30 October 2023
EMA/251450/2023
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Questions and answers on data requirements when transitioning to low global warming potential (LGWP) propellants in oral pressurised metered dose inhalers' (EMA/CHMP/83033/2023)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1.	Noveayr Therapeutics
2.	Mundipharma Research Ltd
3.	Joined comments from: International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) International Pharmaceutical Aerosol Consortium (IPAC) European Federation of Pharmaceutical Industries and Associations (EFPIA)
4.	AstraZeneca Pharmaceuticals
5.	Glenmark Pharmaceuticals Europe Limited, United Kingdom
6.	CHIESI FARMACEUTICI S.p.A. Parma-Italy
7.	Viatris
8.	FLEMING REGULATORY LIMITED
9.	Cipla Ltd.
10.	Medicines for Europe

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1.	We welcome your guidance detailing your thoughts on replacing hydrofluorocarbons at a critical point to allow industry to progress with these activities.	
1.	A novel excipient has been defined is an excipient which is being used for the first time in a drug product, or by a new route of administration (ICH). We would like to understand EMAs position on what would constitute a low global warning potential propellant (LGWP) to become an established LGWP. Would this be once it's been approved within any union state in any pMDI, or once it's been approved in combination with a particular active substance or class of actives?	It will be regarded as established once it is included in an approved and marketed product.
1.	We would like to understand if EMA have considered implementing an excipient master file system to facility the submission of extensive data and aspects of supplier confidential data that are needed? Currently routes for submission of confidential data are only in existence through the Active Substance Master File process for active substances. Data generated by the supplier themselves (such as tox or clinical data aspects) may include some confidential aspects which require direct submission to the agency. There are also only a few suppliers of LGWP so a master file process would facilitate more efficient review of information by the agency using versioned controlled copies of master files.	Under the existing EU regulatory framework, there is only the concept of active substance master file, which is applicable only to a well-defined active substance (as indicated in Annex I of Directive 2001/83/EC) and cannot be used for excipients. The information related to excipients shall be provided within the marketing authorisation application by the applicant and any post-authorisation changes as variations are to be submitted by the Marketing Authorisation Holder.
2.	General comment on section 3.3.2 and 3.4: Is it acceptable that a single study proving non inferior efficacy and similar AE profile of the new formulation (if required as per flow	Please note that the clinical safety data is to document any novel propellant whereas data on therapeutic equivalence of active substances is to be shown for each product. Clinical data to show therapeutic equivalence should be

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	diagram) can be demonstrated through a single, active-controlled study, rather than a specific placebo-controlled safety study for the novel propellant and a clinical efficacy study?	avoided as it is difficult to achieve assay sensitivity in such studies.
3.	Within the Q&A document, there is mention that the data requirements can be reduced when sufficient data have been collected (Section 2, General Principles). How will companies know when the data requirements can be reduced when they are developing their products? How will it be visible that sufficient data on any novel inhaled propellant/excipient has been generated?	It will be regarded as established once it is included in an approved and marketed medicinal product.
3.	SAFETY: Could EMA clarify the situations where new safety studies may be needed to be conducted with active pharmaceutical ingredients (APIs)?	Studies with APIs will only be required in case the exposure to the actives is considerably higher with the new propellant. However, in this situation it is recommended to reformulate the product.
3.	Could EMA establish some pathway to share safety information on new propellants, to avoid repeated studies and redundancies, thereby speeding up the transition?	A propellant will be regarded as established once it is included in an approved and marketed medicinal product.
4.	AstraZeneca appreciates the issuance of this timely and informative Q&A on the data needed when replacing HFCs in pMDIs. AstraZeneca has an established and successful track record of developing novel therapies to address respiratory diseases. As part of our call to action for pharmaceutical companies to address the urgent climate crisis (reference), AstraZeneca has made a commitment to phase out HFCs and replace them with gases that ensure the continued safety and efficacy of our respiratory devices while significantly lowering our carbon footprint. We are actively engaged in precedent setting programs to show how we can	

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	successfully accomplish these goals. We appreciate that EMA is supporting these efforts across industry.	
4.	AstraZeneca would welcome further clarity on Clinical Spacer study requirements.	Requirements for spacer data are the same as for (hybrid) generics. In case of specific questions please ask for scientific advice.
5.	**Comment**: Overall guidance is providing good insight on agency's expectations with intention of earliest use of HFCs in pMDI in favour of low global warning potential propellants. The interpretation of this guidance by Generic Industry is, to follow reference medicinal product composition for the new propellant and/or novel excipient and submit post-approval variation with support of *in-vitro* quality data (in accordance with CPMP/EWP/4151/00 Rev 1) and refer **line 172 – 175, figure 1** to demonstrate therapeutic equivalence. This approach can be used to avoid generation of non-clinical data, safety/tolerance, clinical safety and expose volunteers in these studies unnecessarily. Can agency confirms on this interpretation and/or provide more insights helpful for generic industry.	This is correct. If the product following change of propellant is an exact copy as defined by fulfilling all requirements for waiving in vivo data as outlined in the OIP guideline (CPMP/EWP/4151/00 Rev 1) would be acceptable provided the propellant as such is established.
7.	Viatris is a new kind of healthcare company, empowering people worldwide to live healthier at every stage of life. Viatris brings together scientific, manufacturing, and distribution expertise with proven regulatory, medical, and commercial capabilities to deliver high-quality medicines to patients in more than 165 countries and territories. Our portfolio includes numerous branded and a diverse	

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	range of generic and complex generic medicines, providing patients and healthcare systems important options and savings to make healthcare more accessible regardless of circumstance. Viatris is committed to minimizing our impact on the environment while safeguarding a reliable supply of medicine. Viatris acknowledges and respects the decision made by the European Commission to phase out propellants with higher global warming potential. To maintain patient access to generic or hybrid alternatives, the European Medicines Agency should separately consider data requirements for generic or hybrid medicinal products that are developed to be the same as reference medicinal products with established low global warning potential propellants (LGWPs). The following comments focus on the proposals from a patient access perspective.	
8.	The Q&A seems to propose a formulation by formulation approach. More targeted data requirement should be considered, especially for active substances regarded as safe and established treatments with a long history of use such as Salbutamol.	Not agreed. We find it important that therapeutic equivalence is demonstrated for each product.
8.	To avoid unnecessary repetition of studies and significant delays in the introduction of low global warming potential propellants, a grouping approach is suggested. There is currently no 'master file' for excipients in EU (only existing for active substances). We propose maximising the use of a 'master file' concept for the propellant to enable a single assessment by EU	Under the existing EU regulatory framework, there is only the concept of active substance master file, which is applicable only to a well-defined active substance (as indicated in Annex I of Directive 2001/83/EC) and cannot be used for excipients. The information related to excipients shall be provided within the marketing authorisation application by the applicant and any post-

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	regulators of data which is relevant to multiple Marketing Authorisations.	authorisation changes as variations are to be submitted by the Marketing Authorisation Holder.
9.	The Q&A delineates the requirement of propellant safety and tox studies. More details based upon how usage of existing data can be used will be helpful particularly for differentiated generics and under the 10(3) hybrid pathway.x`x`	Existing data may be used irrespective of legal base for the application. The comment not fully understood.
10.	To maintain patient access to generic or hybrid alternatives, the European Medicines Agency should separately consider data requirements for generic or hybrid medicinal products that are developed to be the same as reference medicinal products with established low global warming potential propellants (LGWPs). The following comments focus on the proposals from a patient access perspective.	Not agreed. Data requirement are irrespective of legal base of the application.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 4-6	3.	Comment: The document's title "*Questions and answers on data requirements when replacing hydrofluorocarbons as propellants in oral pressurised metered dose inhalers*" may need to be revised. One of the next-generation propellants with a low global warming potential is a hydrofluorocarbon (HFC 152a). Furthermore, certain pressurised metered dose inhalers (pMDIs) are intended for delivery to the nose. **Proposed change:** 'Questions and answers on data requirements when TRANSITIONING TO LOW GLOBAL WARMING POTENTIAL (LGWP) ~~replacing hydrofluorocarbons as~~ propellants in oral AND INTRANASAL pressurised metered dose inhalers'	The expression HFC is used in the Kigali Amendment to the Montreal Protocol. However, to avoid confusion we have changed the title. Please note that the advice given in this Q&A document is pursuant to orally inhaled products. Products for delivery in the nose is not covered.
Line 38	3.	Comment: In the text , '…of low global warning potential propellants (LGWP)…', there is a typo: 'warning' should probably be 'warming'. Also, the proposed abbreviation LGWP is confusing because 'P' in 'GWP' is typically used for 'potential' rather than 'propellant'. It would be helpful if the first mention of 'LGWP'	Agreed.

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		included a reference to an authoritative source containing a formal definition and further details. . **Proposed change:** "…low global warming potential (LGWP) propellants". Please also include a reference to the definition of "low global warming potential", e.g., as specified in the F-Gas requlations and the KIGALI amendment of the Montreal Protocol.	
Lines 48 – 51	5.	**Comment**: Variation code, type/category, conditions to be fulfilled, documentation to be supplied can be specified here for better clarity to be able to replace existing propellants quickly. Proposed change (if any): -	Not agreed. Submission is to be made as detailed elsewhere. There is nothing special with the change of propellants when it comes to submission technicalities.
Lines 48 – 53	5.	**Comment:** The data exclusivity/market protection periods related aspects should be discussed. Especially in the case where 8 and 10 years period is completed for the reference medicinal product and to be able to change propellant, MAH of reference product has used novel excipients and performed extensive toxicological and clinical studies. In accordance with Article 6(1) of Directive 2001/83/EC, '*for a reference medicinal product, the start of the data exclusivity and market protection periods is the date when the first marketing*	The data exclusivity period is not impacted by the change of propellants. It is not considered necessary to include aspects related to data exclusivity/market protection as these aspects fall outside the scope of this Q&A. Moreover, it is not necessarily a MAH holding the authorisation for a product used as reference medicinal product that perform the studies of novel propellants.

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		authorisations was granted in the Union in accordance with the pharmaceutical acquis. New additional strengths, pharmaceutical form, administration routes, presentations as well as any variations and extensions do not restart or prolong this period'. Considering above a clear statement in the guidance can be useful for Generic companies to quickly adopt revised formulation/new propellant of reference medicinal product. **Proposed change:** *For the generic/hybrid applications, data exclusivity and market protection rule applies i*n accordance with Article 6(1) of Directive 2001/83/EC, which means data exclusivity and market protection period shall not restart or prolong for reference medicinal product with the effect of new propellant in the approved formulation. Alternatively, a separate Q/A in this aspect can be introduced for better clarity.	
Lines 53 – 56	5.	Comment: Clarity on list of required data and agency's expectation can be provided. Here interpretation is, applicant can use data generated on other approved product, where same propellant being used, where pharmacovigiliance data is available. In addition,	This interpretation is correct, yes. More details are not needed here under general principles.

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		guidance related to aspects like differences in quantity of propellant used by reference medicinal product as compared to generic medicinal product to be outlined. Proposed change (if any):	
Lines 53-56	3.	Comment: It is stated that "If a certain propellant has already been used in an approved medicinal product for the same route of administration, the data requirements for including the said propellant in another medicinal product can be reduced when sufficient data, including pharmacovigilance data, have been collected." **Proposed change:** For further clarity, suggest it be explicitly stated whether the active substance should be the same or whether the active substance can be different from that used in the approved medicinal product.	The section is about data requirements for the propellant as such. It is irrespective of active substance and type of inhaler. Concerns about the active substance is detailed in section 3.4.
Line 78	1.	Comment: Proposed change (if any): ~~**quality data**~~ requirements are to be taken into account	Accepted.
Lines 79 to 81	1.	Comment: Depending on impact of the propellant change on the whole system there could be rational for not repeating	Not accepted. It is not needed to state that all relevant studies should be applicable. Studies relevant to the change should be conducted.

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		some aspects of pharmaceutical development studies. Propose amended wording to take this aspect into consideration if appropriate. Proposed change (if any): All relevant pharmaceutical development studies described in the Guideline on the pharmaceutical quality of inhalation and nasal products (EMEA/CHMP/QWP/49313/2005 Corr) **should be reviewed and repeated if applicable unless suitably justified**	
Lines 82-84	1.	Comment: Would like to understand EMAs position of all intended patient population within this statement. Similar patient demographics between indications (e.g. Asthma and COPD) could support data from a representative demographic of usage to support multiple indications. In addition, spacers are commonly used for specific populations such as paediatric populations which would negate the need to investigate some aspects in these populations. Proposed change (if any): For all the indicated patient populations, propellant aspects which may impact the usability of the product such as expelling pressure, taste, feeling in the mouth and flammability. **A representative demographic which covers usage of the indicated patient population could be utilised if suitability justified**.	Partly accepted. The intension was not to cover different patient groups or indications where the use pattern is similar but rather to cover children and possible other situations when handling and experience becomes important. This could be clarified by adding "as applicable" to the text.
Line 83	6.	Comment:	Not accepted. We find the text appropriate here as it is about the performance of the product as such irrespective of

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		Normally usability studies simulate the use of the inhaler in representative settings however it's in clinical trials that humans are exposed to the formulation that is fired out of the inhaler. **Proposed change (if any):** • We propose to reword "expelling pressure" substituting with "firing force". • We suggest to consider comments on "taste" and feeling in the mouth in sections related to in-vivo studies since in "usability studies" normally the product is not administered	whether the propellant is novel or not and independent on data on therapeutic equivalence.
Lines 85-89	6.	Comment: In case of step-wise approach of clinical development, if only one clinical (PK) study is completed, there might be only one clinical batch to be considered as a reference for re-evaluation of finished product specifications. In this case the use of additional data on process capability and stability studies should be recommended as outlined in the guideline (EMEA/CHMP/QWP/49313/2005 Corr). Proposed change (if any): Re-evaluation of the finished product specifications, at release and at the end of shelf life, in view of the results of the batches used in the studies pivotal for demonstrating therapeutic equivalence and safety and "***also***	Accepted.

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		considering process capability and stability data"	
Lines 90-91	6.	Comment: • Reference to EMEA/CHMP/QWP/49313/2005 Corr (section 4.5) could be considered in particular when no clinical studies are conducted to allow taking into consideration process capability and stability data Proposed change: When no clinical studies have been conducted, the critical quality attributes limits ***should be comparable****, process capability and stability data may also be considered.*	Not agreed. "Should not be substantially changed" is deemed an appropriate level.
Lines 92 to 95	1.	Comment: Definition of device constituent being included here. Not defined in EMA/CHMP/QWP/BWP/259165/2019 and should not be defined here and subject to justification and determination of relevant device constituent for product. Proposed change (if any): Discussion and justification of device related changes (e.g., in the device components ~~**such as valve and**~~	Not accepted. Valve and canister are mentioned as examples of device components that might be changed due to a new formulation (new propellant) and therefore valuable information.

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		~~**canister**~~), taking into consideration the requirements described in the Guideline on quality documentation for medicinal products when used with a medical device (EMA/CHMP/QWP/BWP/259165/2019) and related documents.	
Lines 96 to 97	1.	Comment: Manufacturing method validation should only be needed if there is a change in manufacturing process or in-process controls needed. Proposed change (if any): Pressurised metered dose inhalers are considered as a critical dosage form. Hence, adequate manufacturing method validation **(if there has been in any change in process or controls)** and stability data should be provided.	Not accepted. It is agreed that process validation data is only required if the manufacturing process has been changed. This is sufficiently covered by "...adequate manufacturing method validation...".
Lines 96 to 102	1.	Comment: Although pMDIs are a critical dosage form if the manufacture has expensive experience in manufacturing in that dosage form (and change in propellant does not result in change in manufacturing principle/or change in principle they still have experience in) the process is considered standard to them. In this situation in line with the Guideline on process validation for finished product (EMA/CHMP/CVMP/QWP/749073/2016) it is proposed that the applicant may be exempt for the need for production scale validation data. Proposed change (if any): Pressurised metered dose inhalers are considered as a critical dosage form. Hence, adequate manufacturing	It is agreed that the manufacturing process could be considered as a standard method for a manufacturer with appropriate experience and if justified. The text is updated accordingly.

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		method validation **(if there has been in any change in process or controls)** and stability data should be provided. **The applicant may be exempt for the need for manufacturing method validation data if they can suitably justify that the product process can be considered standard for a particular manufacturer / site taking into account the risk to the patient of failure of the product or process (EMA/CHMP/CVMP/QWP/749073/2016).**	
Line 97	3.	Comment: It is stated that "adequate manufacturing method validation and stability data should be provided." **Proposed change:** For companies that have manufactured MDIs for many years, the manufacturing process is considered a standard process, therefore manufacturing method validation data should not be required.	See comment above.
Lines 97-100	3.	Comment: It is stated that 'Stability data for at least two batches, packed in the commercial container closure system, stored at long-term conditions and in different orientations for a sufficient time should be provided to conclude similar stability profile.' **Proposed change:**	Partly agreed. Other stability data package may be acceptable and therefore "should be provided" is replaced by "is recommended". This is in line with the requirement for changes in composition (B.II.a.3). Minor changes to the container closure system could be assessed as supportive data. However, stability data under ICH conditions (including commercial package) should be started and data available for a sufficient time.

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		Please consider allowing minor changes to the container closure system for commercial supply chain if the changes can be justified as not being quality critical. Also, please consider allowing alternative approaches to the stability data package if justified based on an appropriate risk assessment.	
Lines 101-102	3.	Comment: It is stated that 'Stability data for the new propellant in other finished products could be seen as supportive.' **Proposed change:** Change to 'Stability data for the new propellant in other finished products ~~could~~ *would* be seen as supportive.'	Agreed.
Lines 107-115	3.	Comment: Propellants are volatile (i.e., rapidly dissipating) gases, which makes nonclinical in vitro studies [per ICH M3(R2)] practically challenging to conduct and may not provide reliable results. **Proposed change:** It would be helpful if this could be acknowledged in Section 3.2. and give the applicant scope to provide adequate justification to waive such studies.	Not agreed. There is sufficient scope within ICH M3 (R2) and related guidelines to justify the lack or modification of any studies if they are not considered feasible.
Lines 107-115, 172-175	3.	Comments:	Not agreed. Tox data would be considered irrespective of who conducts them (manufacturers of the propellants or the product developer), this doesn't need to be stated.

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		Would toxicology data from the manufacturers of the propellants be sufficient or does the product developer also need to do tox.studies with the novel excipient? Are environmental non-clinical studies required? Is it a safety study of the novel propellant alone, or of the drug product including both propellant and API? Section 3.2 only references the testing of the propellant alone. **Proposed change:** Please provide clarification. Please also provide some general considerations for when a bridging toxicology study for a drug product may be needed (and timing of this study) and incorporate this into Figure 1 of the stepwise schematic.	Repetition of studies are not encouraged. Full study reports need to be submitted for assessment. Data may be provided with the propellant only. An environmental risk assessment (ERA) is required for all new marketing authorisation applications for a medicinal product through a centralised, mutual recognition, decentralised or national procedure in accordance with the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr 2). The focus of such an ERA is in general the active substance and a stand-alone ERA for an excipient is not currently foreseen. Non-clinical data are not needed to show therapeutic equivalence and therefore not appropriate to add to Figure 1.
Lines 112-115	3.	Comment: The sentence in lines 112-115 seems to refer to excipients yet ends with '…as for any new substance.' **Proposed change** Put a full stop after '…ICH M3 (R2)'. Delete 'as for any new substance'.	Not agreed. It is intended to refer to substance (irrespective of whether it is active or not)
Lines 119-135	2.	Section 3.3.1 requires two studies of local tolerance (ciliary function, airway sensitivity reactions). That section does not indicate numbers of subjects needed. This section requires more detail.	The section is intentionally not very detailed to acknowledge that there might be several alternative acceptable approaches. There is yet no standard study designs. In case of uncertainty please ask for scientific advice.

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Line 122	2.	Ciliary function, should this be with propellant only or vehicle finished product (i.e matching placebo) including excipients. Proposed change (if any):	Vehicle finished product would be preferred. This is clarified.
Lines 122 – 126	5.	Comment: Related to "golden standard" methods, agency's expectation on study design, approaches, methodology can be included; although this topic is evolving with more knowledge in different products. Alternatively, examples of previously accepted methodologies can be mentioned in bracket ***as shown below*** for reference purpose. **Proposed change** (if any): a) '*Data on ciliary function should be preferably collected from a study in non-smoking healthy volunteers as this is deemed the most sensitive population to detect differences between the new and the reference propellant. There is no established and validated "golden standard" method.* As on date (April 2023), different methodologies like xxxx, xxxx, xxxx have been accepted by agency; however applicant can choose different method. In any case, a thorough justification for the choice of the design is needed.	Not agreed. The Agency has not yet been presented with any final study reports for assessment.
Lines 122-128	3.	Comment: Regarding Section 3.3 (a) Data on ciliary function. As noted, there is currently no accepted method to	The sensitivity for picking up adverse effects on ciliary function may be limited especially if studies are conducted with COPD-patients (with reduced function from start) or

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		directly assess the potential of a drug or chemical to impact mucociliary clearance. Conventional safety studies may indirectly indicate whether the test article induces significant treatment-mediated effects on mucociliary clearance. Standard evaluations of clinical signs (such as increased cough) or increased respiratory disease may be used as a surrogate marker for treatment-mediated effects on mucociliary clearance. **Proposed change:** Observation and comparison of clinical signs and symptoms (such as cough, increased respiratory disease) during a clinical safety study using the proposed formulation **or** propellant-only is sufficient evidence for lack of treatment related effects on ciliary function.	with active substances masking the effects. Thus, we find it important to have a focused study as outlined.
Lines 124-128	6.	Comment: Since it is recognised that there is no established and validated "golden standard" method (currently, April 2023) to assess ciliary function and also no defined criteria for assessing non inferiority, it would be difficult or impossible to set a predefined statistical hypothesis with a clinically relevant non-inferiority margin. Proposed change:	Partly agreed. The text is amended to avoid specifically mentioning the non-inf margin.

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		To delete: ~~if statistical aspects such as pre-specification of a primary endpoint with a non-inferiority margin at a relevant level can be justified.~~	
Line 126	2.	Provide guidance regarding ciliary function and how this can be determined by scintigraphy and whether a comparator (before propellant change) is required in study model	Yes, a comparator is needed as already stated ("to detect differences between the new and the reference propellant").
Line 127	2.	In a study where lung deposition is to be determined via a scintigraphic evaluation, further guidance on preferred end-points and non-inferiority margins would be useful. Proposed change (if any):	As the field is new, we prefer to leave the choice of study design open to allow justifications for different study outlines as deemed appropriate for each company.
Lines 129-135	3.	Comment: Regarding Section 3.3 (b) Airway sensitivity reactions. Supportive data for possible bronchoconstrictive effects would be attainable during a safety study (see line 138 "The main objective of this study is to collect adverse events such as bronchoconstriction, hoarseness, and cough"). **Proposed change:** Propose that a standalone airway sensitivity study would only be required if safety studies suggested propensity for the new propellant to increase risk of bronchoconstriction.	Not agreed. This dedicated study could very well be more sensitive picking up differences.
Line 130	2.	What constitutes a supratherapeutic dose. Is it related to a single dose or daily dose and what magnitude of difference is recommended	The intention is to make the study model as sensitive as possible. It is anticipated that this would imply a supratherapeutic single dose.

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		Proposed change (if any):	
Lines 130-131	9.	Comment: The treatment duration of this study is not provided. As the recommendation is to assess supratherapeutic dose, clarification should be provided on the dosage acceptability. Proposed change (if any): Inclusion of requirement whether a single dose study or cumulative dose single dose study would be acceptable.	We don't see a need to specify study duration. Single dose would be acceptable.
Lines 135-159	10.	**Comment:** The guidance requires data from a product exposure study including placebo product. However, there will be rapid transition of these novel propellants to becoming established excipients. Once the LGWPs are established the requirement to provide clinical safety should be waived. **Proposed change (if any):** Clarify that clinical safety studies may be waived when a medicinal product appropriately references an established product with an established LGWP. Include provision that allows reference to exposure data from alternative sources such as a propellant manufacturer.	It would be acceptable if the propellant manufacturer makes these data available. It doesn't need to be specifically stated.
Lines 136 - 159	7.	Comment: The guidance requires data from a product exposure study including placebo product. However, there will be rapid transition of these novel	Not agreed. It is already stated that clinical safety data are needed in case of novel propellants only.

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		propellants to becoming established excipients. Once the LGWPs are established the requirement to provide clinical safety should be waived. Proposed change (if any): Clarify that clinical safety studies may be waived when a medicinal product appropriately references an established product with an established LGWP. Include provision that allows reference to exposure data from alternative sources such as a propellant manufacturer.	
Lines 136-159	2.	Section 3.3.2 clinical safety: a placebo or vehicle, 3 MONTH STUDY for a combination PMDI in asthma pts is challenging and will likely result in compliance issues (as alternative inhalers containing API will be required) and masking of safety events by other asthma products required for pt treatment. If a propellant has been tested in a healthy volunteer study is that acceptable and data can be referenced without need for additional patient exposure. Proposed change (if any):	Comment not understood. The clinical safety study is needed in case of novel excipients irrespective of kinetic data on therapeutic equivalence.
Lines 136-159	2.	Regarding 3.3.2 A 3-month 2x 300 volunteer propellant only study would likely not be approved by ethics committees. In addition, we would think that the airway sensitivity reactions study in a relatively small number of volunteers at higher risk of such	Not agreed. Please consider that the safety study is for novel excipients only. It is irrespective of whether products are shown therapeutically equivalent or not.

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		reactions mentioned in 3.3.1 should suffice for "bronchoconstriction, hoarseness and cough". In our opinion all of section 3.3.2 could be rewritten to simply indicate that a 2x 300 subject simplified safety (and efficacy) study of at least 3 months duration should be performed to demonstrate non-inferiority with respect to safety (and efficacy) of the reformulated product with the original product in actively dosed patients treated as per approved indication. In addition, it should be clarified whether such a study is always required or is only required if in vitro or in vivo pK studies and/or the local tolerability studies mentioned in sections 3.1 and 3.2 have raised concerns. If the pK data support bioequivalence and the local tolerability studies with the propellant have not raised any significant concerns, there would not seem to be a strong argument to require a relatively large safety (and efficacy) study, which could also raise ethical questions.	
Line 136-159	8.	Comment: As stated, evaluation of side effects can be compromised by known effects of active substances. In addition, the design of the proposed clinical safety study (3 months, 300 subjects in each treatment arm, healthy volunteers or patients using dry powder devices for maintenance therapy, product strength where the number of actuation needed is in the higher range) seems to be inapplicable for the evaluation of a rescue therapy.	Partly agreed. It is nevertheless not anticipated that a certain propellant will be used in products intended as rescue medication only.

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		For rescue therapy there is no rational for a 3 months administration on a daily repeated regimen. Moreover, the feasibility of the study in healthy volunteers or patients with asthma receiving higher range of rescue treatment is very uncertain. The bronchoconstriction could be observed with a shorter duration of drug intake. Proposed change: Data requirements on clinical safety as well as study design should be given per therapeutic class (SABA, ICS, …). For SABA, a different design to test the paradoxical bronchoconstriction related to the new oral inhaled drug with a novel propellant with a hyperresponsiveness test study to ensure that the propellant does not induces bronchial hyperresponsiveness should be considered.	
Lines 137-138	9.	Comment: As PFT will measure in the airway sensitivity study, its unclear whether PFT data for assessment of bronchoconstriction is required in the safety study or assessment such as chest tightness, breathlessness, wheezing, cough recorded in diary could be considered as adequate.	

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		Proposed change (if any): Inclusion of information related to usage of PFT data.	
Line 138-139	6.	Comment: Adverse events such as bronchoconstriction can be evaluated within a shorter and separate study as bronchoconstriction usually occur during the first administrations.	The intention with the safety study is not only bronchoconstriction but any adverse reactions.
Line 139	3.	Comment: It is stated that 'Study duration should be at least 3 months.' Adverse events such as bronchoconstriction can be evaluated even within a shorter study as bronchoconstriction usually occur during the first administration or within one week. **Proposed change:** Given the short half-life of SABA medications and the frequency of patient usage, if a sufficient number of adverse events could be collected in a shorter time period, could a shorter duration be possible? Suggest including in the Q&A document a statement '**Other study designs could be acceptable if suitably justified'.**	See above.
Lines 139-140	9.	Comment: The guidance does not provide statistical expectation (descriptive statistics) of this study if any.	The statistical plan might differ dependent on the chosen study design. We would therefore suggest not to give details.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Any comparative descriptive statistics presented for required AE assessments can be considered acceptable and could be included.	
Lines 141-143	3.	Comment: '*The pMDI product at investigation should ideally be a vehicle version of the final formulation to allow detecting adverse effects of the novel propellant while minimising the risk that these are masked by the active substance(s) (thereby compromising any extrapolation of the conclusions to other products).'* Statement and wording 'vehicle version of the final formulation' is confusing and not clear. As indicated in the parenthesis the extrapolation of the safety study results to other products with the same propellant seems to be intended. Hence the following is proposed: **Proposed change:** '*The pMDI product at investigation should ideally be a formulation without active substance to allow….'*	Agreed.
Lines 141-143	10.	**Comment:** The guidance requires data from a vehicle version of the final formulation (line 141), while in line 149 a different final product is allowed for this evaluation. Maybe it is too restrictive to use the term vehicle version while it will lead to unnecessary duplication of studies. If cases with a representative	Not agreed. It says "ideally", thus it is not a strict requirement.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		final formulation are envisaged, this should be adequately justified by the manufacturers of the final product. Hence the following change in the text is suggested. **Proposed change (if any):** The pMDI product at investigation should ~~ideally be a vehicle version of the final formulation to~~ allow detecting adverse effects of the novel propellant…	
Lines 144-145	10.	**Comment:** lines 144-145 mention that bronchoconstriction could be masked by β2-agonists and hoarseness and cough are known side effects from glucocorticoids, complicating the evaluation. This contradicts to lines 149-150 to use a final finished product formulation indicated for daily maintenance treatment, preferably a mono-component product such as a glucocorticoid. **Proposed change (if any):** Nevertheless, as 3-month studies investigating an excipient might prove difficult to conduct in practice, it would be acceptable to use a final finished product formulation indicated for daily maintenance treatment.~~, preferably a mono-component product~~. ~~such as a glucocorticoid~~	Ideally a formulation without active should be used. If this is not feasible the number of included substances should preferably be low, e.g. a glucocorticoid as mono component.
Line 145	6.	Comment: It is not appropriate and also ethically questionable to study the propellant for three months in healthy volunteers. Usually, clinical study involving healthy	Not agreed. Inclusion of healthy volunteers is not mandatory but one option. If not feasible, alternatives could be chosen.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		volunteers have a shorter duration i.e maximum 2 to 4 weeks while the evaluation of a maintenance treatment can only be made though administration of the finished product. Proposed change: The sentence should be modified as follows: "The subjects to be included should be ***patients"***	
Lines 145-147	9.	Comment: This section lacks clarity on whether a study in healthy subjects with Placebo version of test and reference can be considered acceptable for the 3-month safety study. Proposed change (if any): Inclusion of clarification on subject and placebo information.	It would be acceptable to use healthy volunteers. This doesn't need to be stated specifically.
Lines 145-147	9.	Comment: Conduct of this study in asthma patients with placebo version of Test and Ref, with allowance for daily maintenance treatment of any dry powder inhaler drug to the patients need to be clarified to address recruitment challenges. Proposed change (if any): Inclusion of clarity on allowances to address recruitment challenges to be included.	If conducting the study with asthma patients the study could preferably be conducted in healthy volunteers
Lines 148-150	9.	Comment: Clarification on the three below scenarios can help	We don't see a need to update the text as all alternatives would in principle be acceptable. Alternative two would

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		1. Healthy subjects with placebo version of test and reference 2. Asthma patients with placebo version of test and reference 3. Asthma patients with a corticosteroid MDI of Test and reference. Proposed change (if any): Inclusion on clarity related to subject type and active vs placebo formulation inclusion as per various scenarios to be included.	probably not be any company's choice though although in principle, any patients treated with DPIs only could be included in a study where a vehicle only product is used.
Lines 148-150	9.	Comment: Performing study with finished corticosteroid MDI in patients and extrapolation to all products needs clarification. Proposed change (if any): Inclusion of proposal that a study with finished product with corticosteroid MDI in patient and extrapolation to all products being developed with the propellant.	It is clearly stated that the 3-month study is needed only in case of a novel excipient, irrespective of active substance in the formulation.
Lines 148 - 152	7.	Comment: The guidance suggests that if using an active in the clinical safety study preferably the finished product is a mono glucocorticoid product. There is no evidence that short-acting beta-agonists/short -acting muscarinic antagonists/long-acting beta-agonists/long-acting muscarinic antagonists or combination products mask local toleration signals. Additionally, mono-glucocorticoid	Not agreed. It is not a requirement but a preference. Bronchoconstriction could be masked by bronchodilators.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		products may not be the priority for reformulation using LGWP. Proposed change (if any): Remove the requirement that clinical safety studies are performed on mono-component glucocorticoid products.	
Lines 148-152	10.	**Comment:** The guidance suggests that if using an active in the clinical safety study preferably the finished product is a mono glucocorticoid product. There is no evidence that short-acting beta-agonists/short -acting muscarinic antagonists/long-acting beta-agonists/long-acting muscarinic antagonists or combination products mask local toleration signals. Additionally, mono-glucocorticoid products may not be the priority for reformulation using LGWP. **Proposed change (if any):** Remove the requirement that clinical safety studies are performed on mono-component glucocorticoid products.	It is not a requirement and thus no changes to the text is needed. Bronchoconstriction is an important possible sign of local intolerance which could be masked by a bronchodilator.
Lines 149-152	3.	Comment: It is stated that 'it would be acceptable to use a final finished product formulation indicated for daily	Yes, they may be included. It is not anticipated that the clinical safety study will be conducted with any final formulation other than medicines intended for the included population.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		maintenance treatment, preferably a mono-component product such as a glucocorticoid.' **Proposed change:** Can final finished product formulation also be used in the safety study if it is indicated for rescue treatment (for example, a short acting bronchodilator?). Given that well-controlled asthma patients on a daily maintenance regimen of inhaled corticosteroid monotherapy would have little need for SABA reliever medication, and thus may receive insufficient investigative product exposure in a safety study, could regular scheduled SABA use be implemented, to support development of SABA with novel propellant, regardless of symptoms? Given that asthma patients across different levels of severity use SABAs for relief, could well-controlled patients on dual inhaled therapy (ICS/LABA) and triple inhaled therapy (ICS/LABA/LAMA) be included?	
Line 150	2.	States preferably a mono-component product: Please comment on dual or triple products. – are these acceptable? Proposed change (if any):	If such data are available they could be found acceptable if justified yes Mono-component data would nevertheless be preferred.
Lines 153-154	3.	Comment: It is stated that, 'A comparator product which is an approved pMDI product supported by a full dossier should be included.'	We would like the studies to be compared to allow a direct comparison to an approved medicinal product.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Since considerable adverse event data already exists for SABA medications, could a single arm safety study utilizing only the investigative SABA formulation be conducted with an adverse event profile compared to existing historical SABA data? If historical data is acceptable, what data sources could be utilized to derive the baseline incidence of the adverse events to be studied, and thus, subject numbers?	
Lines 153-155	10.	**Comment:** A comparator product which is an approved pMDI product supported by a full dossier should be included. Full dossier seems to be very restrictive and does not justify the rationale for selection of the comparator product. A comparator approved via abridged applications should also be acceptable as long as it can serve its purpose (I.e., does not contain novel propellants). **Proposed change (if any):** A comparator product which is an approved pMDI product in EU ~~supported by a full dossier~~ **containing safe and well-established excipients suitable for this comparison (i.e., old propellants)** should be included	Not agreed. To avoid generic drift the comparator should always be a product supported by a full dossier.
Lines 156-159	9.	Comment: Conducting a study with final finished ICS/LABA combination in asthma patients and extrapolation to all products needs clarification.	Not agreed. There is no need for advice specifically on ICS/LABA combinations as data requirements for novel propellants is irrespective of active substances in the formulation.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Inclusion of proposal that a study with finished ICS/LABA MDI in asthma patients and extrapolation to all products being developed with the propellant.	
Lines 156-159	9.	Comment: Dosage regimen for dosing with placebo MDI is not provided in the guidance document. Proposed change (if any): If this study is conducted with placebo version of test and reference device, inclusion of information related to the expected twice daily regimen with the Placebo MDI as convenient for the 3-month testing period.	The dosing should be such that the amount of propellant inhaled is relevant for the intended use in practice.
Lines 156-159	9.	Comment: Local clearance studies as well as the safety studies can be conducted in any country as applicable for conventional comparative PK or PD studies – the same could be clarified. Proposed change (if any): Inclusion of confirmation whether the safety studies can be conducted in any country as applicable for conventional comparative PK or PD studies.	There are no restrictions with regard to countries where studies may be conducted.
Line 159	2.	States it is recommended to choose a product/strength where the number of actuations needed is in the higher range – Please clarify what 'higher range refers to? Is this highest daily dose? – is this acceptable from a safety perspective?	This is to be justified in each case pending on what would be acceptable.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 167	3.	Comment: This is the first mention of a step-wise approach. The text does not follow the flow diagram. **Proposed change:** Introduce this step-wise approach earlier in the text and insert a more detailed flow diagram earlier in this document as well.	Not agreed. Section 3.4 is the first place where data on therapeutic equivalence (refers to active components) is mentioned. This is where the flow diagram fits in.
Line 168	3.	Comment: The sentence 'Data should be provided both with and without spacer/holding chamber.' presumes that a spacer/holding chamber must be used. Not all products are supplied with a spacer and not all strengths of a particular product supplied with a spacer **Proposed change**: Recommend updating the sentence as follows: *'Data should be provided both with and without spacer//holding chamber* ***where applicable '***	Not agreed. Use of a spacer should be possible (and thus studied) in all cases. The change is nevertheless made in section 3.4.2 as PK-data are only needed if applicable.
Lines 168-169	8.	Comment: It is stated that data should be provided both with and without spacer/holding chamber. For a product to be used with a spacer/holding chamber, would the stepwise procedure also be applicable to studies with a spacer? For instance, waiving a clinical spacer/holding chamber study using in vitro similarity should be possible even if in vitro	A pMDI should normally be approved for use with a spacer as needed. Thus the stepwise procedure applies both with and without spacer. A clarification is made to point out that in case all in vitro requirements are fulfilled either with or without spacer the corresponding PK-study may be waived.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		similarity without a spacer/holding chamber is not demonstrated (and thus a PK study without spacer is needed)? Proposed change: Clarify how stepwise procedure applies for products to be used with a spacer/holding chamber and update Figure 1 accordingly.	
Line 174 (Figure 1)	3.	Comment: It would be useful to include if / when clinical safety & other studies should be conducted when in vitro equivalence is demonstrated. The schematic only speaks to in vitro, PK, and PD studies. **Proposed change:** Please clarify whether the schematic is only applicable to novel excipients? Is it appropriate to enhance the schematic to also speak to if / when clinical safety & other studies should be conducted when in vitro equivalence is demonstrated.	A clinical safety study is needed only to document safety for a novel excipient. It is not needed to show the safety of the novel excipient for each product. The stepwise approach as outlined in the figure is applicable to all products and is independent on whether the propellant is established or not.
Line 174 Figure 1, Step 2	3.	Comment: Step 2 in the flow diagram could be misinterpreted **Proposed change**: Add "of the API" to the first parenthesis, so it would read "(total exposure of the API)".	Agreed. This applies to all steps though and is now stated in the label.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 174 Figure 1, after Step 2	3.	Comment: '*Are test and reference product therapeutic equivalent by means of PK data…*?' It should be clarified that for the PK safety study demonstration of non-inferiority rather than equivalence (i.e. not higher systemic exposure for the test product than for the reference product) is sufficient (in line with EMA PK working party Q&A section 3.4). Clarification could be included in Step 3 as proposed below. **Proposed change:** "*If the PK safety study failed to demonstrate not higher systemic exposure for the test product than for the reference product for any active substance, …*"	In principle agreed. We would nevertheless prefer not to give a lot of details about the stepwise approach in this document as it applies similarly as for abridged applications for new products. There are numerous other details not mentioned here.
Line 174 Figure 1, after Step 3	3.	Comment: Wording included in the last arrow is not accurate and hence we propose a change to indicate that evidence can also be split between efficacy and safety / PK and PD. **Proposed change:** '*PK and/or PD data'.*	Not agreed. It should be PK and (if applicable) PD data as PK should always be provided (unless in vivo data can be waived.
Line 183	3.	Comment: The sentence '……lung deposition / local availability with and without spacer need to be provided' presumes that a spacer must be used **Proposed change**:	Not agreed. A spacer must not be used in all cases but spacer data should always be provided.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Recommend updating the sentence as '*……lung deposition / local availability with and without spacer need to be provided where applicable* '	
Lines 184 and 185-187	2.	There may be an error in line 184 in "As surrogate marker for safety, total exposure (AUC0-t and Cmax) should be used.". We would assume this would be a surrogate marker for efficacy. And in lines 185-187 in "For products where the contribution from the gastrointestinal tract to the systemic exposure following inhalation is negligible (<5%), the systemic safety study could also be used to compare lung deposition.", is "systemic pharmacokinetic study" intended, or was the intent to point to one of the two local tolerance studies?	No, there is not an error. Total exposure is used as a surrogate for safety, not for efficacy as the effect is local. This applies unless there is negligible uptake in the GI-tract (the drug is absorbed through the lung only) then total exposure is accepted as a surrogate also for efficacy. It's correct though that "the systemic safety study" refers to kinetics. This is updated.
Lines 199 - 217	3.	Comment: The Q&A document states 'The conclusion from studies supporting safety of a novel propellant as outlined in question 3.3. above can be extrapolated to children and adolescents even though the studies are conducted in adults only.' **Proposed change:** Does this also apply to any clinical safety or other studies conducted in asthmatic adults? Please clarify.	Yes, it applies to all studies listed in section 3.3 also if conducted in asthmatic adults.
Info not provided, seems it refers to	4.	Comment: **Pediatric extrapolation (adolescents and children)**: Do such studies need to be done in healthy or asthmatic patients?	Sorry, the comment is not understood. There are no specific data requirements for children.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
lines 199-217		Proposed change (if any):	
Line 213	3.	Comment: Wording "*it might be acceptable*" is not very clear as to what is required, i.e., would additional in-vitro studies be sufficient? **Proposed change:** Please provide examples so it is clear when it would and would not be acceptable to keep the age limit.	In many cases it will likely be possible to justify an approved age limit without in vivo data in children. There are yet no examples to be presented though.
Lines 220 - 221	7.	Comment: The change in the product formulation should be evident to HCPs and patients to promote transparency and the use of LGWP-containing products. There is already a precedent for non-CFC-containing medicinal products to highlight this in the product name, for example CO-FLUSALM 250/25 mcg FCKW-Frei Dosier-Aerosol (translates to CO-FLUSALM 250/25 mcg CFC-free metered-dose aerosol). Proposed change (if any): Allow HFC-free to be included in the name of the product.	Not agreed. According to the NRG Guideline on the acceptability of names for human medicinal products processed through the centralised procedure, the (invented) name should not convey a promotional message with respect to the therapeutic and/or pharmaceutical characteristics and/or the **composition** of the medicinal product.
Lines 220-221	10.	**Comment:** The change in the product formulation should be evident to HCPs and patients to promote	See previous comment.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		transparency and the use of LGWP-containing products. There is already a precedent for non-CFC-containing medicinal products to highlight this in the product name, for example CO-FLUSALM 250/25 mcg FCKW-Frei Dosier-Aerosol (translates to CO-FLUSALM 250/25 mcg CFC-free metered-dose aerosol). **Proposed change (if any):** Allow HFC-free to be included in the name of the product.	
Lines 222-227	3.	Comment: Regarding the statement: *'Inclusion of statements such as 'HFC free' on the label: As a general principle, the Summary of Product Characteristics (SmPC) is the basis of information for healthcare professionals on how to use the medicinal product safely and effectively. There is no ground or need to include additional information on elements which are not included in a medicinal product (i.e., absence of a component in the product or in a container), as the information may become extensive and confusing. Therefore, such promotional statement is not allowed'.* **Proposed change:** It is important that information about the environmental benefits of the reformulated product is	Not agreed. In accordance with the articles 11, 54 and 59 of Directive 2001/83/EC, there is no legal basis for listing excipients not included in the composition of the medicinal product.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		visible to HCPs and patients in order to drive the pace and level of change required to meet the environmental goals of the F-Gas legislation. Without this prescribing behaviours will not be challenged/updated resulting in a slow uptake, reduced urgency for the supply base to change and ultimately a slower reduction of targeted emissions from pMDIs.	
Lines 222 - 227	7.	Comment: The change in the product formulation should be evident to HCPs and patients to promote transparency and the use of the LGWP products. When propellants in pMDIs were changed from CFCs to HFCs this was highlighted within Section 6.1 of the SmPC (e.g., Salamol CFC-Free Inhaler) contains a new propellant (HFA-134a) and does not contain any chlorofluorocarbon (CFC) propellants. Proposed change (if any): Allow HFC-free to be included in the SmPC and product labelling.	Not agreed. See above.
Lines 222-227	10.	**Comment:** The change in the product formulation should be evident to HCPs and patients to promote transparency and the use of the LGWP products. When propellants in pMDIs were changed from CFCs to HFCs this was highlighted within Section 6.1 of the SmPC (e.g., Salamol CFC-Free Inhaler) contains a	See previous comment.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		new propellant (HFA-134a) and does not contain any chlorofluorocarbon (CFC) propellants. **Proposed change (if any):** Allow HFC-free to be included in the SmPC and product labelling.	