GMP in active pharmaceutical ingredients development

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MEDICINAL Products are governed to meet the established requirements by European Directive EEC/75/319. The principles and guidelines to use starting materials manufactured in accordance to detailed guidelines on GMP for starting materials is detailed in ICH Q7a document titled 'GMP for Active Pharmaceutical Ingredients.

Active Pharmaceutical Ingredients (API) can be defined in simple term – 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 fulfill the pharmacological activity or other direct effect in the cure, investigations, treatment, improvement or prevention of disease or to affect the structure and function of the body.

The requirements provided as per guidelines should be elaborated for the best knowledge of current practices during the development. All the requirements laid down and interpreted from the guidelines should be complemented by the matrix such as analytical procedures, processes, technology and other quality management systems.

In the current climate though the guidelines are stringent for starting materials, it is not clearly defined for chemical development activities leading to intermediates, therefore during API development ICHQ7a, Good manufacturing practice for Active pharmaceutical Ingredients, ICHQ6a, Specifications test procedures and acceptance criteria for new drug substances and new products : chemical substances, Quality management system for Active Pharmaceutical Ingredients Manufacturers, Good Manufacturing practices guide for bulk pharmaceuticals excipients. 21 Code of Federal Regulations, parts 210 to 211, U.S. Food & Drug administration. Guidance for Industry: Impurities in Drug substances and several other guidelines requirements should be followed. Manufacturer's responsibilities to decided how to implement the set guidelines and recommendations if any based on risk assessment approach.

Setting up of specifications for starting raw materials, intermediates and API should be elaborated throughout the development phase, as per understanding and knowledge based of the process and analytical procedures increase, for Phase I until end of Phase III. The final and layers of specifications for raw materials, intermediates and API should be in place at the end of Phase III and this should be the basis on which the validation of the process should be performed at the site of manufacture.

As a minimum, the API should have defined test procedures for the determination of identity and characterization of impurities and/or assay. It is recommended that an identity test is performed for intermediates. All these procedures should be in place to document and justify the specifications changes of any in the raw materials, intermediates and API followed by approve of API specification changes form Phase I to Phase III

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 should 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.

The methods adopted should be established and 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.

In-Process Checks (IPC) during development is 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.

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.

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

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

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 characterized 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).

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.

Chemical process

Chemical process development is done to optimize the chemical process (e.g. solvents, reagents, reaction conditions) used to manufacture the API. Optimization 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 validated process to the manufacturing site, including procedures for reprocessing, reworking and 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 dependent upon the intended use and development stage of the API (NC, Phase I, Phase II or Phase III).

Chemical/physical characteristics 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.

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.

Definition of chemical synthesis route: At the end of Phase III the chemical synthesis route, as defined by the isolated and no isolated chemical intermediates, should be fixed. This route will be described in the regulatory submission and should identify starting materials as well as intermediates.

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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.

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.

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.

Proven Acceptable Ranges: PARs 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.

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.

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

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

Quality Management

Quality Management , a system for managing quality should be in place. This system should encompass the organizational 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.

Regulatory aspects

Regulatory aspects system for managing quality should ensure compliance with the regulatory submission. It is recommended a development report of equivalent document be compiled and made 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 need not contain all data but refer to more detailed subsidiary reports.

It is recommended that the industry should take care of the development aspects more sincerely and document all the details to meet GMP requirements so that agencies will not find fault and development can avoid huge costs and manpower losses. ◆

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