ANALYSIS OF ALTERNATIVES

and

SOCIO-ECONOMIC ANALYSIS

PUBLIC

Legal name of applicant:	Becton, Dickinson U.K. Limited
Submitted by:	Becton, Dickinson U.K. Limited
Date:	June 2022
Substance:	2-(2*H*-benzotriazol-2-yl)-4,6-ditertpentylphenol (EC No: 247-384-8, CAS No: 25973-55-1), known alternatively as UV-328
Use title:	Use of an imported polymer containing 2-(2H-benzotriazol-2-yl)-4,6-ditertpentylphenol as an additive for UV stabilisation in the manufacturing of a mechanical separator component for blood collection tubes in Becton, Dickinson U.K. Limited's plant in Plymouth.
Use number:	1

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AfA	Application for Authorisation
AoA	Analysis of Alternatives
CBI	Confidential Business Information
CE	Conformité Européenne, meaning the product conforms to EU legislation on Health Safety and the Environment.
CLP	Regulation (EU) 1272/2008 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006
CRO	Contract Research Organisation(s)
CSR	Chemical Safety Report
DNEL	Derived No Effect Level
DU	Downstream User
E&L	Extractable and Leachable
ECHA	European Chemicals Agency
ECS	Environmental Contributing Scenario
EEA	European Economic Area
EU	European Union
EWC	European Waste Catalogue
FDA	Food and Drug Administration
IVD	*In vitro* diagnostics
LAD	Latest Application Date
NHS	National Health System
NPV	Net Present Value
NUS	Non-Use Scenario
OC	Operational Conditions
PBT	Persistent, Bioaccumulative and Toxic
PNEC	Predicted No-Effect Concentration
PST	Plasma Sample Tubes
RMM	Risk Management Measures
SD	Sunset Date
SEA	Socio-Economic Analysis
SST	Serum Sample Tubes
STOT- SE or RE	Specific Target Organ Toxicity- Single Exposure or Repeated Exposure
SVHC	Substance of Very High Concern
TPE	Thermoplastic Elastomer
UV	Ultraviolet
UV-328	2-(2*H*-benzotriazol-2-yl)-4,6-ditertpentylphenol (EC No: 247-384-8, CAS No: 25973-55-1)
UVCB	Unknown or Variable composition, Complex reaction products or Biological materials
vPvB	Very Persistent, very Bioaccumulative
WWTP	Waste Water Treatment Plant

DECLARATION

We, Becton, Dickinson U.K. Limited, are aware of the fact that further evidence might be requested by HSE to support the information provided in this document.

Also, we request that the information blanked out in the "public version" of the Analysis of Alternatives and Socio-economic Analysis is not disclosed. We hereby declare that, to the best of our knowledge as of today (20 June 2022), the information is not publicly available, and, in accordance with the due measures of protection that we have implemented, a member of the public should not be able to obtain access to this information without our consent or that of the third party whose commercial interests are at stake.

Daniel Hopkin

Director – Becton, Dickinson U.K. Limited

20 June 2022, Winnersh, UK

1. SUMMARY

1.1. Background

2-(2*H*-benzotriazol-2-yl)-4,6-ditertpentylphenol (EC No: 247-384-8, CAS No: 25973-55-1), also known as UV-328, is included in the Authorisation List due to its Toxic (PBT) and very Persistent, very Bioaccumulative (vPvB) properties. It has a Latest Application Date of 30 June 2022 and a Sunset Date of 27 November 2023 in the UK.

Becton, Dickinson U.K. Limited (the applicant) uses an imported polymer containing UV-328 in the manufacturing of mechanical separators for their Barricor™ blood collection tubes at their Plymouth plant in the UK. The substance is supplied as a component of the thermoplastic elastomer (TPE) compound used to manufacture the mechanical separator. It is provided in granular form and is processed via injection moulding to form an elastomer top which is then incorporated in the article matrix of the mechanical separator. The applicant expects to import up to [redacted] (100-200) kg of UV-328 a year in the 2023-2027 period.

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1.2. Analysis of alternatives

UV-328 is used as a UV stabiliser in the mechanical separator, preventing degradation of the article from exposure to UV radiation. The mechanical separator is a critical component of the applicant's Vacutainer Barricor™ blood collection tubes, as it enables obtaining a plasma sample with less cellular contamination, no gel globules and no fibrin due to insufficiently clotted serum tubes, compared with conventional gel tubes. The Barricor™ product is unique in the market in that it is the only one using a mechanical separator. It reduces the lab turnaround time and improves laboratory workflow efficiency. UV-328 ensures that the mechanical separator is not impacted when it is exposed to UV radiation and that it maintains its necessary properties, such as elasticity, until the end of the blood collection tube's shelf life.

The applicant has recognised the need to substitute UV-328 from their products and their TPE compound supplier has identified and proposed a potentially suitable alternative. The potential alternative (Alternative 1) is a different benzotriazole that has shown comparable results with UV-328 in initial pre-selection tests and is currently under evaluation at the applicant's site in the UK. Preliminary tests have shown promising results, but the applicant needs to carry out their testing regime in full, including a full-length shelf-life feasibility test, which would push the end of the substitution process beyond the UK Sunset Date.

In general, the applicant needs to follow their due diligence procedures and carry out all necessary validation testing before adopting the new raw material containing Alternative 1. It will not be possible to incorporate Alternative 1 in the manufacturing process before the Sunset Date for UV-328.

Therefore, it is necessary to request a bridging authorisation for the continued use of UV-328 in the UK for four years from the Sunset Date to allow the validation studies to conclude and enable substitution to the alternative. The 4-year review period is anticipated to be critical, considering the already evident delays in the substitution process and other unexpected time-delaying obstacles that may arise.

1.3. Socioeconomic Analysis

In case of a theoretically refused authorisation, the applicant will not be able to manufacture mechanical separators and Barricor™ blood collection tubes using UV-328. As a result, they will stop production of the tubes in their Plymouth plant and all sales to their customers, at least until substitution of UV-328.

The market gap will be taken over by conventional blood collection tubes (Plasma Sample Tubes and Serum Sample Tubes, PST and SST), which can be provided by the applicant and their competitors. This will result in increased blood sample processing times, and potentially prevent the Barricor™ users, which include public and private health organisations, from having a fast, clean high-quality plasma sample that reduces time to results, thus enabling faster clinical decisions.

Overall, there will be a significant impact to the applicant, as they will lose their Barricor™ business, potentially to non-UK based competitors. Part of the loss could be recovered from sales of PST and SST products, but SST will result in a longer processing time and PST sample quality will be inferior to Barricor™. In the Non-Use scenario, the applicant calculates that the total monetised socioeconomic impacts will be approximately £[redacted] (2-10) million over the requested 4-year review period.

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On the other hand, the applicant does not expect any human health or environmental impacts from the continued use of UV-328. There is no occupational risk from the use of UV-328, as all risks are controlled and the risk characterisation ratios for all tasks involving the substance are below 1. Furthermore, there are no emissions to the environment, as it is a closed process and all waste generated is collected and sent for incineration.

In conclusion, there are significant benefits from the continued use of UV-328, while, at the same time, the risks are practically zero. Therefore, the applicant considers that the benefits of continued use vastly outweigh the risks and that an authorisation for a minimum of 4 years is justified.

2. AIMS AND SCOPE

2.1. Background information

2-(2*H*-benzotriazol-2-yl)-4,6-ditertpentylphenol (EC No: 247-384-8, CAS No: 25973-55-1), also known as UV-328, was initially identified as a Substance of Very High Concern (SVHC) by the European Chemicals Agency on 17th December 2014, due to its Persistent, Bioaccumulative and Toxic (PBT) and very Persistent, very Bioaccumulative (vPvB) properties [1].

It was then included in Annex XIV of EU REACH (The Authorisation List) after the 8th Recommendation for Inclusion, in February 2018, with an initial Latest Application Date (LAD) of 27th May 2022 and a Sunset Date (SD) of 27th November 2023 [2].

When UK REACH came into force in the UK on 1st January 2021, the UK retained the Authorisation provisions of EU REACH in full. This includes the substances that were already included in the Authorisation List of EU REACH. UK REACH also retained the same LADs and SDs for the substances in the Authorisation List, with the exception of entries 44-54. The LAD for these substances, which include UV-328, was extended by approximately a month, to 30th June 2022, but retained the same SD as EU REACH (27th November 2023) [3].

2.2. Aim of the report

The aim of the analysis of alternatives (AoA) and the socioeconomic analysis (SEA) is to justify the use of this non-threshold substance in an authorisation following the socio-economic route. The focus is to demonstrate that

a) the emissions of UV-328 are as low as technically and practically feasible;

b) that there will be no suitable/feasible alternatives available by the Sunset Date, even if such alternatives are generally available, and

c) that the benefits to society from continued use outweigh the (costs of the) risks of continued use.

2.3. Scope of the Application for Authorisation

Becton, Dickinson U.K. Limited (the applicant, or BD) uses an imported elastomer containing UV-328 at concentrations above 0.1% (but below 1.0% ([redacted]%)) in the manufacture of a mechanical separator component of blood collection tubes in their Barricor™ product. Manufacture of the mechanical separator takes place at the applicant's manufacturing plant in Plymouth (Figure 2-1). The same plant then uses the mechanical separators to assemble the Barricor™ blood collection tubes.

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Figure 2-1 Location of the applicant's plant near Plymouth (taken from google maps)

The applicant uses an elastomer containing UV-328 in the manufacturing of a medical device. The applicant purchases the elastomer compound containing UV-328 from a US supplier in pellet form. The use applied for is therefore the use of UV-328 in a compound in the formation by injection moulding of an article.

While medical device uses are exempt from the need to apply for a REACH authorisation if the hazard listed on Annex XIV is a human health hazard, such a derogation does not apply in the case of environmental hazards as is the case for PBT and vPvB substances. Therefore, the exemption does not apply for UV-328 (Article 60, par. 3(b) of REACH Regulation).

The applicant must thus apply for an authorisation for their use of UV-328 in manufacturing of the mechanical separators. The mechanical separators are considered an article under REACH, as their function in the blood collection tubes is influenced by their shape rather than their chemical composition. Therefore, the manufacturing and service life steps after the production of the mechanical separator fall out of scope of the authorisation application, but they are of relevance for the Chemical Safety Report (CSR).

This SEA will examine the releases and health (and environmental) impacts of the substance from the whole manufacturing process at the applicant's Plymouth plant.

The applicant manufactures the Barricor™ blood collection tubes only at their Plymouth plant, but sells them worldwide. Any disruption in the supply of UV-328-containing material, in the form of a refused authorisation, would have direct social and economic impacts in the UK and a detrimental effect to the applicant's operations in the country, as well as globally, where Barricor™ blood collection tubes will be sold.

The applicant is committed to substituting UV-328 from their mechanical separators and the Barricor™ blood collection tubes and had discussions in [redacted] with the supplier of the material containing the substance, to remove it from the elastomer. The applicant initiated internal discussion on the qualification process and determined that the qualification including shelf-life aging tests would not be completed before the Sunset Date. The evaluation of impacts in the SEA will include the period deemed necessary for the applicant

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to substitute and, if necessary, gain regulatory approval for the new blood collection tubes. This is further explained in the Substitution Plan in Section 4.1.3.

3. ANALYSIS OF ALTERNATIVES

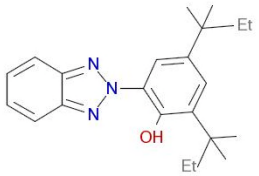
3.1. SVHC use applied for

3.1.1. Substance identity

UV-328 is a phenolic benzotriazole that is substituted with two tert-pentyl groups at the 4th and 6th position of its phenolic moiety. It absorbs the full spectrum of UV light in a fully reversible and non-destructive process, and is thus used as a UV absorber to protect various surfaces against discolouration and weathering under UV light [4].

Table 3-1 shows chemical identifiers and some molecular characteristics of the substance.

Table 3-1 Substance identification of UV-328

Property	Value
Common name	UV-328
Name	2-(2H-benzotriazol-2-yl)-4,6-ditertpentylphenol
CAS / EC Number	25973-55-1 / 247-384-8
Chemical formula	$C_{22}H_{29}N_3O$
Molecular weight	351.5 g/mol
Chemical structure	

The substance does not have a harmonised classification in Table 3 of Annex VI of the CLP Regulation (1272/2008), but the self-classification by the EU REACH registrants declared systemic toxicity for liver and kidney after repeated oral exposure (STOT RE 2) and chronic aquatic toxicity (Aquatic Chronic 4) [5].

UV-328 is persistent in soil and sediment, with disappearance half-lives much higher than 180 days. It has also been found to be bioaccumulative and has been detected in a broad range of biota, including marine mammals, fish and crustaceans. The substance also has the potential for long range environmental transport. UV-328 is also known to be toxic to mammals.

As a result, it is characterised as a Persistent, Bioaccumulative and Toxic (PBT) and a very Persistent, very Bioaccumulative (vPvB) substance under EU REACH. This is also the reason for its characterisation as a Substance of Very High Concern. Recently, UV-328 has been proposed to be listed as a Persistent Organic Pollutant (POP) by the POP Review Committee, after Switzerland submitted a proposal in May 2020 [6].

3.1.2. Description of the functions of UV-328 and performance requirements of associated products

3.1.2.1. Blood collection tubes and plasma / serum separators

The applicant is supplied UV-328 in a thermoplastic elastomer (TPE) which is used to manufacture a mechanical plasma separator for use in the applicant's BD Vacutainer® Barricor™ blood collection tubes.

Blood component separation

Clinical testing in laboratories, to detect pathogens, disease indicators or health metrics, is usually done on blood specimens. Blood specimens for laboratory analysis are collected in glass or plastic tubes in partial vacuum, to ensure that their internal air pressure is lower than atmospheric pressure to facilitate blood collection and prevent contamination of the specimen.

If the blood is stored as collected, the presence of red blood cells and other cellular debris may cause erroneous results for some chemistry tests. Therefore, laboratories typically separate the cellular blood components (e.g. red blood cells) from the liquid fraction of the blood (i.e., serum or plasma) for chemistry testing. Figure 3-1 shows blood components separated in a blood collection tube.

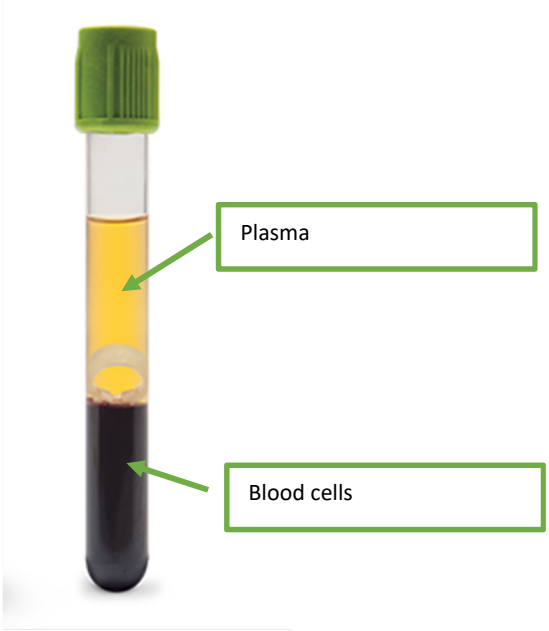


Figure 3-1 Separated blood components in a BD Barricor™ blood collection tube

It is important to make the distinction between serum and plasma.

- *Serum* is the straw-coloured liquid that remains after centrifugation of coagulated blood
- *Plasma* is the straw-coloured liquid that remains after centrifugation of blood with an anticoagulant, which prevents clotting.

Centrifugation of blood samples allows for the separation of serum/plasma from the clot/red-blood cells for subsequent analysis. If blood components stay in touch with the

plasma or serum for a prolonged period of time, red blood cells may lyse (break up), with the remnants (e.g. haemoglobin) interfering with chemistry assays [7].

To facilitate stability of serum or plasma, medical device manufacturers, including the applicant, introduce a separator component in their blood collection tubes. Figure 3-2 shows a typical blood collection tube. The colour of the cap / lid indicates the type of the tube and any potential clotting additives that may have been added by the manufacturer.

Figure 3-2 Blood collection tube components

During centrifugation, the heavier, solid blood components, such as red blood cells are concentrated at the bottom of the tube, while the lighter ones (plasma, serum) move to the top. A separator component in the blood tube ensures that, after centrifugation, the blood components do not mix again.

Plasma / serum gel separators (Figure 3-3) typically use a silicone or polyamide gel that has a density between that of the plasma and the cellular blood components. During centrifugation, when the plasma / serum and blood cells move to the opposite sites of the blood tube, the separator gel remains between the two, thanks to the density difference. Its shape also changes from the centrifugal force and allows the blood components to move in the tube. When centrifugation finishes, the gel expands to the walls of the tube, thus creating a seal that prevents the two fractions from mixing.

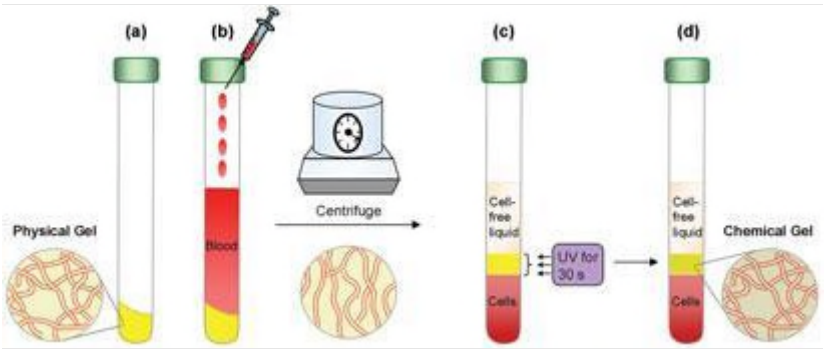


Figure 3-3 How gel separators work in blood collection tubes [8]

BD Barricor™ blood collection tube

BD Vacutainer® Barricor™ Plasma Blood Collection Tubes are used to collect, separate, process, transport, and store venous blood specimens for use in chemistry determinations,

therapeutic drug monitoring, and infectious disease testing in plasma for in vitro diagnostic use.

The applicant's Barricor™ blood collection tubes use a different separator, though its functioning principle is essentially the same as for the gel separators. The "mechanical" separator used by the applicant consists of two parts, as shown in Figure 3-4:

- An elastomer top which contains the UV stabiliser at a [redacted] % (< 1%) w/w concentration, and
- a high-density base.

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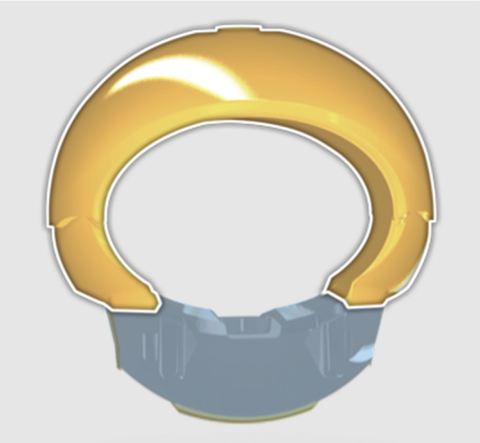

Figure 3-4 Schematic of mechanical separator in BD Barricor™ [9]

When blood is collected in a Barricor™ tube, the mechanical separator rests at the top of the tube. Its ring shape allows the collected whole blood to flow to the bottom of the tube [9]. During centrifugation, the elastomer stretches as a result of the force applied and the separator detaches from the tube walls and drops into the blood. Throughout the centrifugation, the elastomer part remains stretched, thus allowing the blood cells to precipitate to the bottom of the tube through the plasma. At the same time, the difference in density between the top and the base of the mechanical separator keep it positioned properly in the tube. When the centrifuge slows and stops, the elastomer component returns to its original shape and forms a seal between the plasma and the blood cells. This process is shown schematically in Figure 3-5.

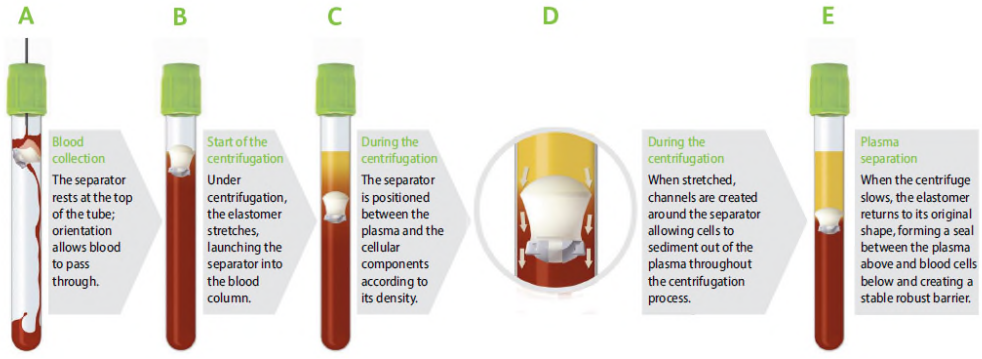

Figure 3-5 Mode of operation of mechanical separator in BD Barricor™ [9]

This configuration provides several benefits to the BD Barricor™ blood collection tubes, compared to conventional tubes with plasma separators [10]:

- Mechanical separators continuously allow the flow of blood cells during centrifugation, resulting in a better separated, cleaner sample. Thanks to this, there is lower cellular contamination in the plasma fraction, compared with gel separators.
- Mechanical separators contribute to greater stability, thus allowing for longer transport times and improved stability of components, such as aspartate aminotransferase (AST), potassium (K), phosphate and lactate dehydrogenase (LDH), compared to conventional plasma sample tubes with gel separator.
- It eliminates the generation of gel artifacts, such as gel globule or smearing, which may appear with gel separators.

Overall, the benefits allow for better processing times and longer transport times, along with better blood sample quality, improving capacity and capabilities of the users in clinical settings.

3.1.2.2. Functionality of UV-328

UV-328 is a component of the raw materials of the mechanical separator of Barricor™ blood sample tubes, manufactured at the manufacturing plant in Plymouth. Barricor™ is the only blood collection tube offered by the applicant to the market for routine clinical use that contains UV-328. Moreover, Barricor™ is the only product with a mechanical separator offered by the applicant.

UV-328 is added into the TPE by the supplier to prevent degradation or yellowing of materials during/after their exposure to UV light. Without proper functioning of the mechanical separator the performance of the product may not meet the requirements. Degradation due to UV light could directly affect properties of the mechanical separator (density and elastic modulus), which are quintessential to barrier formation and barrier integrity. In addition, the overall shelf life of product, which currently is 18 months, could be affected without the material being stable after exposure to UV degradation.

If the properties of the mechanical separator are affected by UV light, it will not be able to perform its function properly. Change in elastic modulus means that the separator will be more rigid and even brittle, which can result in the separator not dropping during centrifugation or not providing a tight enough seal between plasma and blood cells. Furthermore, change in density means that the positioning of the separator during centrifugation is not the correct one, thus affecting effectiveness of the separation of blood cells from plasma.

These functions are essential for the generation of a clean, high-quality blood sample in BD Barricor™ tubes.

3.1.2.3. Performance requirements of blood collection tubes and functionality of mechanical separators

Each BD Barricor™ blood collection tube contains only one mechanical separator. A mechanical separator consists of two main materials, PP (polypropylene) and TPE (thermoplastic elastomer). The UV stabiliser is present as [redacted] (< 1) % w/w in the TPE part of the mechanical separator. The applicant imports it to their UK plant from a US-

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based supplier in the form of granules, containing UV-328. Formulation therefore occurs in the US, at the supplier's plant. This separator is a component of blood collection tubes. UV-328 is not present elsewhere in the blood collection tubes. All other blood collection tubes that the applicant manufactures at their Plymouth plant except Barricor™ do not contain UV-328.

The function of the mechanical separator is to form and maintain a physical barrier between plasma and blood cells after centrifugation of the blood specimen. It is important for the mechanical separator to meet certain mechanical specifications, to ensure it moves in the correct location to allow proper separation of blood components during centrifugation and to maintain the seal between separated plasma and blood cells during storage and transportation after centrifugation. The top, elastomer, part of the mechanical separator must remain flexible during centrifugation, to allow the flow of the blood components. It must also be steady and robust enough that it does not get dislodged during transportation or in case of a drop or other unexpected move. These properties could be affected if the UV stabiliser does not provide stability against UV light exposure and subsequent degradation.

The mechanical separator is an irreplaceable component of the Barricor™ product as it is a key technology that allows unique barrier formation features that distinguish this product from all other blood collection tubes. The mechanical separator enables the blood collection tube with enhanced blood sample quality (cleanliness) and faster turnaround time.

The blood collection tubes must conform to national and international standards (e.g. ISO 13485, ISO 14155), as well as to comply with the requirements of regulations, such as the Medical Device and IVD Regulations in the EU (MDD 93/42/EEC and IVD 98/79/EC or MDR 2017/745 and 2017/746) or 21 CFR 820 and 21 CFR 50, 56 and 812 in the US. The Barricor™ products are CE Marked, but the CE Mark does not follow any specific standard.

3.1.2.4. Technical feasibility criteria for potential alternatives

The alternative UV stabiliser must be assessed on two levels:

1. As a substance, based on its properties and its regulatory profile.
2. As a component in the compound with the TPE, based on the properties and the resulting performance of the compound against the specifications set by the applicant.

Of these two levels, the compound one is the more critical and the one where most of the applicant's efforts are focused.

Evaluation of the substance is carried out by the supplier of the compounded TPE. They evaluate the properties of the different potential alternative UV stabilisers compared to UV-328, based on the criteria detailed in Table 3-2 and which consist of both technical aspects as well as regulatory ones. These pre-selection criteria include a) chemical structural similarity; b) physico-chemical characteristics such as melting behaviour; c) absorption spectra; d) changes in properties and behaviour with time.

Table 3-2 Pre-selection criteria for potential alternative UV stabilisers

Technical criterion	Desired value or performance	Impact area / Justification of importance
Chemical structure	Another substance of a similar structure desired	A similar chemical structure means that the behaviour of the UV stabiliser in the elastomer will be similar, with no unwanted interactions with the other constituents.
Molecular weight	Similar to UV-328	A similar molecular weight would mean that the properties of the TPE would not change significantly, so its processing would not need to change compared to UV-328, allowing for an easier transition to the alternative.
Melting point	Should be sufficiently different from that of TPE	The moulding process must be carried out at a temperature that melts the TPE, but not the UV stabiliser. If the UV stabiliser were to melt at the same (or a lower) temperature as the TPE, it could create uneven distribution in the final article, thus affecting its performance.
Water solubility and reactivity	Little/none desired for both	The UV stabiliser must not react with or dissolve in water, as this could impact the clinical performance of the collected blood. If the UV stabiliser were to leach into the plasma, it could affect the accuracy of the laboratory analyses.
UV light absorption	Within 280 – 420 nm	The UV stabiliser must be able to absorb UV light in the wavelengths that can degrade the elastomer. That way, the elastomer can retain its mechanical properties for longer, thus extending the blood collection tube's shelf-life. A broader wavelength absorption range is typically more desirable.
Regulatory restrictions.	Substance not anticipated to be under any regulatory restrictions at the time of submission of the AfA. Low toxicity	The applicant wants to identify an alternative that reduces the risk arising from UV-328. Hence, the pre-selected alternative should have low toxicity and be available for use without restrictions at the time of submission of the AfA.

Besides the raw material information, the compound with control UV-stabiliser (TPE/UV-328) and the compound with alternative UV-stabiliser must be tested and key parameters related to the product mechanical performance including viscosity, density, yellowness index and elastic modulus must be evaluated. This evaluation is first carried out at the compound supplier's side in the USA, using two types of medical grade TPE, which are different to the TPE that will be used by the applicant. If tests using these compounds are successful, the supplier will provide the applicant with the full compound to be used in the mechanical separator, for additional testing at the applicant's site.

Table 3-3 Pre-selection criteria for compounds with potential alternative UV stabilisers

Technical criterion	**Desired value or performance (based on Barricor™ TPE buy specification)**
Viscosity	[redacted] Pa at [redacted]°C [redacted] /sec shear rate
	[redacted] Pa at [redacted]°C [redacted]/sec shear rate
Density	[redacted] g/ml
Yellowness index	[redacted]
Elastic modulus	[redacted] psi

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Following pre-selection, the identified alternative will need to be validated by the applicant, to ensure that the mechanical separator can be manufactured consistently in their plant and that the final medical device (the Barricor™ blood collection tube) performs according to specifications. The criteria that have to be met by the separator and the blood collection tube fall in two major categories, namely mechanical properties and clinical performance. Non-clinical and clinical studies must be completed demonstrating the product meets required performance, safety and effectiveness claims. Table 3-4 summarises these validation criteria and the tests that need to be carried out.

Table 3-4 Validation criteria

Validation category	**Validation criteria description**	**Qualification criteria**
Mechanical performance	1. Barrier formation test	1. The separator moves to a desired position between plasma and cell interface.
	2. Barrier integrity for centrifuged samples after simulated courier transportation	2. Visible cell separation and plasma quality is maintained.
	3. Barrier integrity for centrifuged samples post drop from benchtop and storage height	3. Visible cell separation and plasma quality is maintained.
	4. Mechanical separator positioning after shipping and prior to product use	4. Minimal movement of the separator from its assembled position.
Clinical performance	Clinical (confirmatory) study to be performed at T=0 (i.e. time of manufacture, without aging) to lower the regulatory risk associated with this change. In addition, extractable and leachable (E&L) will be evaluated, to assess the difference in E&L profiles between the two UV stabilisers (existing and alternative). Any difference will be assessed for clinical impact and, if needed, added to the clinical study test plan.	The clinical study and the E&L profiles must show little difference between the two UV stabilisers.

3.1.3. Market analysis of products manufactured with the Annex XIV substance

Barricor™ sales are expected to grow in the next 5 years in the UK. Barricor™ is an alternative blood collection tube for both the NHS and the private market due to its advantages. Barricor™ provides improved sample quality, reduced turnaround time and increased lab efficiency for the user.

The outlook for Barricor™ in the UK and the rest of Europe is shown in Table 3-5. At the moment, there are no specific forecasts for beyond 2025, but the applicant expects a [redacted]% (1-5%) annual growth across their whole blood collection tubes product portfolio.

Table 3-5 Barricor™ sales forecast

Year	Tubes Units UK (`000 units)	Tubes Units rest of Europe (`000 units)	Tubes Units global (incl. UK and Europe) (`000 units)
2022	[redacted] (100-500)	[redacted] (15,000 – 30,000)	[redacted] (30,000-50,000)
2023	[redacted] (500 – 2,000)	[redacted] (15,000 – 30,000)	[redacted] (30,000-50,000)
2024	[redacted] (500 – 2,000)	[redacted] (15,000 – 30,000)	[redacted] (50,000-100,000)
2025	[redacted] (2,000 – 5,000)	[redacted] (30,000 – 60,000)	[redacted] (50,000-100,000)

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3.1.4. Annual volume of the SVHC used

Table 3-6 shows the quantities of UV-328 that are expected to be imported in the UK in the TPE compound.

Table 3-6 UV-328 imports for use in mechanical separator manufacturing

Year	Tubes Units global (incl. UK and Europe) (`000 units)	Purchased quantities of TPE (in kg)	Maximum imported quantities of UV-328 (assuming [redacted]% content in TPE) (in kg)
2022	[redacted] (30,000-50,000)	[redacted]	[redacted] (10-100)
2023	[redacted] (30,000-50,000)	[redacted]	[redacted] (1-10)
2024	[redacted] (50,000-100,000)	[redacted]	[redacted] (10-100)
2025	[redacted] (50,000-100,000)	[redacted]	[redacted] (100-200)
2026*	[redacted] (50,000-100,000)	[redacted]	[redacted] (100-200)
2027*	[redacted] (50,000-100,000)	[redacted]	[redacted] (100-200)

Notes

*: For 2026 and 2027 there are no forecasts at the moment, so the quantities were calculated assuming the average 4% annual growth expected across the applicant's blood tube products

**: Please note that the amount of UV-328 that is purchased per year is not always completely consumed in one year. It is stored and used up the following year, which is why quantities do not correspond to the increased output in 2023.

CBI 1

CBI 3

The Application for Authorisation covers an annual total amount of [redacted] (100-200) kg of UV-328, corresponding to [redacted] (10,000-30,000) kg of TPE resin (considering the worst case scenario of [redacted] % (0.1-1%) of UV-328 in TPE resin w/w). CBI 3

3.2. Efforts made to identify alternatives

The applicant has focused their efforts to identify a chemical alternative, i.e. an alternative UV absorber / stabiliser. Use of a different technology, removing the need for a mechanical separator altogether, was not considered to be a realistic option. The applicant introduced the mechanical separator as an improvement over the existing blood separator techniques, such as gel separators. Therefore, it is considered unlikely that a technology that can provide equivalent performance would be identified in the same time frame. Furthermore, introduction of a new technology would essentially require the design of a new product to replace Barricor™, and the very high costs and uncertainties associated with such a new product process.

3.2.1. Consultations with customers and suppliers of alternatives

Once UV-328 was added to the Authorisation List, the applicant identified the need to substitute the substance from their product. In [redacted], the applicant began working together with the US supplier of the raw material compound to identify a suitable alternative UV stabiliser. CBI 2

The supplier carried out R&D work, to identify a suitable potential alternative UV stabiliser, which does not have the drawbacks of UV-328. This work was based on the pre-selection criteria described in Table 3-2.

Once a potential alternative raw material-UV stabiliser compound is identified, the supplier tests it in a TPE compound to ensure that the whole compound performs comparably to the control, i.e. the currently used compound with UV-328. Testing is carried out with two different TPE compounds, which are also different to the compound supplied to the applicant. Once these tests are successfully completed, the supplier supplies the applicant with the new compound to be used in the mechanical separator for further evaluation.

3.2.2. Research and development

As mentioned in Section 3.2.1, the applicant did not undertake R&D in-house to identify and pre-select potential alternatives, as this was and is done by the supplier. However, they have to evaluate any alternatives identified by the supplier in their manufacturing process.

Validation is a process that must be carried out by the applicant any time there is a change (major or minor) in any of the parameters of a medical device's manufacturing process. This includes any change in process or materials, even a minor one such as a UV stabiliser in concentration of [redacted]% (<1%) in a component. CBI 1

The applicant needs to ensure that the modified medical device, in this case the BD Barricor™ blood collection tubes using the alternative UV stabiliser, performs according to specifications and can be manufactured at a consistent quality. Details of validation testing are shown in Table 3-4.

3.2.3. Data searches

As the search for an alternative UV stabiliser is undertaken by the US supplier, the applicant did not carry out data searches to identify an alternative themselves.

The US supplier of the TPE-UV stabiliser compound provided general pre-selection criteria, as shown in Table 3-2. As the potential alternative UV stabiliser was provided by the compound provider's supplier of materials, a full list of assessed UV stabilisers was not made available by the supplier.

The applicant therefore carried out desk research as part of this AoA. This research was based on information that is publicly available online and identified a number of alternative UV absorbers. However, as a potentially suitable alternative has already been identified by the supplier, this exercise has mainly an illustrative character.

3.2.4. Identification of alternatives

As discussed in Section 3.2.1, the US supplier of the TPE raw material containing the UV stabiliser performed their own R&D to pre-select potential alternatives to UV-328. The supplier focused on a potential alternative that can be used with the existing elastomer material. Offering a different compound altogether, changing both the TPE and the UV stabiliser was not considered a feasible option. Such an option would have a much higher change factor and, as a result, would require much more extensive (and expensive) validation, both at the supplier and at the applicant sites, which would take much longer. Therefore, substitution with a 'drop in' alternative substance is considered a more streamlined and simpler approach, with little to no anticipated impact on the process and the product. The supplier worked with several known, commercially available, UV stabilisers, focusing on the pre-selection criteria in Table 3-2.

Table 3-7 shows a list of UV absorbers that were identified as part of the desk research [11].

Table 3-7 Indicative list of UV absorbers / stabilisers

Trade Name	Chemical Name	CAS No	Applications
UV-3346	Poly[N,N'-bis(2,2,6,6-tetramethyl-4-piperidinyl)-1,6-hexanediamine-co-2,4-dichloro-6-morpholino-1,3,5-triazine]	82451-48-7	PE/PP film, injection and rotational moulding, (polyoxymethylene, polyamides, polyethylene terephthalate, acrylonitrile styrene acrylate, polynutylene terephthalate, acrylonitrile butadiene styrene, high impact polystyrene, poly(methyl) methacrylate and polyurethane)
NIQ 81 84	UV stabilizer mixture of Nickel quencher and UV531 for outdoor application	N/A	Polyolefins
UV-1130	N/A		Coatings, printing and packaging adhesives and sealants.
UV-80	N/A		Narrow absorption limit for sunglasses lenses resins of polycarbonates and poly(methyl) methacrylate. Also used in adhesive, paint and solvent-based systems.
UV-3050	N/A		Optimum filter effect up to the boundary with visible light. Used in linear polyesters or optical articles, polyurethane systems and alkyd resins.
UV-312	N-(2-ethoxyphenyl)-N'-(2-ethylphenyl)oxamide	23949-66-8	Plastic and other organic substrates, particularly rigid and flexible PVC and polyesters.
MB PS 26P25	UV stabiliser masterbatch	N/A	Extended Polystyrene
UV-3030	Pentaerythritol tetrakis(2-cyano-3,3-diphenylacrylate); 1,3-Bis-[(2'-cyano-3',3'-diphenylacryloyl)oxy]-2,2-bis-[[(2'-cyano-3',3'-diphenylacryloyl)oxy]methyl]propane	178671-58-4	Polymers with high extrusion temperature, e.g. polyamides, polyethylene terephthalate, polycarbonates
UV-3039	2-Ethylhexyl-2-cyano-3,3-diphenylpropenoate	6197-30-4	Strong UV absorbance, especially in UV-B region. Compatible with polyurethanes, styrenic polymers, polyesters, polyamides, and acrylics.
UV-3	N,N'-Bis(4-ethoxycarbonylphenyl)-N-benzylformamidine	586400-06-8	Polyurethanes (Spandex, TPU, RIM etc.), engineering plastics (polyethylene terephthalate, polycarbonates, polycarbonates / acrylonitrile butadiene styrene, polyamides, polybutylene terephthalate, etc.)

Trade Name	Chemical Name	CAS No	Applications
UV-1	N-(Ethoxycarbonylphenyl)-N'-methyl-N'-phenyl formamidine	57834-33-0	Microcellular and integral skin foams, traditional rigid, semirigid and flexible foams, fabric coatings for synthetic leather
UV-1577	2-(4,6-Diphenyl-1,3,5-triazin-2-yl)-5-[(hexyl)oxy]-phenol	147315-50-2	Polycarbonates and polyesters for complex mouldings, fibres, plain and corrugated sheets, twin wall sheets, thin films, co-injected or coextruded semi-finished parts.
UV-3529	N,N'-Bis(2,2,6,6-tetramethyl-4-piperidinyl)-1,6-hexanediamine polymers with morpholine-2,4,6-trichloro-1,3,5-triazine reaction products methylated	193098-40-7	Polyethylene and Polypropylene agricultural films, artificial turf, injection and rotational moulding, polypropylene fibre, polyoxymethylene, polyamides, polyethylene terephthalate, polybutylene terephthalate, acrylonitrile styrene acrylate, acrylonitrile butadiene styrene, high impact polystyrene, rigid and flexible polyvinyl chloride, poly(methyl) methacrylate and polyurethanes
UV-1579	2-(2-Hydroxy-4-methoxyphenyl)-4,6-diphenyl-1,3,5-triazine	106556-36-9	Pet fibre (terylene)
UV-3638	2,2’-p-phenylenebis-4H-3,1-benzoxazin-4-one	18600-59-4	Polyethylene terephthalate film, fibre, containers, polycarbonate-capstock and moulding
UV-3049	2,2’-dihydroxy-4,4’-dimethoxy-benzophenon	131-54-4	Polyester film
UV-1164	2-(4,6-Bis-(2,4-dimethylphenyl)-1,3,5-triazin-2-yl)-5-(octyloxy)-phenol	2725-22-6	Nylon, polyvinyl chloride, polyethylene terephthalate, polybutylene terephthalate, acrylonitrile butadiene styrene and poly(methyl) methacrylate and other high-performance plastics.
CHIM 81	2-hydroxy-4-octoxy benzophenone	1843-05-6	UV absorber containing benzotriazole, suitable for polystyrene, polyurethanes, elastomers, polyvinyl chloride.
NIQ 84A	2,2'-thiobis(4-tert-octylphenolate)-N-butylamine nickel(II)	14516-71-3	Nickel quencher, UV stabilizer developed for outdoor applications in polyolefins
UV-234	2-(2-hydroxy-3,5-di(1,1-dimethyl-benzyl)-2-benzotriazole	70321-86-7	UV absorber containing benzotriazole, suitable for polystyrene, polyethylene terephthalate, thermoplastic elastomers, polyamides, polyoxymethylene, polycarbonates
UV-326	2-(2'-Hydroxy-3'-t-butyl-5'-methylphenyl)-5-	3896-11-5	UV absorber containing benzotriazole, suitable for acrylonitrile butadiene styrene,

Trade Name	Chemical Name	CAS No	Applications
	chlorobenzotriazole		polystyrene, polyurethanes, polyvinyl chloride, polyesters
UV-329	2-(2h-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol	3147-75-9	UV absorber containing benzotriazole, suitable for e.g. polystyrene, polyethylene terephthalate, polyacrylamide, polyvinyl chloride
UV-360	Phenol 2,2'-methylene(6-(2h-benzotriazol-2-yl)-4-(1,1,3,3tetramethylbutyl))	103597-45-1	UV absorber containing benzotriazole, suitable for polyoxymethylene, poly(methyl)methacrylate, polycarbonates, polyamides, polyethylene terephthalate, polybutylene terephthalate, elastomers.
UV-P	2-(2'-hydroxy-5-methylphenyl)-5-benzotriazole	2440-22-4	UV absorber containing benzotriazole, suitable for acrylonitrile butadiene styrene, polystyrene, elastomers, polyesters, polyurethanes, polyvinyl chloride.

The results of the desk research show that there are several UV stabilisers in the market, and not all of them belong to the benzotriazole family, such as UV-328 or UV-350, which are listed in the Authorisation List. However, it appears that not all of the UV stabilisers are suitable alternatives for the application of UV-328 in TPE. As is shown in Table 3-7, the UV stabilisers mentioned as suitable for elastomer or TPE applications appear to be benzotriazoles or benzotriazole-based substances.

A paper presented in a 2018 elastomer conference examined benzotriazole UV stabilisers more closely, following the inclusion of four such substances in the Authorisation List [12]. The paper presented a hazard screening of benzotriazole UV stabilisers and a comparison table. Figure 3-6 shows the assessed benzotriazoles and their hazard scoring, with a lower score indicating a less hazardous substance.

	Acute Toxicity	Carc.	Muta.	Repr. Tox	Dev. Tox	Neurotox.	Chronic Toxicity	Resp. Sens.	Aquatic Acute	Aquatic Chronic	Hazard Score
UV-P	1	1	1	1	1	-	2	-	1	3	3
UV-234	1	-	1	-	1	-	2	-	1	1	2
UV-326	1	1	1	1	1	-	1	-	1	1	1
UV-328	1	-	1	*2*	1	-	3	-	1	-	3
UV-329	1	-	1	*1*	*1*	-	*2*	-	1	1	*2*
UV-360	1	-	1	1	1	-	1	-	1	1	1
UV-928	1	-	1	-	*1*	-	1	-	1	1	*1*

Notes: Endpoint scores and Hazard Scores given in italics are deemed to be of low confidence.

Figure 3-6 Hazard scoring summary for UV-328 and alternatives [12]

Based on this paper, there are several benzotriazoles with a better hazard profile than UV-328, which makes them potentially suitable alternatives.

3.2.5. Shortlist of alternatives

The supplier of the thermoplastic elastomer raw material concluded on a single alternative, based on its structural similarity and its physico-chemical properties, along with its hazard profile, which is preferable to that of UV-328. The identity of this shortlisted alternative is shown in Table 3-8.

Table 3-8 Shortlisted alternatives

No.	Alternative name	CAS or EC Number (where applicable)	Description of alternative
1.	[redacted]	[redacted]	Benzotriazole UV stabiliser – chemical alternative intended as direct 1:1 wt.% replacement of UV-328

CBI 2

3.3. Assessment of shortlisted alternative

CBI 2

3.3.1. Alternative 1: [redacted]

3.3.1.1. General description of Alternative 1

Alternative 1 was identified as a suitable alternative by the applicant's supplier. It is also a benzotriazole, like UV-328. Its substance ID and molecular characteristics are shown in Table 3-9.

Table 3-9 Substance identification of Alternative 1

Property	Value
Common name	[redacted]
Name	[redacted]
CAS / EC Number	[redacted]
Chemical formula	C[redacted]H[redacted]N[redacted]O
Molecular weight	[redacted]g/mol
Chemical structure	[redacted]

CBI 2

3.3.1.2. Availability of Alternative 1

Compounding (i.e. mixing of polymer and additives) of the elastomer is carried out by the applicant's supplier outside the UK, so the supplier is responsible for procurement of Alternative 1. Since the compound supplier has confirmed comparable performance of Alternative 1 in the compound, they have begun supply of the new compound to the applicant for additional evaluation. The first evaluation batch for qualification activities arrived in [redacted]. According to the raw material supplier, and considering the relatively small quantities of UV stabiliser used in the manufacturing of the mechanical separators, there is sufficient supply capacity of Alternative 1 for the applicant's use, though currently there are still delays in supply of the compound as a result of disruptions in the supply chain caused by the Covid-19 pandemic.

CBI 2

As shown in Section 3.1.4, the quantities of UV-328 imported by the applicant in the UK in 2022 are expected to be [redacted] (10-100) and it is expected to increase to [redacted] (100-200) by 2027. It is expected that the required quantities of Alternative 1 would be in the same range, so there would not be any need for registration under UK REACH, which could delay import of larger quantities.

CBI 3

In conclusion, Alternative 1 is readily available from the supplier for use by the applicant and in sufficient quantities.

3.3.1.3. Safety considerations related to using Alternative 1

There is no harmonised classification in EU CLP for Alternative 1. Similarly, the EU REACH registration dossier concluded that the substance is not classified. Some individual Classification and Labelling notifiers have included chronic aquatic toxicity (Aquatic Chronic 3 or 4) or systemic toxicity after a single exposure (STOT SE 3) and acute hazards such as skin and eye irritation [13].

Based on the hazard profile described above, Alternative 1 is less hazardous than UV-328.

Overall, based on currently available information, and as seen in Figure 3-6, the substance has a better toxicological profile than UV-328. Therefore, it can be assumed that its use would comply with the requirements of authorisation.

3.3.1.4. Technical feasibility of Alternative 1

Alternative 1, more precisely the raw material containing Alternative 1 additive, has been initially evaluated for technical feasibility by the US supplier of the raw material. The supplier evaluated the raw material against the technical feasibility criteria discussed in Section 3.1.2.4.

Table 3-10 summarises the findings of the supplier from their evaluation of Alternative 1 in comparison with UV-328.

Table 3-10 Technical feasibility evaluation of Alternative 1 by the raw material supplier

Technical criterion	Impact area	Comparison of Alternative 1 vs UV-328
Chemical structure	Physico-chemical property	Alternative 1 belongs to same class of substances as UV-328. Similar structure ensures that compounding of plastic will require fewer changes and that performance is expected to be equivalent.
Molecular weight	Physico-chemical property	Molecular weight of Alternative 1 is similar to that of UV-328
Melting point	Physico-chemical property	Melting point is not close to that of the elastomer, so there are no anticipated concerns for the moulding process in case of substitution.
Water solubility and reactivity	Physico-chemical property	Alternative 1 is not soluble and has low reactivity with water, similar to UV-328.
Absorption spectra	UV light absorption and product shelf-life	Similar range of absorption spectra as UV-328, at between 280-420 nm wavelength. UV stabilisation performance is thus expected to be equivalent to UV-328.
Restrictions from chemical regulations	No restrictions in use of Alternative 1 in UK at time of submission of AfA	No regulatory restrictions in place that would not allow use of Alternative 1 after the Sunset Date for UV-328. Alternative 1 has no harmonised (or self-) classification.

In addition, besides the raw material information, the compound with control UV stabiliser (TPE/UV-328) and two different compounds with alternative UV stabiliser have been tested and key parameters related to the product mechanical performance including viscosity, density, yellowness index and elastic modulus have also been tested. Testing results have shown that the alternative compounds (containing Alternative 1) perform comparably to the original compound (containing UV-328).

Following the technical feasibility assessment by the supplier, the alternative UV stabiliser was deemed acceptable for use in the elastomer and the new raw material was offered to the applicant. Despite that, the applicant's process also requires that the alternative UV stabiliser is tested for feasibility on yellowness index and elastic modulus in the TPE compound used in the mechanical separator. These tests are currently in progress, but

preliminary results show that control and alternative perform comparably as well. The results are presented in Table 3-11.

Table 3-11 Comparison of compounds containing UV-328 and Alternative 1

Technical criterion	Desired value or performance	UV-328 performance	Alternative 1 performance	Comments
Viscosity	[redacted] Pa at 200°C 11,170/sec shear rate	[redacted] Pa	[redacted] Pa	Higher than UV-328, but within desired limits
	[redacted] Pa at 200°C 223/sec shear rate	[redacted] Pa	[redacted] Pa	
Density	[redacted] g/ml	[redacted] g/ml	[redacted] g/ml	Comparable with UV-328
Yellowness index	[redacted]	[redacted]	[redacted] (preliminary result – testing still in progress)	Lower than UV-328 and within desired limits
Elastic modulus	[redacted] psi	[redacted] psi	[redacted] psi (preliminary result – testing still in progress)	Higher than UV-328, but within desired limits

CBI 1

CBI 2

Before switching to the alternative UV stabiliser, the applicant must carry out their own validation of the mechanical stabiliser and the Barricor™ blood collection tube using the new raw material, to ensure that the performance is acceptable and consistent. The UV stabiliser comprises just [redacted]% of the mass of the elastomer used to manufacture the mechanical separator. As such, the applicant does not need to carry out a full application for regulatory / commercialisation approval.

CBI 1

The applicant is currently engaged in this validation process, which is expected to be completed only after the Sunset Date for UV-328. This means that technical feasibility of Alternative 1 for use in the applicant's mechanical separator has not been confirmed, yet. Considering the small scale of the change, the chemical structural similarity, the positive results from the supplier's evaluation and the applicant's feasibility check, it is expected that validation of the alternative raw material will be successful. However, as it is still ongoing, Alternative 1 cannot be considered a technically feasible alternative, yet.

3.3.1.5. Economic feasibility of Alternative 1

The UV stabiliser is included in the elastomer resin in very low concentration, approximately [redacted]%. Alternative 1 is considered a drop-in alternative to UV-328 so no major modifications in the manufacturing equipment or the process are expected.

CBI 1

The supplier of the raw material has informed the applicant that the price of the elastomer with the new UV stabiliser will be the same as the one with UV-328.

In conclusion, substitution of UV-328 with Alternative 1 will not affect the applicant's operating costs or the price of the Barricor™ product. It is therefore considered economically feasible.

3.3.1.6. Suitability of Alternative 1 for the applicant and in general

Based on the raw material supplier's evaluation and the applicant's feasibility check, Alternative 1 appears to be a technically feasible alternative. This remains to be verified by the applicant, after they carry out the necessary mechanical and performance tests for the mechanical separator and Barricor™ blood collection tube's validation.

As such, Alternative 1 is not confirmed as technically feasible at the moment. The validation testing process is expected to continue until after the Sunset Date, hence the need for an authorisation for the continued use of UV-328 in the UK beyond that date.

Alternative 1 is also considered economically feasible, having essentially the same price as UV-328 in the elastomer raw material. It is also available in sufficient quantities for the applicant's use.

In terms of safety, the substance is not classified as hazardous and there are currently no restriction to its use in the UK or the EU.

3.4. Conclusion on shortlisted alternative

As discussed in Section 3.3.1.6, Alternative 1 is a potentially technically feasible alternative UV stabiliser. However, as the applicant needs to follow their due diligence and carry out all necessary validation testing before adopting the new raw material containing Alternative 1, it will not be possible to incorporate it in the manufacturing process before the Sunset Date for UV-328.

Therefore, it is necessary to obtain a bridging authorisation for the continued use of UV-328 in the UK for four years after the sunset date to allow for the validation studies to conclude and rollout of the alternative.

4. SOCIO-ECONOMIC ANALYSIS

4.1. Continued use scenario

4.1.1. Summary of substitution activities

After the applicant identified the need to substitute UV-328 from their medical device, they communicated with their supplier of the raw material containing the substance and initiated substitution activities at the supplier's end.

The supplier carried out their research for an alternative in-house, based on a set of internal technical criteria and specifications from the applicant. In late [redacted], the supplier came with a proposed alternative that performs comparably to UV-328 and has no regulatory restrictions under UK REACH (referred to as Alternative 1 in this report). The applicant initiated internal discussion on the qualification process and determined that the qualification including shelf-life aging tests would not be completed before the Sunset Date.

CBI 2

Using the identified alternative UV stabiliser in the elastomer, the applicant is currently validating the manufacturing of mechanical separators for their Barricor™ blood collection tubes, preparing test samples and running a series of tests, including stability. These tests are expected to finish after the Sunset Date for UV-328 in the UK.

4.1.2. Conclusion on suitability of available alternatives in general

The applicant is aware that alternative UV stabilisers / UV absorbers are available in the market, although some of them, such as UV-327 and UV-350, are also listed in the Authorisation List and therefore not available.

The applicant is also aware of other substances used as UV stabilisers in the coating or plastics industry, as discussed in Section 3.2.4. These alternatives belong to the benzotriazole family, which also includes UV-328, but also in other chemical groups, as shown in Table 3-7.

Nevertheless, it is the supplier of the TPE raw material who has the means to evaluate an alternative UV stabiliser that best suits the TPE they supply to the applicant. The applicant's supplier of the raw material has already identified a potentially suitable alternative, which is readily available and can be supplied to the applicant in the required quantities. Alternative 1, assessed in Section 3.3.1, is currently under evaluation by the applicant, after it met the preliminary selection criteria the applicant and the supplier set. Preliminary results of testing Alternative 1 in the compound to be used in the mechanical separator are promising, and comparable with the current compound, containing UV-328. However, the applicant cannot use the substance in commercial production, yet, as they must first validate its use in the mechanical separator and the finished product.

In conclusion, the applicant understands that there are suitable alternatives generally available in the market, which can be potentially used in their mechanical separators as UV stabilisers. However, before any of these alternatives can be used in commercial production, they must undergo testing to ensure that they meet the applicant's specifications consistently. At the moment, such tests are not expected to be concluded before the Sunset Date for UV-328, so no alternative can be considered available at the moment.

4.1.3. Substitution plan

This AfA is a bridging application to allow the applicant to safely conclude their validation and qualification procedures with the selected potential alternative. Therefore, the applicant describes a substitution plan in this document.

4.1.3.1. Factors affecting substitution

Applicant's validation and qualification process

To substitute a component of a medical device, such as UV-328 in the mechanical separator of the Barricor™ blood collection tubes, the applicant must follow a long and resource-demanding process. The aim of this process is to ensure that the new component (mechanical separator) and the medical device as a whole (blood collection tube) perform within the applicant's specifications and that this end-use performance can be reproduced accurately and consistently through the manufacturing process.

This is standard industrial procedure in all changes to the manufacturing process or the materials of a medical device, such as Barricor™. The applicant must carry it out step by step, ensuring that previous steps are complete before the following ones commence. Any failure in any of the process phases may push the substitution process back to the beginning, with the need for identification of a new alternative. It is thus critical that the applicant carries out their validation / qualification efforts with the appropriate diligence. More details of the necessary actions are provided in Section 4.1.3.2.

Furthermore, the validation tests also include shelf-life tests, which are necessary to ensure that the medical device will keep performing within specifications until the end of its designated shelf life. These tests are lengthy and must be carried out in real time for the duration of the product's shelf life, as the applicant needs to be certain that there is no impaired performance due to aging of the product.

In conclusion, while a potentially suitable alternative has been identified, the applicant cannot use it in commercial production until all validation phases are complete.

Reliance on supplier for alternative

The applicant does not purchase the UV stabiliser separately. Instead, they purchase the elastomer raw material, which is compounded with the UV-328 additive. The supplier of the raw material carries out compounding of the elastomer. Therefore, the supplier is responsible for identifying and supplying an alternative UV stabiliser, based on selection criteria set jointly with the applicant. This process added some delay to the identification of the alternative, as the applicant did not have control over the pre-selection process.

Theoretically, it was possible for the applicant to approach different suppliers of TPE compounds, in and outside the EU, for alternatives. However, the long cooperation with the existing TPE supplier has built good communication channels and strong trust for the supplier's expertise, which can facilitate a faster substitution. Switching to an alternative supplier altogether would significantly prolong substitution, as the new supplier may have to be qualified before their compound can be used. Furthermore, contractual restrictions with the existing supplier could also result in longer legal negotiations. In short, continuation of the existing cooperation was considered as the most efficient way towards substitution.

4.1.3.2. List of actions and timetable with milestones

The applicant's product development process for the substitution of UV-328 in the mechanical separator of Barricor™ blood collection tubes is broken down in the phases described below. It should be noted that the timing of these phases represents a reasonable best case scenario. In practice, the applicant expects that the substitution timeline may be extended.

CBI 2

- **Phase I – Planning** ([redacted]): In this phase, the applicant specifies the criteria that a potential alternative UV stabiliser should have and works with the supplier to identify a suitable substance. The phase also involves planning of the cross-functional qualification tests and activities to verify that the pre-selected alternative meets those criteria. This phase is currently complete. The applicant has already reviewed the pre-selection criteria of an alternative UV stabiliser with the supplier of the raw material. They have also planned the necessary cross-functional qualification tests and activities.
- **Phase II – Test material request and sample preparation** ([redacted]): In this phase, the supplier provides the applicant with the new raw material and the applicant must use it to manufacture the mechanical separators that will be used in the validation testing. The applicant must manufacture four lots of the product (three using the alternative UV stabiliser and one using UV-328 as control), which must be found to comply with the specifications during the tests in Phase III below. This phase is currently in progress, with the manufacture of the test material initially targeted to be completed by [redacted]. However, due to supply chain delays, the phase is not anticipated to finish until the end of [redacted].
- **Phase III – Test execution** ([redacted]): This is a critical phase, as the results of the testing will determine if the alternative can be accepted to substitute UV-328 or modifications will be needed in the manufacturing process or equipment or even the raw material. If this phase does not produce acceptable results, it is possible that the substitution timeline will be extended. This phase has not started, yet. It will involve the activities depicted in Table 4-1 below.
- **Phase IV – Design review and project closure** ([redacted]): This is the final phase of the substitution process, which will finalise the manufacturing process modifications needed for the integration of the alternative material in the manufacturing of the mechanical separators. It will follow the successful commencement of the tests in Phase III.
  The applicant does not anticipate that they will need to carry out any regulatory submission activities for commercialisation of the Barricor™ with the new UV stabiliser in the mechanical separator. As there is no product performance specification change, due to the minor change in the mechanical separator, no regulatory approval is anticipated to be required. However, the requirement for regulatory approval may be subject to change depending on resulting risks identified during implementation and test.
- **Phase V – Project mitigation & project closure ([redacted] November 2027)**

  Based on the timeline discussed in this section, in an optimistic scenario the applicant expects that they will be able to substitute UV-328 from the mechanical separator of Barricor™ by [redacted]. With the Covid-19 pandemic still ongoing,

the applicant is expecting delays in the delivery of the materials to be used in the qualification lot of between 3 and 6 months. The length of this potential delay is based on the historical timeline of raw material received from the compound supplier's vendor and from the time required for the material to clear customs, but already the current delay is longer. In addition, if the production line in the Plymouth plant will need to be moved and revalidated, it is possible that an additional 3-4 months will be added to the timeline. In total, the applicant expects that these delays can bring the expected end date for substitution to [redacted]. However, as there is uncertainty in the nature and length of any potential delays, which may push completion of substitution beyond the expected time, the applicant includes additional mitigation time in the substitution timeline and, by extension, to the requested review period. This "mitigation phase" is expected to extend to four years after the SD, until **November 2027** giving the applicant sufficient time to implement substitution.

CBI 2

In addition, a longer review period will also avoid a situation in which the applicant has to submit a precautionary review report. Such a report will need to be submitted 18 months before the expiry of the initial review period, with preparations beginning as early as 12 months before then. In this 4-year review period, the applicant will need to start preparing a review report just 1.5 years in, but in a shorter, 2-year review period, work on a review report would have to start immediately after submission of the AfA. This is not efficient and could also lead to increased costs, as the work will need to start earlier.

Table 4-1 Mechanical and clinical tests to be carried out during Phase III

Test	Goal	Timeline
Feasibility check	To check the quality of mechanical separator molding; product assembly and final product; UV light aging effect on yellowness index and modulus due to UV stabilizer change	[redacted]
E&L test	To review the E&L profile between current and alternative stabilizers; any identified difference will be assessed on clinical impact and added for clinical study.	[redacted]
Confirmatory clinical study	To mitigate the regulatory risk by performing the study; no anticipated technical risk due to the change.	[redacted]
Mechanical aging test	To assess the final product's mechanical performance impact due to the UV stabilizer change within product shelf time.	[redacted]

CBI 2

4.1.3.3. Monitoring of the implementation of the substitution plan

The applicant applies all internal project management and monitoring procedures on the substitution project. It is being managed by the change control owner and coordinator, who are also responsible for reporting the progress to the management of the plant and to corporate management.

The project timeline and budget are reviewed and revised as part of the annual budgeting process of the applicant. Additionally, if there is a significant change in project scope, the budget and timeline will be re-evaluated. Changes in scope, timeline and/or budget and confirmation of project plans are addressed in periodic reviews and presentations from the project owner / project manager.

In team meetings, project risks that could impact the project scope, hence also the timeline and budget, risk mitigations and contingency plans, are discussed and documented in meeting minutes. The progress of the project is monitored using commercial software, such as Microsoft Project. The tool provides details on the tasks that need to be carried out in each phase of the project and connects those tasks with the team responsible for them. It is used to keep track of the timing of the milestones for each phase and to ensure that the project is on track for completion. This information can inform the project management about the status of the testing in the project and provide warning of any issues that may arise, which could delay timely project completion.

Table 4-2 Monitoring plan summary and risk mitigation

Phase	Actions	Milestones	Resources	Status / Timeline	Monitoring options	Risks and mitigation
Planning	Alternative specifications defined. Literature and market review on alternatives Pre-selection testing of alternative substance	Identify the potential alternative UV stabiliser	TPE supplier's R&D team Internal R&D teams	Completed	Not relevant – phase complete	Not relevant – phase complete
Test material request & sample preparation	Supply of alternative TPE compound Manufacture of four lots for testing	Manufacture of all necessary TPE lots	TPE supplier Internal manufacturing	In progress (exp. completion by [redacted])	Phase completion	TPE supply delay causing delay in test lot manufacturing -> 3-6 months' delay (critical path) Mitigation: begin testing with existing lots Need for revalidation of production line -> 3-4 months' delay in start of tests
Testing	Feasibility check E&L test Confirmatory clinical study Mechanical aging test	All tests successful, meeting specifications	Program Mgmt, R&D Team, Mfg Eng Team, Product Strategy, Quality	Not started yet Start: [redacted] End: [redacted]	Phase completion Gate Review	Tests fail to produce acceptable results -> fall back to different alternative, leading to significant overall project delay Mitigation: Mitigation phase to allow for sufficient time to turn around the process with a different alternative.

CBI 2

Phase	Actions	Milestones	Resources	Status / Timeline	Monitoring options	Risks and mitigation
Design review and project closure	Agree on manufacturing process modifications needed Integrate new TPE compound in manufacturing process	Product ready for commercial production	R&D Team, Mfg Eng Team, Product Strategy, Production Plant, Quality	Not started yet Start: [redacted] End: [redacted]	Phase completion Gate Review	

4.1.3.4. Conclusions

The applicant's supplier has provided a potentially suitable raw material with the elastomer containing an alternative UV stabiliser. The alternative UV stabilizer is supplied incorporated in the TPE raw material used to manufacture the mechanical separator in the applicant's blood collection tubes.

The alternative has met the pre-selection criteria set by the applicant and the raw material supplier, but cannot be considered technically feasible, yet, as validation trials are in progress. The applicant still needs to carry out tests on the mechanical separator and finished product, using the new raw material with the potential alternative. These tests are essential to ensure that the mechanical separator's, and thus the blood collection tube's, performance is the same as that with the UV-328 separator. This performance must be assessed over the medical device's shelf life. The duration of these tests cannot be shortened, and they are currently expected to finish in [redacted], which is beyond the Sunset Date for UV-328 in the UK.

CBI 2

The applicant needs to include contingency timing to account for potential delays in the supply chain and the production line. Taking this contingency time into account, the applicant currently anticipates a latest end date of November 2027, i.e. four years after the Sunset Date.

4.2. Risks associated with continued use

4.2.1. Impacts on environmental compartments

The applicant is using UV-328 in the injection moulding manufacturing process of the mechanical separators at their Plymouth plant. The substance is used compounded in a thermoplastic elastomer, which is supplied in granular form (pellets).

The individual steps of the manufacturing process, including storage and waste management, are described in detail in the CSR. The applicant estimates that there are no releases of UV-328 to the environment, based on the following:

- UV-328 is supplied to the applicant as an additive of a TPE compound. The compound is supplied in granules, with practically no generation of dust.
- The substance's vapour pressure is extremely low (0.000005 Pa at 20°C), so releases to air during handling are negligible.
- The substance is used in closed systems, from vacuum delivery to the moulding machine, with no direct releases to the environment, and ends up included in the matrix of an article.
- No liquid waste is generated during the process, as the process does not use water.
- Solid waste containing UV-328 can be generated during transfer processes, through empty containers, the moulding process and through unused batches and off-spec products. All solid waste is collected and sent off-site to be incinerated by a licensed contractor.

As there are no emissions to the UK environment from the applicant's use of UV-328, the applicant expects no impact to the environmental compartments for the applied for use.

4.2.2. Impacts on humans

4.2.2.1. Occupational exposure

UV-328 has a harmonised classification for systemic toxicity after repeated dose (STOT_RE 2 for liver and kidneys) to humans. It has a DNEL(inhalation) of 0.7 mg/m^3 and a DNEL(dermal) of 0.3 mg/kg bw/day.

As discussed in Section 4.2.1, there are zero emissions of UV-328 from the applicant's manufacturing operations in their Plymouth plant. Therefore, there is no risk to the general population due to environmental releases from the applicant's use. The human health impact assessment will thus only focus on potential worker exposure at the applicant's manufacturing plant.

Table 4-3 summarises the combined exposure and risk assessment for the workers, as estimated in the CSR and presented in Table 10.1 and Table 10.2 therein.

Table 4-3 Combined risk assessment results from CSR

Scenario	PROC	No of workers	RCR (inhalation)	RCR (dermal)
ES1 – WCS1: Delivery and Storage of Thermoplastic Elastomer (TPE) resin	PROC1	[redacted]	0	0
ES1 – WCS2: Transfer of TPE – Loading into Moulder Machine	PROC8b	[redacted]	<0.01	0.023
ES1 – WCS3: Injection Moulding Process – Producing Mechanical Separator	PROC14	[redacted]	<0.01	0
ES1 – WCS4: Loading of Insertion of Mechanical Separator in assembling machine of Blood Collection Tubes	PROC21	[redacted]	0	0
ES1 – WCS5: Waste treatment	PROC8b	[redacted]	<0.01	0.023
ES1 – WCS6: Sampling	PROC19	[redacted]	<0.01	0.471
ES1 – WCS7: Cleaning and Maintenance of Moulder Machine	PROC10	[redacted]	<0.01	0.091
Combined risk	N/A	[redacted]	**0.018**	**0.61**

CBI 5

As can be seen in Table 4-3, the Risk Characterisation Ratios (RCR) for all tasks are below 1. Even if the workers were carrying out all tasks with potential exposure to UV-328, the overall combined RCR, for inhalation and dermal exposure, would be below 1 (**0.628**). This shows that there is no occupational risk from the use of UV-328 by the applicant in their manufacturing plant.

4.2.2.2. Exposure of Humans via the Environment

Considering that there are no releases of UV-328 from the applicant's use, there is no pathway for the general population to be exposed to the substance. As a result, there is no risk from exposure of humans via the environment.

4.2.3. Compilation of human health and environmental impacts

Table 4-4 and Table 4-5 summarise the human health and environmental impacts from the continued use of UV-328 for the manufacturing of mechanical separators used in the Barricor™ blood collection tubes.

Table 4-4 Summary of additional statistical systemic toxicity cases for human health.

	Excess lifetime (Systemic toxicity)	Number of exposed people	Estimated statistical cases (over 4 years)[5]	Value per statistical case	Monetised excess risk (over 4 years)[5]
Workers					
Directly exposed workers[2]	0	[redacted] (10-50)	0	0	0
Indirectly exposed workers[3]	0	N/A	0	0	0
Sub-total	*0*	[redacted] *(10-50)*	*0*	*0*	*0*
General population					
Local	0	N/A	0	0	0
Regional	0	N/A	0	0	0
Sub-total	*0*	*N/A*	*0*	*0*	*0*
Total	**0**		**0**	**0**	**0**
Latency (years)	No latency considered				

CBI 5

Table 4-5 Summary of remaining releases to the environment

	Over 4 years
Total releases/emissions (in kg per period)	0

4.3. Non-use scenario

4.3.1. Discussion of potential Non-Use Scenarios

A refused authorisation would mean that the applicant will not be able to use UV-328 in the TPE compound used for manufacturing mechanical separators for the Barricor™ blood collection tubes in the UK. Therefore, production of the blood collection tubes will stop in the Plymouth plant after the Sunset Date.

As concluded in the Analysis of Alternatives (Section 3.4), there is a potentially feasible alternative to UV-328. However, the applicant still needs to carry out their performance testing, including full length shelf-life tests, before concluding on the technical feasibility of the alternative and switching to the alternative compound.

The substitution process, as presented in the substitution plan in Section 4.1.3, is expected to conclude after the Sunset Date.

The Plymouth plant is the only BD facility able to manufacture both the mechanical separators and the blood collection tubes. The applicant could theoretically transfer the manufacturing process to a different location outside the UK and the EU. However, the applicant's strategic planning does not consider moving activities to non-UK / non-EU locations. Such a move would require transferring not only the production line equipment, but also the manufacturing know-how to outside the UK. The new line would have to be set up, validated and the production process will need to be optimised before it can

commercially produce the mechanical separator. This means that the new production line will need to obtain regulatory approval before they can sell UV-328 in any market.

The production line transfer is a lengthy process and will also be finished after the Sunset Date, even if it started immediately. It would therefore offer little benefit to the applicant, especially considering that the Applicant is committed to substituting UV-328 from their products and the substitution efforts for UV-328 are already underway.

The other option that the applicant has is to cease production of Barricor™ blood collection tubes. Under this NUS, the applicant will continue the substitution efforts as described in the Substitution Plan and will resume manufacture of mechanical separators and blood sample tubes once the new compound is validated in the manufacturing process.

4.3.2. The most likely non-use scenario

When looking at the two possible non-use scenarios, the applicant believes that the most likely non-use scenario provided is to cease production of Barricor™ in Plymouth. Relocation is not considered likely because it does not align with the strategic planning of the Applicant and is expected to incur additional costs for transferring the process to a different location, while at the same time not mitigating the lost sales of Barricor™ because of the downtime.

Table 4-6 presents the two possible Non-Use Scenarios (NUS) for the applicant in case of a refused authorisation and a high-level description of impacts.

Table 4-6 Possible Non-Use Scenarios

	Non-use scenario	Reasoning
1	Cessation of production of Barricor™ blood collection tubes at BD UK limited. Current BD DU use other blood collection tubes to meet clinical needs.	• In the best-case scenario, without any unexpected delays, an alternative is expected to be assessed and validated by [redacted]. This would be approx. 18 months after the Sunset Date, but the delay may be longer. In the worst-case scenario delays will push the availability of an alternative to up to 4 years after the Sunset date. • Production, sales in the UK and export to the rest of the world of Barricor™ blood collection tubes represents a revenue stream of > £[redacted] (2 to 8) million per year. Without an Authorisation this revenue stream would be a significant loss to the applicant. • UK based DU would need to replace the use of > [redacted] million blood collection tubes annually, which can rise to >[redacted] million across the UK and EEA • UK and EEA based DU would have to replace Barricor™ blood collection tubes by PST and SST tubes. In the current NHS supplies context where SST and PST tubes are in short supply, this depletion of Barricor™ blood collection tubes could further drive the scarcity of SST resulting in delays in diagnoses for patients. • There could also be impacts on the rest of the world, which will bring the shortage of tubes to more than [redacted] million, once the US market is launched.
2	Relocation of production of Barricor™ blood collection tubes outside the UK and EU.	• This would theoretically allow BD's DU to still use Barricor™ blood collection once transfer is complete. • The applicant strategic planning does not consider production activities outside of the UK or EU. This realistically rules out this non-use scenario. • Process transfer would incur additional costs to move equipment, set up, validate and optimise production line. • This would lead to a loss of revenue for the applicant. • Substitution of UV-328 will still proceed

CBI 2

CBI 5

Under the most likely NUS, the applicant will lose the revenue and profit from sales of Barricor™ blood collection tubes until successful substitution of UV-328, at the earliest 18 months after the Sunset Date, but as late as four years after SD.

The applicant's Barricor™ blood sample tubes do not have a direct competitor in the market. In this NUS, the applicant's existing global customers (e.g. NHS, hospitals, blood banks and contract research organisations, etc.) would need to source alternate blood collection tubes. This would mean the EU and UK markets would have to make up a shortfall of more than [redacted] (10-50) million blood collection tubes per year, of which [redacted] (0.1-1) million blood collection tubes are supplied in the UK (based on 2022 numbers, as per Table 3-5). By 2025, these numbers are expected to rise to [redacted] (10-50) million for EEA and to [redacted] (2-5) million for the UK. In addition, the applicant expects they will launch Barricor™ in the US market, with the total volume of units sold reaching more than [redacted] (50-100) million.

CBI 5

BD Plymouth is the sole manufacturer of Barricor™ blood collection tubes, so the market would be significantly impacted if no authorisation is granted. Moreover, it is uncertain how the lack of Barricor™ blood collection tubes would affect the price of other existing blood collection tubes in the UK market. UK based users would then have to replace Barricor™ blood collection tubes by plasma sample tubes (PST) and serum sample tubes (SST).

The applicant is also manufacturing PST and SST, with Barricor™ tubes only comprising a relatively small share of the Plymouth plant's output. As such, the Applicant does not expect that there will be a significant impact to the plant's workforce. The Applicant expects that the personnel related to this production line could be relocated to fulfil other productive activities.

4.4. Societal costs associated with non-use

4.4.1. Economic impacts on the applicant

4.4.1.1. Revenue and profit losses

In the UK, there would be significant economic impacts associated with the NUS for the Applicant.

The removal of the manufacture of Barricor™ blood collection tubes from the applicant's Plymouth plant will have a negative impact on the Applicant's revenue and profits. In 2022, Barricor™ blood collection tubes revenue is expected to be over £[redacted] (1-5) million[1] for the UK and EU markets combined. It should be noted that a share of the profit from this is being used in the development of UV-328-free blood collection tubes.

CBI 5

Table 4-10 summarises the expected revenue and profit from Barricor™ sales in the 2022-2025 period. In the NUS, the loss of revenue and profit will be estimated at over a 4-year review period, namely 2024-2027. As the applicant does not have a detailed sales forecast for beyond 2025, a steady [redacted]% (1-5%) annual increase in sales is assumed. This does not include the launch of the product in the US market, as the actual impact is currently

CBI 5

[1] Conversion rate of 25/01/2022: 1 USD = 0.7424 GBP

uncertain. However, it should be noted that this move is expected to increase global profit and revenue [redacted] from [redacted] onwards.

Table 4-7 Lost revenue and profit from Barricor™ UK and EEA sales

Year	Revenue	Profit
2022	[redacted]	[redacted]
2023	[redacted]	[redacted]
2024	[redacted]	[redacted]
2025	[redacted]	[redacted]
2026	[redacted]	[redacted]
2027	[redacted]	[redacted]

CBI 5

In case of a refused authorisation, the NPV of the applicant's profit loss from unrealised sales of Barricor™ blood sample tubes in the UK and EEA will be approximately £[redacted] (£5-10) million, discounted to 2022 prices using a 4% discount factor, over a 4-year period.

However, it should be noted that the Barricor™ blood sample tubes will be replaced in the market by "conventional" PST and SST, which are also manufactured by the applicant. As a result, the total loss of profit will be lower than what is calculated above.

There are two main factors that need to be considered when estimating the potential recovery of sales by the applicant, through supply of their conventional PST and SST tubes.

CBI 5

Firstly, the applicant is the market leader for blood collection tubes, holding an estimated roughly [redacted]% (>50%) market share in Europe, but it is still expected that their competitors, based outside the UK will still take over some of the lost Barricor™ market. The applicant cannot know whether their competitors will be able to take over their Barricor™ customers and if they have the manufacturing capacity to do so. For the calculations, it will be assumed that the Barricor™ customers will be covered by the applicant and their competitors proportionally, based on their current estimated market shares, i.e. [redacted]% (>50%) by the applicant and the remaining [redacted]% (<50%) by the competition.

For the sales that will remain to the applicant, conventional blood collection tubes have a lower price and a smaller profit per unit compared to Barricor™. Table 4-8 compares the profit margin of Barricor™ and conventional (PST/SST) blood collection tubes.

Table 4-8 Comparison of revenue and profit per unit of Barricor, SST and PST

	Barricor™	SST	PST
Average Revenue per unit 2022-2025 (£)	[redacted]	[redacted]	[redacted]
Average Profit per unit 2022-2025 (£)	[redacted]	[redacted]	[redacted]
Note: The values in this table are indicative, as they are taken as the average over the forecasted revenue and profit for the years 2022-2025. In practice, each year is expected to have a different revenue and profit per unit.			

CBI 5

As can be seen in Table 4-8, Barricor™ blood collection tubes have approximately 50% higher profit per unit sold. Therefore, by substituting them with conventional SST and PST tubes in the NUS, the applicant will end up with a lower profit than in the Applied for Use Scenario.

Furthermore, the applicant's production lines for conventional tubes are running close to capacity and production cannot be ramped up to cover all the additional need that will be generated in case of a refused authorisation. The additional demand for PST and SST tubes

may not be possible to be covered by the applicant and will either be taken over by competition or become shortage.

Table 4-9 summarises the economic situation for the applicant in the NUS over a 4-year review period, taking into account the sales lost to competitors and the different price and profit margin of the different blood collection tubes. In the calculations, it has been assumed that the additional demand for conventional PST and SST tubes will be covered by the Applicant and their non-UK competition in proportion to the currently estimated market shares.

Table 4-9 Lost revenue and profit from Barricor™ sales in NUS

Year	2024-2027
(A) Loss of profit from Barricor™ expected sales (£)	[redacted]
(B) Loss of [redacted]% (<50%) of sales to competition (£)	[redacted]
(C) Profit from remaining Barricor™ sales (£) (A – B)	[redacted]
(D) Profit from sales of SST instead of remaining Barricor™ (£)	[redacted]
(E) Lost profit from sales of SST (£) (C – D)	[redacted]
(F) Economic losses for applicant in NUS (£) (B + E)	[redacted]
(F1) Discounted economic losses for applicant in NUS (£)	[redacted]

CBI 5

Over a 4-year period, the economic losses for the applicant will be approximately £[redacted] (1-5 million), discounted to 2022 values, using a 4% discount factor.

It must be noted that there is uncertainty in the value of the economic costs calculated in Table 4-9, as the calculations involved a number of assumptions, namely that the share of sales taken over by competitors will be the same as the current market share, that the price (and thus profit margin) of conventional tubes will not change. The economic costs will be further assessed in the sensitivity analysis.

4.4.1.2. Other costs

Other costs in a non-use scenario include machinery asset depreciation as well as reputational damage.

The equipment used in the manufacturing of the mechanical separators and the Barricor™ blood sample tubes has not yet been fully depreciated. If manufacturing of the tubes stops after the sunset date, the remaining non-depreciated value of the equipment will be written off as a loss in the Applicant's balance sheets. The Applicant does not believe they can sell the equipment. The remaining asset value is estimated to be approximately £[redacted] (1-5) million and the cost will be incurred in 2024.

CBI 5

There are likely to be other economic impacts. In the EU a significant amount of market activity is managed via a tender process, where the mechanical separator technology provided by Barricor™ blood collection tubes is a tender requirement. The inability to be able to offer Barricor™ blood collection tubes would mean not being able to fulfil contractual commitments. As a result, the financial and reputational impact of the applicant could be significantly broader than the loss of sales itself.

4.4.1.3. Summary of economic costs for the Applicant

Table 4-10 summarises the economic impacts for the applicant in the NUS for the four years after the Sunset Date. The impacts considered are the loss of profit and the asset depreciation. The total NPV of the economic costs for the applicant in the NUS is approximately £[redacted] (2-10) million.

Table 4-10 Summary of economic impacts for the applicant

CBI 5

Economic impact (discounted to 2022 prices, 4% discount factor)	Value (£)
Lost profits	[redacted] (£1-5 million)
Asset depreciation	[redacted] (£1-5 million)
Total economic costs for the applicant	[redacted] **(£2-10 million)**

4.4.2. Economic impacts on the supply chain

No other competitors offer the mechanical separator technology of Barricor™. In the case of a non-use scenario, it would result in the customers returning to the use of standard serum and plasma gel tubes (SST and PST). This would lead to the applicant's customers lacking a significant technological advantage that they have been using for the last four or five years.

As previously stated, the non-use scenario not only impacts the applicant financially, but it also affects the downstream users (DUs). The applicant is working with [redacted] and some of the largest public hospitals across the EU. [redacted], for instance, is the biggest market with [redacted]% (>50%) Share of Category (SoC) and the impact could be estimated at about $[redacted] (5 to 50) million for public tenders, which could have serious consequences on the country's healthcare system.

CBI 4

Furthermore, public healthcare systems have to follow certain procedures for procurement of medical equipment, to ensure transparency. Needing to follow their procurement process could lead to shortage of blood collection tubes, as the hospital or laboratory will not be able to procure any more Barricor™ tubes and they will not yet be allowed to purchase conventional PST and SST. This can be particularly serious in those national healthcare systems which predominantly use Barricor™ tubes.

Additionally, if a laboratory is obliged to switch from Barricor™ blood collection tubes to another kind of blood collection tube, the laboratory would have to undergo the following:

- It will typically need to perform verification studies when changing the blood collection tube(s);
- The scope of these studies will vary based on several factors, including: site/laboratory practices, the number and types of assays involved, required patient populations, storage stability requirements, etc.;
- The study duration may range from a few days or weeks, to several months depending on the study scope;
- These studies typically have a significant labour requirement, to support a range of activities including study design and protocol development, study execution, data management, statistical analysis, and assessment of results and study report. Consequently, site practices or reference ranges would be impacted, notifications to site staff and clinicians may need to be developed and communicated.

Barricor™ blood collection tubes do not have a direct competitor tube, i.e. another tube that offers the very same mechanical separator technology, therefore customers (DUs) would need to switch back to the baseline gel and plasma tubes. If the instrument platforms were not originally validated with Barricor™ blood collection tubes, there would be additional validation costs for the customers.

In the absence of Barricor™ blood collection tubes, a trade-off decision will be required by the customers: namely between high quality but slow serum tubes (as serum tubes require up to 30 minutes to clot) or fast (as it does not require clotting), yet lower quality plasma samples for analysis. The Barricor™ blood collection tube is designed to eliminate/minimise the need for such decisions, as it is designed to generate high quality and fast plasma.

Barricor™ blood collection tubes drive efficiencies and potential cost savings by:

- Reducing centrifugation time (3 minute with Barricor™ blood collection tube as opposed to 10 minutes with serum/plasma gel) and, consequently, energy consumption;
- Eliminating the need to clot the sample (compared to serum tubes)
- Reducing cellular contamination, eliminating gel artefacts, and eliminating fibrin due to insufficiently clotted serum sample, which may impact:
    - Sample inspection and remediation
    - Sample re-collection
    - Retesting of sensitive assays
- Reducing the number of tubes (and blood) collected for therapeutic drug monitoring (TDM) as it enables tube consolidation.

The above arguments outline that the final users of Barricor™ blood collection tubes, i.e. hospitals, clinics and analytical laboratories, are likely to be highly impacted if authorisation is not granted.

Overall, the applicant estimates that, in 2025, there would be need for approximately [redacted] (20-50) million PST and SST in the UK and EEA, and this number could increase to [redacted] (50-100) million or more if the US market is considered. In 2025, the applicant estimates they will be manufacturing approximately [redacted] (500-1,000) million PST and SST tubes and they will be close to output capacity at the plant. If they had to replace the worldwide demand for Barricor™ with PST and SST tubes, it would require an approximately 15% increase in output, which may not be possible immediately. This could mean that part of the applicant's blood collection tube sales could move to (non-UK) competitors or that there will be a shortage of blood collection tubes. CBI 5

4.4.3. Economic impacts on competitors

There are no direct competitors for Barricor™ blood collection tubes. However, for the blood collection tube category, competition is expected to respond to the removal of Barricor™ blood collection tubes in the market. It is expected that the competition will aim to gain the market share left by the lack of Barricor™ blood collection tubes on the market through increased production and commercialisation of gel based SST and PST tubes. As some of these competitors are operating outside the UK, the overall outcome will be a loss for the UK economy, as well as for the Applicant.

The applicant has identified two main competitors for blood collection tubes for their UK and EU markets. In Europe, the applicant's estimated market share for blood collection tubes is estimated to be approximately [redacted] % (> 50%). As discussed in Section 4.4.1.1, it is assumed that the market gap generated from a refused authorisation for UV-328 will be covered proportionally by the applicant and the competition. Therefore, competitors will see a total increase in sales of approximately [redacted] (50-100) million blood collection tubes (PST and SST) in the 2024 – 2027 period. CBI 5

The applicant does not know the pricing and profit margin of their competitors, so the actual economic benefits cannot be calculated with certainty. For indicative purposes, if the same profit per unit as the applicant's is used, the expected total profit gains for the competition in the review period will be approximately £[redacted] (£1-5) million. Most, if not all of these profits will move to non-UK companies.

4.4.4. Social impacts

4.4.4.1. Employment impacts

The applicant has estimated that unemployment due to the non-use scenario is unlikely. Although the applicant manufactures Barricor™ blood collection tubes in the plant in Plymouth in the UK, in a non-use scenario the personnel related to this production line could be relocated to fulfil other productive activities.

On the contrary, given a worldwide overall estimated growth of 4% of the blood chemistry tubes category, the applied for use scenario might imply a social opportunity cost of employment growth.

4.4.4.2. Healthcare impacts

Barricor™ blood collection tubes allow for a faster performance of specialist staff compared to SST and PST tubes, and this allows faster diagnosis results to be obtained. The latter, combined with the risk of scarcity of SST and PST tubes on the UK market, means that the depletion of Barricor™ blood collection tubes would imply delays in diagnosis for patients.

Societal wider consequences due to a market unavailability of Barricor™ blood collection tubes are seen to mainly affect customers and the general public because the following advantages offered would be lost:

- Improved sample quality and therefore diagnostic accuracy;
- Making the diagnostic results available faster (up to 37 minutes of time saved for serum users and 7 minutes for plasma users). The difference could be significant, especially for the STAT testing (without delay) where results are needed immediately for the diagnosis or treatment of the patient (e.g. Troponin results for potential heart attack diagnosis);
- Enabling lower cost for testing as it increases lab efficiency through reducing the time required for sample remediation and enabling tube consolidation (meaning same tube could be used for additional testing such as therapeutic drug monitoring (TDM)).

4.4.5. Wider economic impacts

Table 4-11 examines if acceptance of the non-use scenario would lead to:

- Changes to competition within the UK;
- Changes to competitiveness outside of the UK;
- Changes to international trade; and
- Changes to UK finances.

There is uncertainty on how competitors would be impacted in the non-use scenario. It is unpredictable how competitors in the market target segment of blood collection tubes will respond to the supply stoppage of Barricor™ blood collection tubes. It can be expected

that the competition would compete to gain market share left by the lack of Barricor™ blood collection tubes through increasing production and commercialisation of the gel based tubes of the kind SST and PST. This has been discussed in Section 4.4.3.

Table 4-11 Wider Economic Impacts

Impact	Applied for Use Scenario	Non-Use Scenario
Changes to competition within the UK	**No significant impact** Barricor™ blood collection tubes stay on the UK market providing the same level of cover and analysis to patients	**Yes – significant impact** BarricorTM blood collection tubes are removed from the market and partially replaced by non-UK blood collection tubes
Changes to competition outside the UK	**No significant impact** Barricor™ blood collection tubes stay on the worldwide market providing the same level of cover to patients already using the product.	**Yes – significant impact** See above
Changes to international trade	**No significant impact** Barricor™ blood collection tubes stay on the worldwide market providing the same level of cover to patients already using the product.	**Yes – significant impact** BarricorTM blood collection tubes are used throughout the world. The non-use scenario would mean that these markets couldn't be provided with the product and its use would be replaced by conventional PST/SST products
Changes to UK finances	**No significant impact**	**No significant impact**

4.4.6. Combined socio-economic impacts

Table 4-12 summarises the socioeconomic impacts for the affected stakeholders in case of a refused authorisation. Overall, there will be a significant economic impact for the applicant, but there may also be repercussions in the downstream supply chain, especially for end users of Barricor™ blood collection tubes, which may have to substitute them with conventional ones, that do not share Barricor™'s unique product benefits.

Table 4-12 Combined socioeconomic impacts

Description of major impacts	**Monetised/quantitatively assessed/qualitatively assessed impacts**
1. Monetised impacts	**Over 4 years (in £ million, discounted to 2022 prices)**
Loss of profit	£[redacted] (1-5) million
Machinery Asset Depreciation	£[redacted] (1-5) million
Social cost of unemployment	0
Sum of monetised impacts	**£[redacted] (2-10) million**

CBI 5

Description of major impacts	Monetised/quantitatively assessed/qualitatively assessed impacts
2. Additional qualitatively assessed impacts	
Inability to serve the market	The applicant will not be able to provide the better and faster performing Barricor™ blood collection tubes to the market, potentially resulting in reduced output of blood testing laboratories and delays in patients' testing and results In addition, it is very likely that a significant share of the current market share of Barricor™ will go to competitors not based in the UK
Increased demand for gel based tubes (SST and PST) with potential shortfalls in materials for them	Small likelihood for shortage, considering the relatively small market share of Barricor™ currently (approximately [redacted]%), but it depends on free capacity of manufacturing lines in Applicant and competitor plants
Damage to the reputation of applicant from inability to supply	The applicant will not be able to meet contractual responsibilities with customers, which could result in penalties and loss of future contracts
Customers may need to carry out revalidation activities with new blood collection tubes	If replacement blood collection tubes are not already validated for the particular customers use, the customers will need to carry out validation studies to ensure they can be used effectively and safely
Increased procurement costs and delays for some national healthcare organisations	Costs for public tenders by national healthcare system organisations. E.g., cost for [redacted] could reach £[redacted] (10-50) million.
Loss of benefits provided by Barricor™ to end users	Substitution of use of Barricor™ with conventional (PST / SST) blood collection tubes would result in longer processing times, need for clotting (for SST), and potentially higher risk of blood specimen contamination These are the competitive benefits provided by the Barricor™ blood collection tubes and the services provided by the end users will be worse under the NUS

CBI 5

4.5. Combined impact assessment

4.5.1. Comparison of impacts

The combined societal costs of non-use and risks of continued use are summarised in Table 4-13. The cost of non-use per kg and year is shown in Table 4-14.

The applicant does not expect any human health or environmental impacts from their use of UV-328 in the mechanical separator of the Barricor™ blood collection tubes. The substance is used in a closed system, with no releases to the environment, and ends up contained in the matrix of an article. Any waste generated during the manufacturing process is collected and incinerated. Furthermore, based on the occupational chemical risk assessment carried out in the CSR, using conservative Tier 1 exposure assessment tools, the applicant concluded that there is no risk to workers at the Plymouth manufacturing plant, as the combined exposure Risk Characterisation Ratio is below 1.

CBI 5

On the other hand, the total annual cost of £[redacted] (1-5) million has been used for this assessment; this figure was derived from economic impacts from the non-use scenario, i.e. loss of revenue and machinery asset depreciation. This figure is likely to be a

conservative underestimate of the total impacts as it does not include unquantifiable impacts, such as the disruption to patients, as well as potential validation cots for end users of blood collection tubes.

Even with this conservative estimate, the ratio of comparison of impacts is very high, showing the significant benefits of granting the AfA for the bridging period requested, especially considering that the risk to workers and the general population is zero.

Table 4-13 Societal costs of non-use and risks of continued use.

Societal costs of non-use		**Risks of continued use**	
Monetised impacts (£ - over 4 years)	£[redacted] million loss of profits and Machinery Asset Depreciation	Monetised excess risks to directly and indirectly exposed workers (£ - over 4 years)	0 (no excess risks to workers, as workplace risks are controlled – RCR < 1)
Additional quantitatively assessed impacts	Not applicable	Monetised excess risks to the general population (£ - over 4 years)	0 (no excess risks to the general population, as there are zero emissions of UV-328 to the environment)
Qualitatively assessed impacts (over 4 years)	Cost of reputational damage to applicant Delayed diagnosis for patients Need for validation of new blood collection tubes to replace Barricor™ Loss of market share to non-UK competitors	Qualitatively assessed risks (over 4 years)	None identified
Summary of societal costs of non-use (over 4 years)	**£[redacted] million**	**Summary of risks of continued use**	**0**

CBI 5

Table 4-14 Cost of Non-Use per Kg and Year

	Per year
Total cost (£)	£[redacted] (1-5) million
Total emissions (kg)	0
Ratio (£/kg)	Not possible, due to no emissions to the environment

CBI 5

4.5.2. Distributional impacts

The table below outlines the distributional impacts of the applied for use vs. the non-use scenario.

Table 4-15 Distributional impacts

Affected group	**Economic impact**	**Health and environmental impact**
Economic operator		
Applicant	High – loss of revenue and profit	Negligible
Downstream Users	Medium – cost to purchase new blood collection tubes	n/a
Competition	Medium – profit gains	n/a
Patients	Medium – removal of quality blood collection tubes from the market, potential increase of medical attention fees	Medium
Geographical scope		
UK	Medium – loss of competitiveness in market	n/a
Within the applicant's business		
Owners	High – lost revenue	n/a
Workers	None – no job losses expected	None – no occupational risk from exposure to UV-328 expected

Note: (n/a) not applicable

4.6. Uncertainties and sensitivity analysis

4.6.1. List of uncertainties

The assessment in this report has used a number of assumptions, due to the uncertainties involved in the applicant's substitution efforts and the blood collection tube market. Table 4-16 presents the known uncertainties present in the report, along with an evaluation of their impact and the approach followed.

Table 4-16 Cost of Non-Use per Kg and Year

Uncertainty	Impact for assessment	Approach in report
The applicant's substitution process is expected to conclude by [redacted] or later	Substitution Plan Extensive delays could push the end of the applicant's substitution process to beyond the end of the requested review period	To account for potential delays, the applicant has accounted for contingency timing in their requested 4-year review period
In the calculation of economic impacts for the applicant, the extent to which the applicant's customers will purchase replacement blood collection tubes from the applicant or the competition cannot be known. Many factors play a role, including the dissatisfaction of customers with the applicant and the capacity of non-UK competitors to supply replacement products	Socioeconomic Analysis Inaccurate assumptions regarding the extent to which the Barricor™ market share will be taken over by non-UK competition could result in under- or over-estimation of the economic impacts to the applicant	Considering the uncertainties, it was decided to assume that the Barricor™ market share will be shared between the applicant and their competitors according to the currently estimated market shares in Europe. It was also assumed that all competitors are manufacturing outside the UK The economic impacts under the extremes of these assumptions are examined in the sensitivity analysis
Due to an expected increase in demand for PST and SST with short notice in the NUS, it is possible that their prices will increase. The SEA assumes a stable price for these products	Socioeconomic Analysis If the price of the PST and SST products increases as a result of increased demand, the economic impacts for the applicant will be smaller than currently calculated, as the increased prices would offset part of the lost Barricor™ revenues	The current share of Barricor™ blood collection tubes compared to the PST and SST ones is low ([redacted]%). As a result, it is unlikely that such an increase in demand will result in a meaningful increase in price. So, the SEA assumes stable price for the PST and SST replacement tubes
Releases of UV-328 to the environment are expected to be 0, as per the CSR	CSR – SEA If the releases to the environment are not zero, they will need to be weighed against the benefits of continued use of UV-328, to ensure that these benefits far outweigh the costs to human health and the environment.	The applicant is applying very strict risk management measures in their manufacturing plant, so they are confident that releases of UV-328 to the environment are described accurately in the CSR Nevertheless, for completeness, the applicant will carry out a break-even analysis, to estimate the UV-328 emissions below which granting of the authorisation would be justified from a socioeconomic perspective.

CBI 2

4.6.2. Sensitivity analysis

4.6.2.1. Economic costs for the applicant

The sensitivity analysis will calculate the economic impacts for the applicant for different scenarios pertaining to the suppliers of replacement blood collection tubes. In Section 4.4.1.1, it is assumed that production of the replacement blood collection tubes will be spread proportionately to the applicant and the competition. In order to present the range of economic impacts, the sensitivity analysis will examine the two extreme scenarios for the economic costs:

a. All replacement blood collection tubes will be provided by the applicant. In that case, the losses for the applicant will arise from the difference in profit per unit between PST/SST and the Barricor™ tubes.
b. All replacement blood collection tubes will be provided by non-UK competition. In that case, the loss for the applicant will be the whole forecasted Barricor™ revenue during the review period (2024-2027).

Table 4-17 presents the economic costs in these two extreme cases.

Table 4-17 Sensitivity analysis on economic costs for the applicant

Economic impact	Base NUS	100% Applicant	0% Applicant
Lost profits	[redacted]	[redacted]	[redacted]
Asset depreciation	[redacted]	[redacted]	[redacted]
Total economic costs for the applicant	[redacted]	[redacted]	[redacted]

CBI 5

4.6.2.2. Break-even analysis

This break-even analysis will calculate the maximum quantities of UV-328 emitted to the environment that could be considered acceptable for the purposes of granting an authorisation [14].

As UV-328 is a PBT, the methodology of evaluating the impacts for PBT/vPvB substances published by ECHA will be used. According to that guidance, it is not the cost-benefit ratio that must be calculated, as it is not considered possible to monetise the health or environmental impacts from the continued use of such a substance. Instead, the guidance suggests to use the ratio of costs per kg of emitted substance.

The acceptable values of such a ratio may vary from substance to substance, based on their hazards. An IVM study proposed a benchmark of €50,000 per kg of emitted substance [15].

The total combined socioeconomic costs in the NUS have been calculated at approximately £[redacted] (£2-10) million over the 4-year review period. Assuming a £50,000 per kg of UV-328 emissions as an acceptable threshold, the maximum acceptable releases of UV-328 would be approximately [redacted] (40-200) kg over the 4-year review period. This number is approximately one third of the tonnage of UV-328 expected to be used in these years. Based on this, it is unlikely that the cost per emitted kg ratio would indicate that a refused authorisation is not a cost-effective option.

CBI 5

Furthermore, the study also benchmarks a cost of €1,000 per kg as an unacceptable ratio, with the range between €1,000 and €50,000 being a grey zone, which would require more study. In this case, using the lower ratio would be equivalent to more than [redacted] (2-10) tonnes UV-328 released to the environment, which is practically impossible, considering the Applicant's forecast usage of UV-328.

The applicant thus believes that continued use of UV-328 and its substitution in their manufacturing process over the requested review period is the most effective approach.

4.7. Information to support for the review period

The applicant has already identified a potentially suitable alternative to UV-328 and is working on verifying its technical feasibility, so they can incorporate it in their

manufacturing process. Therefore, this is considered a "bridging" application, to allow the customer to perform the necessary activities and substitute UV-328 with a safer alternative.

The applicant has a detailed substitution plan in place, as discussed in section 4.1.3. According to that plan, the substitution activities can be completed by [redacted]. This date is difficult to be brought forward, as the applicant needs to carry out all necessary testing, including full shelf life feasibility tests, before they can safely substitute UV-328 for the identified alternative, and considering the potential delays.

CBI 2

The applicant expects that there can be delays due to supply chain issues (i.e. inability to procure the new TPE compound needed for validation tests) and factory floor reconfiguration, which could push the end date further in the future. Furthermore, there may still be other sources of delay, not identified at this stage, which could push the end date even further.

Therefore, the applicant considers that a review period of at least 4 years will ensure that the substitution can be successfully completed.

5. CONCLUSIONS

The mechanical separators manufactured using an elastomer containing UV-328 are unique components of blood collection tubes. None of the other blood collection tubes manufactured by the applicant or their competitors contain these mechanical separators. This UV-328-containing mechanical separator is an irreplaceable component of the Barricor™ blood collection tube product, allowing unique barrier formation features.

UV-328 is used as a UV stabiliser in the TPE compound used in manufacturing those mechanical separators. There are suitable alternatives generally available in the market, which can be potentially used in the applicant's mechanical separators. The applicant has identified a potentially suitable alternative UV stabiliser, through their non-EU supplier, and is currently working on validating the new TPE compound containing the alternative in the injection-moulding manufacturing process of the mechanical separators. However, such tests are not expected to be concluded before the Sunset Date for UV-328 in November 2023, so no alternative can be considered to be available at the moment.

In the best-case scenario, without any unexpected delays, an alternative is expected to be assessed and determined to be suitable by [redacted], but it is possible that delays would push that end date further. The applicant considers that a 4-year review period will be sufficient, based on the currently known information.

CBI 2

The socioeconomic analysis concluded that, on balance, the benefits of the applicant's operations for the UK economy far outweigh any potential risk of occupational and environmental exposure to UV-328. According to the exposure and risk assessment carried out in the CSR, practically no risk arises from the continued use of UV-328 by the applicant. There are no emissions to the environment, and the risks at the workplace are controlled, with the combined RCR being below 1.

On the other hand, removing this product from the market, as a result of a refused authorisation will incur significant losses for the applicant, in the form of lost profits, depreciation costs and loss of reputation with their customers.

For the downstream users, a refused authorisation may result in a lengthy process to find a feasible alternative blood collection tube and possibly a return to the baseline gel-based plasma and serum tubes. The advantages offered by Barricor™ will be lost, including increased turnaround time and improved sample quality/diagnostic accuracy as well as potentially lower cost for testing. Such losses would impact the speed and quality of patient care, resulting in additional costs for already stretched health care providers.

The return to conventional blood collection tubes may also introduce other issues, such as the need to clot the sample, inefficient diagnosis and increased number of tubes and blood collected, hence potentially increased costs for the healthcare providers and the consumers.

The applicant is therefore applying for an authorisation for the period of time the business can reasonably expect to continue using the raw material containing the substance in the specific use, while at the same time implementing UV-328-free manufacturing process for the production of Barricor™ blood collection tubes. The review period requested by the applicant is 4 years.

6. REFERENCES

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7. ANNEX – JUSTIFICATIONS FOR CONFIDENTIALITY CLAIMS

Table 7-1 Justifications for confidentiality claims.

Blanked out item reference	Justification for confidentiality
CBI 1	**Demonstration of Commercial Interest:** Proprietary manufacturing and specification information are closely held to prevent competitors from replicating procedures and procedures conditions. These details are only shared under strong non-disclosure agreements and are not made publicly available. **Demonstration of Potential Harm:** If process information were to be revealed, competitors could try to copy the design and process, leading to loss of knowhow and market position. Even a portion of the full process information or the applicant's specifications could be used to "reverse engineer" the process. **Limitation to Validity of Confidentiality:** This claim is valid indefinitely
CBI 2	**Demonstration of Commercial Interest:** Substitution strategy, including potential alternative names, evaluation results and timelines is proprietary knowledge and indicative of the applicant's commercial and development strategy. Furthermore, the alternative UV stabiliser is part of the TPE supplier's proprietary TPE compound and cannot be revealed, as it is covered by a Non-Disclosure Agreement (NDA) signed between the applicant and the supplier. Revelation of the alternative's identity can be considered a breach of the NDA. **Demonstration of Potential Harm:** Dissemination of this information could reveal R&D and marketing details to competitors of the applicant and of their supplier and allow them to engage in aggressive commercial tactics using proprietary knowledge to gain an unfair competitive advantage. This would severely harm the commercial interests of the applicant and their supplier of TPE compound. **Limitation to Validity of Confidentiality** This claim is valid indefinitely

Blanked out item reference	**Justification for confidentiality**
CBI 3	**Demonstration of Commercial Interest:** Volumes of UV-328 imported and used are confidential information that are only to be used for the applicant's planning and operations. Sharing them publicly may also breach anti-trust and competition laws in the UK. **Demonstration of Potential Harm:** If competitors got hold of this information, they could use it to determine the applicant's output and market share or the weight of the particular products on their overall business. Competitors could use such sensitive information to gain a competitive advantage over the applicant. Some of the redacted information could also be used to back-calculate sensitive information. **Limitation to Validity of Confidentiality:** This claim is valid indefinitely
CBI 4	**Demonstration of Commercial Interest:** Customer – supplier relations are proprietary to the companies involved in that relationship and a part of the applicant's strategy. **Demonstration of Potential Harm:** Information on commercial relations (customers and suppliers) can be used by competition to gain an unfair competitive advantage against the applicant. **Limitation to Validity of Confidentiality** This claim is valid indefinitely
CBI 5	**Demonstration of Commercial Interest:** Information on business commercial performance, such as manufacturing output, sales, revenue and profit margins, as well as employment, are commercially sensitive information and are only supposed to be known by the company. If they become publicly available they will distort competition and may even be in breach of anti-trust laws in the UK and the EU. **Demonstration of Potential Harm:** If marketing (production, sales, revenue and profits) information were to be released, it will provide the applicant's competitors with proprietary knowledge of information on the applicant's market share and would give them an unfair competitive advantage. **Limitation to Validity of Confidentiality:** This claim is valid indefinitely