LIKE MANY drug delivery technologies, development of Metered Dose Inhalers (MDIs) is a technical challenge. Formulators must ensure that the finished product is safe, efficacious for the duration of the product shelf life, and that it complies with the requirements of the current regulatory landscape.

There are many factors that need to be assessed and brought together to successfully formulate a new product. MDIs are made up of a number of sub-systems, which are required to work with each other to ensure that the finished MDI product operates appropriately. These sub-systems can be broadly summarised as the formulation, the container closure system, the actuator and the secondary packaging. The development of MDIs must therefore use a total system approach to fully design and optimise these products to be robust and reliable during patient use. In addition to designing a robust product, other considerations must be adhered to, including regulatory and quality requirements.

In light of these rigorous processes and requirements, development of a generic equivalent to a current marketed product brings immense challenges. Companies that seek to develop a generic should work with a partner that has the expertise to help them through this process. Doing so will help ensure the smoothest possible path to commercialization and maximize return on investment. This article will outline the six-stage process in the development of generic MDIs.

THE SIX AREAS OF GENERIC DEVELOPMENT OF MDIS

During the development of any generic MDI product, there are various distinct areas that need to be investigated and characterised. A brief description of each follows:

Inhalable therapies require a systems approach to optimize MDIs

By Richard Moody, laboratory manager, 3M Drug Delivery Systems
ANALYTICAL METHOD DEVELOPMENT
Analytical methodology must be phase appropriate and fit for the purpose. Analytical method development and validation is typically delivered via the Quality by Design (QbD) paradigm, applied from feasibility through product launch.

The concept of a lifecycle model described in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines is applied; the analytical method is the “process” and the process output is the reported result.

All methodology has a defined Analytical Target Profile (ATP) and is subject to risk management and continuous improvement processes. The concept of an ATP parallels that of a Quality Target Product Profile (QTPP), as defined in ICH Q8. An ATP is a predefined objective that stipulates the method performance requirements.

Suitable risk management tools such as Fishbone diagrams, Cause & Effect matrices and Failure Mode Effect Analyses identify controls and required experimentation, for each method variable. The critical variables are investigated further by designed experiments to understand the performance of both the Innovator and generic products. This allows method robustness to be inherently built in, rather than challenged towards the end of the method and product development lifecycle.

Finally, the capability of each method is reviewed throughout its lifecycle to deliver continuous improvement.

REVERSE ENGINEERING
To properly baseline and determine the working design space of a generic product, it is critical to gain a thorough understanding of the physical make up and pharmaceutical performance of the innovator product. To achieve this, the current marketed product must be visually examined for general design, primary/secondary packaging and additional features such as the presence of a dose counter. Measurements are taken of hardware parameters that may influence product performance, including actuator exit orifice and jet length, and the impact of altering these parameters is determined.

Additionally, the design and construction of the container closure system may provide useful insights into the formulation characteristics and stability. For example, if a coated canister is used, there may be potential for drug deposition or an interaction with the base material of the canister.

In the case of a suspension product, visually assessing the emitted dose provides information on the particle size of the Active Pharmaceutical Ingredient (API) and an indication of the route of manufacture or size reduction technique. Understanding and matching the particle size distribution of the marketed product is critical in producing a generic product that meets both the in-vitro and in-vivo regulatory requirements.

A further visual assessment of the formulation offers insight into the suspension characteristics and formulation composition. The rate of creaming or sedimentation is useful to understand when developing robust analytical methods.

Base-lining the marketed product for pharmaceutical performance offers a working target specification. In addition, base-lining of the marketed product is done to understand its batch-to-batch performance and performance over its shelf life to establish targets for key performance indicators. These factors will include characterizing key dosing parameters across multiple batches. Key pharmaceutical performance tests are assessed, including delivered dose and Aerodynamic Particle Size Distribution (APSD). When formulating an MDI product, these base-line parameters ensure that the product is developed to match the current marketed product.

PRODUCT FEASIBILITY
During the initial product feasibility stage, all public domain information is reviewed, and an assessment of project risks is initiated. This ensures that all prioritised factors are included in the work plan. In scoping a project, it is vital that all factors within the plan are considered. While not all options will be required and/or desirable for a given project, the rationale for not performing a certain area of work should be considered.

Following an initial screening, pre-formulation activities are required. These will include a thorough characterization
of the API and any other excipient candidates. Studies may also be required to match the particle size distribution of the API to that of the marketed product.

Once a suitable API is attained, formulation based activities are required to assess and optimize the propellant and formulation system. These studies will include several approaches. The experienced formulator will design a study based on the requirements of a single program. In general terms, activities to be carried out during this phase will include assessing the solubility of the API in formulation compared to the marketed product. This will include aspects to assess the physical (e.g., Ostwald Ripening) and chemical compatibility of the API in formulation.

After the systems are further categorised, more detailed formulation activities are required in order to optimize the test product with that of the innovator. Typically a Design of Experiment (DoE) approach may be employed in order to assess a whole raft of responses compared to the innovator product, with the aim to match as closely as possible. When an acceptable match is achieved, this should be assessed to observe the effect, if any, over time. Typically a short-term informal stability assessment will be included for this purpose.

**Actuator Design**

Actuator design takes place in parallel with other areas in the process. During this time, the marketed product is evaluated on key parameters such as mouthpiece design, spray cone, and orifice and expansion chamber geometry. These listed parameters and variants of the design space are then incorporated into the actuator and mould actuators on a single cavity actuator tool. The actuator variants are tested with the given product to evaluate the performance compared to the marketed product. From testing, the key actuator geometries are determined, which are then implemented into an optimal device to be used in the stability and clinical program. Upon successful completion of this program, the selected actuator is then scaled up for commercial manufacturing.

The valve variant is also evaluated to ensure compatibility with the integrated dose counter (DC) or dose indicator (DI), if applicable. This assessment evaluates if the selected valve, when paired with the DC/ DI, will tend to fire after the dose counter has committed to its count to eliminate undercounting and potential patient misuse. If this evaluation shows that further optimization is required then this can be achieved with modification to the given actuator.

**Development/Bioequivalence**

European Medicines Agency (EMEA) and Orally Inhaled Products (OIP) guidelines stipulate that product performance has to be within specified tolerances relative to the marketed product. These factors include, for example, the same active substance, target delivered dose within ± 15% and for aerodynamic particle size distribution (APSD), it may be considered acceptable to demonstrate therapeutic equivalence by using comparative APSD in-vitro data only, if the product satisfies all of the other criteria outlined in the guidelines.

The APSD data is deemed to be therapeutically equivalent if the calculated 90% confidence intervals for the observed in-vitro differences of the test and reference products are within ± 15% (average bioequivalence). Outside of these limits, a pharmacokinetic and pharmacodynamic assessment must be made to determine that the test product is equivalent to the marketed product.

**Product Scale Up**

Product and process development should be carefully scoped from start to finish, from feasibility to launch, and marketed product support. A capable development partner should have the ability to provide either an off-the-shelf development
service or a more bespoke plan to suit individual project requirements.

Developers should investigate or consider the following elements for product scale up:

- Design
- Prototype
- Assembly
- Manufacture
- Test new products from concept phase through product and process development
- Lab scale manufacture
- Toxicological (TOX) supply
- Pilot manufacture
- Phase I to phase III Clinical Trial (CT) supply and support
- Process scale up
- Stability manufacture and set up
- Technology transfer
- Data analysis
- Final product commercialization

Manufacturing technology should provide pressure and cold fill manufacturing options from small to large scale as well as final packaging facilities. Manufacturers should also have the capability of custom equipment design and on site qualification to suit specific project requirements.

High quality service and an excellent standard of manufacture should be ensured. The principles of QbD, ICH and current regulatory guidelines, Current Good Manufacturing Practice (cGMP) and manufacturing best practices should be implemented from the very start of a project, continuing right through to the day-to-day routine manufacture, testing and packaging.

CONCLUSION

As this overview illustrates, development of generic MDIs is a technically challenging process that requires significant expertise. The growing market trend towards lower cost generic products means that companies need experienced partners to develop robust generic products that meet the requirements of the current regulatory landscape. The most qualified partners will be able to demonstrate significant experience formulating, developing and gaining successful registration of multiple MDI products.

With more than 50 years of experience in inhalation, 3M Drug Delivery Systems has the technical understanding necessary to successfully partner with pharmaceutical companies to work through the process together and get products to market quickly.

3M offers its partners the benefit of its experience spanning the entire system, from feasibility to component selection to commercial production. Because speed to market is especially vital with generics, 3M’s track record of single-cycle reviews is a particular benefit in this area, helping reduce the risk for partners.

With the application of innovation, scientific know-how, state-of-the-art technology, product design expertise and business acumen, pharmaceutical companies and their partners can ensure a smooth and timely project and a robust submission package. ✪

For more information, visit 3M.com/dds or contact 1-800-643-8086