White paper

Why Performing Key CMC Activities Early Can Aid De-risking Your Drug Development Program

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Introduction

Drug development is complex, and high rates of attrition stem from a variety of factors. Chemistry, Manufacturing, and Controls (CMC) issues account for a significant attrition of the molecules during clinical development.[1] Hence it is paramount that proper attention is given at an early stage to the physicochemical properties to identify robust candidate molecules and formulations which could reduce the probability of attrition and enhance the strength of the pipeline. This activity requires coordination between the CMC group and other functions/key stakeholders such as Medicinal Chemistry, Drug Metabolism/Pharmacokinetics (DMPK), Safety Assessment, Clinical Pharmacology, Clinical Operations, Commercial, and Regulatory. This white paper focuses on best practices for developing a CMC strategy for orally administered small molecule drugs.

Key CMC activities to support candidate nomination and IND-enablement

Lead to Candidate (~18-24 months)

- Early Med Chem API Route
- API supplies for efficacy, PK, dose ranging
- Route screening & optimization
- Assess PhysChem properties
- Stable Polymorph
- Prelim Formulations for PK/Tox
- Analytical method development
- Start prep for GLP Tox

Candidate Selection to FIH (~9-12 months)

- Supply requirements for GLP tox, FIH, & formulation development
- CDMO identification & Route finalization for GMP scale up
- FIH Formulation development
- Phase I Specs & Methods
- GMP clinical trial supplies (CTS) Manufacture
- Drug Substance & Drug Product Stability
- Supply stable and radioisotopes as necessary
- Reg documentation

Once a candidate has been selected, it's critical to pick an appropriate formulation for the early development and clinical studies with an acceptable manufacturing process, stability, and bioavailability. It should be able to be developed and scaled up in a reasonable time frame and with an acceptable cost while meeting good manufacturing practice (GMP) quality standards. While the IND-enabling CMC activities need to be 'phase appropriate,' remember that regulatory agencies could grant an 'accelerated pathway' status to certain indications like oncology or rare diseases. The program would then require ramping up the CMC activities quickly.

Drug substance development

During the early phases of drug development, Med Chem Batches are typically produced in the range of <10 g to ~100-200 g to support the early clinical studies. Phase appropriate drug purity profiles (e.g., >95%) should be achieved for these Med Chem batches. The physiochemical characterization outlined in the following sections will discuss the properties of the compound and how they may impact its stability, bioavailability, and reproducibility of the manufacturing process. In parallel to the ongoing synthesis of Med Chem lots, thorough route scouting should be conducted to simplify the drug synthesis route as much as possible, improve product yield, and ensure that the intended form can be reproducibly manufactured. Identify the optimal route, and a suitable Contract Development and Manufacturing Organization (CDMO) for the synthesis of drug substance (DS) in support of the Good Laboratory Practice Toxicology (GLP Tox) and Phase 1 clinical studies by the time of candidate nomination.

The DS batch for GLP Tox studies should have all the key observed impurities present for the purpose of tox qualification. In parallel to GLP tox studies, evaluate sourcing of the key starting materials/raw materials and whether any further modifications are needed for the GMP synthetic route. If separate batches are used for GLP Tox vs Clinic, make every effort to generate an active pharmaceutical ingredient lot that is purer for clinical use. This will help avoid formation of novel impurities which may require repeat or bridging of the Tox studies before use in clinical supplies.

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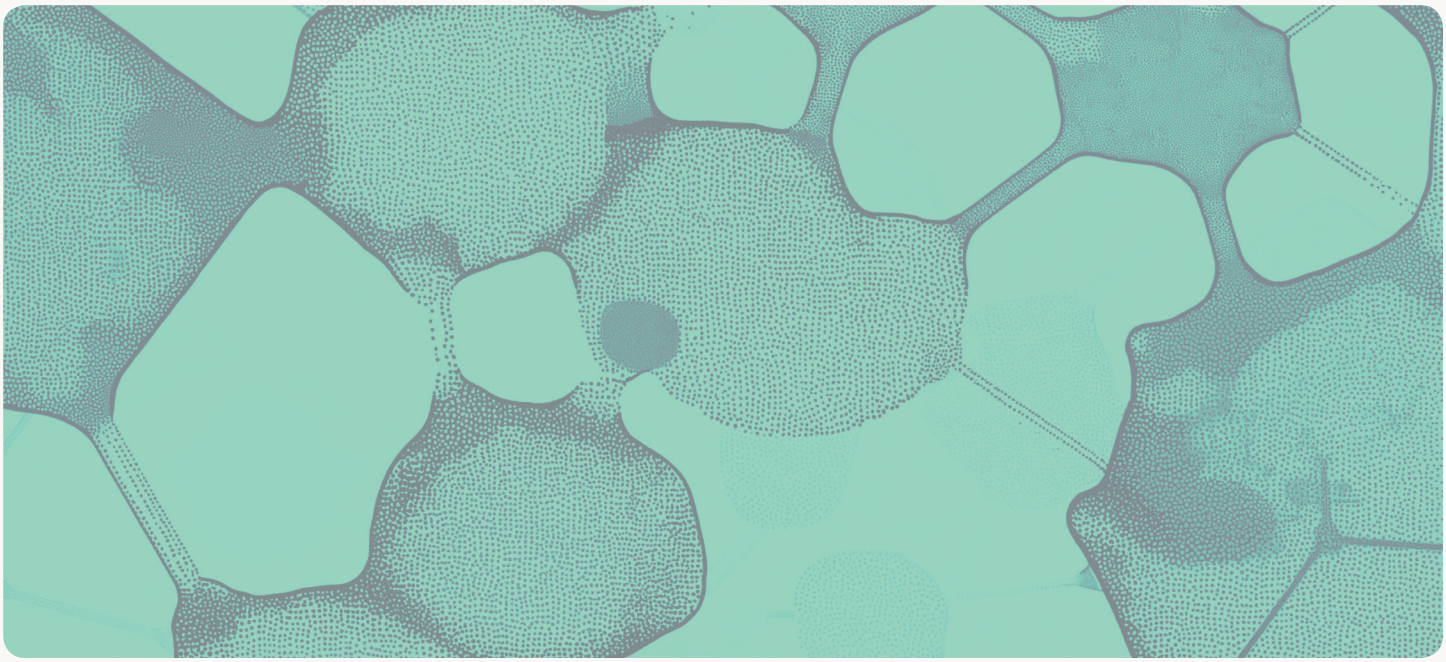
A risk assessment should be conducted for potential genotoxic and nitrosamine-related impurities at this stage. Finally, estimate the preliminary cost of goods at this stage which will be a key consideration especially for the products intended for LMIC ('low- and middle-income countries') regions.



Solid state characterization

Solid state characterization supports a knowledge base that ultimately leads to developing a stable, clinically viable dosage form. A great deal of knowledge could be gained from a limited amount of drug supply in a relatively short period of time.

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Crystalline Form Selection

Different solid-state forms of the same compound could have very different physico-chemical properties such as melting point, solubility, dissolution rate, and stability. X-Ray Powder Diffraction (XRPD) is a very useful technique widely used for both qualitative and quantitative analysis of different solid-state forms.

The amorphous form is metastable and typically has higher solubility when compared with the crystalline material. However, the amorphous form also has reduced stability since it could crystallize over time and thus should be avoided whenever feasible. A crystalline compound may exist in different patterns and therefore demonstrate more than one crystalline form, also known as a 'polymorph' of the compound. Assess the relative stability and bioavailability of different polymorphic forms as early in development as possible. The form of primary interest is typically the crystalline polymorph that is thermodynamically most stable and ideally anhydrous. When water is the solvent associated with the drug, the solvate form is called a hydrate.

Hydrates could be progressed further if they are found to be the most stable form under ambient humidity, routine formulation processing conditions, and have adequate solubility/dissolution characteristics.

Thermal analysis

Thermal analysis of drug substances can provide further useful information regarding the Active Pharmaceutical Ingredient (API) such as melting point, any loss of water or solvent, glass transition temperature (the temperature at which an amorphous polymer changes from a hard/glassy state to a soft/leathery state, or vice versa), etc. which in turn can help us identify any risks for processing, storage conditions, and stability.

Particle size

Particle size is a critical parameter since multiple physical & chemical properties such as drug dissolution rate, bioavailability, content uniformity, flow, compressibility, color, and stability depend on the particle size distribution of the drug substance. If particle size is a critical quality attribute for the product performance, particle size distribution of the API should be optimized and controlled appropriately.

Hygroscopicity

Hygroscopicity refers to the extent of moisture pickup/loss exhibited by an API over a humidity range. Ideally, there should not be any excessive moisture pickup and more importantly, polymorph change over the ambient humidity range (e.g., 40-80% relative humidity (RH)).

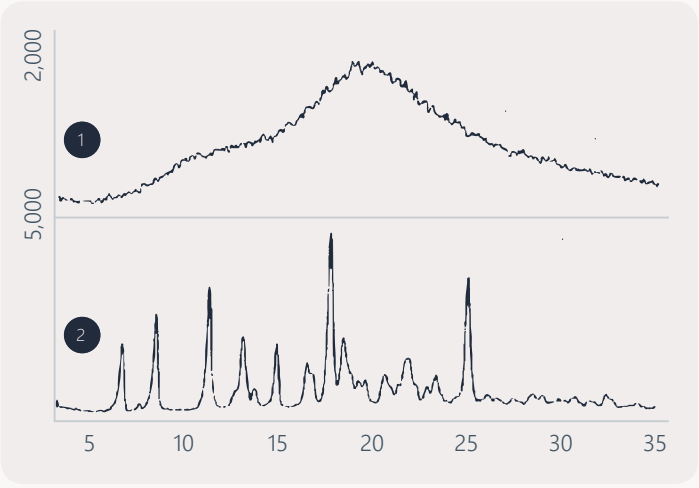

Figure 1. Typical XRPD patterns of amorphous (1) vs crystalline (2) compounds[2]

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Solution state characterization

pKa

This measures the strength of the acid or the base. This is helpful in determining whether a salt formation is feasible and what pH-solubility profile should be expected. It will also help with the counterion selection for the salt formation.

LogP

This reflects the lipophilicity of the molecule. In general, higher lipophilicity results in a higher permeability of the molecule and a better chance of reaching intracellular targets. However, high lipophilicity also results in poor aqueous solubility of the molecule. Both pKa and LogP could be predicted, but it's advisable to generate experimental data for more accurate assessment where feasible.

pH solubility/stability

This provides very useful information on multiple fronts including:

a) Whether the solubility is influenced by changes in pH

b) What is the solubility of the drug across the anticipated pH range in the gastrointestinal tract?

c) Can a suitable formulation for intravenous administration be developed if needed?

d) Whether salt formation is an option for the drug candidate

e) Will the compound be stable during processing conditions or in the in vivo environment?

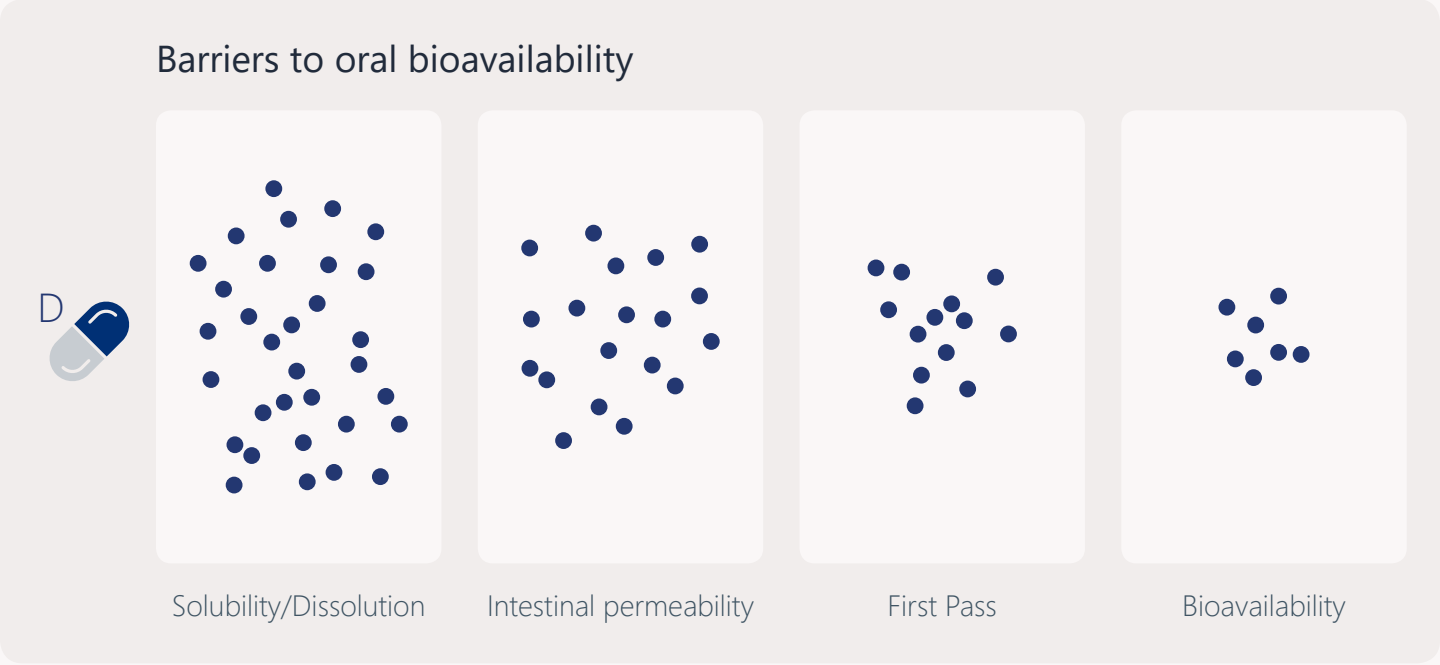

Figure 2. Bio-pharmaceutics assessment

Solubility in bio-relevant media

Solubility in biorelevant media such as simulated gastric fluid (SGF), fasted state simulated intestinal fluid (FaSSIF), and fed state simulated intestinal fluid (FeSSIF) provide a more accurate determination of the soluble fraction available for oral absorption.

Permeability

Along with solubility, permeability of the molecule also has a critical impact on the oral absorption potential of a molecule and could inform about any potential efflux mechanism, which is a barrier to absorption. Permeability is commonly measured across monolayers of Caco-2 cells but other systems such as MDCK and PAMPA can also be used.

Biopharmaceutics Classification System (BCS)

This classification is determined based on the combination of solubility/ permeability profiles. This classification can be used as a basis for determining when in vivo bioavailability (BA) and bioequivalence (BE) studies are needed and can be used to determine when a successful in vitro-in vivo correlation (IVIVC) is likely to predict drug exposure.

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Developability Classification System (DCS)

While BCS is a regulatory tool which is more conservative (e.g., minimum solubility across the entire pH range of 1-7.5) and 250 ml volume available to dissolve the drug), DCS is a more practical and realistic tool as shown below in Fig 4 (e.g., solubility in FaSSIF at pH 6.5, 500 ml volume to dissolve the drug). It can be more realistically used to identify factors limiting oral absorption such as particle size, solubility, dissolution rate. As shown in the figure below, DCS also splits class 2 molecules into class IIa (dissolution rate limited absorption) vs IIb (solubility limited absorption). It can be used to identify key factors limiting oral absorption. It can also help drug developers select the optimal formulation depending on which quadrant the compound falls under. For example, if a compound falls in DCS IIa quadrant, simple approaches such as routine particle size reduction or an alternate salt formation could be utilized to improve the dissolution rate. However, if the compound falls in the DCS IIb quadrant, more complex approaches such as solid dispersion, nano-milling, etc., may be needed.

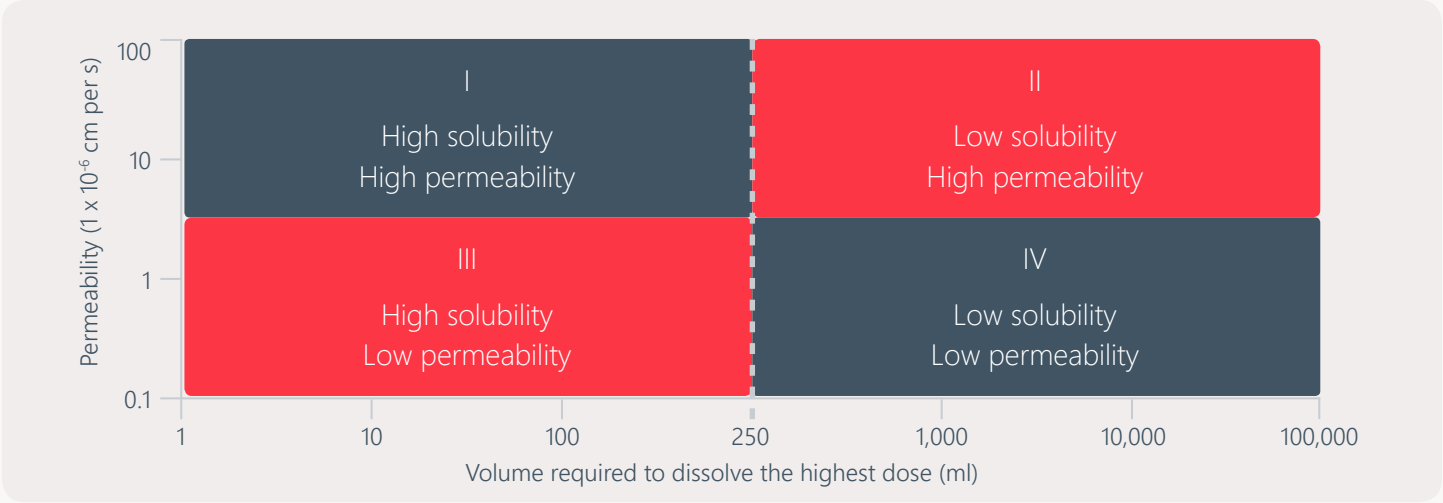

Figure 3. BCS classification system parameters[3]

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Formulation for DMPK/Tox studies

The drug formulation for these should be:

a) able to maintain efficacy in animal pharmacology studies,

b) composed of innocuous or tolerable levels of the selected vehicle,

c) able to 'maximize' bioavailability and achieve dose linearity in PK,

d) and having acceptable processability.

Based on the physico-chemical characteristics mentioned above; diverse formulation approaches can be used to identify an optimal formulation for non-GLP and GLP Tox studies. These could range from simple pH adjustment to routine particle size reduction to more specialized formulations such as amorphous spray dried dispersion & nano-milled suspensions. The vehicle formulations can either be manufactured at the sponsor/CDMO facility and shipped to the PK/Tox study site, and/or a protocol could be provided to the study site for producing the formulation on site. Detailed characterization and stability evaluation of the proposed formulation should be conducted to ensure that it meets the in vitro criteria (e.g. solubility, particle size, etc.) and has adequate stability to support dosing in non- GLP and GLP Tox studies.

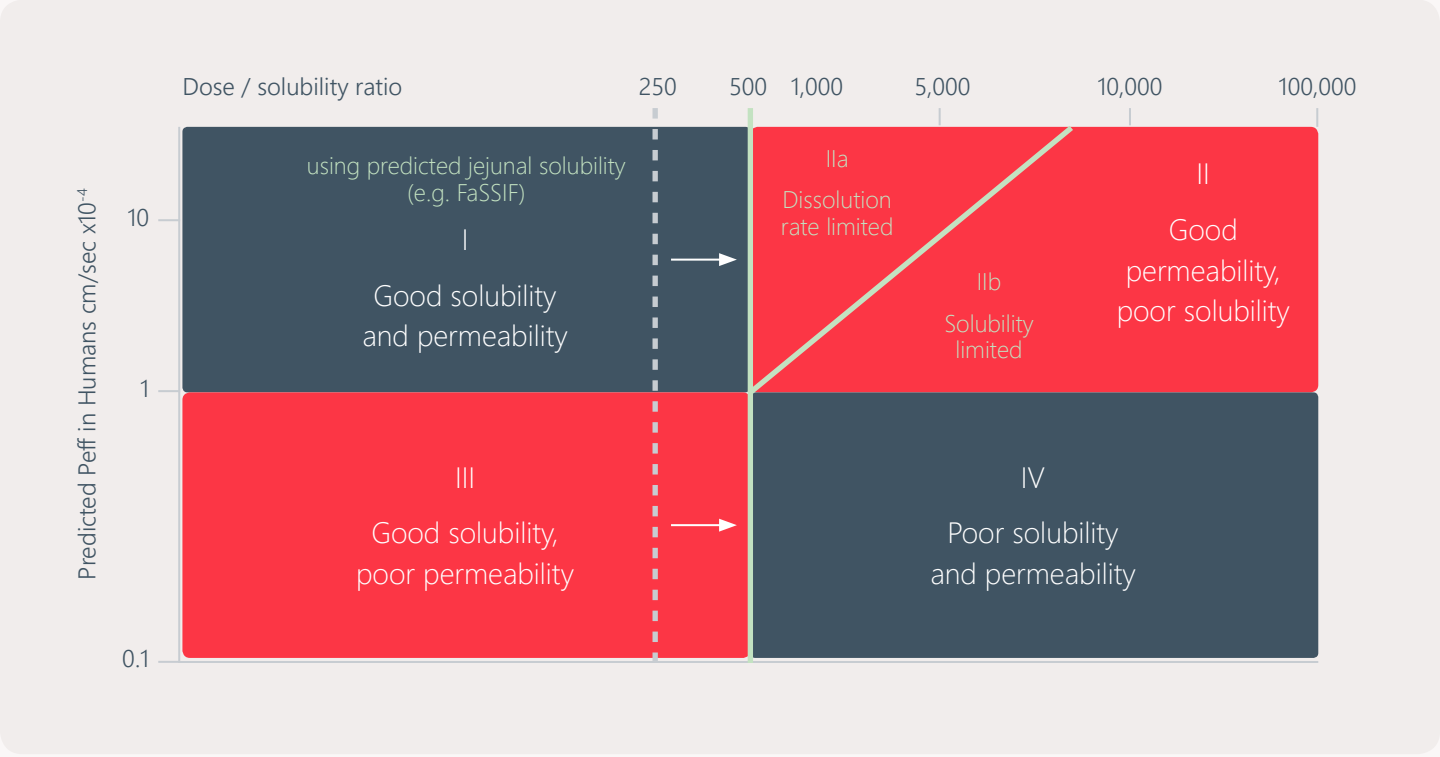

Figure 4. DCS is a modified BCS for more realistic volumes of fluid available in the GI tract and the compensatory nature of permeability on low solubility (modifications from the BCS to DCS are shown in blue).[4]

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Formulation for clinical use

By first intent, a tablet or capsule dosage form should be supplied for the First in Human (FIH) study. Powder in Bottle (PIB), Powder in Capsule (PIC), or Liquid in Capsule (LIC) are also acceptable for Phase 1. Several factors will drive the formulation choice for Phase 1.

There is no 'one size fits all' approach, and the selection of the FIH formulation depends on several factors.

One will be looking for a 'fit for purpose' formulation which can cover the dose range for early clinical studies, could be developed and scaled up relatively quickly, and is expected to have good bioavailability and stability. A simple PIC formulation could provide the fastest path forward. However, the properties of drug substance such as flowability (ability of a powdered material to flow) and ability of the CDMO to handle lower dose ranges will be critical to achieve this formulation without use of any excipients.

Extemporaneous compounding at the clinical site could provide the flexibility of covering a broad range of doses. But this would require a pharmacy setup at the clinical site and is limited to only certain indications and trial designs. If a specialized formulation such as amorphous spray dried dispersion (SDD) is needed, a tablet formulation is preferred for improved stability and dissolution profiles. Regulatory agencies often grant accelerated development pathways for oncology and orphan indications which could require developing a more robust, 'commercial' like formulation (formulated tablet or capsule) earlier on.

Hence there is no 'one size fits all' approach, and the selection of the FIH formulation depends on several factors including API properties, number of intended doses, need for bio-enhancement, trial designs, indication, patient population etc. So rather than making decision in isolation, the CMC, Clin Pharm, Clin Ops, DMPK and other relevant functions should collaborate for a well-informed approach to formulation development. With majority of the early formulation development work being outsourced for small biotechs (and even larger organizations), it is imperative that a suitable CDMO is identified having the facilities, quality systems, bandwidth, and relevant experience of developing the intended formulation.

Analytical methods & specifications

Phase appropriate analytical methods should be developed for early characterization of chemical & physical properties. Forced degradation studies should be performed to understand the key degradation pathways and whether the preliminary method is able to detect and adequately resolve the peaks for active and all potential impurities/degradants. The method should be modified as needed for conducting analysis of the formulations for dose range finding and GLP Tox studies.

For Phase 1 DS & DP batches, phase appropriate method validation should be conducted including specificity, linearity, repeatability, accuracy. Both limit of detection and limit of quantification should be established for the impurities and degradation products.

A quality target product profile (QTPP) should be built based on the available characterization data package, patient unmet need, and intended clinical/commercial targets. This in turn should be able to identify the key physical, chemical, and microbiological attributes for both drug substance and drug product for which specifications need to be established.

Stability

At the time of candidate nomination, minimally 1 month stability should be evaluated for the available drug substance batches in support of the molecule being progressed. Supporting stability data should also be generated for the formulation to be used in the GLP Tox and Safety studies to ensure physical and chemical stability during dosing as well as during formulation storage at the tox site.

For the GMP clinical supplies, a minimum of 1 month stability data is needed for both the drug substance and drug product lots at the time of IND filing with continuation of the stability studies to cover the entire duration of dosing in the clinic.

As outlined in this article, the pre-IND CMC data package is critical for laying the foundation for a robust drug product that can support the compound's clinical development. It involves many interrelated tasks to be conducted in a phase appropriate manner via close collaboration with both internal groups and external CDMOs for drug substance and drug product.

Certara's CMC group is well placed to provide support across all these areas. This could entail a specific gap analysis or in a larger remit, Certara consultants could serve as the CMC steward/project

lead for the clients and provide complete CMC oversight designing studies, providing study cost estimates, and managing activities at the CDMO.

Certara has a dedicated 'Early Development' team which can provide additional needed support in the areas of DMPK, Safety/Toxicology, PK modeling, and Regulatory Strategy. Certara can also provide support for compiling the CMC modules for IND and generating key CMC questions for a pre-IND meeting. Additionally, Certara has state of the art in silico capabilities including the recent addition of Simcyp Discovery Simulator model which could be beneficial in the early stages for formulation selection & PK prediction in an agile manner.

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About the author

Dr. Deven Shah

Dr. Deven Shah is Certara's Chemistry, Manufacturing & Controls (CMC) Vice President helping clients with their drug development CMC needs. Deven also supports the Certara Global Health practice area spending a significant amount of time attending to the Bill & Melinda Gates Foundation work.

Before joining Certara, Deven held positions of increasing responsibility and most recently as the Head of Pharmaceutical Development at Noven Pharmaceuticals and CMC/Preclinical Development Leader at GSK. Deven's impressive background includes extensive experience leading cross-functional matrixed teams comprising of senior leads and hands on experience of CMC development across all phases in formulation development & drug delivery for diverse routes of administration & therapy areas. He also has extensive experience with conducting due diligences, managing biotech alliances, & identifying potential CROs for robust product development. Deven has contributed to regulatory filings spanning from pre-IND to NDA filing stage as well as represented organizations in the regulatory interactions with global agencies.

Deven received his B.Pharm from Jadavpur University in Calcutta, India and Ph.D. (Pharmaceutics & Drug Delivery) from the University of Southern California. He was the recipient of the Procter & Gamble award for excellence in graduate research in Pharmaceutics and Drug Delivery for his Ph.D. work.

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