Koura Zephex®

orbia | Fluor & Energy Materials

DLRC

2024

Whitepaper

Regulatory Landscape for Transition to Low Global Warming Potential (LGWP) Propellants for Pressurised Metered Dose Inhalers (pMDIs)

Authored by

Ian Ashurst, Principal Regulatory Consultant, DLRC

Sharon Robinson, Associate Director & Senior Regulatory Consultant, DLRC

James Murray, Programme Manager, Orbia Fluor & Energy Materials (Koura)

Summary

Introduction

This whitepaper summarises the regulatory requirements for the current transition to low global warming potential (LGWP) propellants in pressurised metered dose inhalers (pMDIs). The focus is on the European requirements: a recent paper by Rik Lostritto[1] has separately given an independent perspective on products regulated by the FDA. The European Medicines Agency (EMA) has recently issued a Q&A on data requirements when transitioning to LGWP propellants[2] and has additionally issued new drafts of key underpinning quality and clinical guidance i.e. the guidelines on the quality requirements for inhaled and nasal products[3] and the guidelines for demonstrating therapeutic equivalence between orally inhaled products (OIP) for asthma and for chronic obstructive pulmonary disease (COPD)[4]. Key aspects of these Q&A and guidance will be explored in this whitepaper.

Background

pMDIs have been used to deliver medicines to the respiratory system since the late 1950s. The 1st generation of pMDIs used chlorofluorocarbon (CFC) based propellants to deliver the aerosol from the formulation; these CFC propellants were found to have a detrimental effect on the ozone layer surrounding earth. The Montreal Protocol[5] drove redevelopment of the CFC based pMDIs and a 2nd generation of pMDIs using hydrofluoroalkane (HFA) propellants, notably HFA-134a and HFA-227ea were developed starting in the late 1980s. These HFA propellants do not have the ozone depleting potential of the CFCs but they do have a high global warming potential (GWP), with HFA-134a having a value of 1430 and HFA-227ea a value of 3220 (AR4, F-Gas 2024/573)[6] corresponding to a 1430-fold or 3220-fold increase in global warming potential over 100 years compared to one kilogram of CO_2. As a result of the Kigali amendment[7] which introduced a rapid hydrofluorocarbon (HFC) phase-down that is to reduce HFC production and consumption by more than 80% over the next 30 years, a 3rd generation of propellants is being developed which are neither detrimental to the ozone layer nor have a high GWP. It is estimated that the Kigali Amendment alone will save up to 0.4 °C of additional warming by the end of this century. (AR4, F-Gas 2024/573)[6].

Two new molecules, HFA-152a with a GWP of 124[6] and HFO-1234ze(E) with a GWP of 1.37 (AR6)[8], are being developed to replace the 2nd generation HFA propellants. The previous transition from 1st to 2nd generation propellants was a prolonged and difficult one for the pharmaceutical industry. Regulatory guidance on the quality of pMDIs was in its infancy when development on this 2nd generation of pMDI products was started and the regulatory guidance was developed as the new products were

developed which meant that the requirements increased as the development progressed. This was further complicated by the low solvency power of the HFA propellants which meant that simple surfactants used in the 1st generation were insoluble in the 2nd generation formulations. Alternatives were found which meant redevelopment of the pMDI valve, can and actuator in many cases had to occur which caused significant complications.

The 3rd generation of propellants have been developed to have a higher solvency power and accordingly it is expected that minimal redevelopment of cans, valves and actuators will be required. The next section of this white paper focuses on the regulatory guidance that applies in Europe and the UK for pMDIs.

Regulatory Requirements

Propellant replacement constitutes a major change to the formulation of established pMDI medicinal products; therefore, data confirming maintenance of product performance and addressing possible toxicity and local tolerance of novel propellants need to be provided to regulatory authorities. The key EU guidance documents on the quality requirements for inhaled and nasal products[3] and the guidelines for demonstrating therapeutic equivalence between orally inhaled products (OIP) for asthma and for chronic obstructive pulmonary disease (COPD)[4] provide a regulatory framework and the new EMA Q&A [Questions and answers on data requirements when transitioning to low global warming potential (LGWP) propellants in oral pressurised metered dose inhalers] supports their interpretation for the specific case of propellant change. The main focus of this whitepaper is to cover the regulatory requirements in the quality, clinical, and nonclinical areas based on the EMA Q&A and guidance documents and also address what should be the legal basis for submissions. Each of the three areas: quality, clinical, and nonclinical, is considered in turn:

Quality Requirements

The quality data requirements for introduction of a new propellant depend on whether the propellant is regarded as novel. The Q&A[2] initially focuses on the first submission for regulatory approval of a novel propellant. This submission will require full quality data in relation to the new propellant according to section 4.6 of the Guideline on excipients in the dossier for application for marketing authorisation of a medicinal product[9]. As for any novel excipient, full details of manufacture, characterisation, and controls should be provided, with cross references to supporting safety data. The quality data should be presented according to the drug substance format, i.e. section 3.2.S of the common technical document (CTD) for the registration of pharmaceuticals for human use: quality (M4Q(R1)).[10] Once the novel propellant has been used in an approved medicinal product with the same route of administration, *with sufficient data available including pharmacovigilance data,* it will become an established LGWP propellant and subsequent submissions would simply need to provide a standard section 3.2.P.4. including suitable excipient specifications.

In addition to the requirements on the LGWP propellant as an excipient, the change of composition will have a significant impact on the drug product functionality and performance and the Q&A pulls out some specific areas to be addressed in terms of pharmaceutical quality:

- All relevant pharmaceutical development studies required that are described in the guideline for the pharmaceutical quality requirements for inhaled and nasal products[3]. The choice of studies should be guided by risk assessment for a potential impact on product quality, safety and efficacy; they are likely to include *in vitro* particle/droplet size and spray characterisation, a reassessment of usability aspects such as priming, cleaning, temperature cycling, and robustness. A change in propellant may also bring differences in moisture sensitivity and ability to leach chemicals from the container.

- Any aspects of the propellant which impact the usability of the drug product such as mouth feel, taste, flammability and expelled pressure should be addressed.
- Update of the finished product release and shelf-life specifications to reflect any changes in characteristics of the reformulated product. However, for a product that is intended to be therapeutically equivalent to the existing formulation, the critical quality attributes should not be substantially changed.
- Discussion of any device related changes with reference to the EMA Guideline on quality documentation for medicinal products when used with a medical device[11]. In addition to functionality-related changes (described in the eCTD dossier) any device changes may require an update to General Safety and Performance Requirements (GSPRs) and therefore may need to build in a notified body reassessment.
- The guideline also notes that applicants can potentially cross refer between products in the MAA documentation, hence, this could be relevant if the same valve/actuator changes are made for several devices for example.
- Manufacturing process validation data, at production scale unless the process can be defined as a 'standard' process.
- Stability data for at least two batches in the commercial container closure system and preferably of production scale to conclude similar stability profile. The Guideline on stability testing for applications for variations to a marketing authorisation recommends these should be of at least 6 months in duration (long term and accelerated conditions).[12]

The *in vitro* characterisation described in the first bullet point may also be used as the first step to establishing therapeutic equivalence between the reformulated and the reference product (see Clinical requirements: section c: Clinical exposure).

Nonclinical Requirements

Before a propellant can be approved for use in pMDI applications it must be shown to have acceptable safety in use. The Q&A[2] focuses on the need for toxicology and pharmacokinetic studies. As excipients, by definition are not expected to have any pharmacological activity, primary and secondary pharmacology studies are not warranted. Safety pharmacology endpoints can be integrated into the toxicology studies.

Full details as given in the excipients guidance[9] should be provided where it states:

- Cross references to supporting safety data should be provided for novel excipients
- Any bibliographical data on the chemistry and on the toxicology and information on where and how the product is currently used should be provided (e.g. industrial application).
- The Community provisions concerning additives in foodstuffs: include criteria based on toxicological data. These criteria ensure that additives are safe for consumption and are supported by thorough toxicological evaluations.
- Data concerning the toxicology of the novel excipient according to the dosage form and the route of administration of the medicinal should be provided in Module 4, the safety section of the dossier.

The Q&A[2] also makes extensive reference to the ICH M3(R2) guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals[13]; this guidance emphasises the importance of providing adequate nonclinical data for any new substance, whether active or excipient. In real terms, this means the following types of toxicology studies should be considered:

- Acute toxicity
- Repeat dose toxicity
- Genotoxicity
- Carcinogenicity
- Reproductive toxicology
- Local tolerance

The general toxicology studies should typically be performed in two species (rodent and non-rodent). In addition, the requirements of ICH S11 (nonclinical safety testing in support of development of paediatric pharmaceuticals)[14] may apply if the drug product is intended for a paediatric population. Lastly, a repeat dose bridging toxicology study with the drug product formulation should be considered.

Clinical Requirements

The introduction of a novel propellant may bring differences in the safety and efficacy of the finished product: either through safety and local tolerance of the propellant, or from changes to local and systemic exposure resulting from differences in delivery of the drug substance(s). These should be addressed: clinical requirements are sub-divided into three specific areas in the Q&A[2]: local tolerance, clinical safety and clinical exposure. These three areas are considered in turn:

a. *Local tolerance* – propellant-only studies should be conducted on both ciliary function and airway sensitivity. Ciliary function studies should be conducted in non-smoking healthy volunteers. For airway sensitivity, lung function studies should be conducted in asthmatic patients, a pilot study may be required if there is no information on the novel propellant in this area.

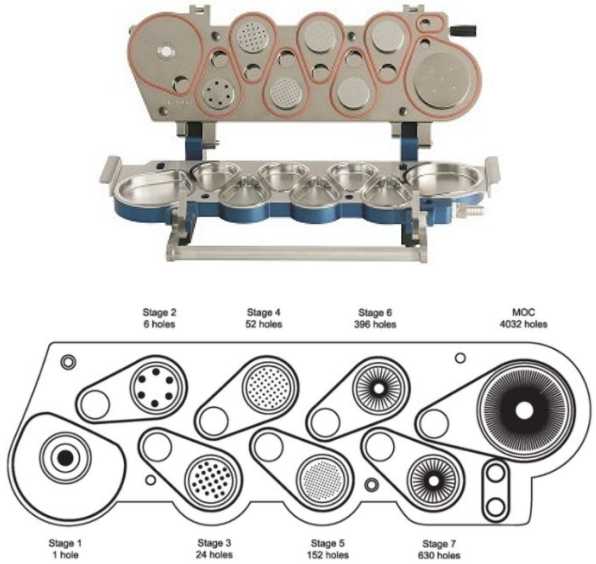
b. *Clinical safety* – a study of at least 3 months in approximately 300 subjects per treatment arm (healthy volunteers or patients) is required to evaluate adverse events such as bronchoconstriction, hoarseness and cough. Ideally, whilst this should be with propellant only to avoid masking of adverse effects of the novel propellant, in practice a 3-month study with propellant only would be hard to conduct so the Q&A recommends that the study be conducted with a single drug substance that is indicated for daily maintenance. This may be interpreted to mean that if propellant-only studies have not been completed, each new combination of drug substance/propellant in the early days of registration of LGWP propellant containing pMDIs would need a 3-month safety study. Combination therapy of 2 or 3 separate drug substances in the same formulation would similarly be affected. A comparator product which is an approved pMDI product supported by a full dossier should be included in the 3-month study.
Subsequent applications for a hybrid version of an approved formulation would not require this 3-month study.

c. *Clinical exposure* – in many cases in the early registrations of LGWP propellant containing pMDIs, the drug product is likely to be a variation of a current product. To demonstrate that the local and systemic exposure of the active substance(s) is not impacted by the propellant change, therapeutic equivalence should be confirmed as outlined in the draft guideline on the requirements for demonstrating therapeutic equivalence between orally inhaled products (OIP) for asthma and chronic obstructive pulmonary disease (COPD).[4] In this guidance, a stepwise procedure is outlined starting with *in vitro* equivalence studies but progressing to pharmacokinetic or pharmacodynamic studies if necessary, which is illustrated graphically in Figure 1.

Figure 1: Schematic overview of the three-step approach for showing therapeutic equivalence for orally inhaled products.

Step 1 – Therapeutic equivalence may be demonstrated using an *in vitro* equivalence study and requirements are laid out in some detail in the draft guideline on the requirements for demonstrating therapeutic equivalence (TE) between OIPs for asthma and COPD[4] rather than being repeated here. The test and reference products should be compared to conclude therapeutic equivalence. The basis for this comparison is an *in vitro* assessment of aerodynamic particle size distribution (APSD); the study should be performed and evaluated using a cascade impactor and a study protocol which includes methods of comparison and acceptance criteria. The general methods are described in Chapter 2.9.18 of the European Pharmacopoeia. A suitable cascade impactor is illustrated in Figure 2 below with a photograph of the opened impactor followed by a schematic of the key stages:

Figure 2: The next generation cascade impactor (NGI)



The NGI is a complex piece of equipment which samples an aerosolised dose according to its particle size in a similar way that the human respiratory system does. In the human respiratory system, the aerosolised dose is inhaled and the larger particles will deposit in the throat and upper airways whilst the smaller particles deposit in the central and peripheral (i.e. alveoli) airways. The NGI mimics this process in sampling an aerosolised dose by drawing it through the impactor at a set flow rate. The impactor is composed of a series of progressively finer screens (stages) where the larger particles deposit on the earlier stages in the impactor and the smaller particles deposit on the middle and later stages. For example, at a flow rate of 30 L/min, the cut-off diameters for each of the 7 stages are given in Table 1 below:

Table 1: NGI Cut-Off Diameters

NGI Stage	Cut-Off Diameter (µm)
1	11.72
2	6.40
3	3.99
4	2.30
5	1.36
6	0.83
7	0.54

Particle sizes typically in the 1 µm to 5 µm range are targeted for the treatment of asthma.

Therapeutic equivalence between two inhaled products is sufficiently demonstrated based only on *in vitro* data, if the applied test product fulfils all the following criteria compared with the reference product:

1. The product contains the same active substance (e.g., same salt, ester, hydrate or solvate).
2. The pharmaceutical dosage form is identical (e.g., pMDI, non-pressurised MDI, dry powder inhaler (DPI)).
3. If the active substance is in the solid state (powder, suspension): any differences in crystalline structure and/or polymorphic form should not

influence the performance of the product (e.g., aerosol particle behaviour, in vitro dissolution with relevant conditions).

4. Any qualitative and/or quantitative difference in excipients must be adequately justified and deemed not to influence relevant Critical Quality Attributes and/or any aspect of product performance other than those that are covered by the comparison of the APSD (e.g. mouth/throat feel, taste, patients' compliance, or safety).
5. Handling of the inhalation devices for the test and reference products in order to release the required amount of the active substance should be similar.
6. For DPI and breath-actuated inhalers, the inhalation device should have the same resistance to airflow (within ±15%).
7. The target delivered dose should be similar (within ±15%).
8. The aerodynamic particle size distribution (APSD) should be similar.

For a change in propellant the evidence for therapeutic equivalence is therefore built largely around the comparison of delivered dose and APSD, but also takes into account the properties of the new excipient, any resulting physicochemical differences and usability aspects.

At least three consecutive batches of the test product and three batches of the reference product should be tested with a minimum of ten inhalers of each batch. The complete APSD profile is required to conduct the test, although stage grouping is allowed for the comparison exercise, if pre-defined and justified. The APSD comparison should be presented as the 90% confidence interval (CI) for the observed ratio of the geometric means of test and reference product and similarity is concluded if the 90% CI is within the acceptance limit of ±15% (85.00-117.65%). Data should be provided both with and without spacer/holding chamber and for all strengths.

If it has not been possible to demonstrate therapeutic equivalence through *in vitro* studies, it is possible to compare the performance of the test and reference products using human pharmacokinetic or pharmacodynamic studies as defined in Steps 2 and 3.

Step 2 – Pharmacokinetic (PK) data are required in the case that the *in vitro* data do not demonstrate therapeutic equivalence. PK studies aim at evaluating pulmonary deposition and total systemic exposure compared to the reference product. PK endpoints are considered valid surrogate markers to adequately predict similarity in the pattern and extent of deposition in the lungs and the systemic exposure and, thereby, equivalence in both efficacy and safety. Detailed guidance on study design, conduct and evaluation is given in the draft guideline on the requirements for demonstrating therapeutic equivalence between OIPs for asthma and COPD.[4]

- For safety, total exposure (AUC_{0-t} and C_{max}) following inhalation in a PK study without charcoal administration should be used.

- For efficacy, exposure (AUC_{0-t}) is also valid as a surrogate marker to reflect the amount of drug that has reached the lungs and C_{max} allows for an assessment of similarity in deposition pattern. Where the contribution from the gastrointestinal tract to the systemic exposure following inhalation is negligible, i.e. <5%, then the total systemic exposure could be used directly as a measure of lung deposition. Otherwise, local exposure could be determined as either exposure (AUC_{0-t} and C_{max}) following charcoal administration to block gastrointestinal absorption or (in case of rapidly absorbed substances) truncated $AUC_{0-30\ min}$ and C_{max} to measure early exposure prior to any gastrointestinal absorption in a study without charcoal administration.

A widening of the acceptance criteria for C_{max} based on high intra-individual variability in line with the recommendations in the Guideline on the investigation of bioequivalence[4] may be possible for substances where a wider difference in C_{max} is considered clinically irrelevant.

Step 3 – If both steps 1 and 2 do not show therapeutic equivalence then any concerns about safety or efficacy arising from the differences observed should be addressed with targeted pharmacodynamic (PD) studies. Appropriate endpoints for efficacy are measures of airway function and/or inflammation, and appropriate endpoints for safety are measures of relevant biochemical and/or physiological parameters. Safety assessments including monitoring of adverse events should always be included in the efficacy studies regardless of design. The Q&A[2] recommends that scientific advice is sought before any PD studies are conducted to ensure that their design is appropriate. It is often difficult to design PD studies due to inadequate assay sensitivity and with some drug substances adequate PD models are not available. At this stage potential reformulation could alternatively be considered to address the lack of therapeutic equivalence via PK studies if a suitable PD study cannot be designed.

In summary, the reformulation of a pMDI with novel propellants requires not only the submission of quality. toxicology, clinical safety and local tolerance data relating to the new excipient (see Section 3 Current Regulatory and Development Status of LGWP Propellants for more on this), but also where an existing pMDI is updated, a careful evaluation of any impact on finished product functionality and performance. In demonstrating therapeutic equivalence between original and reformulated products, developers can show the efficacy and safety profile of the products is sufficiently comparable so that a clinically relevant difference can be reliably excluded. A stepwise approach should be taken for demonstration of therapeutic equivalence, starting with *in vitro* equivalence studies and only progressing to pharmacokinetic or pharmacodynamic studies if necessary. The Q&A on data requirements when transitioning to LGWP propellants in pMDIs[2] provides a helpful overview and roadmap.

This whitepaper focuses on guidance that can support switching propellant for existing medicinal products. For new products that are not relying on the established safety and efficacy of a reference product, these need to be demonstrated through more extensive clinical trials not described here. The principles outlined in the Q&A and supporting guidance should however be followed to support changes made during development.

It is highly recommended that any company intending to develop a pMDI with a novel LGWP propellant should apply for scientific advice to the pertinent regulatory authority throughout the development to discuss the development and regulatory strategy for their product. This will ensure an optimal development in line with the current regulatory guidance and will smooth the path of the regulatory submission. The advice can be sought for quality, nonclinical and clinical strategy and is invaluable in helping companies develop their products.

How is this working in practice? The following section givers a brief summary of the current regulatory and development status of LGWP propellants.

Current Regulatory and Development Status of LGWP Propellants

Nonclinical

Nonclinical programmes for both LGWP propellants to support MAAs are complete or nearing completion. The propellant manufacturers have been working alongside pharmaceutical companies to produce a robust package of data for both propellants and have indicated that regulatory agencies have assessed the development programmes. As a result, both HFA-152a and HFO-1234ze(E) appear to be safe for their intended use as propellants in pMDIs[15-16]

Clinical

Various clinical programmes are well underway or nearing completion for LGWP alterative propellants. Initial clinical investigations for HFA-152a began with a Koura sponsored first in human propellant only trial, where quantitative endpoints to assess safety and tolerability included pulmonary function testing (PFT) and vital signs (HR, BP, RR and SpO_2). Concurrently, taste, clinical observations and PK were performed. Overall, the data showed that following oral inhalation from a pMDI, HFA-152a was well tolerated, had minimal impact on several aspects of taste

scoring and was rapidly cleared from the blood. There were no adverse events during the study.[17]

As mentioned above, the EMA have requested further local tolerance and safety studies be carried out on novel propellants, which includes assessment of mucociliary function and airway sensitivity on propellant only formulations. The assessments of these end points are complete for HFA-152a (NCT05472662, NCT05875025) and HFO-1234ze (NCT05850494, NCT05755932), with indications that these new alternatives have similar safety and tolerability to existing HFAs.[18]

Phase 3 clinical trials that will allow for submission of MAAs to regulatory agencies are either complete or in progress. A major pharma company announced the completion of a HFO-1234ze trial in September 2024 with first submissions expected before the end of the year[19]. Drug product submissions containing HFA-152a are expected to quickly follow in early 2025.[20]

Conclusion

This whitepaper has considered regulatory requirements for the current transition to low global warming potential (LGWP) propellants in pressurised metered dose inhalers (pMDIs). The previous transition to HFA propellants was a prolonged and difficult one for the pharmaceutical industry. In order to navigate the current transition successfully, pharmaceutical companies need to have a good understanding of the current regulations and how to tailor their development and regulatory strategies to be successful. Koura and DLRC can provide expert support based on strong histories working in these areas in both companies.

Support for Companies Developing LGWP pMDI Products

orbia | Fluor & Energy Materials Koura Zephex®

Orbia's Fluor & Energy Materials business (branded as Koura) is a global leader in the development, manufacture and supply of Fluoroproducts that play a fundamental role in enhancing everyday lives and shortening the path to a sustainable, circular economy. Backed by over 35 years of experience, Orbia Fluor & Energy Materials' products are used in a vast range of applications including electric vehicles and energy storage, urban and rural infrastructure, indoor climate management, food and medicine refrigeration and even in treating respiratory conditions through the development of healthy and innovative LGWP propellants for metered dose inhalers. Orbia Fluor & Energy Materials has 1,600 employees and 13 manufacturing facilities worldwide, serving 60 countries through a global sales and distribution network

In addition to this Orbia Fluor & Energy Materials provides contract manufacturing and development services to the inhalation drug product industry. The laboratories based in their Chester site have the capability of providing early phases development to pilot scale with certification to manufacture for clinical trials.

DLRC

DLRC is a dedicated consultancy team of highly qualified and experienced Regulatory Affairs professionals who have come from pharmaceutical company and regulatory agency backgrounds. We have provided our services to over 130

companies of all sizes and backgrounds, enabling them to achieve their strategic and operational development objectives. DLRC's expertise and flexible working approach ensure a highly motivated team that interacts effectively with clients and regulators globally and supports both single-issue and long-term commitment to projects.

We have significant experience in inhaled products and have helped clients develop, write, submit, and approve inhaled submissions for DPIs and Nebules and subsequently manage post-approval regulatory activities for the same clients. In addition, we have managed scientific advice for a number of clients for inhaled products both in Europe and the USA, which includes a number of advice procedures involving LGWP propellants. DLRC also has a device team that will help clients navigate global medical device regulations and assist in the design and development process. The team helps clients meet technical and regulatory requirements while facilitating early interactions with regulatory authorities.

Meet the Authors

Ian Ashurst

Principal Regulatory Consultant, DLRC

Ian Ashurst is a Principal Regulatory Consultant at DLRC. He is a Fellow of the Royal Pharmaceutical Society with a PhD in Pharmaceutics. He is now in his 40th year working in the pharmaceutical industry and has worked in pharmaceutical development for 17 years, CMC technical leadership for 14 years, worked as a quality assessor at the MHRA for three years and is now in his 6th year at DLRC. He has developed and assessed many inhaled products such as Serevent, Flovent, Ventolin, Seretide and Relvar, to name a few. His experience sitting on three sides of the table as a medicine developer, regulator and consultant to medicine developers, gives him a unique perspective and an ability to help clients understand how regulators think and develop strategies likely to succeed. Ian has an excellent record in navigating complex technical and regulatory issues. This record has been honed by many years of working on the propellant transition from CFC to HFA propellants in the 1990s and early 2000s and more recently helping DLRC's clients respond to challenging questions from regulators.

Sharon Robinson

Associate Director & Senior Regulatory Consultant, DLRC

Sharon is a Senior Regulatory Consultant at DLRC with over 20 years of experience and specific expertise in nonclinical regulatory topics. Nonclinical strategy plays a crucial role in the drug development process, and a well-planned nonclinical regulatory strategy can help save time and money. Focusing on nonclinical regulatory topics, Sharon supports clients at all stages of the product life cycle (from early phase development, Scientific Advice, PIPs, and INDs to MAA/NDA/BLA and post-approval procedures) across different research and therapy areas and has experience with both small molecules and biologics. Sharon has held positions in contract research organisations, large pharmaceutical companies, and small biotechs and led the nonclinical regulatory activities for multiple small molecule and biologics filings in the EU and US.

James Murray

Programme Manager, Orbia Fluor & Energy Materials (Koura)

James Murray is a Programme Manager at Orbia Fluor & Energy Materials (Koura) with >10 years' experience. James started life in the R&D labs as a process chemist before moving in to regulated medical propellants. He has a well-rounded knowledge base within the industry, having held roles in quality, validation and development of medical propellants. James now manages the Zephex® 152a nonclinical development programme, contract development & manufacturing capabilities and engages proactively with current and potential customers, covering topics such as regulatory status, stability and quality.

References

1. Lostritto.R., Point of view: MDI propellant switching in the 2020's vs. 1990's: Commentary, perspective and recommendations. Inhalation 18 (4) 22-30, 2024.

2. Q&A on data requirements when transitioning to LGWP propellants. EMA/CHMP/83033/2023. https://www.ema.europa.eu/en/questions-and-answers-data-requirements-when-transitioning-low-global-warming-potential-lgwp-propellants-oral-pressurised-metered-dose-inhalers-scientific-guideline

3. Draft guideline on the pharmaceutical quality of inhalation and nasal medicinal products. EMA/CHMP/20607/2024. https://www.ema.europa.eu/en/pharmaceutical-quality-inhalation-nasal-products-scientific-guideline

4. Draft guideline on the requirements for demonstrating therapeutic equivalence between orally inhaled products (OIP) for asthma and chronic obstructive pulmonary disease (COPD). EMA/CHMP/101453/2024. https://www.ema.europa.eu/en/requirements-demonstrating-therapeutic-equivalence-between-orally-inhaled-products-oip-asthma-chronic-obstructive-pulmonary-disease-copd-scientific-guideline

5. United Nations Environment Programme. The Montreal Protocol https://www.unep.org/ozonaction/who-we-are/about-montreal-protocol

6. REGULATION (EU) 2024/573 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 7 February 2024 on fluorinated greenhouse gases, amending Directive (EU) 2019/1937 and repealing Regulation (EU) No 517/2014 https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32024R0573

7. "Amendment to the Montreal Protocol on Substances that Deplete the Ozone Layer". Kigali, 15 October 2016. https://treaties.un.org/Pages/ViewDetails.aspx?src=IND&mtdsg_no=XXVII-2-f&chapter=27&clang=_en

8. AR6 GWP values: https://www.ipcc.ch/report/ar6/wg1/chapter/chapter-7/#7.6 (Section 7.6.1.1)

9. Guideline on excipients in the dossier for application for marketing authorisation of a medicinal product. EMEA/CHMP/QWP/396951/2006. https://www.ema.europa.eu/en/excipients-dossier-application-marketing-authorisation-medicinal-product-scientific-guideline

10. Common technical document for the registration of pharmaceuticals for human use: quality (M4Q(R1)). https://www.ich.org/page/ctd

11. Guideline on quality documentation for medicinal products when used with a medical device. EMA/CHMP/QWP/BWP/259165/2019. https://www.ema.europa.eu/en/quality-documentation-medicinal-products-when-used-medical-device-scientific-guideline

12. Guideline on stability testing for applications for variations to a marketing authorisation. 21 March 2014 EMA/CHMP/CVMP/QWP/441071/2011- Rev.2. https://www.ema.europa.eu/en/stability-testing-applications-variations-marketing-authorisation-scientific-guideline

13. Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals – ICH M3(R2) https://www.ich.org/page/multidisciplinary-guidelines

14. ICH S11 – Nonclinical safety testing in support of development of paediatric pharmaceuticals
https://www.ich.org/page/safety-guidelines

15. Mohar.I et al, Overview of the Nonclinical Safety Program for 1,1-Difluoroethane (HFA-152a) as a Low Global Warming Potential Metered Dose Inhaler Propellant, DDL 2023

16. Giffen.P et al, The Nonclinical Assessment of Trans-1,3,3,3-tetrafluoropropene (HFO-1234ze (E)), a Near Zero Global Warming Potential Propellant for Use in Metered Dose Inhalation Products, Int J Toxicol, 2024 Jan-Feb;43(1):4-18

17. Kuehl PJ, Corr S, Leach CL: Safety, tolerance and pharmacokinetics of HFA-152a in healthy volunteers. In Respiratory Drug Delivery 2022. Edited by Dalby RN, Peart J, Suman JD, Young PM, Traini D, Watts A. RDD Online; Richmond, VA: 2022: 87–96

18. Laubscher M, Purohit R and Johnson S: Navigating the Transition to Sustainable Medical Propellants: A Supplier's Perspective. In Respiratory Drug Delivery Asia 2024. RDD Online; Richmond, VA: 2024.

19. https://www.astrazeneca.com/media-centre/press-releases/2024/astrazeneca-announces-the-completion-of-the-clinical-programme-to-support-the-transition-of-breztri-to-next-generation-propellant-with-near-zero-global-warming-potential.html

20. https://www.oindpnews.com/2023/11/gsk-announces-upcoming-phase-3-trials-of-hfa-152a-version-of-ventolin-salbutamol-albuterol-mdi/

Contact Us

Koura Zephex®

orbia | Fluor & Energy Materials

DLRC

zephexsales@kouraglobal.com

www.kouraglobal.com

Koura

UK: +44(0)1928 518 880

hello@dlrcgroup.com

www.dlrcgroup.com

DLRC Regulatory Consultancy

UK: +44 (0)1462 372 472

EU: +49 (0)89 44489 311

US: +1 617 851 1438