Initial considerations in the development of "repurposed" drugs for inhalation

Elements to consider when changing the route of administration

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Inhaled administration by nebulizers, metered dose inhalers and dry powder inhalers is a well-established route for effective drug delivery. The advantages of inhaled administration include, but are not limited to: (1) targeted, local delivery to the lungs, thereby maximizing drug concentration in the lung and pulmonary vasculature; (2) potential for systemic drug delivery through the lung periphery; (3) potential for fast absorption into the bloodstream and rapid onset of action; and (4) avoidance of first-pass metabolism. These attributes make inhaled delivery optimal for many diseases, particularly where the lung is the site of disease, rapid access to the pulmonary vasculature is critical, and/or the compound is metabolized or poorly absorbed from the gut.

The inhaled route of administration has been utilized effectively for delivery of medication for many years. However, most compounds are not initially developed for inhalation, despite the fact that it may be the most appropriate treatment option for patients. Well-known inhaled therapies for asthma and COPD, such as bronchodilators and inhaled corticosteriods, were initially developed as oral drugs, but now inhaled formulations are the mainstay of therapy. More recently, products for migraine, bacterial infections, Parkinson's disease, cystic fibrosis, diabetes and pulmonary arterial hypertension have been "repurposed" from oral or parenteral administration, due to the potential advantages of inhaled delivery for product efficacy, safety or convenience. In the future, we may see new therapies for viral and fungal infections, idiopathic pulmonary fibrosis and genetic diseases take advantages of the inhaled route to create more options for management of these serious illnesses [1, 2].

When repurposing oral or parenteral therapies for inhaled administration, there are a number of important factors to evaluate early in the drug development process. Considering these factors may increase chances that a repurposed product could be positioned for successful clinical studies and commercial adoption by patients.

Target product profile (TPP)

When developing a new product, it is a good idea to start with the end in mind. This involves asking questions such as: What product are we developing? Why? Who are the intended users? What are the proposed benefits? What are the risks? What data do we need to generate to demonstrate efficacy, safety and convenience of the product? A target product profile (TPP) provides a starting point for every drug development program, guides the product development process and ensures it stays on track.

For repurposed inhaled drugs, a key question is, "Why are we repurposing the drug for inhalation?" In many cases, this question may seem easy to answer (e.g., to achieve higher local concentrations with low systemic exposure). However, it is important to give this question careful consideration, as the answer will guide foundational activities such as drug and target selection; preclinical activities; clinical studies; chemistry, manufacturing and controls (CMC)/quality and commercial positioning of the product.

Furthermore, it will determine the regulatory strategy. If the new product is sufficiently similar—with respect to patient population, disease and intended use—to an oral or parenteral innovator product, a streamlined 505b2 regulatory pathway may be appropriate, where one can reference published data from an existing,

previously approved innovator product. The 505b2 pathway is attractive because the ability to reference published data may reduce non-clinical and clinical development activities needed for approval, thereby decreasing the time and expense required to develop the product to commercialization. However, in some cases, particularly where a substantial evidence of efficacy or safety may be required to achieve the desired labeling for the product (such as for a new indication, disease or patient population), the 505b2 pathway may not be the best choice. Frequently commercial considerations (sales, product positioning, intellectual property, etc.) can play a role in this decision as well.

Many approaches can be taken to develop a TPP. In its simplest form, a TPP can begin as a "concept statement" that outlines the goals of the development program (therapeutic indication, patient population, mode of administration, etc.). The TPP is a "living document" that gets fleshed out, revised and updated based on scientific, medical and commercial information. The TPP also will guide the CMC/quality aspects of the development program, in the form of a quality target product profile (QTPP), to inform quality-by-design principles for manufacturing. As many inhaled products are regulated as drug/device combination products, the TPP will also influence the design controls (required under CFR part 820) and design history file (DHF) documentation to ensure quality of the inhaler device.

Many document templates are available that can help a sponsor in developing a TPP. For example, the United States Food and Drug Administration (FDA) provides draft guidance for TPP development that may be useful [3]. The FDA describes the TPP as "a summary of a drug development program in terms of labeling concepts" that can be shared with the FDA review staff, stating that submission of a TPP is voluntary. This framework is particularly useful because it outlines the goals of development program in terms of the desired product label. This allows the sponsor to evaluate elements such as indication, patient population, clinical studies, non-clinical studies, etc. and compare them to the innovator product, and to determine where to focus the development program for the novel inhaled dosage form. Typically, some elements may be similar to the innovator product (e.g., indications and usage) but others will be very different (e.g., dosage forms and strengths, non-clinical toxicology). Development of the TPP in this way allows the sponsor to quickly identify potential synergies with the innovator product, as well as differences, and provides a starting point to scope the clinical development program. The TPP may also identify key risks that must be addressed early in the development program for the inhaled compound (e.g., safety of a new formulation, relative bioavailability in animals and humans, local tolerability, etc.)

Choice of active pharmaceutical ingredient (API)

When repurposing a drug for inhalation, an important question is "Which drug should we use?" Though this question may seem trivial, there are frequently multiple potential compounds that could be used to provide the desired therapeutic effect and utilize a common mechanism of action. Each of these compounds may have different potency, pharmacokinetic or pharmacodynamic properties, which may make one compound more attractive than another for inhalation. Furthermore, many compounds also exist in "salt" or "free base" form, and it is worthwhile to consider the effect of the chosen salt form on pharmacokinetics, pharmacodynamics and safety.

When considering "which drug," factors such as supply chain, intellectual property and exclusivity can also be important. A good manufacturing practice (GMP) supply of drug substance will be required for clinical studies so the sponsor will need to manufacture drug or secure GMP active pharmaceutical ingredient (API) from third party vendors. In the case of 505b2 applications, the molecule may also have unexpired patents or regulatory exclusivity. Patents and exclusivity on specific molecules can be searched on the FDA's "Orange Book" website [4] and should be reviewed prior to molecule selection. Though there is a fair amount to evaluate, frequently there is more than one good option, and scientific, commercial, legal and regulatory considerations should be taken into account when choosing which molecule to repurpose for inhalation.

Device and quality considerations

Due to the unique formulation and device requirements of inhaled products, additional product design and development activities may be required to create a dosage form suitable for inhaled administration. As is well known, an inhaled drug/device combination product needs to reliably, consistently and efficiently produce respirable particles in the 1-5 μm size range, in order to ensure consistent lung dose delivery to patients. Nebulizers, soft mist inhalers, metered dose inhalers and dry powder inhalers can all be attractive alternatives for repurposing of oral or parenteral medicines. The pros and cons of each should be discussed in light of the requirements of the patient (e.g., medical indication, inhalation capacity and flowrate, dose, intended users, etc.) and the TPP [5].

For dry powder inhalers and metered dose inhalers, manufacturing processes may need to be developed to produce respirable particles and to fill powders into capsules, blisters or reservoirs for dose administration. Commonly, "particle engineering" or size-reduction technologies are employed to manufacture respirable particles in the 1-5 μm size range. For nebulizers and soft mist inhalers, drug-containing solutions need to be prepared in appropriate container/closure systems.

These drug product and inhaler device manufacturing processes must be controlled in accordance with cGMP standards, and any drug-related and manufacturing-process-related impurities characterized. Finished products must have appropriate drug product stability for long-term storage. Drug/device performance data will need to be generated to demonstrate suitability for intended use and users. Regulatory bodies have established draft guidance that sponsors can utilize during development [6, 7].

During development, the sponsor will likely need to develop additional drug product manufacturing processes and CMC data beyond what is provided by the innovator oral or parenteral product. Though the CMC and quality data required to support a marketing approval is significant, product development activities can be conducted in a "phase-appropriate" manner. Early development should focus on ensuring robust clinical evaluation and product safety. During later clinical trials, the commercial manufacturing processes and product quality specifications can be finalized. Similarly, manufacturing scale for the drug product and the device constituent parts can be expanded in a phase-appropriate manner to meet the needs for Phase I, Phase II and Phase III/commercialization.

Pharmacology, pharmacokinetics, and efficacy

For repurposed drugs, a large body of information is likely known about the product. The mechanism of action may be understood and supporting information regarding relevant *in vitro* and *in vivo* pharmacology may be available. This information can be used to support the design of additional *in vitro* or *in vivo* studies. Additionally, systemic pharmacokinetics and absorption, distribution, metabolism and excretion (ADME) data is likely available from previous studies. These data sets may streamline some of the non-clinical development work needed to support good laboratory practice (GLP) and early clinical studies, particularly if the 505b2 pathway is used to reference published data about the innovator product.

However, the change in the route of administration to inhaled delivery may alter the local and systemic pharmacokinetics and efficacy compared to oral or parenteral administration. The inhaled route of administration is likely to change the dose-dependent and time-dependent concentrations in relevant tissues and plasma. Also, the change in route of administration will likely also require a significant formulation change, which may alter the physical properties and aerodynamic size of the drug particles, causing changes in drug dissolution, deposition and absorption.

Characterizing the local and systemic pharmacology/pharmacokinetics and establishing an effective dose are some of the most critical aspects of developing a repurposed inhaled therapy. Initially, the relevant tissue concentrations and systemic pharmacokinetic profiles can be evaluated in non-clinical models. Both small animal (rodent) and large animal (non-rodent) aerosol *in vivo* studies may be needed to identify the changes from parenteral dosing. Physiologically-based pharmacokinetic (PBPK) models can be useful for extrapolating animal results to humans. In early human clinical studies, dose-dependent pharmacokinetic profiles and local and systemic exposures of the drug can be compared to the innovator product. The local and systemic concentrations and profiles can be used to predict the new "effective dose" of the inhaled drug, which may be significantly different from the oral or parenteral form. For locally acting drugs, the effective dose may be lower than a parenteral or oral dosage. For systemically acting therapies, the inhaled dose may be similar, but drug pharmacokinetic profiles and tissue concentrations may be different due to changes in the route of administration.

Though animal models may be used to establish efficacy and benchmark the pharmacodynamics of the inhaled dosage form against the innovator, in many cases the efficacy of the inhaled product will need to be demonstrated clinically. For some diseases, pharmacodynamic markers can be used to estimate efficacy in early clinical trials, though efficacy will likely need to be demonstrated in pivotal clinical studies. Furthermore, due to changes in local and systemic concentrations and pharmacokinetic profiles, repurposed inhaled drugs may also require a modified dosing regimen (either more or less frequent administration) compared to the oral or parenteral product. The acceptability of the inhaled dose and dosing frequency should match the TPP for the product. In many cases, a different administration profile from the innovator product may be appropriate given the PK profile and the mechanism of action of the drug, but the acceptability of this change should be considered in light of the patient population and intended use.

Toxicology, device biocompatibility and safety assessment

From a safety and toxicology perspective, the innovator product may have established the systemic safety of the orally or parenterally delivered product, and safety pharmacology, carcinogenicity and reproductive toxicity studies may have been performed. The systemic exposure margins of the orally or parenterally delivered compound may be sufficient to cover the drug exposures expected via inhaled dosing, and drug interactions and use in special populations may be understood. Use of the 505b2 pathway allows the sponsor to reference published systemic safety data for the product in order to support safety of the new, inhaled dosage form.

However, changing the route of administration from oral or parenteral delivery to inhaled delivery may require a significant amount of local (respiratory tract) non-clinical safety assessment, particularly since the

lung is typically regarded as a sensitive tissue. Furthermore, the change in route of administration will likely require a change in formulation and manufacturing process, and therefore the systemic safety of any new excipients and manufacturing-related impurities will need to be evaluated.

Non-GLP and GLP animal studies can be useful to understand the effect that changing the route of administration may have on product safety. PK studies can be used to compare exposures of the inhaled dosage form to a comparable oral or parenteral product, in order to reference systemic safety data and design GLP safety studies. Short term, inhaled, dose-range finding studies are also useful to examine local toxicity of the inhaled drug product. Ultimately, GLP studies will be required to demonstrate local safety of the drug product in acute, sub-chronic or chronic settings, dependent upon the patient dosing regimen (short term vs. chronic use). Typically, large safety margins (up to 10x) are preferred for demonstrating local safety of the inhaled drug product [8]. Additionally, special safety endpoints, such as respiratory function testing, may be needed to show that there are no additional complications from inhaled administration of the drug product. In the clinical setting, safety and tolerability of the repurposed inhaled drug will be monitored to understand the risk/benefit ratio of the therapy. The design of non-clinical and clinical safety studies should be discussed with regulatory authorities and/or other qualified persons to ensure that all applicable safety endpoints are met.

Because inhaled products are likely to be classified as drug/device combination products by regulatory authorities, additional safety/biocompatibility evaluation may be needed to establish safety of the inhaler device. Extractables/leachables testing and other chemical characterization may be required to assess safety risks associated with the device contact and duration, particularly on the mouthpiece and other components that may contact mucosal membranes. Gas pathway assessment of particulates and volatile organic compounds (VOCs), as well as other biocompatibility endpoints outlined in appropriate regulatory guidances, may be important to address [9].

Early clinical evaluation

The primary endpoints of early clinical evaluation are safety/tolerability and pharmacokinetic evaluation of the repurposed product. These studies can be single dose or multiple dose and are critical to understanding the tolerability, dose proportionality and pharmacokinetic profile of the inhaled product. Furthermore, early clinical studies allow comparisons to the oral or parenteral innovator product, including comparisons of the pharmacokinetic profile, relative bioavailability and treatment-emergent adverse events (TEAEs) that may be related to the inhaled route of delivery. These early studies help provide a basis for additional clinical studies to further evaluate safety, clinical pharmacokinetics and efficacy in Phase II and beyond.

Summary

"Repurposing" of oral or parenteral products to the inhaled form is a promising way to develop products for treatment for many serious diseases, particularly in cases where the lung is the natural site of action or optimal location for drug delivery. When considering repurposing medications, factors such as TPP, product quality, pharmacology and clinical strategy should be taken into account. These can help facilitate a development program that provides a new, "repurposed" inhaled medication that may be a valuable option for patients, offering enhanced efficacy, safety and convenience.

References

1. Cipolla D and Chan HK. Current and Emerging Inhaled Therapies of Repositioned Drugs. Advanced Drug Delivery Reviews 2018; 133: 1-4.

2. Cipolla D and Gonda I. Formulation Technology to Repurpose Drugs for Inhalation Delivery. Drug Discovery Today: Therapeutic Strategies. 2011; 8(3-4): 123-130.

3. United State Food and Drug Administration Draft Guidance. Target Product Profile—A Strategic Development Process Tool. April 2007. https://www.govinfo.gov/content/pkg/FR-2007-03-30/pdf/E7-5949.pdf.

4. United State Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm.

5. Kaplan A and Price D. Matching Inhaler Devices with Patients: The Role of the Primary Care Physician. Canadian Respiratory Journal 2018; Article ID 9473051.

6. United State Food and Drug Administration Draft Guidance. Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products—Quality Considerations. April 2018. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/metered-dose-inhaler-mdi-and-dry-powder-inhaler-dpi-drug-products-quality-considerations.

7. United State Food and Drug Administration Guidance. Applying Human Factors and Usability Engineering to Medical Devices. February 2016. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/applying-human-factors-and-usability-engineering-medical-devices.

8. Tepper JS, et al. Symposium Summary: Breathe In, Breathe Out, Its Easy: What You Need to Know About Developing Inhaled Drugs. International Journal of Toxicology 2016; 35(4): 376-392.

9. United State Food and Drug Administration Guidance. Use of International Standard ISO 10993-1, Biological Evaluation of Medical Devices—Part 1: Evaluation and Testing Within a Risk Management Process. September 2020. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-international-standard-iso-10993-1-biological-evaluation-medical-devices-part-1-evaluation-and.

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