Application of EXCiPACT GMP Standard To Pharmaceutical Auxiliary Materials

A Guide for manufacturers and auditors

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EXCiPACT asbl, Rue Marie de Bourgogne 52, 3rd Floor, B-1000 Brussels, Belgium
E: info@excipact.org **W**: www.excipact.org **T**: +32 2 213 74 49 VAT: BE0545 771 884 IBAN: BE50 3631 3158 8018
RPM Brussels Capital Region

1. INTRODUCTION

Pharmaceutical Auxiliary Materials (PAMs) are materials used in processes to make medicinal products, active pharmaceutical ingredients (APIs) and drug substances[1]. They are not intentionally included in the final product and so not administered to the patient. However residual levels which cannot be removed may remain in the medicinal product, API or drug substance. Therefore, PAMs may need to be manufactured in accordance with GMP principles, including the avoidance of contamination.

PAMs include for example inert gases, used during chemical synthesis, other processing aids[2] and, in biotechnology led manufacturing, cell culture media. The United States Pharmacopoeia has published a general chapter (<1043> concerning Ancillary Materials for Cell, Gene and Tissue-Engineered products. Such Ancillary Materials are also PAMs, but PAMs are not restricted for application only for biotechnology derived drug products, but chemically derived ones too. Thus this document is also applicable to USP Ancillary Materials.

Manufacturing processes used for PAMs may not follow traditional chemical manufacturing processes, so hazards to product integrity and quality could be different. The risk –based approach underpinning EXCiPACT GMP for pharmaceutical excipients can be applied to provide an appropriate and proportionate GMP for these materials.

This guide has been prepared by experts in the pharmaceutical industry to provide advice on how EXCiPACT GMP can be applied to the manufacture of PAMs.

It is also intended as supplemental information for auditors of PAM manufacturers to assess compliance to the EXCiPACT GMPs.

2. DEFINITION

Pharmaceutical Auxiliary Materials (PAMs) are either:

a) materials which are not intentionally included in the medicinal product, but are essential in the manufacturing process, or
b) processing aids used during the manufacture of medicinal products or APIs.

PAMs may have a final bioburden reduction step in their manufacture.

Notes: This definition applies to APIs and medicinal product manufacturing. For example, this includes cell culture media, industrial gases, and ion exchange resins, but excludes packaging components, packaging, other equipment, and similar items.

Note: PAMs are not Auxiliary Medicinal Products (AMPs) which, according to EU 536/2014, is a medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product (e.g., challenge agents, medicinal products used for background treatments).

[1] PAMs may be used in the manufacture of excipients, but it is for each excipient manufacturer to decide if this definition of GMP is suitable and should be applied to those materials.

[2] IPEC Glossary definition: *Materials, excluding solvents, used as an aid in the manufacture of an intermediate, excipient or API that do not themselves participate in a chemical or biological reaction (e.g., filter aid, activated carbon, etc.). See also IPEC Composition Guide.*

EXCiPACT asbl, Rue Marie de Bourgogne 52, 3rd Floor, B-1000 Brussels, Belgium
E: info@excipact.org **W**: www.excipact.org **T**: +32 2 213 74 49 VAT: BE0545 771 884 IBAN: BE50 3631 3158 8018
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3. GUIDANCE

This section provides guidance, in two parts, for manufacturers and auditors of PAMs. The first part is aligned to the section headings in the EXCiPACT GMP Standard. The second part summarises several optional techniques to reduce the bioburden of finished PAMs post synthesis, their principles of operation and the controls needed to have assurance of the correct operation. Such techniques may not be used as frequently in traditional excipient manufacture and so some familiarisation is required for auditors. References to "Sections" refer to the relevant parts of the EXCiPACT GMP Standard.

3.1 Applicability of EXCiPACT GMP

The EXCiPACT GMP annex to ISO 9001 is applicable to excipients. When applying the EXCiPACT GMP Annex to PAMs, all references to excipients should refer to PAMs.

There is no need for a different definition of the starting point of GMP in the manufacture of PAMs (Section 4.3).

With regard to outsourced services, including analytical testing, best practice is to perform a risk assessment (Section 4.4.3.c) to determine the criticality of the service to PAM quality. In critical cases a quality agreement with the provider is a good way to mitigate risks (Section 4.4.3 b).

Where the PAM is referenced in the marketing authorisation dossiers or API drug master files, then it is more likely that customers will have to approve any significant changes. This should be considered both in terms of implementation of the change and in giving as much advance notice to customers as possible. The IPEC Significant Change Guide can be applied to changes impacting PAMs in the same way as described for excipients (Section 6).

The requirement for risk assessments of Infrastructure (Section 7.1.3) and Environment (Section 7.1.4) applies equally to PAMs. Risk assessments need to consider threats to PAM purity and quality and to identify suitable measures and practices to minimise those risks.

The choice of water quality used in the manufacture of PAMs should not only consider the impact on the purity and quality, but also the intended uses. Higher quality than potable water may be required where a PAM is required to have a very low bioburden prior to use. In such cases it is more important to apply best practice controls to monitor and measure water quality. Design of water systems should include best practices to minimise microbial and other contamination (Section 7.1.3).

The requirement for a risk assessment to consider the risk to quality from utilities, lubricants, processing aids and cleaning agents also applies to PAMs. Removal of such materials should be proportionate to the purpose of the PAM, for example in the case of cell culture media removal of sterilising agents.

Where reference is made to the end patient (e.g., Section 7.2.g) iii), this should be interpreted as the medicinal product manufactured using the PAM.

The organisation should ensure that any final steps to reduce bioburden are planned, implemented, and controlled (Section 8.5.1). Where required, verification of low bioburden levels should be included. Where testing cannot demonstrate suitable control then the requirements for validation and periodic revalidation will be necessary (as defined in ISO 9001 Section 8.5.1., f).

There are no specific observations concerning PAMs in other sections of the EXCiPACT GMP Annex.

EXCiPACT asbl, Rue Marie de Bourgogne 52, 3rd Floor, B-1000 Brussels, Belgium
E: info@excipact.org **W**: www.excipact.org **T**: +32 2 213 74 49 VAT: BE0545 771 884 IBAN: BE50 3631 3158 8018
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3.2 Guidance on specific post manufacturing techniques to reduce bioburden

Appendix 1 provides details about various techniques that can be applied to reduce or eliminate the bioburden in the product.

Each section is structured consistently as follows:

- Principles of Operation - Description / Applications.
- Critical Quality Attributes / Testing Requirements - Acceptance Criteria.
- Risks to Effective Bioburden reduction (known threats to product assurance quality and purity).
- Expected Supporting Information / Evidence (specific to bioburden reduction type where possible).

A summary of the principles of operation is provided highlighting critical quality attributes of the techniques used to reduce bioburden. This enables auditors without specialist knowledge to assess whether quality critical attributes are effectively controlled, and to determine the impact of any deviations at these and other steps in the process.

Additionally, the sections may benefit those using these techniques in aiding the design and implementation of the correct controls to maximise assurance of product purity and quality.

4. APPENDIX I

Commonly used methods for bioburden reduction

These methods can be applied to reduce bioburden during or at the end of manufacture. In some cases, they might also achieve sterility, although it might not be intended to maintain sterility after that point, for example when applied to bulk material that is subsequently packaged. In other cases, such as irradiation in the final pack, sterility may be maintained until the pack is opened. The suitability of packaging to be subjected to the treatment should be verified. The manufacturer should communicate the treatment and to what extent it provides assurance of the bioburden levels in the PAM.

The organisation should have evidence of the suitability of the method for each specific PAM.

The following sections provide guidance for manufacturers and EXCiPACT auditors for some commonly used methods to reduce bioburden:

- Autoclave.
- Dry Heat Treatment.
- Filtration.
- Gamma Irradiation.
- Vapourised Hydrogen Peroxide Fumigation.

EXCiPACT asbl, Rue Marie de Bourgogne 52, 3rd Floor, B-1000 Brussels, Belgium
E: info@excipact.org **W**: www.excipact.org **T**: +32 2 213 74 49 VAT: BE0545 771 884 IBAN: BE50 3631 3158 8018
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Autoclave

Bioburden reduction Type Summary

Principles of Operation - Description / Applications

An autoclave is a secure, leak free chamber that uses steam at defined pressure, temperature, and contact time to reduce bioburden.

Main stages of bioburden reduction operation are:

- **Purge** - Steam flows through the autoclave and air is removed until the vents automatically close and a pre-determined temperature and pressure is reached.
- **Bioburden reduction** - Steam permeates the chamber and contents contacting all surfaces and will hold for a pre-set time.
- **Exhaust** - Pressure is released and the interior restored to ambient conditions.

Instruments used to measure temperatures and pressures should be calibrated in accordance with Section 7.1.5.2. Control instrumentation should be independent of monitoring instrumentation and chart recorders.

Items, other than products in sealed containers, should be wrapped in a material that allows air and steam to permeate freely and will prevent recontamination after bioburden reduction. All parts of the defined load should be in contact with sterilising steam at the required temperature for the required time.

Biological indicators may supplement methods to demonstrate the effectiveness of the operation.

Critical Quality Attributes / Testing requirements - Acceptance Criteria

- Temperature measurements for example, **>15 minutes at 121°C - 124°C,** to confirm effective bioburden reduction.
- Negative growth of independently verified biological indicators after a minimum of **24-hour incubation at 55 to 60°C.** Standard biological indicators, e.g., *Geobacillus stearthermophilus* are commonly used.
- During the Holding Time, the temperature recorded for each load item should not fluctuate by more than +/- 1°C and should not differ from other load items by 2°C.
- Defined load quantities and orientation of PAMs within the chamber.

Risks to Effective Bioburden reduction (known threats to product assurance quality and purity)
After the high temperature phase of the cycle, precautions should be taken against contamination during cooling. If containers are found to be damaged or leaking after treatment, they should be discarded and the impact on the load evaluated.

Care should be taken to ensure that steam used for bioburden reduction is of suitable quality and does not contain additives at a level that could cause contamination of product or equipment. This should be verified at defined intervals.

Expected Supporting Information / Evidence (specific to bioburden reduction type where possible)

Quality Documentation / Records for proof of reduced bioburden

- Operation Procedures.
- Operation and Maintenance Manuals.
- Minimum and maximum loads.
- Load configuration and load record.

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E: info@excipact.org **W**: www.excipact.org **T**: +32 2 213 74 49 VAT: BE0545 771 884 IBAN: BE50 3631 3158 8018
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- Validation or qualification report demonstrating that the Critical to Quality Attributes are met by the operation.
- Record of bioburden reduction cycle for temperature and pressure.
- Calibration certification for instruments.
- Biological Indicators (if used) Certificate of Analysis.
- Biological Indicators (if used) negative laboratory results.
- Leak Test Results.
- Air removal test results (e.g., Bowie Dick indicator strips added to the load)

Certification for Bioburden reduced Material (if applicable)
A statement may be included on the PAM Certificate of Analysis concerning the treatment applied. A separate certificate is not usually issued.

Equipment Maintenance / Calibration
Leak tests should be performed at defined (regular)intervals to ensure vacuum capability.

Bioburden reduction cycles, for worst-case loads, should be periodically validated, and documented to confirm continued effectiveness.

Cleaning Instructions and Schedules
No specialised cleaning instructions are required.

Applicable Industry Regulations / Standards
Applicable Standards can be applied where appropriate, with the acknowledgement that specific industry and geographical requirements may also apply.

- **EN 285** Sterilisation. Steam sterilisers. Large sterilisers.
- **EN 13060** Small Steam Sterilisers.
- **EN ISO 17665-1** Sterilisation of health care products - Moist heat.

Storage for Bioburden reduced Material.
Any treated items, including those contained within autoclave bioburden reduction paper, should remain sealed during storage. An expiry date is usually be assigned for treated PAMs during which time they are expected to maintain reduced bioburden.

EXCiPACT asbl, Rue Marie de Bourgogne 52, 3rd Floor, B-1000 Brussels, Belgium
E: info@excipact.org **W**: www.excipact.org **T**: +32 2 213 74 49 VAT: BE0545 771 884 IBAN: BE50 3631 3158 8018
RPM Brussels Capital Region

Dry Heat Treatment

Bioburden reduction Type Summary

Principles of Operation - Description / Applications

Dry heat treatment uses HEPA filtered sterile air circulation within a chamber, at defined temperature for a defined period to reduce bioburden. The process maintains positive pressure to prevent entry of non-sterile air. Any air admitted should be passed through a HEPA filter. Where the process is also intended to remove pyrogens, endotoxin challenge tests should be used as part of the validation.

Main stages of bioburden reduction using dry heat treatment are:

- **Drying** - The chamber is heated up and air is vented.
- **Heating** - Vents are closed, air re-circulates inside the chamber and the temperature builds to the pre-set sterilising temperature.
- **Sterilising** - The temperature is held for a pre-set time.
- **Cooling** - The chamber returns to ambient temperature by circulation either of cooling water or air.

Critical Quality Attributes / Testing requirements - Acceptance Criteria

The required temperature and time for dry heat bioburden reduction is **250°C for 30 minutes** or **200 °C for 60 minutes**.

- During the Holding Time, the recorded temperature recorded for each load should not fluctuate by more than +/- 1°C and should not differ from other load items by 2°C.
- PAMs loading and orientation within the chamber should be defined based on studies showing the effectiveness of the treatment.

Note*: Bacillus atrophaeus* ATCC 9372 NCIMB 8058, with a D value of not less than 2.5 minutes is commonly used for routine monitoring.

The grade of HEPA filter used to admit air should be defined.

Risks to Effective Bioburden reduction (known threats to product assurance quality and purity)

The moisture content of loads should be defined before treatment since water will interfere with the process.

Expected Supporting Information / Evidence (specific to bioburden reduction type where possible)

Quality Documentation / Records for proof of bioburden reduction

- Operation Procedures.
- Operation and Maintenance Manuals.
- Minimum and maximum loads.
- Load configuration and load record.
- Bioburden reduction temperature cycle.
- Calibration certification for instruments.
- Biological Indicator (if used) Certificate of Analysis.
- Biological Indicators (if used) negative laboratory results.

Certification for Bioburden reduced Material (if applicable)

Dry heat sterilisers are used to process parts, medical devices, and materials. No Certification other than batch processing records are required when used for this purpose.

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E: info@excipact.org **W**: www.excipact.org **T**: +32 2 213 74 49 VAT: BE0545 771 884 IBAN: BE50 3631 3158 8018
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Equipment Maintenance / Calibration

Bioburden reduction cycles, for worst-case loads, should be periodically validated, and documented to confirm continued effectiveness.

Cleaning Instructions and Schedules

No specialised cleaning instructions are required.

Applicable Industry Regulations / Standards

- **ISO 11138-4** Sterilisation of health care products — Biological indicators — Part 4: Biological indicators for dry heat sterilisation processes).
- **ISO 20857** Bioburden reduction of health care products — Dry heat.

Storage for Bioburden reduced Material

Any bioburden reduced items, should remain sealed during storage. An expiry date is usually assigned during which time they are expected to retain reduced bioburden.

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E: info@excipact.org **W**: www.excipact.org **T**: +32 2 213 74 49 VAT: BE0545 771 884 IBAN: BE50 3631 3158 8018
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Filtration

Bioburden reduction Type Summary

Principles of Operation - Description / Applications
Sterile filtration uses very fine filters to remove microbial contaminants from products that cannot be treated in the final container. Solutions, liquids or gases may be filtered through a sterile filter with **nominal pore size of 0.22 micron (or less)**, or with at least equivalent microorganism retention properties, into a previously bioburden reduced container. Such filters remove most bacteria and moulds, but not all viruses or mycoplasmas. A final sterile filtration should be carried out as closely as possible to the filling point.

Critical Quality Attributes / Testing requirements - Acceptance Criteria
Successful pre and post filter integrity testing to demonstrate that the filter meets specification both prior to, and after use.

Risks to Effective Bioburden reduction (known threats to product assurance quality and purity)
Sterile filtration depends highly on filter integrity, and this should be verified before and after use by an appropriate method. Suitable methods for verification include a bubble point, diffusive flow or pressure hold testing.

Filters may be bioburden reduced in an autoclave prior to use.

The same filter should not be used for more than one product batch unless re-use has been validated.

Fibre-shedding characteristics of filters should be minimal.

The filter should not affect the product by removal of ingredients or release of substances. An extractables and leachables study and report should be available for each filter type.

Expected Supporting Information / Evidence (specific to bioburden reduction type where possible)

Quality Documentation / Records for proof of bioburden reduction
For Test Equipment

- Operation Procedures.
- Operation and Maintenance Manuals.
- Test Programme Parameters.
- Calibration certification for instruments.

For Filter

- Filter Integrity Test record pre and post filtration (part of batch record).
- Filter Certificate of Analysis.
- Extractables and leachables study report

For filtered material

- Bioburden test results, both pre and post filtration (as defined).

Certification for Bioburden reduced Material (if applicable)
Certificate of Analysis for final product.

Equipment Maintenance / Calibration
Filter Integrity Test equipment requires defined and periodic calibrations.

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E: info@excipact.org **W**: www.excipact.org **T**: +32 2 213 74 49 VAT: BE0545 771 884 IBAN: BE50 3631 3158 8018
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Cleaning Instructions and Schedules
Not applicable.

Applicable Industry Regulations / Standards

- WHO Annex 6 GMP for sterile pharmaceutical products.

Storage for Treated Material
Filtered into containers subject to an equivalent bioburden reduction treatment and then sealed.

EXCiPACT asbl, Rue Marie de Bourgogne 52, 3rd Floor, B-1000 Brussels, Belgium
E: info@excipact.org **W**: www.excipact.org **T**: +32 2 213 74 49 VAT: BE0545 771 884 IBAN: BE50 3631 3158 8018
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Gamma Irradiation

Bioburden reduction Type Summary

Principles of Operation - Description

Gamma radiation bioburden reduction is performed by exposing material to a radiation source, typically a Cobalt 60 isotope. It eliminates microorganisms by breaking the covalent bonds of bacterial DNA and inhibiting their division. Changes at the molecular level cause the death of microorganisms or render them incapable of reproduction. The process does not create residues or impart radioactivity in the processed items. The gamma radiation dose may be measured in each batch of material using detectors (dosimeters).

Applications

Gamma Irradiation is suitable for the treatment of a wide range of other materials including, for example, active pharmaceutical ingredients (API), excipients, healthcare products, medical devices, and components. The effective dose at which the material in its packaging is effectively treated must be established and validated in accordance with appropriate standards.

Critical Quality Attributes/ Testing requirements - Acceptance Criteria

- The applied radiation dose.
- Delivery and absorption of radiation dose by the material is determined by product density, packaging size, dose rate, and exposure time as well as facility design.
- A procedure should be in place describing process parameters, cycle specifications, loading configuration, tote/pallet pattern, and descriptions of dosimeter placement.

Risks to Effective Bioburden reduction (known threats to product assurance quality and purity)

- A material's tolerance to gamma radiation must be documented and its effects known, including the impact on the primary packaging.
- Damaged packaging should not be irradiated without customer consent.
- Changes made to the weight and volume of the material may affect the validated range.
- Dosimeters must be calibrated and traceable to national standards and should be purchased from an approved source with a unique reference number to ensure full traceability.
- Dosimeters should be read within a defined period of processing.

Expected Supporting Information / Evidence (specific to bioburden reduction type where possible)

Quality Documentation / Records for proof of bioburden reduction.

A quality agreement and /or contract should be in place defining roles and responsibilities between the contract provider and contract acceptor.

- The following should be agreed between all parties:
  - Pack format and content for items to be bioburden reduced.
  - Cycle parameters, including minimum dose required and maximum acceptable dose.
  - Load configuration and position, number, and type of dosimeters.
  - Product packaging and handling both pre and post bioburden reduction.
  - Validated loading maps should be in place.

Certification for Bioburden reduced Material

The certificate of irradiation should include as a minimum:

- The name and address of the customer.

EXCiPACT asbl, Rue Marie de Bourgogne 52, 3rd Floor, B-1000 Brussels, Belgium
E: info@excipact.org **W**: www.excipact.org **T**: +32 2 213 74 49 VAT: BE0545 771 884 IBAN: BE50 3631 3158 8018
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- Material description or code.
- Item and batch number.
- Date of material receipt.
- Date of irradiation.
- Certified dose.
- Irradiator location.

Equipment Maintenance / Calibration
Each batch of dosimeters must be calibrated, and a system should be in place to ensure that calibrated status is maintained.

Spectrophotometers and measuring gauges should be calibrated.

There should be an annual recalibration of the radiation source and, consecutively, a dose mapping exercise should be performed to confirm any impact to validation.

A review of Irradiation validation should be performed on a periodic basis to determine if requalification is needed.

A procedure should be in place to ensure that any deviations or out of tolerance/specification results which may have an impact on the customer's product are communicated to the customer.

Cleaning Instructions and Schedules.
Plant cleaning frequencies should be documented and include the material handling system (aluminium carriers/ pallets/totes) and the conveyor system that transports the materials into the irradiation chamber.

Applicable Industry Regulations / Standards

- International Atomic Energy Agency (IAEA) Specific Safety Guide – Radiation Safety of Gamma, Electron and X Ray Irradiation Facilities.
- ISO 11137 is the international standard governing bioburden reduction by irradiation.

  The standard is in 3 sections
- ISO 11137 Part 1 – Covers the requirements for development, validation and control of the gamma irradiation process using the most commonly used isotopes (Cobalt 60 and Caesium 137).
- ISO 11137 Part 2 – Provides information regarding methods manufacturers use to determine the minimum necessary dose to achieve sterility.
- ISO 11137 Part 3 – Offers guidance for manufacturers to meet the requirements of part 1.

Storage for Bioburden reduced Material
There should be segregation between non-irradiated and irradiated items.

EXCiPACT asbl, Rue Marie de Bourgogne 52, 3rd Floor, B-1000 Brussels, Belgium
E: info@excipact.org **W**: www.excipact.org **T**: +32 2 213 74 49 VAT: BE0545 771 884 IBAN: BE50 3631 3158 8018
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VHP Fumigation

Bioburden reduction Type Summary

Principles of Operation - Description / Applications

Vapourised Hydrogen Peroxide (VHP) exhibits properties that allow it to be used as a low-temperature antimicrobial sterilising agent. It is applied in enclosed areas where the vapour can contact all accessible surfaces making it suitable for isolators, cleanrooms, and workstations. If the vapour is evenly distributed it is effective against viruses, bacteria, yeasts, and bacterial spores. A Process Challenge Device (PCD) is usually treated alongside the load to demonstrate effectiveness.

Main stages of bioburden reduction are:

- **Dehumidification** - this might not be applicable for mobile units.
- **Conditioning** - injection or fumigation of the VHP.
- **Decontamination** - VHP concentration is maintained and circulated for a specific pre-determined period.
- **Aeration** - VHP is stopped and removed via vacuum to degrade to water and oxygen, providing a low risk of toxicity.

Critical Quality Attributes / Testing requirements - Acceptance Criteria

The bioburden reduction performance needs to be evaluated and documented. Effectiveness is dependent on:

- The quality characteristics of the VHP.
- The time of exposure.
- The concentration of VHP.
- Temperature and relative humidity in the enclosed space.
- Load patterns.

PCDs have a variety of types and sizes and can include a self-contained biological indicator (BI) test microorganism (*Geobacillus stearothermphilus* is usually used) to demonstrate effectiveness. The PCD type and its location within the enclosed space is designed to represent the worst-case scenario in order to demonstrate the efficacy of the bioburden reduction performance.

Risks to Effective Bioburden reduction (known threats to product assurance quality and purity)

- VHP does not reach all surfaces requiring bioburden reduction.
- Residual hydrogen peroxide in process materials such as tubing or other equipment that could impact the product.

Expected Supporting Information / Evidence (specific to bioburden reduction type where possible)

Quality Documentation / Records for proof of bioburden reduction

- Operation Procedures.
- Operation and Maintenance Manuals.
- Loading Pattern (if applicable).
- VHP Specification and Certification.
- Time, temperature, and humidity measurements for exposure.
- PCD specification.
- Biological Indicator Certificate of Analysis.
- Biological Indicators negative laboratory results.

Certification for Bioburden reduced Material (if applicable)

EXCiPACT asbl, Rue Marie de Bourgogne 52, 3rd Floor, B-1000 Brussels, Belgium
E: info@excipact.org **W**: www.excipact.org **T**: +32 2 213 74 49 VAT: BE0545 771 884 IBAN: BE50 3631 3158 8018
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The process is applied to equipment and enclosed spaces. Bioburden reduction exercises should have details of the proof of bioburden reduction as described above.

Equipment Maintenance / Calibration

Bioburden reduction units should be maintained by service contract with appropriate certification available.

Specialist VHP contractors should be certified.

Cleaning Instructions and Schedules

Areas prior to bioburden reduction should be clean and dry. VHP Bioburden reduction does not condensate or leave toxic residue on surfaces.

Applicable Industry Regulations / Standards

None

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5. APPENDIX II

Glossary of Terms

Bowie Dick

This is a test to evaluate the performance of pre-vacuum sterilizers by confirming adequate air removal from the sterilizer chamber both before and during operation. Air within a steam sterilizer is a non-condensable gas (NCG)which does not condense when touching the item to be treated, which is cold. The NCGs acts as insulator between the steam and the item and reduces the efficiency of the treatment.

Reference: ANSI/AAMI ST79 *Comprehensive Guide to steam sterilization and sterility assurance in health care facilities* potentially shielding bacteria and preventing proper sterilization.

Acknowledgement: Steris Healthcare.

D-Value

This a measure of the time taken at a given temperature to reduce the population of exposed microorganisms by 90% or achieve a 1-log reduction. A known concentration of the specified organisms is added to the equipment and after the period of the D-Value (e.g., 2.5 minutes) the remaining viable organisms are determined.

References: ISO 11138-4:2017, Ph Eur 5.1.2 Biological Indicators

EXCiPACT asbl, Rue Marie de Bourgogne 52, 3rd Floor, B-1000 Brussels, Belgium
E: info@excipact.org **W**: www.excipact.org **T**: +32 2 213 74 49 VAT: BE0545 771 884 IBAN: BE50 3631 3158 8018
RPM Brussels Capital Region

6. APPENDIX III

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Contributor	**Affiliation**
Sue Calhoon	Millipore Sigma, QA/QC, Cell culture
Roberto Mastrantonio	Eli Lilly
Ian McKeown	PQ Corp and PQG
Jim Harper	Merck, Scotland, Cell Culture media
Frederic Brehon,	Evonik
Ingrid Snella	AJA
Bev Stout	GSK, excipients, IPEC Europe
Alyssa Colon	Thermofisher
Bree Wang	Merck China, IPEC China
Rosa Ria Riyadi	ex BASF USA
Hank Karayan	SGS
Sophie Moreau	SGS
Michael Snella	AJA
David Klug	Sanofi, EXCiPACT
Herbert Nagorski	DQS
Angelica Rambaldi	Cargill
Sarah Jennings	Thermo Fisher
Hank Narayan	SGS
Francois Jodogne	SGS
Becca Hawthorne	Biogen raw materials
Aasif Hanfi	Sanofi, North America quality,
Sylvie Fokin	Dupont Ion Exchange Business,
Yuan Yaozou	China, Jiangzu packing and excipient association, GMP inspector

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EXCiPACT asbl, Rue Marie de Bourgogne 52, 3rd Floor, B-1000 Brussels, Belgium
E: info@excipact.org **W**: www.excipact.org **T**: +32 2 213 74 49 VAT: BE0545 771 884 IBAN: BE50 3631 3158 8018
RPM Brussels Capital Region