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**INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES**Available online at: <http://www.iajps.com>**Review Article****COMPREHENSIVE APPROACH OF QBD FOR IMPURITIES IN DRUG
SUBSTANCES AND DRUG PRODUCTS****¹Savkare Anand D*, ²Badhe Nanda R.**¹Asst. Prof. Department of Pharmaceutics, NDMVP College of Pharmacy, Gangapur Road, Nashik 2, (422002) Maharashtra, India.²M. Pharmacy, Department of Quality Assurance Techniques, NDMVP College of Pharmacy, Gangapur Road, Nashik-2, (422002) Maharashtra, India.**Abstract:**

In this era of competition quality has been given prime magnitude for pharmaceutical product development. Pharmaceutical industries are regulated by various regulatory authorities like ICH, USFDA, Canadian Drug and Health Agency are emphasizing on the purity requirements and the identification of impurities in API's. Qualification of the impurities is the process of acquiring and evaluating data that establishes biological safety of an individual impurity; thus, revealing the need and scope of impurity profiling of drugs in pharmaceutical research. Quality by Design (QbD) is "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management" and has the aim of improving product quality and of increasing regulatory flexibility. Impurity level is a critical quality attribute for a drug substance or a drug product because levels higher than the toxicologically qualified amount could affect the safety and efficacy of the product. Control of impurities in drug substance and drug product is described in ICH Q3A, Q3B and with thorough product and process knowledge gained from pharmaceutical development under QbD paradigm, an efficient and comprehensive overall impurity control strategy can be developed to achieve the desired quality of the drug substance/ product.

Keywords: Impurity Profiling, Regulatory requirements, QbD approach, Critical Quality Attributes, Control Strategy.

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INTRODUCTION:

In the pharmaceutical world, an impurity is considered as any other organic material, besides the drug substance, or ingredients, arises out of synthesis or unwanted chemicals that remain with API's. Impurity profile is the description of identified and unidentified impurities present in new drug substances [1]. Impurities are found in API's unless; a proper care is taken in every step involved throughout the multi-step synthesis. Impurities in pharmaceutical products do not offer any therapeutic benefit for the patient and sometimes they are potentially toxic. Impurity level is a critical quality attribute for a drug substance or a drug product because levels higher than the toxicologically qualified amount could affect the safety and efficacy of the product. Control of impurities in drug substance and drug product is described in ICH Q3A, Q3B and Q3C guidance documents. Generally, acceptable limits for impurities are indicated by threshold values and impurities exceeding the qualification threshold should be toxicologically qualified. Control of impurities by end-product testing used to be the typical approach. Instead of controlling the impurities by exhaustive testing of the end-product, the QbD paradigm allows strategic and science based approaches to control impurities at various stages. QbD is defined as "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding based on sound science and quality risk management"[2]. The QbD approach which is based on scientific and methodical product development was included in the quality guidelines of International Conference on Harmonization (ICH) from 2005 onwards. This approach includes, ICH Q8 (Pharmaceutical Development), Q9 (Quality Risk Management), and Q10 (Pharmaceutical Quality System) guidelines. The pharmaceutical products quality was also emphasised in Process Analytical Technology (PAT) guidelines for new pharmaceutical product development and quality[3].

How Impurities Can Be Controlled?

-By understanding the formation, fate and purge of the impurities during the manufacturing process.

-By setting up appropriate controls at places where they either enter or form during the manufacturing process of drug substance and/ or drug product

-Based on the knowledge of the types of impurities and their potential sources, a comprehensive control strategy is designed via material quality control and process control steps and ultimately by drug substance/product specifications.

Types of Impurity

- (1) Inorganic impurities.
- (2) Organic impurities.
- (3) Residual Solvents.

1) Organic Impurities

The actual and potential impurities most likely to arise during the synthesis, purification, and storage of the drug substance should be summarized, based on sound scientific appraisal of the chemical reactions involved in the synthesis, impurities associated with raw materials that could contribute to the impurity profile of the drug substance.

2) Inorganic Impurities

Inorganic impurities may also arrive from manufacturing processes used for bulk drugs.

They are normally known and identified and include the following:

a) Reagents, ligands and catalysts- The chances of presence of these impurities are rare.

b) Heavy metals- The main sources of heavy metals are the water used in the processes

And the reactors (if stainless steel reactors are used), where acidification or acid hydrolysis takes place. These impurities of heavy metals can easily be avoided using demineralized water and glass-linked reactors.

c) Other materials (filter aids, charcoal)-The filters or filtering aids such as centrifuge bags are routinely used in bulk drug manufacturing plants and in many cases activated carbon is also used [4].

3) Residual Solvents

Residual solvents are organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products. The control of residues of solvents used in the manufacturing process for the drug substance should be discussed. Acceptance criteria should be based on pharmacopeial standards, or ICH guidelines or known safety data, depends on the dose, duration of treatment, and route of administration.

The residual solvents are classified as follows:

Class 1 Solvents: Solvents to be avoided in pharmaceutical products Known human carcinogens, strongly suspected human carcinogens and environmental hazards.

Table 1: Solvents to be avoided In Pharmaceutical Products

Solvent	Concentration limit(ppm)	Concern
Benzene	2	Carcinogen
CCl4	4	Toxic and environmental hazard
1,2-Dichloroethane	5	Toxic
1,1-Dichloroethane	8	Toxic
1,1,1-Trichloroethane	1500	Environmental hazard

Table 2: Solvents to be limited in pharmaceutical products

Solvent	Permitted Daily Exposure a (mg/day)	Concentration limit (ppm)
Acetonitrile	4.1	410
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cyclohexane	38.8	3880
1,2-Dichloroethane	18.7	1870

Class 2 Solvents: Solvents to be limited in pharmaceutical products. Non-genotoxic animal carcinogens or possible causative agents of other irreversible toxicity such as neurotoxicity or teratogenicity. Solvents suspected of other significant but reversible toxicities shown in table 2.

Class 3 Solvents: Solvents with low toxic potential Solvents with low toxic potential to man; no health-based exposure limit is needed. These solvents are less toxic in acute or short term studies and negative in genotoxic studies. The amount of these residual solvents of 50mg or less would be acceptable. Examples for this class of solvents are Acetic acid, Acetone, Anisole, 1-Butanol, 2-Butanol etc.

Class 4 Solvents: Solvents for which No adequate toxicological data was found. The solvents of this class may be of interesting to manufacturers of excipients, drug substances or drug products. But there was no adequate toxicological data on which to base a Permitted Daily Exposure was found. Examples for this class of solvents are 1,1-Diethoxy propane,1,1-Dimethoxy propane,2,2-Dimethoxy propane, Isooctane etc [5].

Sources of Impurities

From the preceding discussion, it is clear that impurities can originate from several sources; such as;

- Crystallization-related impurities
- Stereochemistry-related impurities
- Residual solvents
- Synthetic intermediates and by-products
- Formulation-related impurities,
- Impurities arising during storage
- Method related impurity
- Mutual interaction amongst ingredients
- Functional group-related typical degradation [6].

Quality by Design Approach:

QbD has its perspectives to contribute the drug design, development, and manufacture of high-quality drug products.

Different elements of pharmaceutical development

- Defining an objective
- Determination of critical quality attributes (CQA)
- Risk assessment
- Development of experimental design

- Designing and implementing control strategy
- Continuous improvement.

Define an Objective

Quality target profile (QTP) forms the basis of QbD, which is in relation to the predefined objective criteria mentioned in the definition of QbD.

For Ex. Intended use in clinical setting, route of administration, dosage form, delivery Systems, Dosage strength(s), Drug product quality criteria like sterility, purity, stability and drug release as appropriate for dosage form the intended for marketing.

Determination of Critical Quality Attributes. (CQA)

According to ICH Q8 R2 “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”. CQAs are generally linked with the drug substance, excipients, intermediates (in-process materials) and drug product. For example CQAs of solid oral dosage forms are typically those aspects affecting product purity, strength, drug release and stability whereas for parenterals they are Sterility and clarity.

Risk Assessment

It is commonly understood that risk is defined as the combination of the probability of occurrence of harm and the severity of that harm. Risk assessment helps to increase quality of method or process.

Development of Experimental Design

Experimental design is the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality.

Designing and Implementing Control Strategy

Control strategy is required to ensure that material and process are within the expected lower and upper limits. Parameter and material are routinely controlled during production in order to assure reproducibility. The control space should be within the design space. Generally scale up is trial and

error basis. During scale up processes parameters may differ but attributes which affect quality remains the same hence control strategy is required.

Continuous Improvement throughout Product Life Cycle

Product quality can be improved throughout the product lifecycle; companies have opportunities to opt inventive approaches to improve quality. Process performance can be monitored to make sure consistency in quality [7].

Control Strategy: For impurity

The control strategy in the QbD paradigm is established via risk assessment that takes into account the criticality of the CQA and process capability. A control strategy is what a generic sponsor uses to ensure consistent quality as they scale up their process from the exhibit batch presented in the ANDA to commercial production. Every process has a control strategy right now. The finished drug products are tested for quality by assessing if they meet specifications [8].

A control strategy for impurities may include, but is not limited to, the following: (ICH Q8, ICH Q11)

- Control of input material attributes (e.g., starting materials, API, reagents, intermediates, excipients, primary packaging materials) based on an understanding of their impact on processability or product quality;
- Control of in-process materials;
- Product specification(s);
- Controls for unit operations that have an impact on downstream processing or product quality (e.g., the impact of drying on degradation);
- In-process or real-time release testing in lieu of end-product testing (e.g. measurement and control of CQAs during processing);
- A monitoring program (e.g., full product testing at regular intervals) for verifying multivariate prediction models.

CS for Impurities in Process Materials for API Synthesis

Starting materials: First check point where we can control the impurities that can enter into the API synthetic route. Impurity profile for starting materials can be developed based on knowledge of manufacturing process used to synthesize it.

Materials other than Starting Materials: These include reagents, process aids and solvents used in various steps of manufacturing of API

-Impurities in Starting Materials and Reagents can be controlled by Release Specification and Supplier Qualification Protocol.

CS For Impurities Formed During API Synthesis

Identification of impurities (CQAs) that can be formed during the manufacturing process is a critical step in manufacturing a high quality of drug substance. Development of robust process which can minimize or eliminate these unwanted impurities can be achieved by performing series of experiments. Impurities in API synthesis can be controlled at incoming stage, in process stage and at the end of synthetic process with appropriate specification based on acceptance limits (ICH Q3A).

CS for Impurities from Excipients

Excipients are components of DP other than API which do not have any therapeutic value but are intentionally added to bulk up the dosage form. Impurities from excipients may include starting materials, solvents, reagents and intermediates. No formal guidance for controlling of impurities in excipients but QbD approach can help. For known excipients, compendial monographs can be source for impurity specifications and acceptance limits. However, additional tests may be needed on case by case basis. For new ones FDA & EMA require toxicological qualification to the same level as a new drug substance.

CS for Impurities from Container Closure System (CCS)

Impurities in DS or DP can be formed not only during the manufacturing process but also during storage. Therefore, it is important to select appropriate CCS for the dosage form. Impurities with Container closure system also include leachable and extractable of the CCS into the Drug Product. Critical CCS parameters for compatibility should be identified early on so that there are no unacceptable changes in the quality of dosage form or interactions such as loss of potency, degradation, changes in pH, absorption/adsorption, precipitation, discoloration and of course leaching. The CCS materials can be evaluated for these quality attributes, taking into consideration the interaction between the critical component extractable and drug product leachable Guidance for Industry titled – “Container Closure Systems for Packaging of Human Drugs and Biologics” provides guidance on the information of packaging materials needed on drug products. Attachment C of the guidance provides information on various extraction studies. USP <661> and USP <381> for the characterization of plastics and elastomers, respectively, and USP <87> and USP <88> for the biological reactivity of plastics and elastomers, respectively. The leachable can also come into the product from an indirect contact (e.g., imprinting

on the bottle or adhesives, inks or varnish from labels) or from surrounding air.

Limits for Impurities:

According to ICH guidelines on impurities in new drug products, identification of impurities below 0.1% level, is not considered to be necessary, unless potential impurities are expected to be unusually potent or toxic. According to ICH, the maximum daily dose qualification threshold to be considered is as follows as shown in table no.2-5;< 2g/day 0.1 % or 1 mg per day intake (whichever is lower) >2g/day 0.05% [8].

CONCLUSION:

This study outlines the development of an efficient overall CS for impurities by utilizing QbD principles and the knowledge of the types of impurities and their potential sources. Overall control strategy is achieved by incorporating controls in the material quality control and process control steps and ultimately by drug substance/product specifications. A systematic control of impurities via QbD approach has following benefits.

For Patients: They receive product of high quality

For Regulators: A clear control strategy from the manufacturers provides transparency and added assurance that risk of impurity has been adequately controlled.

For Pharmaceutical companies: A clear control strategy is identified which ultimately facilitates successful launch of product and also various post approval supplements like scale ups, tech transfers etc.

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