Modern Analytical Techniques in Pharmaceutical Industry
A tool to support pharmaceutical quality
Pavia, October 21, 2016

DEFINITION AND ANALYSIS OF CRITICAL PARAMETERS OF AN API TO ASSURE PHARMACEUTICAL QUALITY

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Yesterday the pharmaceutical quality……

In some pharmacies, since the 16th century, compounds for sale were prepared. So, we can say that in the sixteenth century in Italy a rudimentary form of the pharmaceutical industry already existed , which took more secure expression in the eighteenth century" (Pages of pharmacy history, 1934, p . 320).

Only in the late nineteenth century the preparation of drugs has become a real industry, then it took off in the early decades of the 20th century. Before that, the preparation of drugs was entrusted mainly to individual pharmacies, continuing the long tradition of the apothecaries.

Yesterday the pharmaceutical quality……

The remedies were made up mainly of organic substances extracted with different procedures and mixed according to the advice of doctors or the wisdom of the pharmacist himself. Especially, before the advent of therapeutic molecules obtained by chemical synthesis, there was the difficulty of maintaining uniform quality standards. Suffice it to say that, at least until the first two decades of the twentieth century, in many pharmacopoeia chemically reliable standards were not present to test the quality of drug products and drug substances.

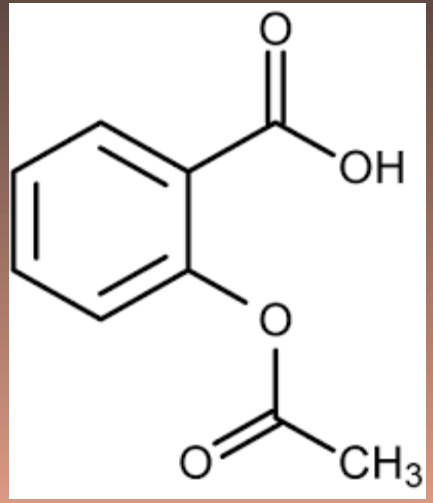
«Pharmacopoeia» as quality standards source……

-1140: the «Antidotarium» by Nicolaus Praepositus (School of Salerno) as official text of medicamenta preparations;
-1498: in Florence following the initiative of Consuls of the Apothecaries University was printed the «Ricettario Fiorentino»;
-1771: a progress in the evolution of the «pharmacopoeia» is the «Antidotarium Bononiense»;
-1892: in Italy the first official edition of Kingdom of Italy was published;
-2nd War: in Italy the VI edition of pharmacopoei was in force (with biological testing of Vitamins A and D);
-1969: the European Pharmacopoeia comes in force as first edition

Evolution of quality standards……

The synthesis of aspirin is classified as an esterification reaction. Salicylic acid is treated with acetic anhydride, an acid derivative, causing a chemical reaction that turns salicylic acid's hydroxyl group into an ester group (R-OH → R-$OCOCH_3$). This process yields aspirin and acetic acid, which is considered a byproduct of this reaction.

Aspirin, in the form of leaves from the willow tree, has been used for its health effects for at least 2,400 years.
The first study of an extract from the bark for fever was completed in 1763 by Edward Stone.
Felix Hoffmann, a chemist at Bayer, has been credited with first chemically making aspirin in 1897.
Acetylsalicylic Acid appeared the first time in 1914 BP.



Evolution of quality standards……

EP 9.0 current edition

- Identification (IR and melting point)
- Related substance by HPLC
- Sulfated ash

Yesterday…..but in certain cases also today

- identification by colorimetric testing
- Readily carbonizable substances
- Chloride
- Sulfates
- Heavy metals
- Limit of free salycilic acid (colorimetric)
- Assay (classical acido-base titration)

Impurity A: 4-hydroxybenzoic acid
Impurity B: 4-hydroxybenzene-1,3-dicarboxylic acid
Impurity C: 2-hydroxybenzenecrboxylic acid (salicylic acid)
Impurity D: acetylsalicyl-salicyic acid
Impurity E: salicylsalicylic acid
Impurity F: acetylsalicylic anhydride

About criteria of acceptance.....

Q6A: Specifications: Test Procedures and Acceptance Criteria for the New Drug Substances and New Drug Products : Chemical substances

October 1999

This guideline is intended to assist to the extent possible, in the establishment of a single set of global specifications for new drug substances and new drug products. It provides guidance on the setting and justification of acceptance criteria and the selection of test procedures for new drug substances of synthetic chemical origin, and new drug products produced from them, which have not been registered previously

About Criteria of acceptance.....

Specifications are chosen to confirm the quality of the drug substance and drug product rather than to establish full characterization, and should focus on those characteristics found to be useful in ensuring the safety and efficacy of the drug substance and drug product.

About criteria of acceptance.....

The experience and data accumulated during the development of a new drug substance or product should form the basis for the setting of specifications. It may be possible to propose excluding or replacing certain tests on this basis.

About criteria of acceptance.....

Limited Data Available at Filing

It is recognized that only a limited amount of data may be available at the time of filing, which can influence the process of setting acceptance criteria. As a result it may be necessary to propose revised acceptance criteria as additional experience is gained with the manufacture of a particular drug substance or drug product (example: acceptance limits for a specific impurity). The basis for the acceptance criteria at the time of filing should necessarily focus on safety and efficacy

About criteria of acceptance.....

Pharmacopoeial Tests and Acceptance Criteria

References to certain procedures are found in pharmacopoeias in each region. Wherever they are appropriate, pharmacopoeial procedures should be utilized. Whereas differences in pharmacopoeial procedures and/or acceptance criteria have existed among the regions, a harmonized specification is possible only if the procedures and acceptance criteria defined are acceptable to regulatory authorities in all regions.

About criteria of acceptance.....

Justification of Specifications

When a specification is first proposed, justification should be presented for each procedure and each acceptance criterion included. The justification should refer to relevant development data, pharmacopoeial standards, test data for drug substances and drug products used in toxicology and clinical studies, and results from accelerated and long term stability studies, as appropriate. Additionally, a reasonable range of expected analytical and manufacturing variability should be considered. It is important to consider all of this information.

About criteria of acceptance.....

-description
-identification
-assay
-impurities
-specific tests (phisico-chemical properties, polymorphism, inorganic impurities, etc.)

About criteria of acceptance.....

Evolving Technologies

New analytical technologies, and modifications to existing technology, are continually being developed. Such technologies should be used when they are considered to offer additional assurance of quality, or are otherwise justified.

Today the pharmaceutical quality……

ICH Q11

Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)

for adoption since 2012

Today the pharmaceutical quality……

This guideline describes approaches to developing and understanding the manufacturing process of the drug substance …..It addresses to development and manufacture that pertain to drug substance, including the presence of steps designed to reduce impurities.

The key issue……design and development

A company can choose to follow different approaches in developing a drug substance……

TRADI TIONAL APPROACH: the drug substance control strategy is tipically based on demostration of process reproducibility and testing to meet the established acceptance criteria.

ENHANCED APPROACH: risk management and scientific knowledge are more extensively used to identify and understand process parameters and unit operations that impact critical quality attributes (CQAs) and develop appropriate control strategies applicable over the life-cycle of the drug substance……

The key issue……design and development

The intended quality of the drug substance should be determined through consideration of its use in the drug product as well as from knowledge and understanding of its physical, chemical, biological and microbiological properties or characteristics, which can influence the development of the drug product. The Quality Target Product Profile (QTPP), potential CQAs of the drug product and previous experience from related products can help to identify CQAs of the drug substance. Knowledge and understanding of the CQAs can evolve during the course of development.

The key issue……design and development

Manufacturing process development should include, at a minimum, the following elements:

- Identifying potential CQAs associated with the drug substance so that those characteristics having an impact on drug product quality can be studied and controlled;
- Defining an appropriate manufacturing process;
- Defining a control strategy to ensure process performance and drug substance quality

The key issue……design and development

A systematic approach to evaluating, understanding and refining the manufacturing process, including:

- Identifying, through e.g. prior knowledge, experimentation and risk assessment, the material attributes (e.g. of raw materials, starting materials, reagents, solvents, process aids, intermediates) and process parameters that can have an effect on drug substance CQAs;
- Determining the functional relationships that link material attributes and process parameters to drug substance CQAs.
- Using the enhanced approach in combination with QRM to establish an appropriate control strategy which can, for example, include a proposal for a design space(s).

Drug Substance Critical Quality Attributes

A CQA is a physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range or distribution to ensure the desired product quality. Potential drug substance CQAs are used to guide process development. The list of potential CQAs can be modified as drug substance knowledge and process understanding increase.

Drug Substance Critical Quality Attributes

Drug substance CQAs typically include those properties or characteristics that affect identity, purity, biological activity and stability. When physical properties are important with respect to drug product manufacture or performance, these can be designed as CQAs. In the case of biotechnological/biological products, most of the CQAs of the drug product are associated with the drug substance and thus are a direct result of the design of the drug substance or its manufacturing process.

Drug Substance Critical Quality Attributes

Impurities are an important class of potential drug substance CQAs because of their potential impact on drug product safety. For chemical entities, impurities can include organic impurities (including potentially mutagenic impurities), inorganic impurities e.g., metal residues and residual solvents (see ICH Q3A and Q3C). For biotechnological/biological products, impurities may be process-related or product-related (see ICH Q6B). Process related impurities include: cell substrate-derived impurities (e.g.DNA); cell culture-derived impurities (e.g. media components) and downstream-derived impurities (e.g. column leachables).

Linking Material Attributes and Process Parameters to Drug Substance Critical Quality Attributes

The manufacturing process development program should identify which material attributes (e.g. of raw materials, starting materials, reagents, solvents, process aids, intermediates) and process parameters should be controlled. Risk assessment can help identify the material attributes and process parameters with the potential for having an effect on drug substance CQAs. Those material attribute and process parameters that are found to be important to drug substance quality should be addressed by the control strategy.

Linking Material Attributes and Process Parameters to Drug Substance Critical Quality Attributes

The risk assessment used to help define the elements of the control strategy that pertain to materials upstream from the drug substance can include an assessment of manufacturing process capability, attribute detectability and severity of impact as they relate to drug substance quality.

For example, when assessing the link between an impurity in a raw material or intermediate and drug substance CQAs, the ability of the drug substance manufacturing process to remove that impurity or its derivatives should be considered in the assessment.

The risk related to impurities can usually be controlled by specifications for raw material/intermediates and/or robust purification capability in downstream steps. The risk assessment can also identify CQAs for which there are inherent limitations in detectability in the drug substance. In this case, such CQAs should be controlled at an appropriate point upstream in the process.

Linking Material Attributes and Process Parameters to Drug Substance Critical Quality Attributes

For chemical entity development, a major focus is knowledge and control of impurities.

It is important to understand the formation, fate (whether the impurity reacts and changes its chemical structure) and purge (whether the impurity is removed via crystallisation, extraction, etc) as well as their relationship to the resulting impurities that end up in the drug substance as CQAs.

The process should be evaluated to establish appropriate controls for impurities as they progress through multiple process operations.

Control strategy

A control strategy can include, but is not limited to, the following:

- Controls on materials attributes (including raw materials, starting materials, intermediates, regents, primary packaging materials for the drug substance, etc.);
- Controls implicit in the design of the manufacturing process (e.g. sequence of purification steps or order of addition of reagents);
- In-process controls (including in-process tests and process parameters);
- Controls on drug substance (e.g. release testing)

Control strategy

A control strategy should ensure that each drug substance CQA is within the appropriate range, limit or distribution to assure drug substance quality. The drug substance specification is one part of a total control strategy and not all CQAs need to be included in the drug substance specification. CQAs can be:

- Included on the specification and confirmed through testing the final drug substance

or

- Included on the specification and confirmed through upstream controls

or

- Not included on the specification but ensured through upstream controls.

Upstream controls may be: in-process controls or use of measurements of process parameters and/or in process material attributes that are predictive of a drug substance CQA. In some cases PAT can be used and made to enhance control of the process

Control strategy

Upstream controls should be based on an evaluation and understanding of the sources of variability of a CQA.

Downstream factors that might impact the quality of the drug substance, such temperature changes, oxidative conditions, light should be taken into consideration.

The quality of each raw material used in the manufacturing process should be appropriate for the intended use . Raw materials used in operations near the end of the manufacturing have a greater potential to introduce impurities into the drug substance than raw materials used upstrem. There fore, manufacturers should evaluate if the quality of such materials should be more tightly controlled than similar materials used upstream.

Conceptually…….

Since 1999 to now: focus on quality of drug substance

Shift from acceptance attributes of drug substance defined on the basis of a limited experience.

to critical attributes indentified based on designed and intended use tailored quality

Increasing the control with modern analtical techniques


THANK YOU