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A Review on Stability Development Guidelines and Impurities Profile Consideration in Solid Oral Dosage Form

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ABSTRACT

In the pharmaceutical industry an impurity is considered, defined the any other organic material besides the drug substance or pharmaceutical ingredients. The impurity may be formed during the formulation or upon aging of two APIs in medicines. Stability testing is an integral part of pharmaceutical development. The primary purpose of stability testing is to provide supporting evidence on stability behavior of pharmaceutical drug products. Stability is the capacity of a drug product to remain within specifications established to ensure its identity, strength, quality and purity.

Keywords Impurity, Stability, ICH, Annexure.

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INTRODUCTION

Impurity is defined as any substance coexisting with the original drug, such as starting material or intermediates or that is formed, due to any side reactions. Impurities present in excess of 0.1% should be identified and quantified by selective methods. The suggested structures of the impurities can be synthesized and will provide the final evidence for their structures, previously determined by spectroscopic methods. Therefore, it is essential to know the structure of these impurities in the bulk drug in order to alter the reaction condition and to reduce the quantity of impurity to an acceptable level¹. Impurity profile is description of the identified and unidentified impurities present in a typical batch of API produced by a specific controlled production process²⁻⁴. It is one of the most important fields of activity in contemporary industrial pharmaceutical analysis. The International Conference on Harmonization (ICH) has published guidelines on impurities in new drug substances, products and residual solvents³⁻⁵ although acetaminophen is considered to be safe for use by pregnant women, new research suggests that fetal exposure to the medication may increase the risk for behavioural problems related to attention-deficit/hyperactivity disorder (ADHD) in children. ADHD makes it difficult for people to inhibit their spontaneous responses—responses that can involve everything from movement to speech to attentiveness. To provide evidence on how the quality of the drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light and establish the degradation curve that could be used to establish the expiration dating period and guarantee the effectiveness and safety of the drug products.

Common Terms of Impurities⁶⁻⁸

Following terms are used by various regulatory bodies and ICH to describe the impurities:

1. Intermediate
2. Penultimate intermediate
3. By-products
4. Transformation products
5. Interaction products
6. Related products
7. Degradation products

Intermediate: The compounds produced during synthesis of the desired material or as a part of the route of synthesis.

Penultimate Intermediate: It is the last compound in the synthesis chain prior to the production of the final desired compound.

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.

Transformation Products: They are related to theorize and none theorized products that can occur in are action. They are similar to by-products except that more is known about these reaction products.

Interaction Products: These products formed either intentionally or unintentionally interaction between various chemicals involved.

Related Products: These are chemically similar to drug substance and may even possess biological activity.

Degradation Products: They are formed by the decomposition of active ingredient or other material of interest by the effect of external factors like heat, light and moisture.

Need of Stability Testing

- To ensure quality, safety, efficacy
- To establish shelf life for the drug product
- Determine the recommended storage conditions
- To verify that no changes have been introduced in the formulation or manufacturing process that can adversely affect the stability of the product
- To Supports label claim

ICH guidelines ¹⁰

The ICH is an International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. It was created in 1990. ICH is a joint initiative involving both regulators and research-based industry representatives of the European Union, Japan and the USA in scientific and technical discussions of the testing procedures required to assess and ensure the safety, quality and efficacy of medicines.

Goal of ICH ⁷⁻¹¹

- Ensure a timelier introduction of new medicinal products and their availability to patients.
- Work towards more economical use of human, animal and material resources.
- Maintain safeguards on quality, safety and efficacy, and regulatory obligations to protect public health.
- Share knowledge about revised ICH Procedures and Med-DRA development
- Understand the background for ICH reforms

- Discuss the status of active electronic and pharmacovigilance topics
- Discuss the status of evolving safety and quality topics

ICH Topics Considerations

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

Terminology – Adapted from ICH

- Selection of batches
- Container closure system
- Testing Frequency
- Storage condition
- Bracketing & Matrixing
- In-use stability testing
- Variation
- On-going Stability Studies

ICH News ¹⁰⁻¹²

(ICH Information Day at the Euro DIA)

On 28 March 2014, DIA and EFPIA (one of the funding member of ICH) are organizing an “Information Day on ICH” to provide an update on the status of active topics and potential new topics to be harmonized. Participants will be updated as well on recent discussions related to the ICH reforms, including increased transparency, new membership, restructured governance and future funding models.

The various regulatory guidelines regarding impurities are as follows:

1. ICH guidelines “stability testing of new drug substances and products”- Q1A
2. ICH guidelines “Impurities in New Drug Substances”- Q3A
3. ICH guidelines “Impurities in New Drug Products”- Q3B
4. ICH guidelines “Impurities: Guidelines for residual solvents”- Q3C
5. US-FDA guidelines “NDAs -Impurities in New Drug Substances”
6. US-FDA guidelines “ANDAs – Impurities in New Drug Substances”
7. Australian regulatory guideline for prescription medicines, Therapeutic Governance Authority (TGA), Australia.

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

Table 1: ICH Stability guidelines

Sr. no.	Types	Topics
1	Q1A(R2)	Stability Testing of New Drug Substances & Products
2	Q1B	Stability Testing : Photo stability Testing of New Drug Substances & Products
3	Q1C	Stability Testing for New Dosage Forms
4	Q1D	Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products
5	Q1E	Evaluation for stability data
6	Q1F	Stability Data Package for Registration Applications in Climatic Zones III and IV
7	Q2(R1)	Validation of Analytical Procedures Text and Methodology
8	Q3A(R2)	Impurities in New Drug Substances
9	Q3B(R2)	Impurities in New Drug Products
10	Q3C(R4)	Impurities: Guideline for Residual Solvents
11	Q4B	Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH regions
12	Q5A(R1)	Viral Safety Evaluation of Biotechnology Products Derived from Cell lines of Human or Animal origin
13	Q5B	Quality of Biotechnology Products: Analysis of the Expression Construct in Cells used for Production of R-DNA Derived Protein Products
14	Q5C	Quality of Biotechnology products: Stability testing of Biotechnological/ Biological products
16	Q5E	Comparability of Biotechnological/ Biological products subjects to changes in their Manufacturing process
17	Q6A	Specifications: Test procedures and Acceptance criteria for New Drug Substances & New Drug Products: Chemical substances
18	Q6B	Specifications: Test procedures and Acceptance criteria for Biotechnological/ Biological products
19	Q7	Good Manufacturing Practice guide for Active Pharmaceutical Ingredients
20	Q8(R2)	Pharmaceutical Development
21	Q9	Quality Risk Management
22	Q10	Pharmaceutical Quality System

Table 2: List of Current ICH Quality Guidelines (Q4B)

Sr. no.	Annexure	Recommendations
1	Q4B Annex 4 A(R1)	Microbiological examination of non- sterile products: Microbial Enumeration Tests
2	Q4B Annex 4 B(R1)	Microbiological examination of non- sterile products: Test for Specified Microorganisms

3	Q4B Annex 4C(R1)	Acceptance Criteria for Pharmaceutical Preparation & Substances for Pharmaceutical Use
4	Q4B Annex 1(R1)	Residue on Ignition Sulphated Ash
5	Q4B Annex 2(R1)	Test for Extractable Volume of Parenteral Preparation
6	Q4B Annex 3(R1)	Test for Particulate Contamination: Sub-visible particles
7	Q4B Annex 5(R1)	Region on Disintegration Test
8	Q4B Annex 6(R1)	An Uniformity of Dosage Units
9	Q4B Annex 7(R2)	Region on Dissolution Test
10	Q4B Annex 8(R1)	On Sterility Test
11	Q4B Annex 9(R1)	On Tablet Friability
12	Q4B Annex 10(R1)	On Polyacrylamide Gel Electrophoresis
13	Q4B Annex 11	On Capillary Electrophoresis
14	Q4B Annex 12	On Analytical Sieving
15	Q4B Annex 13	On Bulk density & Tapped density of powders

CONCLUSION

It is necessary that the stability testing practice all over the world be oriented toward uniformity. Guideline will provide manufacturer's confidence to go for international marketing. This article provides the valuable information about the impurities types and its classification, qualification of impurities and critical factors to be considered while preparation of the bulk drugs. Now a day, it is mandatory requirement in various pharmacopoeias to know the impurities present in APIs and finished drug products. Thus impurity profiling can act as a quality control tool. There is strong requirement to have unique specifications/standards with regard to impurities.

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