ASSURE INHALER SAFETY & PERFORMANCE: POLYMERS, COLOUR & ADDITIVES

Here, Stephen J Duckworth, Global Head, Healthcare Polymer Solutions, Clariant Plastics and Coatings, describes some of the application of polymer colourants and additives in respiratory drug delivery devices, highlighting the strict regulatory environment.

According to WHO studies, chronic respiratory diseases (CRDs) affect more than 300 million people. In many cases, these diseases are incurable, but their symptoms can be treated by patient-administered medications, orally inhaled and nasal drug products (OINDPs), that use hand-held delivery devices such as dry powder inhalers (DPIs) and metered dose inhalers (MDIs). As the market for inhaled medications continues to grow, the inhaler segment of the medical device market will continue to be an important consumer of plastics.

> "Device manufacturers have come to realise that any material or formulation change during the lifetime of the product, or at any point in a complex materials supply chain, can invalidate product approvals while introducing the risk of leaching or contamination. Thus, the demand for change control over every ingredient in the manufacturing process becomes a formidable challenge."

The plastic components used in inhalers for OINDPs are often manufactured using a wide range of polymers and additives to achieve vital visual, physical, mechanical, and performance properties. For example, a DPI may be comprised of a combination of polymers such as polypropylene (PP), ABS, polycarbonate (PC) and modified acetal (POM) polymers and the like.

While there are more polymer and additive options available than ever before, the choices open to medical device manufacturers can be circumscribed by strict regulatory demands. The US FDA and relevant EU authorities, for example, require detailed information on material components, formulations, packaging, and manufacturing processes, backed by extensive supporting data with respect to physical and mechanical properties, biocompatibility and toxicity. Once this extensive documentation is complete, device manufacturers can use the specified materials and ingredients in their products with the confidence that they meet with regulatory and application requirements.

However, such documentation is a "point-of-time" submission, covering only the specified materials and formulations. Device manufacturers – and their supply chain managers – have come to realise that any material or formulation change during the lifetime of the product, or at any point in a complex materials supply chain, can invalidate product approvals while introducing the risk of leaching or contamination. Thus, the demand for change control over every ingredient in the manufacturing process becomes a formidable challenge, and one that often is assumed rather than actual.

It becomes essential, then, for device manufacturers not only to select materials that meet necessary criteria and offer complete and appropriate documentation, but also to select material suppliers with great care. Ideally, manufacturers will select suppliers whose facilities, manufacturing processes, and operations are dedicated to ensuring uninterrupted, change-controlled, and continuously compliant material supplies from the early phases of product design and development phases through the lifecycle of the product.

Stephen J Duckworth
Global Head, Healthcare
Polymer Solutions
T: +41 61 469 61 71
E: steve.duckworth@clariant.com

Clariant Plastics and Coatings AG
Rothausstrasse 61
CH4132 Muttenz
Switzerland

www.clariant.com/mevopur

DEMANDING REGULATIONS

There are two major classes of inhalation devices for OINDPs. MDIs (Figure 1) emit a metered dose of medication, carried by an aerosol charge, into the user's mouth and lungs. DPIs (Figure 2) dispense a small amount of a finely powdered drug formulation into an outlet chamber, which is then inhaled by the user through the mouthpiece.

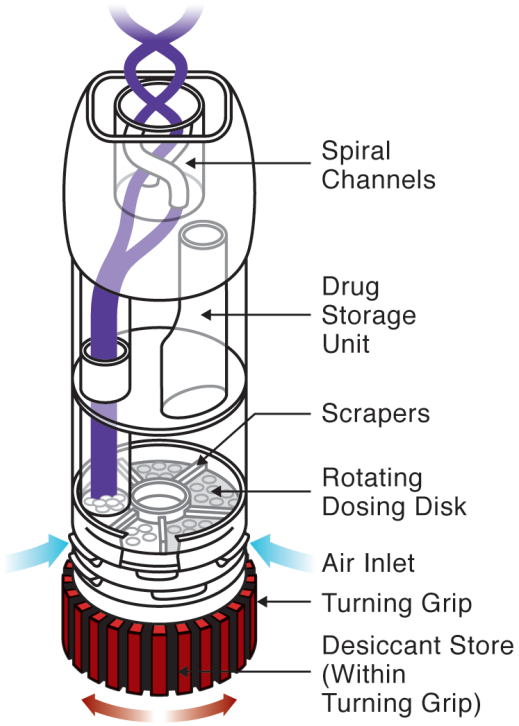

Figure 2: Main components of a typical dry-powder Inhaler.

Concern about the potential risks of materials, additives, and leachables or other contaminants in inhalers is magnified by several factors:

- The FDA rates oral inhalation (together with injection) as the drug administration method associated with the highest concern for risk. This administration method puts the inhaled dosage into direct contact with mucous membranes so it is rapidly absorbed into the body (Table 1).
- The design of both MDIs and DPIs puts plastic components into direct contact with active pharmaceutical ingredients, thus generating the risk of extractables or leachables. MDIs are thought to pose a somewhat higher risk because their aerosols contain solvent compounds that could react more aggressively with polymer components (Table 1).

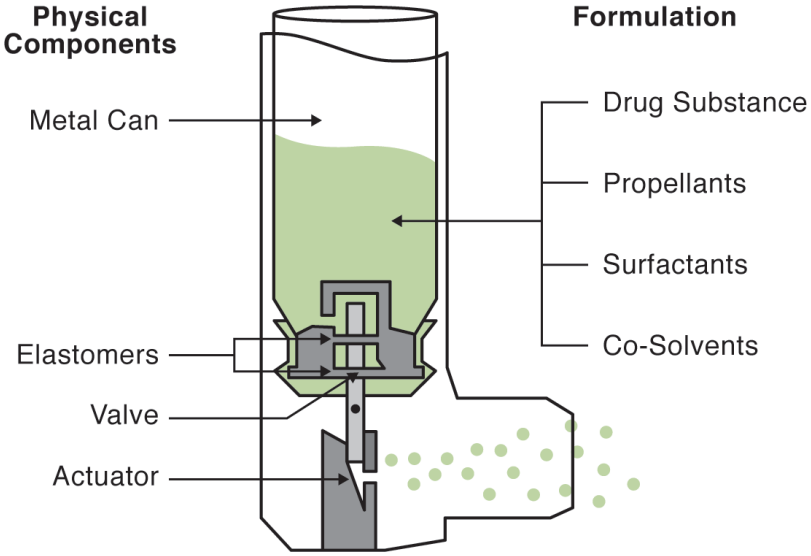

Figure 1: Main components of a typical metered-dose inhaler.

Degree of concern associated with the route of administration	Likelihood of interation (packaging component / dosage form)		
	High	Medium	Low
High	Inhalation aerosols and solutions; injections and injectable suispensions	Sterile powders; Powders for injections; inhalation powders	
High	Ophthalmic solutions and suspensions; Transdermal ointments and patches; nasal aerosols		
Low	Topical soljutions and suspensions; topical and lingual aerosols; oral solutions and suspensions	Topical powders; oral powders	Oral tablets and oral (hard and soft gelatin) capsules

Table 1: Drug Administration, Dosage, and Packaging Interactions. Detail excerpted from "Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics." Published by U.S. Food and Drug Administration, 1999. Found at: https://www.fda.gov/downloads/drugs/guidances/ucm070551.pdf

- Inhalers are designed for repeated usage, so patients may be exposed to inhaler contents 30, 60, or even more times.

To maximise safety, standards and regulatory bodies worldwide are working continuously to update material testing and compliance requirements. For example, the US Pharmacopeia (USP) is in the process of tightening key standards governing plastic packaging materials (USP <661.1>), plastic packaging systems (USP <661.2>), plastic in manufacturing systems (USP <661.3>), and drug delivery devices (USP <661.4>) between now and 2020. These will apply to all materials used in pharmaceutical packaging, including so-called combination devices.

Another international group, the International Pharmaceutical Aerosol Consortium for Research and Science (IPAC-RS) has been working on new, more rigorous testing and control recommendations specific to materials and ingredients used in OINDPs. Published in February 2017, these "Recommended Baseline Requirements for Materials used in OINDPs" make clear that manufacturers

and suppliers must be prepared to implement even higher levels of change controls or risk increased product delays and testing costs. (Full text can be found at: http://ipacrs.org/news-events/news/ipac-rs-updates-recommended-baseline-requirements-for-materials-used-in-oindps.)

COLOUR AND ADDITIVES

This increased regulatory scrutiny comes at a time when – or more likely because – OINDP manufacturers are actually trying to do more and more with colour, functional additives, and other materials in their devices.

Increasingly, treatments are self-administered where compliance to a regular regime is important. US studies indicate only 28% patient-adherence to treatment programs. The cost of wasted medication and follow-on treatment is significant, leading companies to seek out new ways to make their devices more attractive and easier to use. This has led many manufacturers to begin applying techniques perfected in consumer-product design. Colour, for instance, can be used to make OINDPs more appealing to patients so that they are more likely to carry the devices with them and feel comfortable using them as prescribed.

As the market expands, device makers also need to ensure that inhalers are easy to identify and select. Several industry groups have begun recommending that inhalers be colour-coded to indicate the types of medication that they contain. More subtle colour differences can be used to indicate different dosages or other variations. Table 2 shows a coding system typical of those being considered.

Just about any colour imaginable can be developed for OIDNPs and other medical devices, provided that the material properties, regulatory requirements and change management are addressed in the design phase. Suppliers have developed specific product ranges that offer a palette of "standard" or customised colourants already biologically evaluated to ISO10993-1 and USP23 chapters <87> and <88> (Class VI) and, as mentioned in the IPAC-RS guideline, all manufactured with strict quality- and change-control procedures already in place. The same applies to special-effects pigments, which have been used for many years to enhance the look and market appeal of personal-care and consumer goods. When added to plastics, special-effect pigments can give product surfaces a pearlescent, sparkly, or metallic look. Testing has been completed to confirm that the ingredients in these new materials conform to medical and pharmaceutical norms.

Inhaler Colour	Medication Type
Blue	Bronchodilator
Aqua/Green	Long-acting, β_2 agonist
Grey	Muscarinic antagonists
Brown	Corticosteroids
Purple	Compound preparations

Table 2: Example colour coding system for different OINDPs.

> "Though estimates vary widely, the WHO has estimated that more than 8% of the medical devices in circulation are counterfeit, posing not only a significant liability to their manufacturers, but also a risk of harm to patients or healthcare providers."

At the same time, inhalers are mechanical devices. They depend on mass-produced moving parts that must fit together consistently, actuate easily, and reliably deliver a precise dosage of medication anywhere, under any extreme of weather or environment. Achieving and maintaining this level of part-to-part consistency and performance often requires manufacturers to utilise specialised polymer additives. A growing number of functional additives are now available to manufacturers, including:

- Lubricants, which are used to reduce the surface friction between plastic components. These may be part of the original design, or to solve problems encountered during scale-up. Friction reduction plays a vital role device reliability and ease of use in OINDP devices.
- Stabilisers, which prevent certain polymers from losing mechanical properties or prevent the yellowing/discoloration due to gamma or e-beam sterilisation.
- Nucleating agents, which limit the degree of dimensional change in components that can occur when different colours are used. Nucleating agents, which affect how some plastics harden during processing, can help prevent warping due to differential shrinkage. In addition, they can help speed up the process cycle or reduce weight of the component, reducing costs.
- Laser-friendly additives make plastic materials more receptive to laser marking so that the technology can be used for precise, permanent marking even on small, nearly inaccessible surfaces. This type of marking will become increasingly important as unique device identification (UDI) programs are rolled out in both the US and Europe over the next few years.

UDI helps protect patient safety by providing traceability, but is only one weapon to combat the growing problem of counterfeiting, which impacts not only high-value drugs but consumable medical devices like inhalers. Though estimates vary widely, the WHO has estimated that more than 8% of the medical devices in circulation are counterfeit, posing not only a significant liability to their manufacturers, but also a risk of harm to patients or healthcare providers.

One of the most effective ways to protect a reputable product brand is to use multiple level security. This involves the use of covert (hidden) and visible coding on medical devices and their packaging. For plastics, the covert approach employs taggants – unique ingredients that are incorporated into plastic components to provide immediate and incontrovertible proof of the genuine article. Taggants, like other ingredients, are subject to compliance and change-control regulations. Fortunately, solutions are available to meet this challenge.

MOISTURE PROTECTION

Quite often, the medications dispensed through inhalers, particularly DPIs, are moisture-sensitive. Keeping these medications dry, or at a particular relative humidity, is essential not only to maintaining product stability and prolonging shelf life, but to the reliable functioning (e.g. accurate dosing) of the device.

To meet this need, Clariant manufactures a range of controlled atmosphere packaging solutions, including pharmaceutical desiccants, equilibrium sorbents, adsorbent polymers and pharmaceutical closures and containers with these products built in. These products help to protect the drug from moisture even under the severe temperature and humidity conditions used in accelerated shelf-life stability studies.

For example, Clariant's sorbents can maintain humidity equilibrium in pharmaceutical packaging where specific relative humidity conditions are needed, such as in DPI packages. In these packages, equilibrium products perform simultaneously as humectants (desorbers) and desiccants (adsorbers) to maintain an ideal equilibrium relative humidity (ERH). Other desiccant products may be incorporated as washer- or wafer-shaped inserts within inhaler parts, such as the turning grip shown earlier, in Figure 2.

MINIMISING RISK

Device designers, developers, and manufacturers can employ an array of options to add colour and performance to plastic components used in inhalers for OINDPs and other medical devices. The key to successfully employing these options is to understand and manage the regulatory and supply-chain risks that are involved in selecting, sourcing, and controlling these materials through the lifecycle of the product.

Approximately 10 years ago, Clariant Masterbatches recognised supply-chain challenges confronting the healthcare industry and reorganised its approach to the medical device and pharmaceutical packaging markets to help its customers rationalise their approach to risk. This involved creating a network of three global manufacturing plants (one each in the US, Europe, and Asia) and managing them under the ISO13485 quality system with change-control protocols. This is important because, firstly, production of a medical device may be required in different regions or be transferred and, secondly, back-up supply is normally a requirement.

Then came standardisation of raw materials in terms of chemistry and supplier. This process involved the technical, product stewardship and supply chain functions that assess each raw material not only on performance characteristics, but on regulatory criteria such as RoHS, REACh, BSE/TSE and so on, and whether the supply was available in each of the three sites. Each plant uses the same defined raw material ingredients, the same formula, and the same key product quality parameters. The measurements not only include typical tests such as colour and physical properties, but also ISO 10993 part 18 extraction, biological evaluation (ISO10993 and USP <87>, <88>) and batch comparison to a chemical "fingerprint" of a reference product.

CONCLUSION

Whether the issue is regulatory compliance, change control, UDI, counterfeiting prevention, patient acceptance, or usability, there are polymer and additive solutions readily available to help manufacturers get a better OINDP to market more quickly. Once some of the uncertainty that is part of the global material sourcing process has been eliminated, manufacturers can concentrate more on making devices that are more functional, more attractive and, thus, more effective at giving patients around the world greater access to better and safer treatment.

ABOUT THE AUTHOR

Stephen Duckworth is a graduate in Applied Chemistry with over 30 years spent in the polymers and compounding industries in R&D, marketing and operations functions in the US, Europe and Asia, with leading international companies such as Raychem, General Electric (now SABIC), DSM, PolyOne and also as an independent consultant for market analysis, M&A, and Asia entry strategies. He joined Clariant in 2007.

In 2008, Mr Duckworth initiated and led a global project to address the medical, pharmaceutical and healthcare sector that radically changed how Clariant approached this market, and the creation of a new brand MEVOPUR®. Since January 2011, he is the head of a newly formed segment focused on Healthcare, and leads a team of dedicated specialists based in the US, Europe and Asia. This global team initiates and manages developments with pharmaceutical and medical devices companies and their supply chain in areas such as drug packaging and delivery devices, IVD, and invasive devices, focused around an approach of minimisation and management of risk of changes.

Mr Duckworth is Vice-Chairman and Executive Board Member of the cross-industry group MedPharmPlast Europe, and member of the regulatory affairs committee of this association. MedPharmPlast monitors and analyses potential legislation and provides expert insights to the European Commission / legislators, and to the membership.