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WHITEPAPER

Rising to the rare disease challenge: Key considerations in large-molecule orphan drug development

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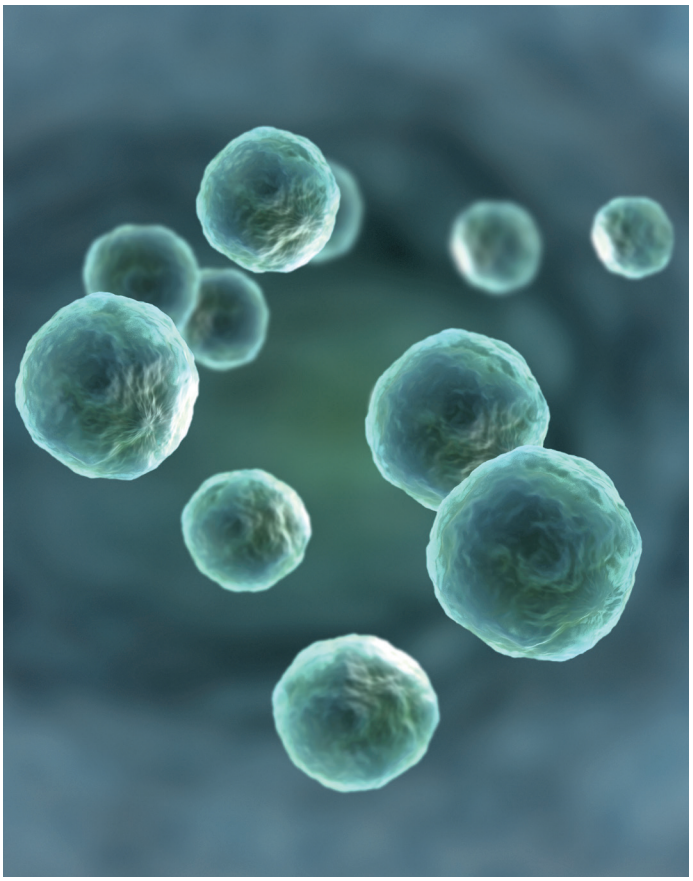
Executive summary

The development landscape for orphan drugs has changed dramatically over the past four decades. Prior to the passage of the Orphan Drug Act (ODA) in 1983 – which incentivized the development of drugs to treat rare diseases – only 35 orphan products had been approved by the FDA. Since that time, the FDA has granted orphan designation to more than 5,099 drug applications and has approved more than 950 orphan drugs.[1]

In addition to the financial incentives for orphan drug research and development, advances in basic and translational science and a greater understanding of disease processes at the molecular level have also contributed to the increased development activity.[2]

Prior to the passage of the Orphan Drug Act (ODA) in 1983, which incentivized the development of drugs to treat rare diseases, only 35 orphan products had been approved by the FDA.

Despite the surge in product development, approved treatments are available for only 5% of the estimated 7,000 known rare diseases.[3] Closing the gap between available treatment options and the needs of patients living with rare diseases requires navigating issues and obstacles typically not encountered in traditional biopharmaceutical product development. In particular, small sample sizes, incomplete knowledge of disease pathology and natural history, and the lack of established clinical end points make it difficult to collect enough high-quality data to draw definitive conclusions. The obstacles are even greater for development of biological products, which account for 40% of the orphan drug applications designated between 1983 and 2019, because of the unique analytical needs and formulation challenges associated with complex, large molecule drugs.[4, 5]



This whitepaper provides targeted guidance for overcoming these challenges and ensuring that enough high-quality data is generated from the start of your orphan drug program to guide evidence-based decision making, based on the following:

- Process design decisions for clinical batches across the three stages of validation
- Key formulation considerations for sterile dosage forms based on the physical, chemical, and biologic characteristics of the drug substances
- Optimal API quantities for preclinical development and Phase 1 studies

Moving the needle in the fight against rare disease requires innovative and flexible drug development approach that spans API production phases to sterile product manufacture and takes into account the data limitations of orphan drug research and the inherent vulnerability of biologics at every stage of the development process.

Introduction

Regulatory incentives initiated by the passage of the Orphan Drug Act in 1983 have sparked considerable growth in the orphan drug market. These novel products are defined by the FDA as "one that affects less than 200,000 persons in the U.S. or meets cost recovery provisions of the act."[6] In 2020, 20 of the 22 therapies receiving breakthrough designation by the Center for Drug Evaluation and Research (CDER) also carried an orphan drug designation, highlighting not only the growing percentage of these novel drugs in the current market but also the potential for their future.[7] A recent report by EvaluatePharma estimates the value of the orphan drug market will reach $217 billion by 2024 after four years of consistent growth.[8]

Bringing biological treatments for rare diseases to market involves facing some steep data collection and process design obstacles. Overcoming these obstacles requires early and careful planning to ensure the collection of sufficient high-quality data needed to inform decisions at each inflection point across the asset lifecycle. To ensure alignment with the policy considerations of orphan drug designation, development teams should consult the FDA throughout the process, prior to application submission, to confirm that the data being generated fulfills their requirements.

The challenge with limited patient data small patient numbers require new dosing and TPP approaches

A new era of biologics that provide treatment to patients suffering from rare disease is a marked difference from the traditional one-size-fits-all blockbuster drugs that have historically filled the industry's pipelines. This focus on smaller patient populations also means smaller batch sizes and clinical studies, which leads to less data. A lack of information about the product creates challenges when trying to understand the dosing and target product profile (TPP), which is critical for orphan indications. While five or six prototypes may be used to identify the most robust and stable TPP for traditional products, many times only two to three prototypes are prepared for orphan drugs.

Without the additional pre-clinical research, it can be difficult to understand a product's long-term stability. Developing laboratory batches that mimic clinical batches are also recommended when possible so that those vials provide a good representation of what will be made in the GMP space for human use. The stability conducted on non-GMP laboratory batches will provide the necessary data to select the best formulation and move into human clinical studies.

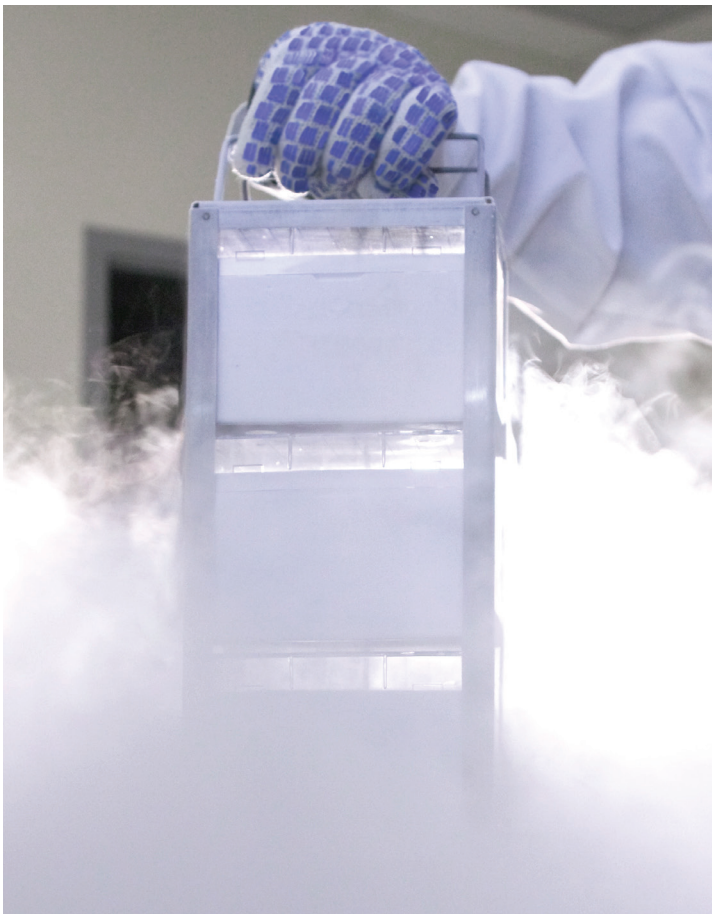
Decisions about the process design for clinical batches should be made once preliminary data from formulation development is available. Some important considerations include:

- **Line selection** – Because small-scale production is required for most orphan drug products, look for small-scale lines already approved for commercial products, which may help with FDA approval. A scale-up strategy should be considered in the early phase to ensure any stability data generated is from a process that closely matches the commercial process.
- **Early phase clinical planning** – Critical process parameters should be established prior to validation (Phase II or III). In some cases, one of the clinical batches should be stress tested to assess the risk of sample holds or worst-case scenarios.
- **Preparation for validation** – It is essential to plan for validation in the early phases because there may be only one batch for each clinical phase, which limits the amount of data available going into validation. For this reason, it's necessary to outline suitable control strategy that will support process validation for both drug substance and drug product.

One of the most important aspects of developing an orphan drug is to ensure good documentation and data collection from the start of the program. Let the data results drive decisions and clearly show a strong rationale for decision making.

Sterile dosage forms: Key formulation considerations

Selecting the right formulation, dosing range, and route of administration can be a difficult challenge in the development of orphan drugs, where time, long-term data, and patients may be limited. The first factor you must consider when developing a formulation for a sterile dosage form is the presentation or component for primary packaging. Typical formats for most sterile injectable drugs include liquid vials, lyophilized vials, prefilled syringes, cartridges, and dual-chamber syringes. For secondary packaging, there are pens and auto-injectors to which syringes and cartridges can be loaded. Liquid vials are the easiest format to use and, therefore, a good place to start. They are the most straightforward presentation in terms of product contact compatibility. Working with a CDMO partner has already pre-qualified many of these systems can shorten overall timelines and eliminate start-up expenses. Liquid vials are also the easiest to manage in terms of inspection and transportation and are good candidates for molecules that are stable either at refrigerated or room temperature conditions long term.



For products that are not stable in solution at room temperature or refrigerated conditions, lyophilized vials can be considered. The transition to a lyophilized formulation will require the addition of excipients as cryoprotectant and bulking agents. The downside of developing a lyophilized formulation is that formulation, cycle development, and characterization will add several months to the overall project timeline. Other options like prefilled syringes and cartridges are utilized for ease of use in the clinic or potentially at home. These are for applications that are low dose (one milliliter or less) and delivered through subcutaneous or intramuscular infusion.

Typically, it is suggested to begin with a frozen liquid vial, if possible, because this is the fastest, easiest, and least-expensive presentation to use when beginning FIH studies. For orphan drugs, there are several considerations that need to be made before choosing a frozen liquid vial as the starting presentation.

Developing a frozen drug product may not be considered the best option due to the difficulty with maintaining frozen conditions during shipment and long-term storage. Depending on the logistics of distribution and use, it may be worth the time and effort to execute sufficient formulation and process development work in the laboratory prior to FIH studies to determine a suitable long-term formulation and presentation. In many cases, a frozen liquid is chosen due to insufficient data at 5°C. In this case, two storage conditions could be explored simultaneously to determine if a refrigerated liquid vial is acceptable.

It is also possible to move forward with frozen liquid vials initially and change to lyophilized vials once the dose is better understood, although there are challenges and costs associated with post-approval changes that can be especially damaging to an orphan drug program. If moving from a vial to a prefilled syringe, compatibility and stability studies must be conducted and should be completed as early as possible, especially if the timeline is compressed, in order to ensure enough data is available at the time of filing.

API quantities for preclinical and Phase I trials: How much is enough?

A question often asked by drug sponsors is how much API is needed for preclinical development and Phase 1 studies. Figure 1 outlines the amount needed for formulation and process development work (left) and for clinical batches (right), which can be problematic for companies with limited materials available. The tables assume a 10mg/mL formulation and 10mL fill volume.

Formulation and process development	
Analytical method development	2g
Solubility studies	10g
Buffer studies	10g
Lyophilization development	15g
Process studies	20g
Lab batch for stability	20g
Totals	77g

Clinical batches	
Line loss	500mL
Pre-filtration bioburden	50mL
BFP validation	250mL
In-process testing (assay/pH, etc)	50mL
Finished product testing	30 vials
Stability	1000 vials
Clinical needs	500 vials
Totals	8.5L or 85g

Figure 1: API needed for Preclinical and Phase 1

The API needed for analytical testing is based on the limit of detection. Two grams is a conservative estimate; the amount could be as low as hundreds of milligrams. The table indicates 10 grams for solubility testing; however, this is necessary only if there is no other information about the molecule. If solubility studies have already been completed, this step can be skipped or modified to confirm the existing data.

Other optional studies prior to the process studies include API-to-API compatibility, API-to-excipient compatibility, and lyophilization development. Lab batch studies should be conducted to ensure stability for the short and long term before going into the first clinical trial materials (CTM) batch. Some of the process studies could potentially be delayed until later stages, although this depends on the customer's timeline. In total, the API needed for formulation and process development is about 80 grams.

For clinical batches, line losses as well as in-process tests and microbiological tests must be accounted for. Vials (liquid and lypholized) for finished product testing required for release must be considered as well. Stability is estimated at 1,000 vials, although this is based on the length of the trial and required tests at each time point. Usually, stability studies are conducted for at least one time point past the length of the trial; therefore, if the trial duration is nine months, 12 months of stability testing would be required. The need for stability also depends on the conditions, and at least two conditions--storage and accelerated, for example—should be tested. Clinical needs are estimated at 500 vials, which accounts for the small patient populations typically targeted with orphan drugs. The total API for clinical batches is about 8.5 liters, or 85 grams (for 10mg/mL product with 10mL fill volume).

Conclusion

The most important consideration for successful commercialization of orphan biological products for is careful early planning to ensure adequate data is generated from the start of development activities. The data limitations associated with clinical research for rare diseases and the complexity of large molecule production processes require substantial contingency planning across the asset lifecycle to understand and prepare for all of the potential impacts on manufacturing and distribution.

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