Analysis of Alternatives to PFOB

Date March 2018

TABLE OF CONTENTS PAGE

1. INTRODUCTION AND SUMMARY

Perfluorooctyl bromide (PFOB) is used by AstraZeneca as a processing aid in the manufacture of pressurised metered-dose inhaler (pMDI) medicines. This substance is safe to use and is exempt from restrictions, but its supply is threatened by the recently adopted REACH Restriction on PFOA, its salts and PFOA-related compounds[1]. The PFOB typically contains up to 200 ppm of perfluorooctyl iodide (PFOI), which is considered a PFOA-related substance. The PFOB is currently purchased from Daikin who manufacture it in Japan from PFOI by-product derived from a C6 telomer process. Daikin would otherwise incinerate the PFOI by-product.

The PFOB is used as a processing aid in the manufacture of porous particles, which are a functional excipient in pMDI products. The porous particles have very specific properties that would be compromised by using a different processing aid and this would affect the performance of the final drug product.

This document discusses potential alternative scenarios to the current use of PFOB in the manufacture of the pMDI medicines. Even if an alternative agent was identified, this would require significant marketing regulatory activity and re-approvals, plus it is also likely that repeat clinical trials would be required. The baseline position is therefore that substitution will be very difficult to achieve for a pharmaceutical product, even if an alternative agent was readily available.

All medicines must undergo extensive clinical trial programmes before seeking marketing approvals. A process to develop, test and validate alternatives to PFOB would require an extensive programme of work and involve significant research and development costs. As such, the work to identify an alternative is on-going and the viability of this may depend on whether repeat clinical trials are required. For example, any change in product performance (enhanced or otherwise) will require repeat clinical trials, which could cost hundreds of millions of dollars across the product range and delay access to medicines for patients.

The risks with the use of PFOB are well managed by AstraZeneca as summarised in the Chemical Safety Report, hence there is no significant benefit with switching to an alternative substance, which would require repeat clinical trials and development costs. These trials may be totally unviable from an economic perspective with any restrictions simply resulting in the products being withdrawn from patient use. AstraZeneca presents four alternative scenarios in this report, these are:

1. PFOB which is further purified to reduce residual levels of PFOI
2. PFOB that is manufactured via alternative synthetic routes
3. PFOE used instead of PFOB
4. Use of structurally different alternatives to PFOB

Significant work has already been conducted and the following pages illustrate the challenges. The analysis presented includes the following elements:

- Availability and suitability
- Risks to human health and the environment
- Technical and economic feasibility

It is anticipated that the remaining work to develop an alternative would incur significant research and development (R&D) costs and take between 5-10 further years to complete. This is based on

[1] Commission Regulation (EU) 2017/1000 of 13 June 2017, which will come into force in July 2020. This restricts use of any substance, mixture or article that contains greater than 1000 ppb of PFOA-related substances.

typical pharmaceutical development costs and timelines, particularly as it can take up to 3 years to receive product approval authorisation in some global markets.

Some of the information is sensitive and has been presented at a high level only to protect intellectual property interests.

2. ANALYSIS OF SUBSTANCE FUNCTION

2.1 Overview

AstraZeneca uses PFOB as a processing aid in the manufacture of porous particles, which are a functional component in a new generation of AstraZeneca pressurised metered-dose inhaler (pMDI) medicines. These medicines use a novel Co-Suspension™ Technology that contains low-density phospholipid porous particles. These porous particles are designed to provide a uniform suspension inside a pMDI, which is able to deliver an optimal distribution of drug crystals in the lungs for alleviation of lung diseases such as COPD[2].

The Co-suspension™ Technology also enables consistent delivery of multiple active ingredients from a single pMDI. The technology is utilised in Bevespi Aerosphere which was approved by the FDA in April 2016 for the treatment of COPD. Bevespi Aerosphere is also under marketing review by the authorities in the European Union. There are also other AstraZeneca projects currently in clinical development, such as the fixed-dose triple combination of LAMA/LABA/Inhaled corticosteroid (PT010)[3]. Positive late stage clinical results were announced for PT010 in January 2018, hence AstraZeneca anticipates making regulatory submissions in Japan and China in the second half of 2018, followed by submissions in the US and Europe.

The manufacture of the porous particles uses perfluorooctyl bromide (PFOB) as a processing aid, which is critical to delivering the unique aerodynamic properties of the porous particles, which ensure the efficient delivery of the medicine to the lungs. The PFOB is produced in Japan and typically contains up to 200 ppm perfluorooctyl iodide (PFOI), which is a PFOA related substance. It is not possible to source PFOB which meets the EU regulation as all synthetic routes proceed via prohibited substances, hence trace amounts inevitably remain in the PFOB.

3. PROCESS DESCRIPTION

The porous particles are constructed from a binary mixture of calcium chloride and phospholipid. The properties of the porous particles are controlled by spray drying precipitation from an emulsion of PFOB and water. The emulsion properties can affect the macroscopic size (diameter) of the porous particles and can also influence the size of the pores and the density and aerodynamic properties of the material. All of these properties are critical to the final performance of the pMDI product.

[2] COPD = Chronic obstructive pulmonary disease, which is the name for a group of lung diseases that cause breathing difficulties over time. These breathing difficulties tend to worsen over time and affect quality of life.

[3] LAMA/LABA = long-acting muscarinic antagonist/long acting β2 agonist and are the active ingredients in Bevespi Aerosphere. LAMA decreases bronchoconstriction, LABA promotes bronchodilation. PT010 also contains an inhaled corticosteroid that suppresses airway inflammation.

The emulsion properties are controlled by homogenization and intrinsic reagent properties and the spray drying parameters are carefully controlled to ensure product quality.

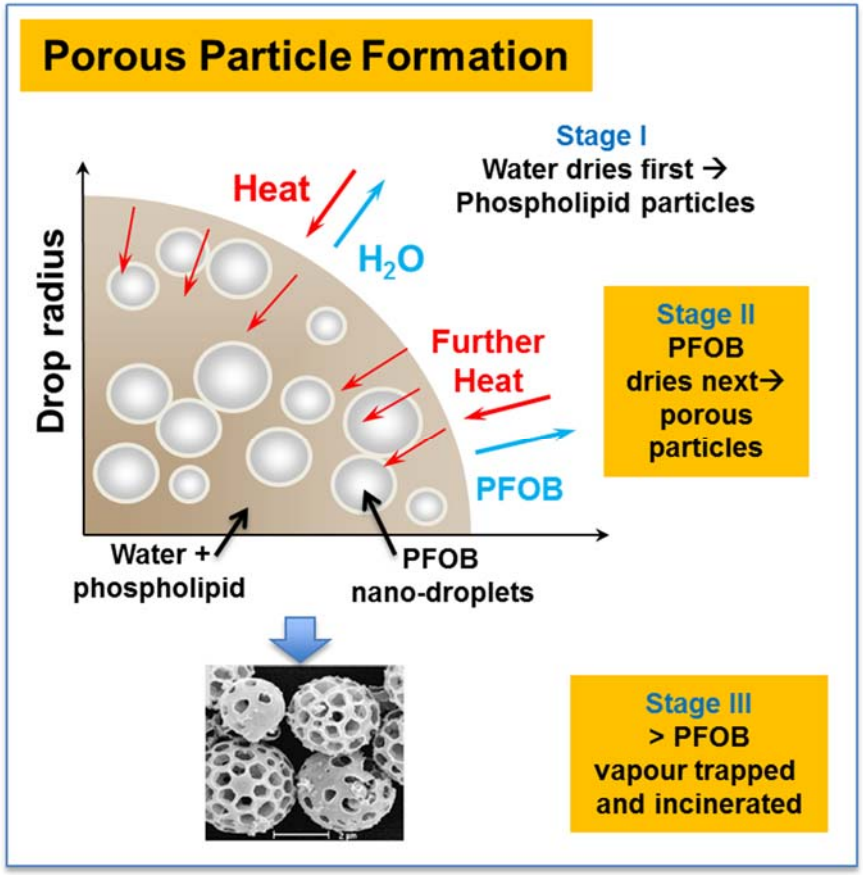
3.1 Tasks Performed by the Substance and Substance Function Data

In analysing the substance function, consideration has been given to the task performed by PFOB. The restricted substance, PFOI, represents a very low proportion (typically <200 ppm) and has no significant impact on the properties of the PFOB.

The PFOB forms a stable emulsion in water with a phospholipid ingredient that is compatible with the lung. The boiling point of PFOB is significantly greater than that of water, such that water can be preferentially spray dried and PFOB subsequently dries away with greater heat to give the well controlled macrostructure and porous properties of the porous particles. Spray drying allows for various levels of control over critical particle features such as particle size and distribution, particle density, surface energy, surface rugosity, porosity and microstructure[4].

[4] Future Med. Chem. (2011) 3 (13).

Functional Aspect	Information
Substance ID and properties	Chemical Name: 1-bromoheptandecafluorooctane / perfluorooctylbromide (PFOB) IUPAC Name: 1-bromo-1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluorooctane CAS Number: 423-55-2 EC Number: 207-028-4 % (w/w): 100% (typically up to 200 ppm PFOI) Appearance: colourless liquid Classification of the substance (EC 1272/2008, Self classification): Aquatic Chronic Category 4 – H413).

Functional Aspect	Information
Description of function	PFOB is very insoluble in water and able to form an aqueous emulsion that delivers the specific properties of the porous particles that are key to the performance of the Co-suspension™ products. The boiling point of PFOB is significantly greater than water, such that water can be preferentially spray dried and PFOB subsequently dries away with greater heat to give the well controlled structure of the porous particles. The role of PFOB in the emulsion spray drying process is illustrated in the diagram below: 

Functional Aspect	Information
Process and performance constraints	The process and performance constraints are summarised as follows: • Liquid substance (PFOB melting point is 6°C) • Insoluble in water for emulsion formation (PFOB is insoluble in water) • Boiling point higher than water (PFOB boiling point is 142°C) • Boiling point amenable to spray drying away of the substance (PFOB boiling point is 142°C)
What customer requirements affect the use of the substance in this use?	The porous particles are a functional component in the next generation of AstraZeneca pMDI medicines. Aerosol medicines are very sensitive to subtle differences in the particle properties of the ingredients. The pharmaceutical industry is heavily regulated in all markets - detailed product quality attributes and specifications are registered with the authorities. Alternatives to PFOB are expected to prompt repeat clinical trials and would certainly require complex regulatory updates as the manufacturing processes and specifications are registered with the authorities. The AstraZeneca requirements are driven by the desire to maintain quality products on the market for patients and to ensure adherence to strict regulatory requirements. Updates to the registered manufacturing processes and specifications can take up to 3 years to complete in some markets outside the European Union.
Are there particular industry sector requirements or legal requirements for technical acceptability that must be met and that the function must deliver?	The PFOB is used in the manufacture of pharmaceutical products, which are closely regulated worldwide. Details of the manufacturing process are registered with the medicines/health regulators in each territory including specifications for residual PFOB. It will not be possible to substitute PFOB without re-registering the product(s) in the relevant markets. Substitution of PFOB is very likely to require clinical trials in all markets. Any change in final product performance would result in the product not meeting the required specifications.

Functional Aspect	Information
Stages to introduce an alternative substance	For the introduction of alternative substances to PFOB, the potential stages are summarised as: Stage 1: Identification of alternative agent and proving: • Process concept proposed with scientific foundation • Applicability and validity of concept described and vetted, or demonstrated • Experimental proof of concept completed • Process validated in laboratory using representative development equipment Stage 2: Safety Assessment • Demonstration that the alternative agent is safe. Stage 3: Dose ranging and clinical assessment • Assuming that the alternative agent has an impact on the properties of the porous particles, it is assumed that clinical trials will be needed to verify that the correct dose is being used. • It is likely that clinical trials would be required to demonstrate therapeutic benefit. Stage 4: Marketing Approvals • Marketing approvals will be required globally, this would involve significant effort to gain approvals in every market. Approval times can exceed 3 years in some markets.

4. IDENTIFICATION OF POSSIBLE ALTERNATIVES TO PFOB

4.1 List of Possible Alternatives & Factors Affecting Suitability of Alternatives

The identification of possible alternatives examines 4 different scenarios.

The following scenarios are examined in turn:

- PFOB which is further purified to reduce residual levels of PFOI.
- PFOB that is manufactured via alternative synthetic routes
- Use of similar molecules to PFOB.
- Use of structurally different alternatives to PFOB

5. SUITABILITY AND AVAILABILITY OF POSSIBLE ALTERNATIVES

5.1 Option 1: Reduction of PFOI levels in PFOB

5.1.1 Substance ID and Properties

Perfluorooctyl bromide, properties described in Section 3.

5.1.2 Technical Feasibility

Daikin supplies PFOB with typical residual levels of PFOI at 200 ppm. PFOI is an intermediate in the PFOB synthesis, hence trace levels remaining are inevitable. Daikin has already taken steps to optimize the process and reduce the level of PFOI.

The chemical conversion is already 99.9% efficient, which is exceptional and there is little scope to improve this conversion rate. The PFOB is distilled to purify it further, repeated distillations may have marginal impact on purity while creating alternative risks to the environment.

The PFOB currently used is already 99.98% clear of PFOI, which is exceptionally pure.
Efforts will continue to reduce levels of PFOI, but it should be recognized that the process is already very well optimized.

5.1.3 Economic Feasibility

Option 1 will be progressed on an ongoing basis. Economic feasibility does not apply to Option 1 as the limitations are mainly technical. There is a very low probability that PFOB can be manufactured to the purity demanded by the EU regulation regardless of the levels of financial investment made.

5.1.4 Reduction of Overall Risk due to Transition to the Alternative

Not applicable this option will be pursued on an ongoing basis.

5.1.5 Availability

Not applicable.

5.1.6 Conclusion on Suitability of Option 1

This option will be pursued in any case but is very unlikely to provide PFOB that meets the impurity thresholds in the European Union regulation.

5.2 Option 2: Manufacture of PFOB via Alternative Synthetic Routes

5.2.1 Substance ID and Properties

Perfluorooctyl bromide, properties described in Section 3.

5.2.2 Technical Feasibility

PFOB could be manufactured via analogous molecules such as sulfonic equivalents, but this could be considered even less desirable than the current intermediate, PFOI. It is also highlighted that the current route for PFOB uses a by-product that would otherwise need to be incinerated. There is a risk that alternative chemical routes will force the synthesis of undesired chemicals for use as intermediates, whereas the existing process consumes an inevitable by-product that is otherwise incinerated.

From a technical perspective, alternative synthetic routes to make PFOB are possible but these are less desirable than the current synthetic route.

5.2.3 Economic Feasibility

Use of alternative synthetic routes will mean identifying a supplier who is able to supply alternative intermediates that can be converted to PFOB. This will infer uncertain costs which may result in a less desirable situation than now.

5.2.4 Reduction of Overall Risk due to Transition to the Alternative

The alternative synthetic route is unlikely to reduce risks to the environment as it would synthesise PFOB via alternative chemicals that are considered even more harmful to the environment than PFOI. As such, Option 2 results in an 'undesirable alternative' status and is not favoured from a risk management perspective.

5.2.5 Availability

Not evaluated further as the alternative has been discounted on the grounds of technical feasibility.

5.2.6 Conclusion on Suitability and Availability for Alternative 2

This is not considered a candidate for substitution due to the shortfalls in technical suitability and potential risks with the use of less desirable chemical intermediate.

5.3 Option 3: Use of Similar Molecules to PFOB

5.3.1 Substance ID and Properties

Perfluorooctyl ethane. The physical properties, e.g. solubility and boiling point are comparable to PFOB.

5.3.2 Technical Feasibility

PFOB related molecules have been assessed for viability as alternative processing aids. Only the ethane analogue of PFOB (perfluorooctyl ethane) was considered suitable. This material can form stable emulsions, etc, but the following issues were identified:

- PFOE can bioaccumulate and is metabolized in the human body.
- PFOE is less stable than PFOB.
- PFOE is made from PFOI so the switch makes little sense.

5.3.3 Economic Feasibility

Not applicable as PFOE is not considered suitable from a technical perspective.

5.3.4 Reduction of Overall Risk due to Transition to the Alternative

Use of PFOE fails to eliminate any risks with use of PFOB containing trace levels of PFOI, while also introducing new risks.

5.3.5 Availability

Not applicable, this option is not viable.

5.3.6 Conclusion on Suitability and Availability for Alternative Option 3

Use of PFOE fails to address any of the current risks while introducing new risks.

5.4 Option 4: Significantly Different Processing Aids

Option 4 encompasses totally different chemicals that are structurally unrelated to PFOB.

5.4.1 Substance ID and Properties

No suitable substances have been identified to date. The physical properties, e.g. water solubility/miscibility and boiling point should be comparable to PFOB otherwise there would be a significant change to the properties of the porous particles.

Water and PFOB are used to form an emulsion for the current process, hence it is unlikely that a mixture of substances can be used as a direct alternative to PFOB.

5.4.2 Technical Feasibility

The initial development of the porous particle process evaluated a large number of alternative substances. The fluorinated substances were chosen because of the very low solubility in water and a boiling point that is significantly higher than water, but still amenable to removal by spray drying. Switching to similar molecules poses a risk of undesirable alternatives, which must be avoided for pharmaceutical products where the clinical trials are very expensive.

Significantly different molecules are likely to affect the properties of the porous particles, which would make clinical trials necessary. The following summarises the clinical trials that might be necessary:

Stage 1: Identification of alternative agent and proving:

- Process concept proposed with scientific foundation
- Applicability and validity of concept described and vetted, or demonstrated
- Experimental proof of concept completed
- Process validated in laboratory using representative development equipment

Stage 2: Safety Assessment

- Demonstration that the alternative substance is safe for human dosing.

Stage 3: Dose ranging and clinical assessment

- Assuming that the alternative agent has an impact on the properties of the porous particles, it is assumed that clinical trials will be needed to verify that the correct dose is being used.
- Clinical trials would be required to demonstrate therapeutic benefit.

Stage 4: Marketing Approvals

- Marketing approvals will be required globally, this would involve significant effort to gain approvals in every market. Approval times can exceed 3 years.

5.4.3 Economic Feasibility

Prohibitively expensive with no guarantee of success. This could result in removal of medicines from the market (or reduced access due to supply chain constraints). If new trials were funded, this could be at the expense of clinical trials for completely new medicines.

Pharmaceutical products undergo rigorous safety and efficacy studies that can last in excess of 10 years from the date a potential new medicine is discovered. The remaining process to develop, test and validate genuine alternatives to PFOB is estimated to require at least 5 to 10 years and involve significant research and development costs. In practice, this could remove funding from potential new products or result in Bevespi Aerosphere being removed from the market.

Care must also be taken to prevent use of regrettable alternatives, particularly considering the long timescales and costs of the substitution activities.

For reference on clinical trials, the initial registration of Bevespi Aerosphere was based on two pivotal 24 week trials with a total of 3699 patients. This demonstrated superior improvements in lung function relative to its individual components and placebo.

5.4.4 Reduction of Overall Risk due to Transition to the Alternative

Minimal reduction in risk, considering that the current risk management results in very low (4g per annum) being released to the environment.

5.4.5 Availability

Not known at this stage.

5.4.6 Conclusion on Suitability and Availability for Alternative Option 4

Use of alternative agents is expected to be prohibitively expensive because this would necessitate clinical trials. Given the financial risks associated with clinical trials and the potential to limit funding for new medicines, it is more likely that the supply chain would be constrained until such time that AstraZeneca could manufacture porous particles with current risk mitigations in territories that have not imposed regulations that prevent the handling PFOB.

6. ALTERNATIVES ASSESSMENT MILESTONES

6.1 Description of Efforts Made to Identify Possible Alternatives

6.1.1 Research and Development

Research and Development activities in this area are confidential. Historical efforts and recent research show that porous particle properties will be affected by any substitution, hence confirming that clinical trials would be required to make any substitution of PFOB with alternative agents.

6.1.2 Data Searches

Data searches has been performed for substances with similar properties to PFOB. Closest matches are similar fluorinated molecules that could result in an undesirable substitution situation. While it might be possible to identify alternative chemicals which totally different structures that perform a similar function to PFOB, these do result in different properties of the porous particles.

7. OVERALL CONCLUSIONS ON SUITABILITY AND AVAILABILITY OF POSSIBLE ALTERNATIVES

Alternatives to PFOB are not readily available and even if an alternative was found, any substitution is likely to require repeat clinical trials and regulatory approvals worldwide, which could take many years to complete. AstraZeneca has risk mitigation in place which ensures the use of PFOB is not harmful to the environment with less than 4 g per annum of the prohibited component (PFOI) being released to the environment. An enforced search for alternatives is not well balanced against the low environmental risks given the high cost of substitution, low probability of success, long timelines and strong risk management processes in place for use of PFOB.

In October 2017, the United Nations Environment Programme Persistent Organic Pollutants Review Committee proposed an exemption until 2036 for the use of perfluorooctane iodide in the production of perfluorooctane bromide for the purpose of manufacturing pharmaceutical products. If alternatives to PFOB are not identified, this would mean these medical products are no longer manufactured from 2036, which could result in patients struggling to manage their medical condition.