**SimpliFiH® Solutions for Accelerated Pharmaceutical Development**
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Lonza
Small Molecules

# SimpliFiH® Solutions for Accelerated Pharmaceutical Development

## INTRODUCTION

With the pharmaceutical industry's focus on accelerating all aspects of drug discovery and development, it is crucial to reduce the time from initial product concept to first-in-human clinical completion. Numerous factors can slow this process, but challenges can be overcome by aligning with a single, integrated Contract Development and Manufacturing Organization (CDMO) to reduce the time, complexity, risks, and costs associated with engaging multiple partners.

The CDMO choice has never been more important given aggressive development timelines for candidate molecules, especially those targeting specialty and orphan applications. Important considerations include (1) the increasing complexity of drug compounds that may require special processing or "enabling" technologies to meet target product profiles (e.g., to increase bioavailability); and (2) the fact many of the new compounds are being developed by smaller and even virtual companies that may lack access to all of the equipment and expertise needed to bring a product to clinical trials and, ultimately, to market.

One study showed that interacting with a single CDMO service partner may shorten the first-in-human clinical timeline by an average of 14 weeks, reducing costs by nearly $21 million and increasing net revenues by almost $24 million.[1] Potential advantages include a streamlined contract process; consistent reporting mechanisms; coordinated design and development for the active pharmaceutical ingredient (API), drug-product intermediate(s), and finished drug product; and simplified data sharing, technology transfer, and validation.

## THE SimpliFiH Solutions APPROACH: INTEGRATED SERVICES

To this end, Lonza has developed SimpliFiH Solutions, an integrated service package designed to simplify and accelerate the development pathway, even for APIs with challenging properties such as low aqueous solubility and poor bioavailability. The flexible package is specifically designed to reduce timelines to as little as 32 weeks from API delivery to drug-product delivery for first-in-human testing in a phase-appropriate format. This approach has been shown to reduce Phase I timelines by at least 3 months compared with traditional approaches, while providing the flexibility required to fit customers' specific needs.

This approach, illustrated in Figure 1 for a Phase I project to enhance bioavailability, is designed to meet the needs of most Phase I programs and provide integrated drug substance and drug product in as little as 32 weeks. It incorporates

- a single project manager for ease of communication;
- simple and phase-appropriate service agreements, terms, and conditions;
- fit-for-purpose process development;
- Phase I qualified drug-product methods;
- Good Manufacturing Practice (GMP) documentation;
- suitable packaging to ensure drug-product stability; and
- options for program customization.

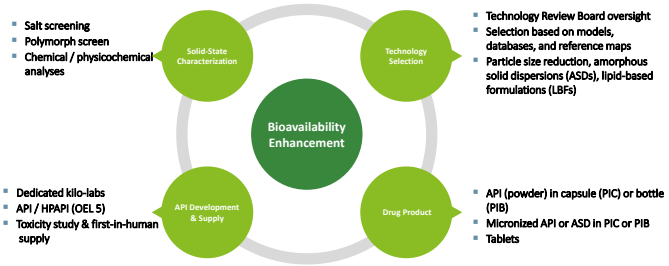


**Figure 1**
SimpliFiH Solutions services for Phase I studies

## THE BUILDING BLOCKS

Some of the main building blocks contributing to the success of the integrated SimpliFiH Solutions package include the following.

*API development and supply:* Dedicated kilogram-scale labs and teams in place to provide the quantities needed for toxicity studies and first-in-human studies for a wide range of compounds, including high-potency API (HPAPIs) (i.e.,

[1] DiMasi, J.A., Z. Smith, K.A. Getz, "Assessing the Economics of Single-Source vs. Multi-Vendor Manufacturing," Tufts University report, October 2017, https://static1.squarespace.com/static/5a9eb0c8e2ccd1158288d8dc/t/5aa2ffa7c830258399bddd82/1520631721090/DiMasi_17.pdf.

compounds with safety ratings up to Occupational Exposure Limit [OEL] 5).

*Solid-state characterization*: Services for API physicochemical characterization, aqueous solubility, and salt and polymorph screening to determine the most progressible solid form. These services play an integral role in Investigational New Drug (IND) studies and later clinical-phase development (Figure 2).

*Technology selection:* Technology review board oversight, proprietary modelling, databases, and reference maps to select technologies and produce drug products that meet target product properties. Enabling technologies include particle engineering (e.g., particle-size reduction), and amorphous solid dispersions (ASDs) produced either by spray drying or holt melt extrusion.

*Drug product:* Ability to provide formulations in many phase-appropriate formats—e.g., tablet, powder in capsule (PIC), or powder in bottle (PIB).

Lonza's SimpliFiH Solutions also includes regulatory services throughout the development process: e.g., providing final Investigational Medicinal Product Dossier (IMPD) and IND Chemistry, Manufacturing, Controls (CMC) sections.

Two case studies are presented below that demonstrate application of the SimpliFiH approach to save time and money throughout the drug-development process.

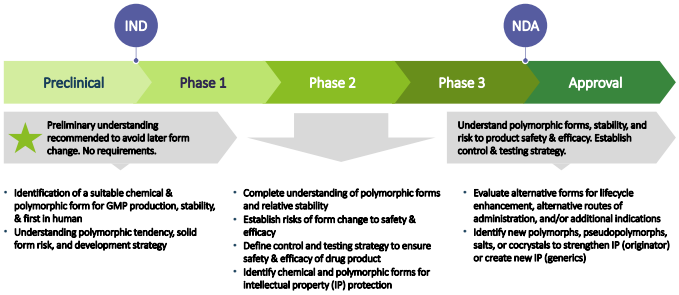


**Figure 2**
Depiction of solid-state services

## CASE STUDIES

### Case 1: Rapid Clinical-Phase Timeline

In the first case study, Lonza was asked to meet a rapid clinical-phase timeline for a HPAPI oncology drug that had promising results in Phase I work. The drug had been granted "breakthrough therapy" designation by the FDA, so the development timeline was accelerated. A different CDMO had been used for early kilogram-scale manufacturing using a multi-step process, so the goal was to transfer this process to Lonza, scale it up, and mount a campaign to manufacture hundreds of kilograms of material for Phase III clinical testing, which was scheduled to start within 4 months.

Lonza collaborated closely with the customer, creating clear project objectives and a focused project plan that was adapted as the project moved forward. The SimpliFiH framework, the strong technical background and expertise of the Lonza project lead, and the clear communication with the customer, resulted in project success.

Clinical material was ready when the Phase III tests began and more than 500 kg of Phase III clinical material was manufactured and delivered within 10 months. This was followed immediately by a successful Product Validation campaign. The timeline from dosing of the first patient to process approval was only 2 years and 8 months.

### Case 2: Technology Selection and Drug Product

In the second case study, the SimpliFiH approach was focused on choosing the correct technology to improve the bioavailability of a high-dose, poorly soluble molecule in a single unit dose.

Based on the physical-chemical properties of the molecule and measurements of its solubility in water and select solvents/lipids, the solubility of the molecule in select lipid vehicles was sufficiently poor that a lipid approach would not lead to a single unit dose. Similarly, based on dissolution rate measurements of a micronized sample, a physiologically based pharmacokinetic (PB/PK) model predicted micronization would not overcome the bioavailability challenge.

To determine the suitability of an ASD approach to improve the molecule's bioavailability, an amorphous solubility measurement was performed. This measurement showed a ten-fold improvement in solubility in simulated intestinal fluid (SIF) relative to that of the crystalline compound. By subsequently measuring drug solubility in the presence of select concentration-enhancing polymers, several lead ASD compositions were identified.

These compositions were manufactured on a scalable, small-scale spray dryer and evaluated using *in vitro* dissolution tests and rapid physical-stability tests. From these evaluations, a 50% drug:Eudragit-L100 formulation was chosen for further scale-up and inclusion into a high-loaded dosage form (HLDF) that contained an equivalent amount of hydroxypropyl methylcellulose acetate succinate (HPMCAS-H) as a concentration-enhancing polymer. Using this composition, the required dose could be administered in a single dosage form that increased exposure in an animal model two-fold relative to the crystalline compound.

The SimpliFiH technology selection program and drug product development provided a clinical-image formulation and *in vivo* animal supplies in just 8 weeks.

## SUMMARY

Careful selection of the right CDMO can make the difference between project success and failure, reducing time, cost, risk, and project complexity. Lonza's SimpliFiH approach offers a comprehensive suite of services and rational approach that capitalizes on the company's extensive expertise across the continuum of drug-product development, manufacture, and approval. The customized approach is based on rational technology selection and capabilities in all the areas needed for a successful CDMO partnership: a full chemistry toolkit, HPAPI capabilities, phase-appropriate processing, enabling delivery technologies, specialized drug-product development and manufacturing, and flexible business models. To learn more, please visit our website.