Good Manufacturing Practices in Active Pharmaceutical Ingredients Development

November 1999

APIC Active Pharmaceutical Ingredients Committee

Table of contents

1 Contents……. 2

2 Acknowledgements……... 2

3 Introduction…….. 3

4 Glossary……. 3

5 Scope…….. 6

6 Legal requirements…….. 6

7 GMP in API Development…….. 6

8 Matrix…… 12

9 Benefits……. 14

10 Literature/References…….. 14

2. Acknowledgements

We thank the "GMP in R&D Working Group" members of the APIC (CEFIC), for their work and effort, as well as for their kindly co-operation, warm friendship and fruitful comments:

- Mercè Bessa (URQUIMA)
- Lothar Hartmann (HOFFMANN-LA ROCHE)
- David Haywood (Astra-Zeneca)
- John van Meurs (DIOSYNTH)
- Paul Michielsens (SOLVAY Pharmaceuticals)
- Han Op't Land (SOLVAY Pharmaceuticals)
- Hanif Patel (GLAXO-WELLCOME)
- Jordi Ruiz (BIOIBERICA)
- Pierre Sarlet (OMNICHEM)
- Giancarlo Scuderi (BRACCO)
- Jacques Vermeulen (UCB-Pharma)
- Allert Wiersema (DSM Anti-Infectives)

We would also express our gratitude to N.C.Franklin (Interactive Consulting), R.Kirrstetter (HMRAG) and J.E.Mänsson (NORDIC SYNTHESIS), for their comments on 3rd draft and valuable suggestions.

3. Introduction

Principles basic to the formulation of this guideline are:

- Development should ensure that all products meet the requirements for quality and purity which they purport or are represented to possess and that the safety of any subject in clinical trials will be guaranteed.
- During Development all information directly leading to statements on quality of critical intermediates and APIs must be retrievable and/or reconstructable.
- The system for managing quality should encompass the organisational structure, procedures, processes and resources, as well as activities necessary to ensure confidence that the API will meet its intended specifications for quality and purity. All quality related activities should be defined and documented.

Any GMP decision during Development must be based on the principles above.

During the development of an API the required level of GMP control increases.

Using these guidelines, the appropriate standard may be implemented according to the intended use of the API. Firms should apply proper judgement, to discern which aspects need to be addressed during different development stages (non-clinical, clinical, scale-up from laboratory to pilot plant to manufacturing site).

Suppliers of APIs and/or critical intermediates to pharmaceutical firms should be notified on the intended use of the materials, in order to apply appropriate GMPs.

The matrix (section 8) should be used in conjunction with text in section 7, as is only intended as an initial guide.

4. Glossary and abbreviations

Terms are according to ICH Q7A draft 6 whenever possible, but adapted to Development if required. If not included below, the definition of the cited document would apply.

4.1. Terms

4.1.1. Active Pharmaceutical Ingredient: Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that when used in the production of a drug becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to effect the structure and function of the body.

4.1.2. Approval: Formal acceptance by QU.

4.1.3. 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.

4.1.4. Cleaning Procedure*:* Procedure that, when applied, result in the effective cleaning of plant or equipment, so it meets predetermined criteria.

4.1.5. Critical*:* A material, process step or process condition, test requirement or any other relevant variable is considered to be critical when non-compliance with predetermined criteria directly influences the quality attributes of the API in a detrimental manner.

4.1.6. Deviation*:* Any non-adherence to a written protocol, procedure, instruction or specification.

4.1.7. Equipment qualification: Action of proving that any equipment is properly installed, works correctly, and actually leads to the expected results

4.1.8. In-process *Control*: Checks performed during production in order to monitor and if necessary to adjust the process and/or to ensure that the intermediate or API conforms to its specification.

4.1.9. Intermediate: A material produced during steps of the processing of an API which must undergo further molecular change or purification before it becomes an API.

4.1.10. Justification: Explanation of the basis for a proposed change with potential impact on product quality, including the technical evaluation of its effect.

4.1.11. Non-clinical studies*:* All animal and *in-vitro* studies in which an API is examined to obtain data on its properties and on safety, intended for submission to appropriate regulatory authorities.

4.1.12. Out of specifications (OOS): Analytical result not meeting predetermined specifications.

4.1.13. Phase I Clinical Trials*:* Short-term studies usually performed with normal healthy volunteers to generate pharmacokinetic and pharmacologic information about a new substance/application/dosage form.

4.1.14. Phase II Clinical Trials*:* Controlled studies with patients to determine initial efficacy and dose of the new substance/application/dosage form.

4.1.15. Phase III Clinical Trials*:* Controlled trials with patients to gather additional information on the safety and efficacy of the new substance/application/ dosage form.

4.1.16. Pivotal Batches: All API batches used for pivotal studies, that is, trials used to prove pharmacokinetics/bioequivalence, if necessary, and efficacy and safety.

4.1.17. Process Scale-up: The significant (usually more than10 fold) increase in scale of production. This typically occurs when a chemical process is transferred from the laboratory into pilot plant, and then further on transfer to production.

4.1.18. Product: API or critical intermediate.

4.1.19. Proven Acceptable Ranges*:* Ranges for critical process variables shown to result in product which meets specification.

> *Note*: The use of these ranges, obtained from small scale tests, does not necessarily extend to full scale manufacturing. However, these ranges provide the basis for parameter setting mentioned in the protocol for (full scale) process validation.

4.1.20. Recovery: Any treatment of materials by a process inteded to make them suitable for further use.

4.1.21. Reference Standard, Primary*:* A substance that has been shown by an extensive set of analytical tests, to be authentic material of high purity. This standard may be obtained from a recognised source or may be prepared by independent synthesis or by further purification of existing production material.

4.1.22. Reference Standard, Secondary (synonym: Working Standard): A substance of established quality and purity, as shown by comparison to a Primary Reference Standard, used as a standard for routine laboratory analysis.

4.1.23. Reference Substance (synonym: qualitative standard): A substance of established identity and composition representative for degradation or by-products of the material studied.

4.1.24. Reprocessing: Repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g., distillation, filtration, chromatography, milling, etc.) that are part of the established manufacturing process. Continuation of a chemical reaction after an in-process control test shows the reaction to be incomplete is considered to be part of the normal process, and not reprocessing.

4.1.25. Reworking*:* Subjecting an intermediate or API that does not conform to standards or specifications, to one or more processing steps that are different from the current manufacturing process so that its quality may be made acceptable (e.g. recrystallisation with a different solvent).

4.1.26. A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting pre-determined acceptance criteria and that the specific process, procedure or system is suitable for its intended use.

4.1.27. Verification: confirmation that a process, procedure, method or system has produced a result or product meeting defined criteria.

4.2. Abbreviations

API	Active Pharmaceutical Ingredient
GMP	Good Manufacturing Practices
DR	Development Report
ICH	International Conference on Harmonisation
IPC	In Process Checks
OOS	Out Of Specification (for analytical result)
P-I, P-II, P-III	Phase I, Phase-II, Phase-III (in Clinical Trials)
NC	Non-clinical (phase, studies)
PAR	Proven Acceptable Ranges
QU	Quality Unit
RD	Registration Dossier

R&D	Research and Development
SOP	Standard Operating Procedure

5. Scope

To provide a document describing appropriate GMP requirements during APIs development from Non-clinical studies to the submission of the Registration Dossier. It covers the supply of the test material and the development of the process, including process operations, analytical tests and methods and equipment.

This guideline was elaborated taking into consideration APIs produced by chemical synthesis, but can be applied to other APIs obtained by different processes, with the pertinent adaptations. It would not apply to sterilisation processes.

6. Legal requirements[1]

Currently medicinal products are governed by European Directive EEC/75/319. Article 19 (f) of this directive is to be amended to require the compliance with the principles and guidelines to use starting materials manufactured in accordance to detailed guidelines on GMPs for starting materials.

Those guidelines will be in the form of the future ICH Q7a document titled "GMP for Active Pharmaceutical Ingredients", chapter 19 of which covers "APIs for Use in Clinical Trials", and deals with the same matter as discussed in this document

7. GMP in API development

The recommendations provided below have been elaborated from the best knowledge of current practice. These points are complemented by the matrix included in Section 8.

7.1. Analytical Matters

7.1.1. Setting of Specifications

Specifications for raw materials, intermediates and API will be elaborated throughout the development phase, as understanding and knowledge of the process and analytical procedures increase, from Phase I until end of Phase III. It is expected that the final and full specification for raw materials, intermediates and API will be in place at the end of Phase III and this will be the basis on which the validation of the process is performed at the site of manufacture.

[1] According to the information available at the time of the publication of this document.

As a minimum, the API should have defined test procedures for the determination of identity and characterisation of impurities and/or assay. It is recommended that an identity test is performed for Intermediates.

A procedure should be in place to document and justify the specification changes to raw materials, intermediates and also to approve API specification changes from Phase I to Phase III.

For additional information on specifications see References section.

7.1.2. Analytical methods

The analytical methods should be developed in parallel with the development of the process, to control and/or check the appropriate specification at each phase of the development programme. It is expected that the final analytical procedures will be in place at the end of Phase III and this will be the basis on which the final validation of the process is performed at the site of manufacture.

A procedure should be in place to document and justify the changes to analytical procedures from Phase I to Phase III.

7.1.3. Validation of analytical methods

Analytical methods must be proven to be appropriate at each phase to give assurance that the data generated is valid and suitable for its intended use. The final validation of the analytical procedures to ICH guideline (Q2a and Q2b) should be done at the end of Phase III when the specification has been fully developed.

Official methods, such as the ones in pharmacopoeias, don't require full validation, provided that method’s suitability can be demonstrated in the laboratory of the intended user.

7.1.4. In-Process Checks (IPC)

During development, IPC may be developed to determine the performance of the process. As the knowledge of the process increases, these IPC may be eliminated or other checks may be added. Any change should be documented.

7.1.5. Cleaning process verification

Procedures need to be developed to clean process equipment. In the development phase, cleaning validation is not usually necessary and thus cleaning verification is used to assess cleanliness of equipment.

In early development (NC and Phase I) a good starting point can be visual inspection, a non-specific test (e.g. residue on evaporation) or any other general test which can determine the level of contamination.

7.1.6. Calibration

All critical equipment should be calibrated at regular intervals in accordance with a written procedure.

7.1.7. Out of specification procedure

As soon as a specification exists, a general written procedure for dealing with Out of Specification (OOS) results must be available and followed.

OOS results level of investigation should be dependent on the stage of development and criticality of the specification

7.1.8. Reference standards and reference substances

These have to be developed in parallel with the development of analytical procedures. At the end of Phase III, a well characterised and defined Primary Reference Standard should be in place. If possible reference substances for main impurities should be available, including degradation products (mixtures of impurities for identification purposes may be suitable).

7.1.9. Stability testing

Stability indicating analytical procedures should be developed for use in analysis of stability samples. These should be able to determine process related impurities and degradation products.

In the early development phase, accelerated stability studies should be undertaken to determine the initial stability of the API and from this the retest date and storage conditions determined.

As the route of the process is fixed then real-time stability studies should be undertaken in accordance with ICH guidelines Q1a, Q1b and Q6a.

7.2. Process matters

Chemical process development is done to optimise the chemical process (e.g. solvents, reagents, reaction conditions) used to manufacture the API. Optimisation would be carried out to improve quality and yields, enhance operability, reduce costs, and control any potential health, safety or environmental effects. The objective of chemical process development is to deliver a validatable process to the manufacturing site, including procedures for reprocessing, reworking, recovery or cleaning, if applicable.

During development and scale-up studies, batches of API used for the clinical development programme may be prepared in pilot plants; these are usually dedicated

R&D facilities. The API may need to be produced to different levels of control dependant upon the intended use and development stage of the API (NC, Phase I, Phase II or Phase III).

7.2.1. Chemical/physical characteristics

The composition of the API (e.g. whether a free-base, salt, solvate, hydrate etc.) and its physical form (e.g. amorphous, crystalline form / polymorphs), controllable by the process and analytical methodology, should be defined at Phase I. However, there must be opportunity to change the characteristics of the API in an evolutionary process. These must be fixed at the end of Phase III. When there are changes, these must be evaluated to determine if toxicology studies should be repeated and bio-equivalence demonstrated.

7.2.2. Process description

Process description will develop throughout the development process, as understanding and knowledge of the process increases. It is expected that the final process instructions will be in place at the end of Phase III and this will be the basis on which the final validation of the process is performed at the site of manufacture.

7.2.3. Definition of chemical synthesis route

At the end of Phase III the chemical synthesis route, as defined by the isolated and non-isolated chemical intermediates, should be fixed. This route will be described in the regulatory submission and should identify starting materials as well as intermediates. However, it should be noted, that the earlier the route is fixed, the fewer problems are likely to arise. Different routes may be acceptable during development. The impurity profile changes have to be qualified according to ICH Q3a (e.g. by toxicity studies). Changes to the impurity profile and/or physical characteristics of the API should be verified, taking into consideration any impact on bioavailability.

7.2.4. Stability studies and definition of storage conditions and packaging materials

Stability studies on the API should form the basis for the proposed storage conditions, packaging materials and retest or shelf life period and so justify operational practices. Retesting the material prior to use is an acceptable practice.

7.2.5. Critical process variables

Process variables which need to be controlled in order not to compromise the quality of the intermediate and/or API, need to be investigated and identified as critical. This study normally starts in Phase I and should be finished prior to the end of Phase III. These data are related to PARs.

7.2.6. Proven Acceptable Ranges (PARs)

PAR apply to critical process parameters and need to be defined during process development and scale-up. These ranges should be included in the process validation protocol.

7.2.7. Process deviations

As soon as process instructions exists, a general written procedure for dealing with process deviations must be available and followed.

Process deviations level of investigation should be dependent on the stage of development and criticality of the specification.

7.2.8. Qualification of production equipment

Production equipment and associated instrumentation, when appropriate, should be identified and qualified for its intended use. In Phase I an II the use of nonqualified laboratory equipment is acceptable.

7.2.9. Calibration and Maintenance

All measuring and control equipment critical to product quality should be calibrated and maintained at appropriate intervals according to written procedures.

7.2.10. Cleaning procedures

Cleaning procedures may be either specific (i.e. developed for particular vessels and chemical stages) or generic and should be developed as integral part of the process in order to achieve effective cleaning of plant and equipment.

All should be capable of validation when transferred to production sites. The applied procedures should have associated testing methods and release procedures, if appropriate.

7.2.11. Utilities

Utilities in direct contact with the API should be of controlled quality and their systems should be validated.

7.2.12. Process validation

Process validation is not required during development, but a process validation strategy should be available at the end of Phase III.

7.3. Quality Management Systems, QU, Training and Responsibilities

7.3.1. Quality Management.

A system for managing quality should be in place. This system should encompass the organisational structure, general procedures (and specific protocols where required), processes and resources as well as actions necessary to ensure confidence that the API for Non-Clinical and Clinical studies will meet its intended (predetermined) specifications for quality and purity in relation to its intended use.

7.3.2. Regulatory aspects

The system for managing quality should ensure compliance with the regulatory submission.

It is recommended a Development Report o equivalent document be compiled, and to be available at the end of phase III. While it isn't a GMP requirement, it is a regulatory expectation, which could be reviewed during a Pre-approval Inspection.

This document will resume all background information on the selected route, the development of the chemical process, the chosen equipment and the development of analytical methods and specifications. The Development Report needs not contain all data but refer to more detailed subsidiary reports.

7.3.3. Documentation of changes

The system for managing quality should ensure that, beginning from an early stage, all planned changes are documented and justified.

7.3.4. Selection and documentation of (raw) material suppliers

The system for managing quality should ensure that, at the end of the development, suppliers of (raw) materials are identified, selected, approved and monitored.

Selected suppliers of (Raw) materials for Phase I and Phase II need to be identified only, whereas the requirements for Phase III include approval and monitoring of the supplies by QU.

7.3.5. Outsourcing and supply

Outsourcing and/or external supply are sometimes needed. Strategic and tactical plans should be developed concerning to the use of external companies to carry out contract development and/or supply of materials. The contracted firm must meet appropriate GMP requirements.

Access to raw data and technology transfer should be agreed and laid down in the formal contract.

The QU should approve service providers.

7.3.6. Data integrity review

A procedure should be in place for data integrity checking at milestones, in house or as defined in the formal contract between the company and the contractor. Responsibility for such checks should be defined, and could be part of the auditing system of the company.

It is advisable to conduct a formal review prior to any regulatory submission.

7.3.6. Training/Competence

Training on tasks to be performed, including GMP, should be given, evaluated, recorded and kept for further review.

7.3.7. Labelling

The label should at minimum contain:

- the identification of the compound
- batch number
- storage conditions
- retest date
- safety information, as appropriate, for external transport (a legal requirement, not a GMP requirement)

Assignment of storage conditions should be based on results of available stability data.

7.3.8. Documentation and retained samples

To support the GMP-status of work done, documentation and retain samples should be available. Documentation on production and testing of the API should be kept to allow for traceability. For the same reason, samples of all pivotal batches are to be retained.

A procedure should be in place to define the storage and retention time of the documents and samples.

7.4. Technology transfer

A procedure should be in place describing the transfer of technology (process and analytical) from R&D to manufacture. This procedure should include responsibilities and criteria for a successful transfer.

Technology transfer during development should ensure availability and accessibility of information obtained earlier.

8. Matrix

This section is provided for the correlation of information for the selected topics. It can be used as a quick guide, but should be read with the corresponding point of section 7.

Related matters are indicated, for easy comparison. The Phase where it is recommended a requirement to be implemented is marked "**X**". The Phase were it is believed a requirement will be

mandatory, is marked "⊗". Such requirements needed for Registration Dossier(RD) or (A)NDA, are included as mandatory in the last (extreme right) column.

ANALYTICAL MATTERS

POINT	PROCEDURE	Related to	PHASES NC	P-I+II	P-III	RD
7.1.1	Setting of specifications	7.2.1		X	X	⊗
7.1.2	Analytical methods	7.2.1	X	⊗	⊗	⊗
7.1.3	Validation of analytical methods For API Other materials	7.2.12		X	⊗ X	⊗
7.1.4	In-Process Checks	7.2.5		X	X	⊗
7.1.5	Cleaning process verification	7.2.10		X	⊗	
7.1.6	Calibration	7.2.8 7.2.9	X	⊗	⊗	
7.1.7	Out Of Specification procedure	7.1.1		X	X	
7.1.8	Reference standards and reference substances			X	X	⊗
7.1.9	Stability testing	7.2.4	X	X	X	⊗

PROCESS MATTERS

POINT	PROCEDURE	Related to	PHASES NC	P-I+II	P-III	RD
7.2.1	Chemical/physical characteristics	7.1.1	X	X	X	⊗
7.2.2	Process description	7.1.2	X	X	X	⊗
7.2.3	Definition of final chemical synthe- sis route	7.1.1		X	X	⊗
7.2.4	Stability studies, storage conditions and packaging materials.	7.1.9	X	X	X	⊗
7.2.5	Critical process variables	7.1.4		X	X	⊗
7.2.6	Proven Acceptable Ranges	7.2.12		X	X	⊗
7.2.7	Process deviations	7.1.7		X	X	
7.2.8	Qualification of manufacturing equipment	7.2.9 7.1.6		X	⊗	
7.2.9	Calibration and maintenance	7.1.6	X	⊗	⊗	
7.2.10	Cleaning procedures	7.1.5	X	X	⊗	

7.2.11	Utilities			X	X	⊗
7.2.12	Process validation	7.2.5 7.2.8 7.2.10				X

QUALITY MANAGEMENT, QU, TRAINING AND RESPONSIBILITIES

POINT	PROCEDURE	Related to	PHASES			
			NC	P-I+II	P-III	RD
7.3.1	Quality Management			⊗	⊗	
7.3.2	Regulatory aspects. Development report.		X	⊗	⊗	⊗ X
7.3.3	Documentation of changes	7.3.9	X	X	X	
7.3.4	Selection and documentation of (raw) material suppliers		X	X	X	
7.3.5	Outsourcing and supply		X	X	X	X
7.3.6	Data integrity review			X	X	X
7.3.7	Training/Competence		⊗	⊗	⊗	
7.3.8	Labelling		X	X	X	X
7.3.9	Documentation and retained samples		⊗	⊗	⊗	

TECHNOLOGY TRANSFER

POINT	PROCEDURE	Related to	PHASES			
			NC	P-I+II	P-III	RD
7.4.	Technology transfer	7.3.2	X	X	X	⊗

9. Benefits

In the current climate of no clear guidance for chemical development activities leading to APIs, this document aims to provide guidance regarding GMP activities and recommendations for the implementation.

Any company has the responsibility to decide how to implement these recommendations, based on risk assessment.

10. Literature/References

"ICH Q7a. Good Manufacturing Practice for Active Pharmaceutical Ingredients" (Draft 6, October 19th, 1999, section 19).

"ICH Q6a. Specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances".

"Good Manufacturing Practices for Active Pharmaceutical Ingredients" (EFPIA / CEFIC Guideline, August, 1996).

"Quality Management System for Active Pharmaceutical Ingredients Manufacturers" (APIC/CEFIC May 1998).

"Good Manufacturing Practices Guide for Bulk Pharmaceutical Excipients", The International Pharmaceutical Excipients Council (October 1995).

"21 Code of Federal Regulations, parts 210 to 211", U.S. Food & Drug Administration.

"Guide to inspection of Bulk Pharmaceutical Chemicals", U.S. Food & Drug Administration, (Revised Edition: May 1994).

"Guidance for Industry. ANDAs: Impurities in Drug Substances", U.S. Food and Drug Administration, CDER (June 1998).

"Guideline on the Preparation of Investigational New Drug Products", U.S. Food & Drug Administration, CDER (March 1991).

"EC Guides to GMP, Annex 13: Manufacture of Investigational Medicinal Products" (Revised Dec. 1996).

"GMP Compliance during Development", David J. DeTora. *Drug Information Journal*, **33**, 769-776, 1999.

FDA Guidance documents on internet address: http://www.fda.gov/cder/guidance /index.htm

EMEA Guidance documents on internet address: http://www.eudra.org.

Copyright and disclaimer

* Please contact the secretary of APIC at CEFIC