BRAS Advanced Course Module 3

May 12-13, 2022

Summary results of case studies on variations

For the description of the case studies, please refer to the documents that were distributed during the course.

Please not that this document only summarises the results of the exercise presented by the working groups during the meeting and should not be considered as a formal guideline.

Case study N° 1
Update of drug product specifications & stability issue

Remark: The proposed changes may be classified as follows:

- **a type II variation B.II.d.1.e) (change outside the approved specification limits) for the dissolution test**
- **a type IB variation B.II.d.2.d) (other changes to a test procedure (including replacement or addition)) for the replacement of the HPLC method for related substances**
- **a type IB variation B.II.d.1.g) (Addition or replacement (excluding biological or immunological product) of a specification parameter as a result of a safety or quality issue) for the new limits for related substances.**

1. List of requested changes (current vs. proposed)

- The current and proposed drug product shelf life specifications for dissolution and impurities are shown below:

Current:

Related substances by current HPLC

Indiv imp ≤ 0.2%
total < 3.0%

In vitro dissolution test
t= 1h ≤ 25%
t= 4h 45-65%
t= 8h ≥ 85%

Proposed:

Related substances by new HPLC

impurity B	≤	0.2 %
impurity D	≤	1.0 %
impurity E	≤	0.5 %
unidentified RRT 0.8	≤	0.4 %
unidentified RRT 1.3	≤	0.2 %
any other	≤	0.2%

In vitro dissolution test

t=1 h	≤ 25%	
t=4 h	40-65%	
t=8 h	release:	≥ 85%
	shelf life:	≥ 75%

- New gradient HPLC method for degradation products in the finished product (to replace the current method).

2. Relevant guidance documents to be consulted

Impurities in New Drug Products
CPMP/ICH/ 2738/99-ICH Q3B (R2)

Validation of Analytical Procedures: Text and Methodology
CPMP/ICH/381/95 - ICH Q2 (R1)

Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances
CPMP/ICH/ 367/96-ICH Q6A

General chapter on dissolution Q4B annex 7
CHMP/ICH/645469/08

Quality of oral modified release products
EMA/CHMP/QWP/428693/2013

Stability Testing of Existing Active Ingredients and Related Finished Products.
CPMP/QWP/ 122/02 Rev. 1 corr

Evaluation of stability data
CPMP/ICH/420/02-ICH Q1E

Annex: Declaration of Storage Conditions for Medicinal Products Particulars and Active Substances
CPMP/QWP/ 609/96 Rev. 2

3. Summary of the documentation to be presented in support of the variation

I. Change in limits and test method for related substances.

B.II.d.1.g):

Documentation
1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).
2. Comparative table of current and proposed specifications.
3. Details of any new analytical method and validation data, where relevant.
4. Batch analysis data on two production batches (3 production batches for biologicals, unless otherwise justified) of the finished product for all specification parameters
5. Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch complying with the current and proposed specification. For herbal medicinal products, comparative disintegration data may be acceptable.
7. Justification of the new specification parameter and the limits

B.II.d.2.d)

Documentation
1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including a description of the analytical methodology, a summary of validation data, revised specifications for impurities (if applicable).
2. Comparative validation results or if justified comparative analysis results showing that the current test and the proposed one are equivalent.; This requirement is not applicable in case of an addition of a new test procedure.

3.2.P.5 Control of Drug Product

- 3.2.P.5.1 Specifications: Updated release and shelf life specifications.

- 3.2.P.5.2 Analytical procedures: Description of new HPLC method (including reference standards).

- 3.2.P.5.3 Validation of analytical procedures: Validation of new HPLC method: specificity for all relevant impurities and excipients, precision, linearity, range, Limit of Quantification (LoQ), accuracy at LoQ, robustness, extraction method from the matrix

polymer. Stress studies: these studies are intended to demonstrate that the method is suitable for the detection of the degradation products. Mass-balance results should be presented.

- 3.2.P.5.4 Batch analysis: batch results should be presented.

- 3.2.P.5.5 Characterisation of impurities: identification of the impurities; discussion of the degradation pathway.

- 3.2.P.5.6 Justification of specifications: the new proposed limits should be discussed and justified, taking into account the batch and stability results as well as the identification and qualification thresholds (including stability data).

3.2.P.2.6 Reference standards for the related substances.

3.2.P.8 Stability

- 3.2.P.8.1 Stability summary and conclusion

- 3.2.P.8.3 Stability data: stability results should be provided to support the requested changes.

II. Change in dissolution limits

3.2.P.2 Pharmaceutical Development

- The dissolution results obtained with the original batches / clinical batches should be included.

3.2.P.5 Control of Drug Product

- 3.2.P.5.1 Specifications: Updated release and shelf life specifications (including acceptance criteria of the dissolution test).

- 3.2.P.5.6 Justification of specifications: the new proposed limits should be discussed and justified, taking into account the potential impact on the in vivo availability as well as batch and stability results (Reference should be made to the data provided in pharmaceutical development).

3.2.P.8 Stability

- 3.2.P.8.1 Stability summary and conclusion
- 3.2.P.8.3 Stability data: stability results should be provided to support the requested changes.

4. Critical issues / Pitfalls / Specific considerations

I. Change in limits and test method for related substances.

Critical issues for related substances:

- Discussion of synthesis / degradation impurities: imp. B is a synthesis impurity and should not be included.
- Set limits for total impurities
- The release specifications should be provided
- Discussion of the proposed limits in function of the batch / stability results
- Discussion of identification / qualification threshold in accordance with the guideline on impurities in new drug products (impurities should be identified or qualified if present at a level greater than the threshold):

Maximum daily dose	100 mg
Identification threshold	0.2% or 2 mg, whichever is lower
Qualification threshold	0.5% or 200 µg, whichever is lower
Real identification threshold	0.2% *(0.2% is lower than 2 mg of a 100 mg dose corresponding to 2.0%)*
Real qualification threshold	0.2% *(200 µg of a 100 mg dose is 0.2% and lower than 0.5%)*
Limits to be discussed / modified	Qualification of impurities D & E & F because the limits are above the 0.2% threshold. Impurities D & E are already identified. Impurity F should be identified. Identification and qualification of impurity G are not necessary (limit at the thresholds).

For qualification, the limit can be justified

- by toxicological/safety studies or
- by clinical experience or
- if the impurity is a metabolite or
- by compendial limit (Ph. Eur./British Pharmacopoeia/USP – drug product monograph if any) or
- since the product is already on the market and if no adverse event has been reported by pharmacovigilance, the impurity is considered qualified on condition that the proposed limit represents the real levels observed in the marketed batches (historical results will be requested).

If the impurities are qualified by one of the above mentioned possibilities → OK
Otherwise, discussion of the following alternatives to reduce degradation level and allow lower limits:

- Reduction of shelf life

- change of storage conditions (the specified unidentified degradation products are only observed at accelerated conditions)
- use of a more protective packaging (e.g. PVDC/aluminium blister, aluminium/aluminium blister,…)
- setting stricter limits at release to guarantee lower levels of impurities at shelf life
- change manufacturing parameters (e.g. relative humidity, drying temperature)

II. Change in dissolution limits

Critical issues for dissolution limits:

- The specifications for drug release should be derived from batches used in the clinical trials showing acceptable in vivo performance.

- The applicant should present a discussion regarding the investigation of the possible cause of the decrease observed for dissolution during stability. What happened between registration and now to explain the observed changes? E.g. changes in minor manufacturing parameters / conditions; change in excipients suppliers…

- If the widening is requested on the basis of the results obtained at accelerated and/or intermediate conditions, a change in storage conditions is recommended.

- The proposed limits are not in line with the recommendations of the guideline on modified release products: range higher than 20% at 4 h and last point lower than 80%. Therefore, the following is recommended:
  - ✓ Discussion of the following alternatives to reduce the range at 4h and increase limit to 80% at 8h:
    - * to study other packaging material,
    - * to set stricter limit at release (for the 4-hour time-point)
    - * to change storage conditions and/or shelf life.
  - ✓ If maintenance of the current criteria is not possible, a bioequivalence study will be requested, in accordance with the guideline on Modified Release Oral and Transdermal Dosage Forms: Section II (Pharmacokinetic and Clinical Evaluation) (CPMP/EWP/280/96).

Remark: the 'Guideline on Quality of Oral Modified Release Products' (EMA/CHMP/QWP/428693/2013), section 2.4 ('Variations to products') states the following: 'The supporting data requirements for variations to the Marketing Authorisation will depend upon the significance of the change, whether or not a Level A IVIVC exists and whether or not the dissolution method/limits is to be changed. If bioavailability/bioequivalence data have not been submitted their absence should always be justified.
When a Level A IVIVC has been established and the release specification is not changed, changes may be accepted on the basis of in vitro data, the therapeutic index of the drug substance and predictive capability of the IVIVC. In this case, waiver of a bioequivalence study should be based on comparison of the predicted plasma concentration-time profiles and associated pharmacokinetic parameters (Cmax, AUC and a shape parameter) for the formulations before and after changes, calculated utilising the in vitro data and the validated IVIVC.
In general, bioavailability/bioequivalence data are needed for products with an established Level B or C correlation or no IVIVC, unless justification is provided for absence of such data.'

Note: An in vitro in vivo correlation (IVIVC) is a mathematical model describing the relationship between an in vitro property of a dosage form (mainly dissolution or drug release) and a relevant in vivo response (mainly drug plasma concentration or amount absorbed). It is self-evident that such a relationship is only likely to exist when the formulation controls the rate of appearance of drug in plasma. A level A IVIVC can be used to support biowaiver claims in later phases of clinical development or post-authorisation if there are changes in formulation.

Case study n°2:
Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container' (EMA/CHMP/CVMP/QWP/850374/2015)

The new EMA Guideline came into effect on 1 October 2019. It provides guidance on the documentation expected for sterile finished products, sterile active substances, sterile excipients and sterile primary containers in a new marketing authorisation application or a variation application for a medicinal product, (called quality dossier throughout the guideline).

The five exercises in the case for sterile medicinal products illustrate common deficiencies observed in quality dossiers. Using the new Guideline, and based on the presentations given during the first day of this course, the BRAS participants are asked to identify these deficiencies and how to avoid them.

Exercise 1 – Justification of sterilisation method

A type II variation is introduced to change the sterilisation method from terminal steam sterilisation (121°, 15 min) to sterile filtration with aseptic processing. The Applicant has justified this change due to the heat sensitivity of the active substance. Unknown degradation products are observed above the identification threshold at release and out-of-specification results are observed for some specified degradation products after 4 years storage.

With aseptic processing no such increase in impurities is observed. Still, questions were raised by the Authorities in the first round, and after the second round the proposed change was refused.

Questions:

a) What could be the possible explanations for this refusal ?

No demonstration that the product could be sterilised by steam sterilisation with lower heat input, e.g. $F_0 \geq 8$ minutes achieving SAL of 10^{-6}.

Terminal sterilisation should not be ruled out based on unidentified or unqualified impurities. Efforts to be made to identify unknown degradation products, specified degradation products could be metabolites, observed levels could already be qualified.

Instead of changing the sterilisation method one could solve the out-of-specification issue by reducing the shelf life and storage conditions.

No discussion if adaptation to formulation, container closure system or manufacturing process could allow terminal sterilisation.

b) The selection of a sterilisation method is documented in which CTD section of the quality dossier.

3.2.P.2 Pharmaceutical development

- **3.2.P.2.3 Manufacturing process development**

Discussion how the required SAL of 10^{-6} is achieved. Cross-reference can be made to the detailed validation data in section 3.2.P.3.5.

Impact of heat or irradiation on drug product (degradation products, radiolysis impurities), or container closure system (polymer degradation, integrity, functionality, intended use etc.)

➢ 3.2.P.2.4 Container closure system

The sterilisation approach for the empty containers (i.e. those subsequently used in aseptic manufacturing process could be discussed here)

Exercise 2 – Validation of sterilisation processes

Indicate for each of the claimed sterilisation processes if validation data should be included in the quality dossier.

- Steam sterilisation with $F_0 \geq 15$ min; process hold temperature ≥ 121°C.

  No. Ph. Eur. reference conditions fulfilled.

- Steam sterilisation based on the reference cycle of the USP Pharmacopoeia (i.e. $F_0 > 12$ min).

  Yes. Even though the reference cycle of the USP pharmacopoeia is used, EU does not accept such cycle without validation data.

- Terminal gamma irradiation cycle at 15 kGy and compliance statement with ISO 11137.

  Yes. Irrespective of ISO compliance, data as requested in Note for Guidance "The use of Ionization Radiation in the Manufacture for Medicinal Products" and in compliance with Ph. Eur. chapter 5.1.1 should be provided. The irradiation dose is also below the Ph. Eur. reference dose (25 kGy).

- Dry heat sterilisation at 170°C for 60 minutes.

  Yes. Irrespective of the temperature, lower time exposure than the exposure time of 120 minutes in the Ph. Eur.

- Ethylene oxide sterilisation (routine monitoring with Ph. Eur. compliant biological indicator)

  Yes. Gas sterilisation should always be documented.

Exercise 3 – Purchased sterile drug substance

A drug product manufacturer submits a type II variation to replace the current manufacturer of the sterile drug substance (Ph. Eur.) with a new one who has obtained a CEP from the EDQM for this sterile drug substance.

Note: The sterilisation process is described in detail in the CEP application submitted to the EDQM, together with full data on the validation of the sterilisation method. When granted, the CEP will include the relevant subtitle ("sterile"), it will specify the sterilisation method used and will refer to the test for sterility. It will also be mentioned that the sterilisation process has been assessed and approved.

Method of sterilisation: sterile filtration with aseptic processing.

Questions:

a) Which CTD section(s) are impacted by this variation ?

3.2.S.2 Manufacture

- **3.2.S.2.1 Manufacturer(s)**
- **3.2.S.2.2. Description of manufacturing process and process controls**
- **3.2.S.2.5 Process validation**

  Sterilisation of the active ingredient is regarded as part of finished product manufacture. Therefore data on the sterilisation process of the active substance (including validation data) should be submitted to the Marketing Authorisation applicant/holder for inclusion in the dossier submitted for the finished product and approval by the national licensing authority(ies).

- **3.2.S.4 Control of drug substance**

  Specifications in line with the new CEP, batch analysis data.

3.2.P.3 Manufacture

- **3.2.P.3.1 Manufacturer(s)**

  The manufacturing site performing the sterilisation of the drug substance should be included.

- **3.2.P.3.3 Description of manufacturing process and process controls, 3.2.P.3.4 Control of Critical steps and Intermediate(s), 3.2.P.3.5 Process Validation**

  2 options: description and validation data could be retaken here, or, a more practical solution is to make a cross-reference to section 3.2.S.2.

b) Similar question, this time the new manufacturer uses an ASMF to describe the synthesis and the sterilisation of the drug substance.

Same approach.

In agreement with existing quality guidelines, The sterilisation of the drug substance is described in section 3.2.S.2.5 Process Validation

Problem: This section is normally included in the Restricted Part of the ASMF !

The ASMF holder should make this information available in the Applicant's part of the ASMF !

Exercise 4 - Sterile filtration with aseptic processing – Data for the sterilising filter

An Applicant was asked to provide the missing documentation on the 0.22 µm sterilising filter used in the manufacturing process

The next answer was received from the Applicant:

The sterilising filter used in the manufacturing process used is a PES membrane filter (10 inch). The quality characteristics and validation criteria stated in the table below meet the requirements laid down in table 3 of the "Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container' (EMA/CHMP/CVMP/QWP/850374/2015)"

Cartridge Filters

	5-inch Cartridges	Per 10-inch Cartridge
Nominal Dimensions		
Diameter:	6.9 cm (2.7 in.)	6.9 cm (2.7 in.)
Length:	12.5 cm (5 in.)	25.4 cm (10 in.)
Filtration Area	0.29 m² (3.1 ft²)	0.54 m² (5.8 ft²)
Materials of Construction		
Filter membrane:	Hydrophilic polyethersulfone	
Film edge:	Polypropylene	
Supports:	Polypropylene	
Cage and end caps:	Polypropylene	
Core:	Polysulfone	
O-rings:	Silicone, EPDM or Fluoroelastomer	
Maximum Differential Pressure		
Forward:	5500 mbar (80 psi) at 25 °C	
	1700 mbar (25 psi) at 80 °C	
	300 mbar (5 psi) at 135 °C	
Reverse:	1400 mbar (20 psi) at 25 °C	
	69 mbar (1 psi) at 135 °C	
Air Diffusion at 23 °C	Through a water wet membrane at 2800 mbar (40 psi):	
	≤ 16.4 cc/min.	≤ 30.0 cc/min.
Bacterial Retention	Quantitative retention of 10^7 CFU/cm² Brevundimonas diminuta ATCC® 19146 per ASTM® methodology	
Bacterial Endotoxin	Aqueous extraction contains <0.25 EU/mL as determined using the Limulus Amebocyte Lysate (LAL) test.	
TOC/Conductivity	Autoclaved cartridge effluent meets the WFI criteria for USP <643>, Total Organic Carbon, and USP <645>, Conductivity, after a WFI flush of:	
	5.5 L at 25 °C	10 L at 25 °C
Sterilization	Autoclave: May be autoclaved for 15 cycles of 60 minutes at 126 °C	
	In-line Steam: May be in-line steamed forward for 15 cycles of 30 minutes at 135 °C or forward for 12 cycles and reverse for 3 cycles of 30 minutes at 135 °C	
Toxicity	Component materials meet the criteria for the USP Class VI Biological Test for Plastics.	
Non-fiber Releasing	Component materials meet criteria for a "non-fiber releasing" filter as defined in 21 CFR 210.3 (b) (6).	
Component Material Toxicity	Component materials were tested and meet the criteria of the USP <88> Reactivity Test for Class VI plastics.	
Indirect Food Additive	All component materials meet the FDA Indirect Food Additive requirements cited in 21 CFR 177-182.	
Good Manufacturing Practices	These products are manufactured in a facility which adheres to FDA Good Manufacturing Practices.	

Questions:

a) Is the answer from the Applicant satisfactory ? (Table 3 from the Sterilisation guideline referred to, is included on the next page)

General information on the filter is given as required by the guideline together with quality characteristics for the given filter from the filter manufacturer.

However, the filter should be validated taking the medicinal product and worst-case manufacturing process conditions into account. This validation is mostly outsourced to the filter manufacturer himself, or, it could be performed in-house by the drug product manufacturer. In both cases, detailed validation reports should be submitted.

Table 3 Filter data to be provided in the quality dossier for filters in contact with the drug product or components of the drug product

Parameter	Filter		Comment	
	Non-sterilising[1]	Sterilising[1]		
General information on filter				
Type of material, nominal pore size	X	X		
Number of filters	X	X		
Filter area	-	X		
Filter integrity test	-	X	Principle of the test, details on when the tests are performed, solution(s) used in the test and acceptance criteria before and after filtration should be described.	
Filter validation			**Solution used**	**Comment**
Potential sorption of solution components to filter	X	X	Product	
Solution Compatibility	X	X	Product	Worst case conditions with regards to for instance sterilisation process, contact time, filtration time, pressure, filtered volume.
Filter retention capacity	-	X	Product [2]	Minimum 10^7 CFU/cm^2 using a justified indicator organism and the actual solution.
Filter integrity test limits	-	X	Product [3]	
Extractable and leachable substances from the filter	X	X	Product [4]	Justified surrogate solution may be used.

[1] As defined in GMP, Annex 1
[2] Validation of filter retention capacity may be combined with solution compatibility. If the product solution affects the indicator organisms negatively, it should be neutralised before adding the organisms. For validation, a suitable challenge microorganism representing the worst-case challenge to the filter should be used.
[3] If the test is performed using a different solution in routine manufacture (for instance water for injections), the limits should be established in this solution.
[4] Data on leachables is relevant only if the extractables data indicate that toxic components may leach into the solution to be filtered.

b) Which CTD sections should be completed ?

3.2.P.3 Manufacture

➢ 3.2.P.3.3 Description of manufacturing process and process controls, 3.2.P.3.4 Control of Critical steps and Intermediate(s)

General information on the filter.

Filter integrity test limits and method. The filter integrity is part of the validation yet the proposed acceptance criteria should be included under the critical process steps.

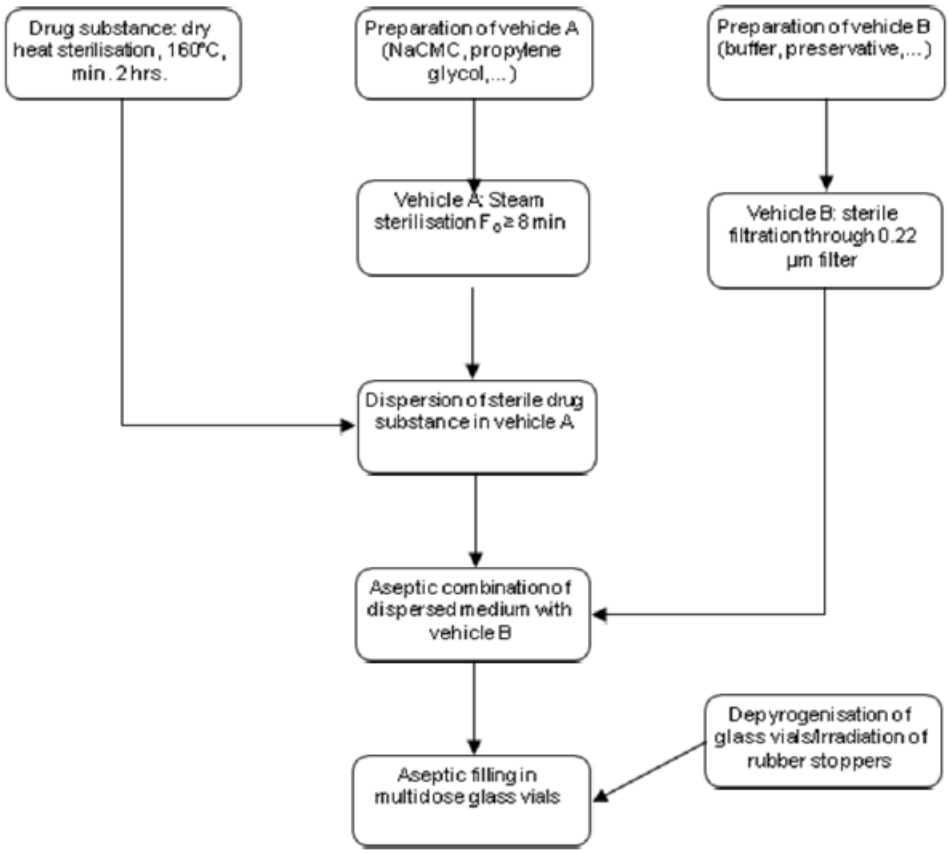
➢ 3.2.P.3.5 Process Validation

The detailed validation reports (compatibility, microbial retention, extractables/leachables) for the sterilising filter. (Note: validation is frequently outsourced to the filter manufacturer)

Exercise 5: Change in composition of a parenteral dosage form

A variation is introduced to revise the formulation of the drug product (suspension for injection). The preservative phenol is replaced with a different preservative excipient.

Manufacturing flow-chart:



Questions

a) Impact on CTD section 3.2.P.2 Pharmaceutical development ?

3.2.P.2.1 Components of the drug product

Justification of selection and concentration of preservative excipient.

3.2.P.2.2 Drug product formulation

Justification for changing the formulation.

3.2.P.2.4 Container closure system

Compatibility of the multidose container with the revised formulation should be demonstrated. In this case particular attention should be paid to the interaction of new preservative with the rubber stopper. The easiest way to demonstrate this, is by performing formal stability studies. Vials should be stored in both upright and inverted position to examine possible adsorption of the preservative to the rubber stopper. Cross-reference with stability section 3.2.P.8 can be made.

3.2.P.2.5 Microbiological attributes

Preservative efficacy testing in accordance with the Ph. Eur. 5.1.3 monograph Efficacy of antimicrobial preservation at the lower limit in the shelf life specification, e.g. 90-110% or 85-110%.

Relevant quality guidance documents:

- *ICHQ8(R2) Pharmaceutical Development*
- *Guideline on Excipients in the dossier for Application for marketing Authorisation of a Medicinal Product EMEA/CHMP/QWP/396951/2006*
- *Ph. Eur. 5.1.3 monograph - Efficacy of antimicrobial preservation*

b) Discuss the validation strategy needed for this change (# batches, batch size ?)

There are two important aspects which determine the type and amount of validation data. Firstly, the drug product is a suspension for injection which is a specialised pharmaceutical dosage form (dose uniformity is critical). Secondly, the manufacturing process involves aseptic processing which is known to be complex. Consequently, both the product and manufacturing process must be considered non-standard.

The Guideline on process validation for finished products - information and data to be provided in regulatory submissions (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1, Corr.1) states

"Full production-scale data should be provided in the dossier for non-standard products or processes which are validated using traditional process validation. In these cases, data should be provided in the dossier on a number of consecutive batches at production scale prior to approval. The number of batches should be based on the variability of the process, the complexity of the process / product, process knowledge gained during development, supportive data at commercial scale during technology transfer and the overall experience of the manufacturer. Data on a minimum of 3 production scale batches should be submitted unless otherwise justified. Data on 1 or 2 production scale batches may suffice where these are supported by pilot scale batches and a justification as highlighted above".

c) Discuss the stability program needed for this change (# batches, batch size ?)

Supportive stability studies

Guideline on stability testing for Applications for Variations to a Marketing Authorisation EMA/CHMP/CVMP/QWP/441071/2011-Rev2:

"For critical dosage forms or when the active substance is known to be unstable, comparative stability data 6 months in duration, long term and accelerated stability testing conditions on at least three primary batches are recommended. Two of the three batches should be at least pilot scale, the third batch may be smaller".

Comment: Since production scale batches need to be produced anyway, it is appropriate to place samples from these batches on stability. It is acknowledged that at the time of submission, 6-month stability results may not be available yet for three production batches (case-by-case assessment).

Multidose vials > In-use stability studies

Note for Guidance on In-Use Stability Testing of Human Medicinal Products CPMP/QWP/2934/99

"A minimum of two batches should be subjected to the test. At least one of the batches should be chosen towards the end of its shelf life. If such results are not available, one batch should be tested at the final point of the submitted stability studies."

Comment: supportive development data may also demonstrate the efficacy of the preservative at lower concentration level.

Relevant quality guidance documents:

- *ICH guideline Q8 (R2) on pharmaceutical development EMA/CHMP/ICH/167068/2004*
- *Guideline on process validation for finished products - information and data to be provided in regulatory submissions EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1,Corr.1*
- *Stability Testing of Existing Active Ingredients and Related Finished Products CPMP/QWP/122/02 Rev.1 corr.*
- *Annex: Declaration of Storage Conditions for Medicinal Products Particulars and Active Substances CPMP/QWP/609/96 Rev.2*
- *Guideline on stability testing for Applications for Variations to a Marketing Authorisation EMA/CHMP/CVMP/QWP/441071/2011-Rev2.*
- *Note for Guidance on In-Use Stability Testing of Human Medicinal Products CPMP/QWP/2934/99*

Case study n°3:
Registration of a new API supplier using its own route of synthesis

1. What is the potential impact of requested changes on the quality of the product?

Addition of new API supplier implies potential changes in

a. chemistry or physico-chemical properties of the drug substance (e.g. particle size profiles, polymorphic form) → drug product development, manufacture or performance
b. synthetic route/manufacturing process
c. qualitative and quantitative impurity profile
d. applicant's specifications and control test methods (reference standards)
e. packaging material of the drug substance
f. stability and re-test period of the drug substance
g. stability of the drug product

Which parts of CTD Module 3 will have to be amended?

3.2.S. DRUG SUBSTANCE (NAME, MANUFACTURER)

3.2.S.1. General Information (name, manufacturer)

3.2.S.2. Manufacture (name, manufacturer)
- 3.2.S.2.1. Manufacturer (name, manufacturer)
- 3.2.S.2.2. Description of Manufacturing Process and Process Controls
- 3.2.S.2.3. Control of Materials
- 3.2.S.2.4. Controls of Critical Steps and Intermediates
- 3.2.S.2.5. Process Validation and/or Evaluation
- 3.2.S.2.6. Manufacturing Process Development

3.2.S.3. Characterisation (name, manufacturer)
- *3.2.S.3.1. Elucidation of Structure and other Characteristics*
- 3.2.S.3.2. Impurities

3.2.S.4. Control of Drug Substance (name, manufacturer)
- 3.2.S.4.1. Specification
- 3.2.S.4.2. Analytical Procedures
- 3.2.S.4.3. Validation of Analytical Procedures
- 3.2.S.4.4. Batch Analyses
- 3.2.S.4.5. Justification of Specification

3.2.S.5. Reference Standards or Materials (name, manufacturer)

3.2.S.6. Container Closure System (name, manufacturer)

3.2.S.7. Stability (name, manufacturer)
- 3.2.S.7.1. Stability Summary and Conclusions
- 3.2.S.7.2. Post-approval Stability Protocol and Stability Commitment
- 3.2.S.7.3. Stability Data

3.2.P. DRUG PRODUCT (NAME, DOSAGE FORM)

3.2.P.2. Pharmaceutical Development (name, dosage form)
- 3.2.P.2.1. Components of the Drug Product
  - 3.2.P.2.1.1. Drug substance
- 3.2.P.2.2. Drug Product
  - 3.2.P.2.2.3. Physicochemical and Biological Properties

3.2.P.5 Control of the drug product (name, dosage form)
- 3.2.P.5.1 Specifications
- 3.2.P.5.2 Analytical procedures
- 3.2.P.5.3 Validation of analytical procedures
- 3.2.P.5.5 Characterisation of impurities
- 3.2.P.5.6 Justification of specifications

3.2.P.8 Stability (name, dosage form)
- 3.2.P.8.3 Stability data

2. What would be the best procedure to use for the medicinal product manufacturer to file Supplier 2 (ASMF, CEP or full data in MA dossier)

The best way to submit the API data from Supplier 2 is integration of full scientific data in the registration file. The API Supplier 2 is part of the BRAS group owned by the applicant. The ASMF procedure is not relevant as there is no know-how to be protected. CEP (only possible once monograph is officially published in the Ph. Eur.) would mean a longer cycle time before approval is granted since a 2 step procedure needs to be followed (request CEP to EDQM and submit CEP as variation to the National Authorities, (this would be a Type IAIN, so can be submitted when the change is implemented).

For the change (addition) of manufacturer of the active substance, a single, major type II variation can be applied for since the newly proposed manufacturer uses a different route of synthesis, which has a potential impact on the quality characteristics of the active substance such as impurity profile (see Annex II of the regulation). No Ph. Eur. certificate for the active as produced by its supplier is available at the moment.

B.I.a.1 Change in the manufacturer of a starting material/reagent/ intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved	**Procedure type**

	dossier		
☒	c)	The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions, which may have a potential to change important quality characteristics of the active substance, such as qualitative and/or quantitative impurity profile requiring qualification, or physico-chemical properties impacting on bioavailability.	II

3. Make a proposal for the unique list of drug substance specifications that can be used by the medicinal product manufacturer (BRAS, Poland) to control the API from both Suppliers 1 & 2

A single compiled specification list of the drug substance sourced from both API suppliers including common test parameters and supplier specific test parameters should be established. BRAS company shall test the API from Supplier 1 & 2 according to the specification list since it has full responsibility on the quality of the API for use in its drug products.

A proposal for such an API specification list is given in the table below:

Test	Specification limit
Appearance	white or almost white crystalline powder or colourless crystals
Identification A. IR-spectrum	Conforms to standard
Sulphated ash	NMT 0.1%
Loss on drying	NMT 0.5%
Assay (Titration)	98.5-101.0%
Particle size (Laser diffraction) (if tested)	D90: NMT 30 µm D50: NMT 15 µm D10: NMT 5 µm
Polymorphic form (XRD) Identity & purity (if tested)	Ratio of peak at 2θ=xx to peak at 2θ=yy : NMT 5%
Related substances (HPLC) *Impurity A* (1) *Impurity B* *Impurity C* (2) *Any other* *Total*	 ≤ 0.25% ≤ 0.10% ≤ 0.40% ≤ 0.10% ≤ 1.0%
Residual solvents (GC) *Methanol*(2) *THF* (2)	 ≤ 500 ppm ≤ 4,000 ppm

(1) only tested for supplier 1

(2) only tested for supplier 2

Appearance: qualitative statement about API in solid state (stability indicating)
Identification: IR-test specific enough;
Sulphated ash : general, non-specific limit tests to control inorganic impurities
Loss on drying: adequate for moisture and Class 3 solvents
Assay (titration): non-specific but precise test to determine API content in combination with stability indicating HPLC test for related substances (see Ph. Eur.)
Particle size: may affect process ability, dissolution and bioavailability, stability of the drug product; testing possibly relevant for tablets by direct compression (unless otherwise justified)
Polymorphism: tested if it affects drug product performance, bio availability and/or stability
Impurity A: impurity present from synthetic route A, > ICH qualification threshold, Ph. Eur. limit qualified at 0.25% level
Impurity B: impurity limited at 0.10% level as in the Ph. Eur. monograph
Impurity C: not on Ph. Eur. transparency list, but arising from synthetic route B, > ICH qualification threshold, should be qualified at 0.40% level
Any other: any unspecified impurity NMT ICH identification threshold
Ethanol (Class 3 solvent): controlled with general non-specific LOD test (NMT 0.5%)
Methanol (Class 2 solvent): 500 ppm is < 3,000 ppm (option 1 ICH limit)
THF (Class 2 solvent): 4,000 ppm > 720 ppm (option 1 ICH limit); but max. administered daily dose of active in drug product is 0.06g, this means that the max. daily intake of THF would be 0.24mg, which is below 7.2mg/d (PDE, option 2 ICH limit)
Pd: from the risk assessment on the intentionally added Pd, the maximum daily intake of Pd from the drug product is calculated at 0.9 µg, which is below 30µg/d (30% of PDE). Consequently, Pd should not be included in the drug substance specification. The only source of Pd is the drug substance (catalyst used during synthesis).

Some additional considerations related to this variation

The approval of the variation will come at different time points since the drug products are registered partly through MRP and partly through NP. MRP timelines are established, but clock start is not. NP timelines are not established in all countries.
The BRAS company will need a detailed implementation plan and a system to distinguish between drug product batches produced with API from Supplier 1 (which can be brought to the market) and drug product batches produced with its own API (which can only be brought to the market as soon as variation approval).

According to Art 20 of Regulation No 1234/2008 as amended, the same type II variation affecting more than one marketing authorization from the same holder can be grouped in a worksharing procedure. In this case, worksharing is possible since:

1) The same type II variation is applicable to the MRP products and all purely national products
2) The MRP products and all purely national products belong to the same MAH
3) There is no or limited need for assessment of a potential product-specific impact

As an MRP product is combined with several purely national marketing authorizations from different Member States, the letter of intent for the submission of a WS should be

addressed to CMDh, at least 6 weeks before the planned submission. The request should include a proposal for the preferred reference authority. Supposing the preferred reference authority is BE and the WS is accepted at CMDh, a procedure number (e.g. BE/H/xxxx/WS/22) will be assigned and communicated to the applicant after which the WS application can be introduced in BE, NL, LU, FR, UK, IE, ES and IT.

In this case, it seems logical that a full data procedure is used to file Supplier 2 since there is no intellectual property to protect and it is the fastest way to get approval within a limited time frame. However, it has to be remarked that, once the monograph is officially published in the Ph. Eur., the submission of a CEP is a recommendable alternative to apply for the new API supplier 2 (however, a longer approval cycle has to be taken into account). This is indeed the preferred way to demonstrate the suitability of the Ph. Eur. (and additional specifications) to control the drug substance in relation to its manufacturing process used (see NfG on summary requirements for active substances in the quality part of the file). Once a CEP is granted by the EDQM, this should be fully accepted by the competent authorities without further justification or questions. Additional data such as stability data to support a re-test period (only if not mentioned on CEP) and physico-chemical characteristics (e.g. particle size and polymorphism) may be requested.

The product-specific requirements of the drug substance (e.g. particle size, polymorphism) may affect drug product performance, safety or efficacy. The drug substance particle size and polymorphism are only relevant for the 5 mg or 10 mg tablet produced by direct compression. None are required for the oral solution.

If changes to the drug substance (changes in synthetic route, raw materials, processes equipment, container closure system or facilities) have the potential to change the elemental impurity content of the drug product, the risk assessment (including controls for elemental impurities) should be re-evaluated. The risk assessment has to be done by the drug product manufacturer taking into account the actual use of the drug substance in the drug product.

For information, the list of reference documents used during compilation of the case is provided here:

References to EU guidelines and Ph. Eur. Monographs are provided to assist applicants when compiling the chemical, pharmaceutical and biological part of the application.
The guidelines referenced below are available on the EMA website: http://www.emea.europa.eu
and the website of the European Commission (under topic 'Health'):
https://ec.europa.eu/health/medicinal-products_en

Regulatory guidelines and regulations

Current Variation Regulation *Regulation EC 1234/2008*	https://ec.europa.eu/health/system/files/2016-11/reg_2012_712_en_0.pdf

Notice to Applicants	https://ec.europa.eu/health/system/files/2016-11/ctd_05-2008_en_0.pdf

General Guidelines:

Document Title	Number/*version*
GMP for API	ICH/Q7A

Active Substance Guidelines

Document Title	Number/*version*
Guideline on the chemistry of active substances	EMA454576/2016
Guideline on Control of impurities of pharmacopoeial substances: Compliance with the European Pharmacopoeia general monograph "Substances for pharmaceutical use" and general chapter "Control of Impurities in substances for pharmaceutical use"	CPMP/QWP/1529/04
Note for Guidance on impurities testing: Impurities in new drug substances (revision of CPMP/ICH/142/95) (Q3A)	CPMP/ICH/2737/99 – ICHQ3A (R2)
Impurities: residual solvents (Q3C)	EMA/CHMP/ICH/82260/2006
Note for Guidance and specifications – Test Procedure and acceptance criteria for new drug substances and new drug products – Chemical substances (Q6A)	CPMP/ICH/367/96 – ICH Q6A
Q3D Impurities: guideline on elemental impurities	CHMP/ICH/353369/2013
Guideline on stability testing: Stability testing of existing active substances and related finished products	CPMP/QWP/122/02 rev 1 Corr.
Guideline on summary of requirements for active substances in quality part of the dossier	CPMP/QWP/297/97/rev1Corr
Guideline on Active Substance Master File Procedure	CPMP/QWP/227/02/rev4 Corr
Template for the qualified person's declaration concerning GMP compliance of active substance manufacture " The QP declaration template"	EMA/334808/2014

Medicinal Product Guidelines

Document Title	**Number/*version***
Note for guidance on pharmaceutical development	CPMP/ICH/167068/2004 – ICH Q8 R2
Guideline on stability testing for applications for variations to a marketing authorisation	EMA/CHMP/QWP/441071/2011-rev2