



Stability Development Strategies and Impurities Profile Consideration in Pharmaceuticals: A Review

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ABSTRACT

The advance progression in the pharmaceuticals brought a new era in human health. These pharmaceutical preparations might serve their envisioned solitary if they're free from impurities and as long as are administered in suitable quantity. With intensifying regulatory stringency on the control of medicines, impurities and their degradation constituents in unadulterated and formulated products, a strong emphasis is being placed on the need of the stability viewing systems/methods to measure the drugs and their impurities by utilizing assortment of common analytical instrumental strategies. Every single procedure has its one unique impact in assessing the pharmaceutical preparations, and investigating their impurities, which could have a hazard to human existence. In the drug manufacturing an impurity is measured, characterized any other organic substances in addition to the drug substance or pharmaceutical ingredients. The impurity can be fashioned in the course of the drug preparation or upon ageing of two APIs in drugs. Stability checking is a fundamental essential part of pharmaceutical improvement. The main reason of stability testing is to provide supportive indication on stability behavior of the pharmaceutical preparations. Stability is the potential of a drug product to remain within conditions established to make sure its strength, identity, purity and quality. This review write-up was for the study of pharmaceutical impurities, stability study and products degradation in pharmaceuticals.

Keywords: Pharmaceutical Impurities, Stability, Degradation, ICH.

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INTRODUCTION

Impurity is described as any substance/material coexisting with the authentic drug, consisting of beginning material or intermediates or this is formed, because of any lateral aspect reactions. Impurities found in excess of 0.1% have to be recognized and quantified with the aid of using selective procedures. The counseled establishments of the impurities may be synthesized and could provide the concluding proof for structures, formerly determined with the aid of using spectroscopic methods. Therefore, it's far vital to understand the shape of those impurities withinside the bulk drug in order to alter the condition of the reaction and to diminish the quantity of impurity to an appropriate level¹. Profile of the Impurity is description of the recognized / identified and unidentified impurities found in batch of API produced by a certain specific controlled manufacturing process²⁻⁴. It is one of the greatest significant fields of activity in contemporary modern pharmaceutical industrial analysis.

The ICH (International Conference on Harmonization) has printed rules and guidelines on impurities in new drug preparation substances, formulations, products and enduring solvents despite the fact that acetaminophen is taken into consideration to be safe to be used with the aid of using pregnant women, new studies shows that fetal exposure to the medicine might also additionally rise the risk for behavioral troubles associated with ADHD (attention-deficit-hyperactivity disorder) in children⁵. ADHD makes it threatening for individuals to inhibit their natural responses that could include the whole from motion to speech to attentiveness. To give proof on how the purity of the pharmaceutical substance or drug product differs with time affected by an assortment of ecological factors like temperature, light, humidity and establish the degradation graph that would be utilized to found the expiration relationship duration and assure the viability effectiveness and safety of the pharmaceutical products.

Common words/terms of pharmaceutical Impurities⁶⁻⁸

The ICH and several regulatory agencies are using the following terms to describe the pharmaceutical impurities:

I. Intermediate:- The composites or compounds formed during synthesis of the preferred material or as a component of the route of synthesis.



II. Penultimate intermediate: - Prior to the production of the final desired compound it is the preceding compound in the synthesis chain.

III. By products: - The compound produced in the reaction other than the required intermediates. They can occur through a variety of side reactions, such as overreaction, incomplete reaction, demonization and rearrangement, unwanted reactions between starting materials or intermediates with chemical reagents or catalysts.

IV. Transformation products: - They are associated to speculate and none hypothesized products that can take place in are actions. They may be similar to by product apart from that additional is known in relation to these reaction products.

V. Interaction products: - These products are produced either deliberately or involuntarily interaction between various chemicals involved.

VI. Related products: - Which are chemically analogous to medicine substance and might be have a biological activity.

VII. Degradation products: - They are framed by the deterioration of dynamic component or other material of attention by the impact of exterior factors like temperature, moisture and light.

Need of Stability Testing⁹

In the process drug approval stability testing as an important step, the persistence behind testing is to give proof on how the nature of a medication substance or product changes with time affected by an assortment of ecological factors like heat, light and humidity, and to lay out a re-trial for the substance or a timeframe of realistic usability or shelf life for the medication.

- To confirm quality, efficacy, safety of the pharmaceutical product
- To establish shelf life for the drug product
- To determine the suggested stockpiling conditions
- To confirm that no progressions have been presented in manufacturing process or in the formulation process that can antagonistically influence the stability of the product
- To Supports name, guarantee or label claim

Guidelines of ICH¹⁰⁻¹¹:

The ICH is an “International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use”. It was established in the year of 1990. ICH is a joint initiative including the binary regulators and scientific based industry representatives of the Japan, European Union and the USA in logical scientific and specialized technical conversations of the testing methods expected to evaluate and guarantee the wellbeing, quality and viability of medications.

Objective of ICH¹¹

- i. Ensure an appropriate overview of novel therapeutic products and their obtainability or availability to patients.
- ii. Effort has in the direction of more efficient economical use of animal, human and material resources.
- iii. Withstand safety measures on quality, efficacy and safety and regulatory responsibilities to safeguard the health of public.
- iv. Share information about modified Procedures of ICH and Med DRA advancement
- v. Comprehend the background for ICH-reforms
- vi. Deliberates the standing of active electronic and pharmaco-vigilance topics
- vii. Deliberates the standing of evolving quality and safety topics

Subsets of ICH:

The topics of ICH are allocated into 4 categories and codes of ICH are assigned consistent with these classes.

- Quality Guidelines Topics-Q
- Safety Guidelines Topics-S
- Efficacy Guidelines Topics-E
- Multidisciplinary Guidelines Topics-M

Adapted Terminology from ICH

- Selection of batches - for stability study
- Container closure system- for human drug packing
- Frequency of Testing
- Storage and its condition
- Bracketing and Matrixing
- In use stability testing
- Variation
- Ongoing Stability Study

ICH News¹²

(Information Day on ICH at the DIA Euro)

On 28th March 2017, EFPIA (one of the funding member of ICH) & DIA are organizing an “Information Day on-ICH” to deliver an updates on the standing of active topics & potential novel topics to be harmonized. Members will be updated in addition on current discussions connected to the ICH reforms, including improved transparency, new participation, reorganized governance and prospect funding models.

The various regulatory guidelines regarding impurities



are as follows:

- I. "stability testing of new drug substances and products"- ICH-guidelines - Q1A
- II. "Impurities in New Drug Substances" - ICH-guidelines - Q3A
- III. "Impurities in New Drug Products" – ICH- guidelines - Q3B
- IV. "Impurities: Guidelines for residual solvents" – ICH-guidelines - Q3C
- V. "NDAs -Impurities in New Drug Substances" US FDA-guidelines
- VI. US FDA guidelines "ANDAs – Impurities in New Drug Substances" - US-FDA-guidelines
- VII. TGA - Therapeutic Governance Authority -Australian regulatory guideline for prescription medicines.

This Guidelines or Rules has been established by the appropriate ICH-Expert Working Group and has been subject to consultation by the administrative parties, as per the ICH Process. At 4th Step of the Process the concluding draft is suggested for adoption to the regulatory bodies of the EU-European Union, USA and Japan.

Table 1: Stability guidelines of ICH

No	Topics
Q1A- R2	Stability Testing of New Drug Substances & Products
Q1B	Stability Testing : Photo stability Testing of New Drug Substances & products
Q1C	Stability Testing for New Dosage Forms
Q1D	Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products
Q1E	Evaluation for stability data
Q1F	Stability Data Package for Registration Applications in Climatic Zones III and IV
Q2-R1	Validation of Analytical Procedures Text and Methodology
Q3A-R2	Impurities in New Drug Substances
Q3B-R2	Impurities in New Drug Products
Q3C-R4	Guideline for Residual Solvents
Q4B	Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH regions
Q5A – Q5E	Quality of Biotechnology Products
Q6A	Specifications: Test procedures and Acceptance criteria for New Drug Substances & New Drug Products: Chemical substances
Q6B	Specifications: Test procedures and Acceptance criteria Biotechnological/ Biological products

Q7	Good Manufacturing Practice guide for Active Pharmaceutical Ingredients
Q8-R2	Pharmaceutical Development
Q-9	Quality Risk Management
Q-10	Pharmaceutical Quality System

Table 2: Current Quality Guidelines of ICH (Q4B)

S.No	Annexure	Recommendations
1	Annex 4: A(R1) - Q4B	Microbiological examination of non-sterile products: Microbial Enumeration Tests
2	Annex 4: B(R1) - Q4B	Microbiological examination of non-sterile
3	Annex 4: C(R1)- Q4B	Acceptance Criteria for Pharmaceutical Preparation & Substances for Pharmaceutical Use
4	Annex 1: (R1)-Q4B	Residue on Ignition Sulphated Ashes
5	Annex 2: (R1)-Q4B	Test for Extractable Volume of Parenteral Preparation
6	Annex 3: (R1)- Q4B	Test for Particulate Contamination: Sub- visible particles
7	Annex 5: (R1)- Q4B	Disintegration Test
8	Annex 6: (R1)- Q4B	Uniformity of Dosage Units
9	Annex 7: (R2)- Q4B	Dissolution Test
10	Annex 8: (R1)- Q4B	Sterility Test
11	Annex 9: (R1)- Q4B	Tablet Friability
12	Annex 10: (R1)-Q4B	Polyacrylamide Gel Electrophoresis
13	Annex: 11-Q4B	Capillary Electrophoresis
14	Annex: 12- Q4B	Analytical Sieving
15	Annex: 13- Q4B	Bulk density & tapped density of powders

CONCLUSION

It is essential and compulsory that testing practice of stability of the pharmaceutical preparations everywhere in the global be orientated towards uniformity. Standard guideline will afford manufacturer's assurance to head for global promotion. This article presents the treasured data about the impurities and its types and its categories, criterion type of impurities and important elements to be taken into consideration at the time of bulk drugs preparation. Therefore, as now it is very essential to know the impurities present in APIs and also in finished drug products. Now an afternoon, it's far obligatory requirement in diverse pharmacopoeias to recognize the impurities present in APIs and finished drug merchandise. Thus, impurity profiling can act as a pleasant manage device. There is robust requirement to have particular specifications or requirements in regards to impurities.



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