease in the D90. Before selection of the final process parameter and performing the stability, the nanomaterial was analyzed with regard to potential physicochemical changes like the formation of an amorphous drug or different polymorphic forms. Subsequently, the nanoparticles in a suspension formulation were subjected to a stability study at 25°C/60% RH and 40°C/75% RH, confirming 2 weeks stability at accelerated conditions (table 1).

➢ (A) Particle size before and after milling

	Particle size distribution (µm)		
Timepoint	d(0,1)	d(0,5)	d(0,9)
Before milling	1,565	2,757	4,967
Afte milling	0,064	0,125	0,255

Effective size-reduction

➢ (B) Particle size stability in suspension

		Particle size distribution (µm)		
	Timepoint	d(0,1)	d(0,5)	d(0,9)
	T0	0,064	0,125	0,255
25°C/60%RH	T2weeks	0,066	0,130	0,268
	T1M	0,070	0,133	0,271
	T2M	0,073	0,136	0,271
40°C/75%RH	T2weeks	0,068	0,133	0,273
	T1M	0,070	0,134	0,277
	T2M	0,065	0,129	0,281

Stable nanosuspension

Table 1:
Particle size reduction by milling (A) and particle size stability of the nanoparticles under accelerated conditions (B)

In preparation for the Phase 1 clinical trial and IND/IMPD documentation, a bioequivalence study of the nano-suspension against the reference suspension (i.e. with the unmilled API) was performed in Beagle dogs. The nanoparticles showed a 5-fold increase in bioavailability after oral administration (Figure 2).

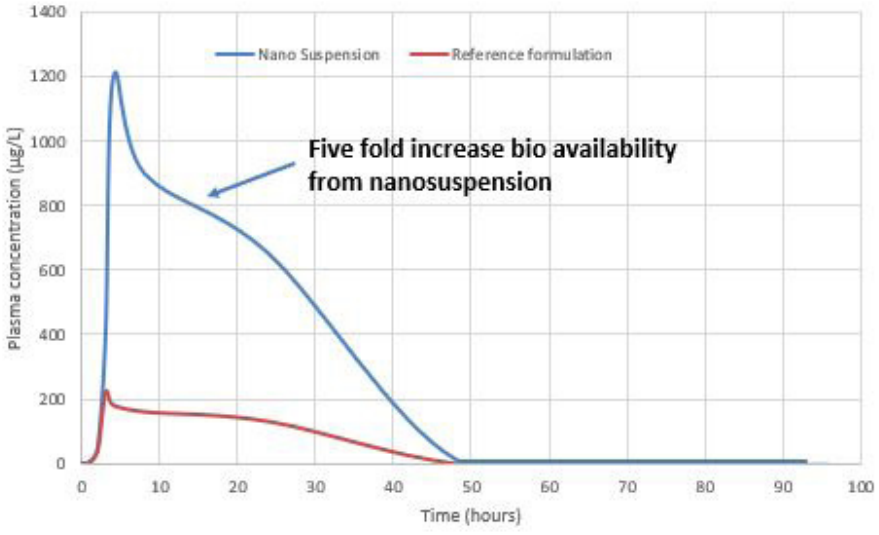

Table 2:
Preclinical study: results

These data constituted an important part of the CMC documentation that Ardena's regulatory experts addressed with the FDA in the pre-IND meeting and contributed to the success of the IND submission. In case of a positive clinical PoC, the collaboration will continue with the development of a solid oral dosage form based on the established nanoparticle technology.

Conclusion

Drug discovery is the source of pharmaceutical innovation driven by scientists from virtual companies through large pharmaceutical companies. The key objective and milestone of drug discovery is the clinical proof of concept. An important step towards this goal is the approval of the first clinical trial application. This requires not only the non-clinical pharmacology, toxicology, and kinetics studies, but also sufficient and phase appropriate CMC work and documentation, the relevance of which is often underestimated. As indicated in the FDA review of IND filings, the likelihood of success also depends heavily on sponsor experience and pre-IND meeting advice. However, through timely consideration of CMC, appropriate expertise, and collaboration, CMC can also be instrumental for milestone decisions contributing to the overall success of a project. Combining the expertise from chemical synthesis and characterization, analytical method and formulation development, clinical supply, and regulatory expertise, partnering with Ardena can accelerate your drug development program, support science based milestone decisions, mitigate the risk, and prepare for a successful market entry from the early stages of development.

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