# APIC GUIDE FOR AUDITING REGISTERED STARTING MATERIAL MANUFACTURERS

**Version February, 2018**

## 1. PREAMBLE

This original version of this guidance document has been compiled by a subdivision of the APIC 3rd Party Audit Task Force on behalf of the Active Pharmaceutical Ingredient Committee (APIC) of CEFIC.

The Task Force members are:
Tom Buggy, DSM, Netherland
Danny De Scheemaecker, Janssen Pharmaceutica Division of J&J, Belgium
Anthony Storey, Pfizer, U.K.
Gemma Feenstra-Bielders, Abbvie, Netherland
Dieter Vanderlinden, S.A. Ajinomoto Omnichem N.V.
Francois Vandeweyer, Janssen Pharmaceutica Division of J&J, Belgium
Alejandro Sureda Salvado, Farmhispania group
Mohan Ganapathy, Merck, United States of America

With support and review from:
Betsy Fritschel, J&J, US and member of ICH Q7 EWG and IWG

Luisa Paulo, Hovione FarmaCiencia SA, Portugal
Rainer Fendt, BASF, Germany
Pieter van der Hoeven, APIC, Belgium
Annick Bonneure, APIC, Belgium
The APIC Quality Working Group during the Tallinn APIC general assembly meeting in September 2016. Following companies were represented:
*AbbVie, Teva, CU Chemie, BASF SE, AFAQUIM, Novacyl, DSM Sinochem, DSM Nutritional Products, Infagroup, Hovione, Merck KGaA, BASF Pronova, EGIS Pharmaceuticals, Janssen Pharmaceutica, S.A. Ajinomoto Omnichem N.V.*

The reason for the development of this guidance is related to following:
- The potential disagreements between applicants and quality assessors on the suitability of proposed Registered Starting Materials (RSM).
- Another trend is more and more often the registered starting material manufacture is outsourced to third parties. There is concern that the use of external sources may lead to a higher degree of risk to quality of the final active substance than would be expected when the RSM process is carried out by the applicant.
- The filing description of the manufacturing process of the RSM should be sufficiently detailed to demonstrate that the process and its associated control strategy will consistently provide active substance of satisfactory quality.
- The manufacture of the registered starting material is not in the scope of ICH Q7 guideline on Good Manufacturing Practices for API, but some of the principles of control can be applied to RSM

- The expectation from Health Authorities is that the applicant has adequate control on the "good manufacturing process principles" implemented at the RSM manufacturer to control the final API quality. This guide will help industry in performing audits at RSM manufacturers to assure expectations of the health authorities.
- Quality Risk Management Processes as described in the ICH Q9 Guideline on Quality Risk Management should be applied as appropriate.

  This document is based on the applicable chapters of ICH Q7 and is intended to give guidance on appropriate quality system controls. Manufacturers of RSM are expected to have a quality system in place to control their manufacturing processes. It is also recommended to have a Quality Agreement between the API manufacturer and the RSM manufacturer detailing requirements related to process, changes to process, materials, test methods, deviations (non-conformances), how rejects are handled, reprocessing, rework, blending activities, recovery of solvents, etc.

## 2. INTRODUCTION

### 2.1 Objective

Auditing of registered starting material (RSM) suppliers is a primary activity used by the API Industry in its evaluation of suppliers/materials and as part of the ongoing quality oversight of such suppliers/materials. A written Quality Agreement between the API manufacturer and the RSM manufacturer also helps to clarify expectations, roles and responsibilities. Such a Quality Agreement can help assure the consistent quality of the RSM and the eventual API resulting from the RSM.

The API industry and health authorities understand the importance of having an appropriate robust quality management system in place at such suppliers to ensure the quality of the RSM to support its use throughout the lifecycle of API(s).

The quality of the RSM is intrinsically linked to the quality of the final API, hence, some key aspects of the RSM quality management system such as change control and production controls are key parameters to be evaluated in such audits. This guideline has been prepared to aid the industry (RSM manufacturer and customer) to:

- Consider key areas of focus for such audits
- Consider the application of risk management principles in their audit process
- Consider key parameters of a quality management system needed for the manufacture of such materials

A key dilemma/ concern of the industry (both RSM manufacturer and RSM customer) is what should be evaluated in an audit of RSM facilities.

As a result, APIC has generated this guide to cover topics that are important to ensure the quality of RSM. This document can be used by both the API industry and RSM

manufacturers as an aide in audits of the quality management systems implemented at the RSM manufacturers.

Some key points that were considered on the generation of this document are as follows:

There is currently no written requirement or good manufacturing practice (GMP) standard that is specific to the manufacture and control of RSMs. The concepts in ICH Q7 were used as a starting point to develop this guideline taking into consideration the following:

ICH Q7 does not apply to steps prior to the introduction of the defined RSM. Table 1 in ICH Q7 shows the increase in GMP from the introduction of the API Starting Material to the final API. This same principle can be applied in the case of RSM allowing industry to use an incremental approach for the implementation of quality systems based on quality risk management principles in ICH Q9 to define the key elements of a quality system that are appropriate for RSMs.

It should be stated that RSMs are manufactured by many different techniques and can be complex or simple materials. The type of process needs to be considered in the auditing/evaluation of such materials.

This guideline allows the industry to determine which controls are appropriate and critical to the specific RSM in order to ensure quality of the final API and to support the uninterrupted supply of the RSM, hence reducing the possibility of drug shortages.

### 2.2 Regulatory Applicability

As previously indicated there is no written regulatory requirement describing controls for the manufacturer of RSMs. However, as indicated in the preamble there are expectations from health authorities that in order to control the final API quality the applicant has adequate control over the good manufacturing process principles implemented at the RSM manufacturer.

This guide supports the API Industry to control the use of RSMs in their API processes and hence supporting applicant's submissions of RSMs.

### 2.3 Scope

This Guide applies to the manufacture of RSMs for APIs for use in human drug (medicinal) products. The principles outlined in this document can apply equally for RSMs for API's in veterinary drug (Animals).

This Guide covers RSMs used for APIs that are manufactured by chemical synthesis, extraction, fermentation, by recovery from natural sources, or by any combination of these processes. Specific guidance for starting materials for APIs manufactured by fermentation is described in Section 18.

The Guide does not apply to the manufacturing of raw materials (chemicals) but could be applied for chemicals identified as critical – in the process related criticality

assessment - for the API manufacturing process used in process steps after introduction of the RSM in the process.

An “API Starting Material” is a raw material that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. More guidance on identifying and selecting an API starting material is given in the EU document EMA/CHMP/CVMP/QWP/826771/2016 Corr.1 of July 3rd, 2017, (Reflection paper on the requirements for selection and justification of starting materials for the manufacture of chemical active substances).
An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API Starting Materials normally have defined chemical properties and structure. Additional clarification and guidance regarding the selection of API Starting Material is provided in ICH Q11 and the ICH Q11 Q&A document.

This document is designed as a guide and does not imply that all topics shown should be in place. The topics and stringency of adherence to these topics should be based on a risk assessment and process knowledge of the potential impact to the RSM and the eventual impact to the quality of the final API.

**Table of Contents**

## 3. QUALITY MANAGEMENT

### 3.1 Principles

3.10 Quality should be the responsibility of all persons involved in manufacturing.

3.11 Each manufacturer should establish, document, and implement an effective system for managing quality.

3.12 There should be a quality unit(s) that can act independently in releasing or rejecting RSM outside the control of the manufacturing company.

3.13 All quality related activities and responsibilities should be defined and documented.

3.14 All quality related activities should be recorded at the time they are performed.

3.15 Quality critical deviations from established procedures should be documented and evaluated prior to release. Where appropriate, the deviations should be investigated and the conclusions documented.

### 3.2 Internal Audits (Self Inspection)

3.20 The organization shall conduct internal quality related audits of the relevant departments and systems at planned intervals. These audits should be documented.

3.21 The audit should be performed by person(s) independent from the area audited.

## 4. PERSONNEL

### 4.1 Personnel Qualification

4.10 There should be an adequate number of personnel including temporary personnel and contractors qualified by appropriate education, training and/or experience to perform the manufacture of RSM.

4.11 Training should be documented.

### 4.2 Personnel Hygiene

4.20 Personnel should practice good sanitation and health habits.

4.21 Smoking, eating, drinking, chewing and the storage of food should be restricted to certain designated areas separate from the manufacturing areas.

## 5. BUILDINGS AND FACILITIES

### 5.1 Design and Construction

5.10 Buildings and facilities used in the manufacture of RSM should be designed and constructed to facilitate cleaning, maintenance, and operations as appropriate to the type and stage of manufacture.

5.11 There should be defined areas/systems for the following activities including but not limited to:

- Receipt, identification, quarantine and release of incoming materials;
- Rejected materials;
- Sampling of RSM;
- Production Operations;
- Laboratory Operations;
- Storage of final RSM.

**5.2 Water**

5.20 Water used in the manufacture of RSM should be demonstrated to be suitable for its intended use.

**5.3 Containment**

5.30 Appropriate measures should be established and implemented to prevent contamination or cross-contamination.

5.31 As a general principle production activities of highly toxic materials, herbicides and pesticides should not be conducted in the same equipment and area as used for the production of RSM unless there are circumstances where the RSM manufacturer has appropriate controls in place and the customer agrees.

**5.4 Lighting**

5.40 Adequate lighting should be provided in all areas to facilitate cleaning, maintenance, and proper operations.

**5.5 Sanitation and Maintenance**

5.50 Buildings should be properly maintained and repaired and kept in a clean condition.

5.51 Sewage, refuse, and other waste (e.g., solids, liquids, or gaseous by-products from manufacturing) in and from buildings and the immediate surrounding area should be disposed of in a safe, timely, and sanitary manner. Containers and/or pipes used for waste material should be managed in order to avoid contamination of the RSM.

5.52 As a minimum all production areas as from the RSM final isolation should be subject to pest control. A suitable pest control system should be implemented for RSM, product contact materials and packaging materials storage areas.

## 6. PROCESS EQUIPMENT

### 6.1 Design and Construction

6.10 Equipment used in the manufacture of RSM should be of appropriate design, material construction and size adequate for its intended use, cleaning and maintenance.

6.11 Major equipment (e.g. reactors, storage containers) used during the production of a RSM should be appropriately identified.

6.12 Where open equipment is used, or equipment is opened, appropriate precautions should be taken to minimize the risk of contamination.

### 6.2 Equipment Maintenance and Cleaning

6.20 Schedules should be established for the preventative maintenance of major equipment.

6.21 Written procedures should be established for cleaning of equipment. Cleaning procedures should contain sufficient details to enable operators to clean each type of equipment in an effective manner. These procedures should include:

- Cleaning agents and minimum volume;
- Acceptance criteria
- When appropriate, instructions for disassembling and reassembling each article of equipment to ensure proper cleaning;
- Instructions for the protection of clean equipment from contamination prior to use;
- Inspection of equipment for cleanliness immediately before use.

6.22 Where equipment is assigned to continuous production or campaign production of successive batches of the same RSM, equipment and utensils should be cleaned at appropriate intervals to prevent build-up and carry-over of contaminants (e.g. degradants).

6.23 Non-dedicated equipment and utensils should be cleaned between production of different materials to prevent cross-contamination.

6.24 Acceptance criteria for residues should be defined based on the risk of carryover into the next product and as a minimum include a visual inspection for cleanliness. If only visual inspection is applied as routine verification, sufficient analytical data should be generated to support the routine visual inspection (e.g. TOC, UV, TLC)

### 6.3 Calibration

6.30 Process and measuring equipment that is critical for assuring the quality of RSM should be calibrated covering the operating range according to written procedures and an established schedule. Calibration data should be documented.

6.31 Calibrations should be performed using standards traceable to certified standards, if existing.

6.32 The current calibration status of critical equipment should be known and verifiable.

6.33 Deviations from approved standards of calibration on critical equipment should be evaluated for potential impact on the quality of the RSM manufactured using this equipment since the last successful calibration.

### 6.4 Computerized Systems

6.40 Appropriate verification should be documented to demonstrate the suitability of computer hardware and software related to critical activities.

6.41 Computerized systems should have sufficient controls and/or procedures to prevent unauthorized access and/or actions (such as making changes, deletion of data etc.).

6.41 When electronic records are part of batch documentation they should be handled as described below in Section 7

## 7. DOCUMENTATION AND RECORDS

### 7.1 Documentation System and Specifications

7.10 All documents related to the manufacture of RSM should be prepared, reviewed, approved and distributed according to written procedures. Systems should be in place to ensure that only the latest version of the documents in paper or electronic form are in use.

7.11 The retention period of the manufacturing and quality records should be defined in writing.

7.12 Good documentation practices should be established and followed.

7.13 Specifications should be established for raw materials and RSM's.

### 7.2 Master Production Instructions (Master Production and Control Records)

7.20 To ensure uniformity from batch to batch, master production instructions for the production of RSM should be present. The master production instruction should be reviewed and approved by relevant personnel.

7.21 Master production instructions for the RSM should include but not be limited to:

- The name of the RSM being manufactured
- A complete list of raw materials and intermediates of the RSM;
- The quantity or ratio of each raw material or intermediate to be used, including the unit of measure;
- The production location and major production equipment to be used;
- Detailed production instructions, including the:
    - sequences to be followed,
    - ranges of process parameters to be used,
    - in-process controls with their acceptance criteria, where appropriate,

- sampling.
- The instructions for storage of the RSM to assure its suitability for use.

### 7.3 Batch Production Records (Batch Production and Control Records)

7.30 Batch Production Records should be prepared and completed for each batch of RSM and should include complete information relating to the production and control of each batch. The Batch Production Record may be electronic or paper and should include at least but not be limited to:

- Dates and when appropriate times,
- Equipment used,
- Record of equipment cleanliness,
- batch numbers and quantity of the raw materials,
- actual values of the process parameters,
- description of packaging

In case of continuous production, records should be available on the control of the process.

7.31 For batch production processes these records should be identified with a unique batch number. For continuous production, an identification system should be in place.

7.32 Dates and time of completion of each critical step in the batch production records and the employees involved should be recorded on paper or retained electronically.

7.33 Deviations should be documented in the batch production record and evaluated for impact.

### 7.4 Laboratory Control Records

7.40 Laboratory control records should include all tests conducted to ensure compliance with established specifications; the documentation should include but is not limited to:

- A record of samples received for testing;
- A statement of or reference to each test method used;
- A record of the actual weight or measure of sample and reference standards, if applicable, used for each test;
- Raw data generated during each test;
- A record of all calculations performed in connection with the test;
- The signature of the person who performed each test and the date(s) the tests were performed; and
- The date and signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established specifications before release.

7.41 Complete records should also be maintained for:

- Any modifications to an established analytical method;
- Periodic calibration of laboratory instruments; and
- Out-of-specification (OOS) evaluations.

### 7.5 RSM Batch Documentation Review and Batch Release

7.50 Written procedures should be established and followed for the release of a batch. This includes the review and approval of the production and laboratory control records, including outsourced test results to determine compliance of the RSM with established specifications.

7.51 All critical deviations and OOS records should be reviewed before the batch is released.

## 8. MATERIALS MANAGEMENT

### 8.1 General Controls

8.10 There should be written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing, and approval or rejection of materials.

8.11 Materials should be purchased against a specification.

8.12 Changing the source of supply of critical raw materials should be assessed and documented.

### 8.2 Receipt and Quarantine

8.20 Upon receipt and before acceptance, each pack or grouping of packs should be examined visually for correct labelling and packaging damage.

8.21 Incoming materials should be assessed for compliance with the specifications, tested if appropriate, and released prior to use.

8.22 Before incoming materials are mixed with existing bulk stocks (e.g., solvents or stocks in silos), they should be identified as correct, tested if appropriate, and released. A process should be in place to prevent mix-ups during discharging and to identify the status of each batch.

8.23 If sampling is required, sampling procedures should be in place to guarantee a representative sample.

### 8.3 Storage

8.30 Materials should be handled and stored in a manner to prevent degradation, contamination, and cross-contamination.

8.31 Materials stored in fiber drums, bags, or boxes should be stored off the floor.

8.32 Certain materials in suitable containers can be stored outdoors, provided identifying labels remain legible and containers are appropriately cleaned before opening and use.

8.33 Rejected materials should be identified and controls should be in place to prevent the use of rejected materials.

## 9. PRODUCTION AND IN-PROCESS CONTROLS

### 9.1 Production Operations

9.10 Raw materials for RSM manufacturing should be handled under appropriate conditions to prevent contamination and cross-contamination.

9.11 Prior to use, production personnel should verify that the materials are those specified in the batch record for the RSM.

9.12 Written procedures should be established for documenting and evaluating critical deviations. The evaluation should be extended to other batches that may have been associated with the specific deviation.

9.13 Materials to be reprocessed or reworked should be appropriately controlled to prevent unauthorized use.

9.14 In case blending is performed the homogeneity of the batch should be assured and full traceability to the individual batches should be documented. As a general principle, there should be no blending of Out of Specification material unless the customer agrees.

### 9.2 In-process Sampling and Controls

9.20 If in-process controls are performed written procedures should be followed and the outcome should be documented.

9.21 The monitoring tests and measuring devices should be appropriate for their intended use.

### 9.3 Contamination Control

9.30 All production stages should be conducted in a manner that will prevent contamination of RSM.

9.31 Higher precautions to avoid contamination should be considered at the final stages of the manufacture of RSMs (isolation, physical processing, filling/packaging).

## 10. PACKAGING AND IDENTIFICATION LABELLING OF RSM

### 10.1 Packaging Materials

10.10 Primary packaging materials and functional secondary packaging (example an Aluminum bag to protect hygroscopic product) for RSM should conform to a specification.

10.11 Verification of each order of primary packaging materials should be performed and documented.

### 10.2 Packaging and Labelling Operations

10.20 Labelling operations should be designed to prevent mix- ups.

10.21 There should be documented procedures to ensure that correct packaging materials and labels are used.

10.22 Labels used on containers should indicate the name or identifying code of the RSM, the name and address of the manufacturer, the batch number of the product, and the storage conditions, when such information is critical to assure the quality of RSM.

10.23 Packaging should assure the integrity of the RSM.

## 11. STORAGE AND DISTRIBUTION

### 11.1 Warehousing Procedures

11.10 Facilities should be available for the storage of all materials under appropriate conditions. Records should be maintained of these conditions if they are critical for the quality of the RSM.

### 11.2 Distribution Procedures

11.20 RSM should only be distributed to third parties after they have been released.

11.21 RSM should be transported in a manner that does not adversely affect the quality and integrity.

## 12. LABORATORY CONTROLS

### 12.1 General Controls

12.10 The RSM manufacturer should have at its disposal adequate laboratory facilities.

12.11 There should be documented procedures describing sampling, testing, approval or rejection of the raw materials and RSM, and recording and storage of laboratory data. Laboratory records should be maintained in accordance with Section 7.4.

12.12 Appropriate specifications including acceptance criteria for impurities (e.g. residual solvents, elemental impurities, related substances) should be established for RSM consistent with the Starting Material manufacturing process.

12.13 All testing methods should be suitable for their intended use and verified under actual conditions of use.

12.14 Laboratory controls should be followed and documented at the time of performance.

12.15 Any deviations from the above described procedures should be documented.

12.16 Any out-of-specification result of the RSM obtained should be evaluated and documented according to a procedure. If an OOS result is to be invalidated by a new result, this should be supported by a scientific justification.

12.17 If reference standards are used for testing of RSMs, they should be stored under the defined conditions if required. The identity and the purity of the reference standard should be established and documented.

### 12.2 Testing of RSM

12.20 For each batch of RSM, appropriate laboratory tests on a representative sample should be conducted to determine conformance to specifications.

### 12.3 Certificates of Analysis

12.30 Certificates of Analysis should be issued for each batch of RSM.

12.31 Information on the name of the RSM, the batch number, and the date of manufacturing should be provided on the Certificate of Analysis. For RSM with a retest/expiry date that date should be provided on Certificate of Analysis.

12.32 The Certificate should list each test performed in accordance with the specifications, including the acceptance limits, and the numerical results obtained (if test results are numerical).

12.33 Certificates should be dated and signed by authorized personnel and should show the name and address of the original manufacturer.

12.34 If new Certificates are issued by or on behalf of repackers/reprocessors, agents or brokers, these Certificates should show the name and address of the laboratory that performed the analysis. They should also contain a reference to the name and address of the original manufacturer and to the original batch Certificate, a copy of which should be attached.

### 12.4 Expiry and Retest Dating

12.40 The expiry or retest date should be supported by documented data.

### 12.5 Reserve/Retention Samples

12.50 Reserve samples of each RSM batch should be retained for a predefined period.

12.51 The reserve samples should be stored in a packaging that is equivalent to or more protective than the commercial packaging system.

## 13. VALIDATION

13.10 The full validation program that is typically performed in the API manufacturing industry may not always be carried out by the RSM manufacturer. However the RSM manufacturer should demonstrate the consistent and robust operations of the processes (e.g. production process, analytical method, equipment, cleaning). Documented evidence should be generated to support the consistency, robustness and reproducibility of the current processes

## 14. CHANGE CONTROL

14.10 A formal change control system should be established to evaluate all changes that may affect the production and control of the RSM.

14.11 Significant changes that potentially impact the quality of the RSM and/or the provided process description should be managed by the formal change control procedure and communicated to the customers.

## 15. REPROCESSING OR REWORK OF MATERIALS

### 15.1 General

15.10 RSM failing to meet established specifications should be identified as such and quarantined. These RSM can be reprocessed or reworked.

15.11 Rework must be performed under change control as it differs from the established process description and should be approved by the customer

### 15.2 Recovery of Materials and Solvents

15.20 Recovery (e.g. from mother liquor or filtrates) of reactants, solvents and RSMs is considered acceptable, provided that approved procedures exist for the recovery and the recovered materials meet specifications suitable for their intended use.

15.21 Fresh and recovered solvents and reagents can be combined if adequate testing has shown their suitability for all manufacturing processes in which they may be used.

15.22 The use of recovered solvents, mother liquors, and other recovered materials should be adequately documented.

### 15.3 Returns

15.30 Returned RSM should be identified as such and quarantined.

15.31 Records of returned RSM should be maintained.

15.32 Records of the disposition of returned RSMs should be maintained.

15.33 If there is doubt on the quality of the returned goods, appropriate actions should be taken. (reprocess-rework-destruction)

## 16. COMPLAINTS

16.10 All quality related complaints should be recorded and investigated according to a written procedure.

16.11 Records of complaints should be retained.

## 17. CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

17.10 Contract manufacturers (including laboratories) should be evaluated by the contract giver (RSM manufacturer) to ensure compliance of the specific operations occurring at the contract sites.

17.11 The roles and responsibilities of each party should be defined in a written and approved contract between the contract giver and the contract acceptor.

17.12 Where subcontracting is allowed, the contract acceptor should not pass to a third party any of the work entrusted to him under the contract without the contract giver's prior evaluation and approval of the arrangements.

17.13 Significant changes in the process, equipment, test methods, specifications, or other contractual requirements should not be made unless the contract giver is informed and approves the changes.

## 18. SPECIFIC GUIDANCE FOR RSM MANUFACTURED BY FERMENTATION

### 18.1 General

18.10 Section 18 is intended to address specific controls for RSMs manufactured by fermentation that may not have been covered adequately in the previous sections. It is not intended to be a stand-alone Section. In general, the quality principles in the other sections of this document apply.

18.11 While Q7 addresses GMP for both biotechnological processes and fermentation processes, this APIC guide only addresses RSM for fermentation. Controls for cell banks used in biotechnological processes are described in the ICH Q5 series and details regarding establishment of the master cell bank and working cell banks are required in the dossier. So APIC has chosen to only address RSM for fermentation in this section.

18.12 The term “classical fermentation” refers to processes that use microorganisms existing in nature and/or modified by conventional methods (e.g. irradiation or chemical mutagenesis) to produce RSMs.

18.13 Depending on the source, method of preparation, and the intended use of the RSM control of bioburden, and/or endotoxins during manufacturing and monitoring of the process at appropriate stages may be necessary.

18.14 Appropriate controls should be established at all stages of manufacturing to assure RSM quality.

18.15 Appropriate equipment and environmental controls should be used to minimize the risk of contamination. The acceptance criteria for quality of the environment and the frequency of monitoring should depend on the step in production and the production conditions (open, closed, or contained systems).

18.16 In general, process controls should take into account:

- Control of the critical operating parameters during fermentation;
- Monitoring of the process ;
- Harvest and purification procedures protect the RSM from contamination (particularly of a microbiological nature) and from loss of quality;

- Monitoring of bioburden and, where needed, endotoxin levels at appropriate stages of production.

18.17 Where appropriate, the removal of process-related impurities, product-related impurities and contaminants should be demonstrated.

### 18.2 Fermentation

18.20 Where aseptic addition of materials, media, buffers, and gases is needed, closed or contained systems should be used where possible. If the inoculation of the initial vessel or subsequent transfers or additions (media, buffers) is performed in open vessels, there should be controls and procedures in place to minimize the risk of contamination.

18.21 Where the quality of the RSM can be affected by microbial contamination, manipulations using open vessels should be performed in a biosafety cabinet or similarly controlled environment.

18.22 Personnel should be appropriately gowned and take special precautions handling the cultures.

18.23 Critical operating parameters (for example temperature, pH, agitation rates, addition of gases, pressure) should be monitored to ensure consistency with the established process.

18.24 Fermentation equipment should be cleaned, and sanitized or sterilized.

18.25 Culture media should be sterilized before use when appropriate.

18.26 There should be appropriate procedures in place to detect contamination and determine the course of action to be taken. This should include procedures to determine the impact of the contamination on the product and those to decontaminate the equipment and return it to a condition to be used in subsequent batches. Foreign organisms observed during fermentation processes should be identified as appropriate and the effect of their presence on product quality should be assessed, if necessary. The results of such assessments should be taken into consideration in the disposition of the material produced.

18.27 Records of contamination events should be maintained.

18.28 Shared (multi-product) equipment may warrant additional testing after cleaning between product campaigns, as appropriate, to minimize the risk of cross-contamination.

### 18.3 Harvesting, Isolation and Purification

18.30 Harvesting steps should be performed in equipment and areas designed to minimize the risk of contamination.

18.31 Harvest and purification procedures should be adequate to ensure that the RSM is recovered with consistent quality.

18.32 All equipment should be properly cleaned and, as appropriate, sanitized after use. Multiple successive batching without cleaning can be used if the RSM quality is not compromised.

18.33 If open systems are used, purification should be performed under environmental conditions appropriate for the preservation of product quality.

## 19. GLOSSARY

**Acceptance Criteria**
Numerical limits, ranges, or other suitable measures for acceptance of test results.

**Batch (or Lot)**
A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval.

**Batch Number (or Lot Number)**
A unique combination of numbers, letters, and/or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined.

**Bioburden**
The level and type (e.g. objectionable or not) of micro-organisms that can be present in raw materials, API starting materials, intermediates or APIs. Bioburden should not be considered contamination unless the levels have been exceeded or defined objectionable organisms have been detected.

**Calibration**
The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements.

**Computer System**
A group of hardware components and associated software, designed and assembled to perform a specific function or group of functions.

**Computerized System**
A process or operation integrated with a computer system.

**Contamination**
The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material or RSM during production, sampling, packaging or repackaging, storage or transport.

**Contract Manufacturer**
A manufacturer performing some aspect of manufacturing on behalf of the original manufacturer.

**Critical**
Describes a process step, process condition, test requirement, or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the RSM meets its specification.

**Cross-Contamination**
Contamination of a material or product with another material or product.

**Deviation**
Departure from an approved instruction or established standard.

**Expiry Date (or Expiration Date)**
The date placed on the container/labels of a RSM designating the time during which the RSM is expected to remain within established specifications if stored under defined conditions.

**Impurity**
Any component present in the RSM that is not the desired entity.

**In-Process Control**
Checks performed during production in order to monitor and, if appropriate, to adjust the process and/or to ensure that the RSM conforms to its specifications.

**Lot**
See Batch

**Lot Number**
See Batch Number

**Manufacture**
All operations of receipt of materials, production, in-process monitoring, packaging, repackaging, labelling, relabeling, quality control, release, storage, and distribution of RSMs and related controls.

**Material**
A general term used to denote materials, reagents, catalysts, solvents, RSM and packaging and labelling materials.

**Mother Liquor**
The residual liquid which remains after the crystallization or isolation processes. A mother liquor may contain unreacted materials, levels of the RSM and/or impurities. It may be used for further processing.

**Packaging Material**
Any material intended to protect a RSM during storage and transport.

**Procedure**
A documented description of the operations to be performed, the precautions to be taken and measures to be applied directly or indirectly related to the manufacture of RSM.

**Process Aids**
Materials, excluding solvents, used as an aid in the manufacture of an intermediate or API that do not themselves participate in a chemical or biological reaction (e.g. filter aid, activated carbon, etc.).

**Production**
All operations involved in the preparation of a RSM from receipt of materials through processing and packaging of the RSM.

**Registered Starting Material (RSM)**
A material that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. See for more information ICH Q11 and ICH Q11 Q&A.

**Quality Control (QC)**
Checking or testing that specifications are met.

**Quarantine**
The status of materials isolated physically or by other effective means pending a decision on their subsequent approval or rejection.

**Raw Material**
A general term used to denote reagents, catalysts and solvents intended for use in the production of RSM.

**Reference Standard**
A substance of established quality and purity, used as a reference standard for routine laboratory analysis.

**Reprocessing**
Introducing a RSM including one that does not conform to standards or specifications, back into the process and repeating a crystallization step or other appropriate chemical or physical manipulation steps that are part of the established manufacturing process.

**Retest Date**
The date when a material should be retested to ensure that it is still suitable for use.

**Reworking**
Subjecting a RSM that does not conform to standards or specifications to one or more processing steps that are different from the established manufacturing process to obtain acceptable quality RSM (e.g., recrystallizing with a different solvent).

**Specification**
A list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the test described. It establishes the set of criteria to which a material should conform to be considered acceptable for its intended use. “Conformance to specification” means that the material, when tested according to the listed analytical procedures, will meet the listed acceptance criteria.