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Impurities from degradation of Drug Substances

REFERENCE

1. ICH - IMPURITIES IN NEW DRUG SUBSTANCES - Q3A(R2)
2. ICH - IMPURITIES IN NEW DRUG PRODUCTS - Q3B(R2)
3. ICH - VALIDATION OF ANALYTICAL PROCEDURES: TEXT AND METHODOLOGY - Q2(R1)
4. U.S. FDA Guidance for industry - Q3A IMPURITIES IN NEW DRUG SUBSTANCES
5. EMA – February 2004 – GUIDELINE ON THE CHEMISTRY OF NEW ACTIVE SUBSTANCES (CPMP/QWP/130/96 Rev 01)
6. EMA – STABILITY TESTING PHOTOSTABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS – CPMP/ICH/279/95 (ICH Topic Q 1 B)
7. EMA - NOTE FOR GUIDANCE ON STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS - CPMP/ICH/2736/99 (ICH Topic Q 1 A (R2))
8. EMA- GUIDANCE ON STABILITY OF ESTABLISHED ACTIVE INGREDIENTS AND FINISHED PRODUCTS - CPMP/ICH/556/96

OBJECTIVE

- The objective of the presentation is to give an overview of the current guidelines and regulatory requirements for evaluation, identification and quantification of degradation impurities in NEW and ESTABLISHED DRUG SUBSTANCES

ICH Q3A(R2)
IMPURITIES IN NEW DRUG SUBSTANCES

- **Impurity**: Any component of the new drug substance that is not the chemical entity defined as the new drug substance.
- **Impurity Profile**: A description of the identified and unidentified impurities present in a new drug substance.

ICH Q3A(R2)
IMPURITIES IN NEW DRUG SUBSTANCES

Organic impurities can arise during the manufacturing process and/or storage of the new drug substance. They can be identified or unidentified, volatile or non-volatile, and include:

- Starting materials
- By-products
- Intermediates
- **Degradation products**
- Reagents, ligands and catalysts

ICH Q3A(R2)
IMPURITIES IN NEW DRUG SUBSTANCES

Regulatory Requirements

The applicant should summarise the actual and potential impurities most likely to arise during the synthesis, purification, and storage of the new drug substance.

This summary should be 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 new drug substance, and **possible degradation products**.

This discussion can be limited to those impurities that might reasonably be expected based on knowledge of the chemical reactions and conditions involved.

ICH Q3B(R2)
IMPURITIES IN NEW DRUG PRODUCTS

- **Degradation Product**: An impurity resulting from a chemical change in the drug substance brought about during manufacture and/or storage of the new drug product by the effect of, for example, light, temperature, pH, water, or by reaction with an excipient and/or the immediate container closure system.
- **Degradation Profile**: A description of the degradation products observed in the drug substance or drug product.

GUIDELINE ON THE CHEMISTRY OF NEW ACTIVE SUBSTANCES (CPMP/QWP/130/96 Rev 01)

«3.2.S 3.2 Impurities

Information on impurities should be provided...

Possible routes of degradation should be discussed please see section 3.2.S 7.1...»

«3.2.S 7.1 Stability Summary and Conclusions

... The summary should include results, for example, from forced degradation studies and stress conditions (light stress, higher temperature, etc) ...»

Little guidance on strategies and principles (ICH Topic Q 1 A (R2))

Stress testing of the drug substance (2.1.2)

- can help identify the likely degradation products, which can in turn help establish the degradation pathways and the intrinsic stability of the molecule
- validate the stability indicating power of the analytical procedures used.

Little guidance on strategies and principles (ICH Topic Q2 (R1))

ICH Q2 recommends to use samples from forced degradation studies to prove specificity.

Specificity is a key factor in determining whether or not the analytical method is stability indicating.

Co-elution of peaks or components being retained on the column will underestimate the amount of degradation products formed and could compromise quality and increase risk to the patient

Little guidance on strategies and principles (ICH Topic Q 1 A (R2))

- The nature of the stress testing will depend on the individual drug substance and the type of drug product involved.
- Stress testing is likely to be carried out on a single batch of the Drug Substance.

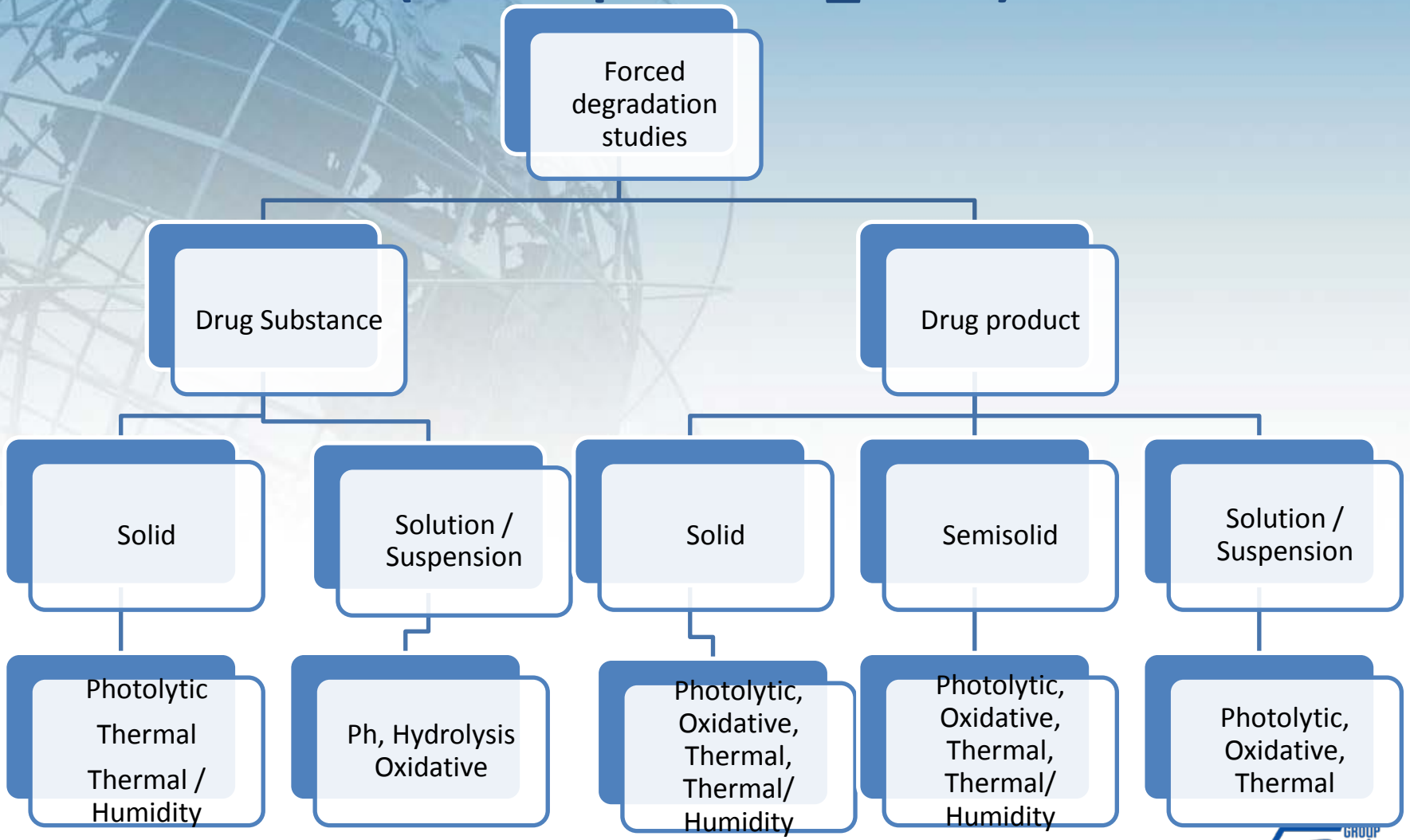
Little guidance on strategies and principles (ICH Topic Q 1 A (R2))

The recommendations are to examine the effects of temperature (above that for accelerated testing, i.e., >50°C), humidity (≥75% relative humidity), oxidation.

Testing in solution should also be performed across a wide pH range either as a solution or suspension.

Photostability testing should be an integral part of stability testing.

Little guidance on strategies and principles (ICH Topic Q1A _ Q1B)



Little guidance on strategies and principles (ICH Topic Q 1 A (R2))

However, it may not be necessary to examine specifically for certain degradation products if it has been demonstrated that they are not formed under accelerated or long-term storage conditions.

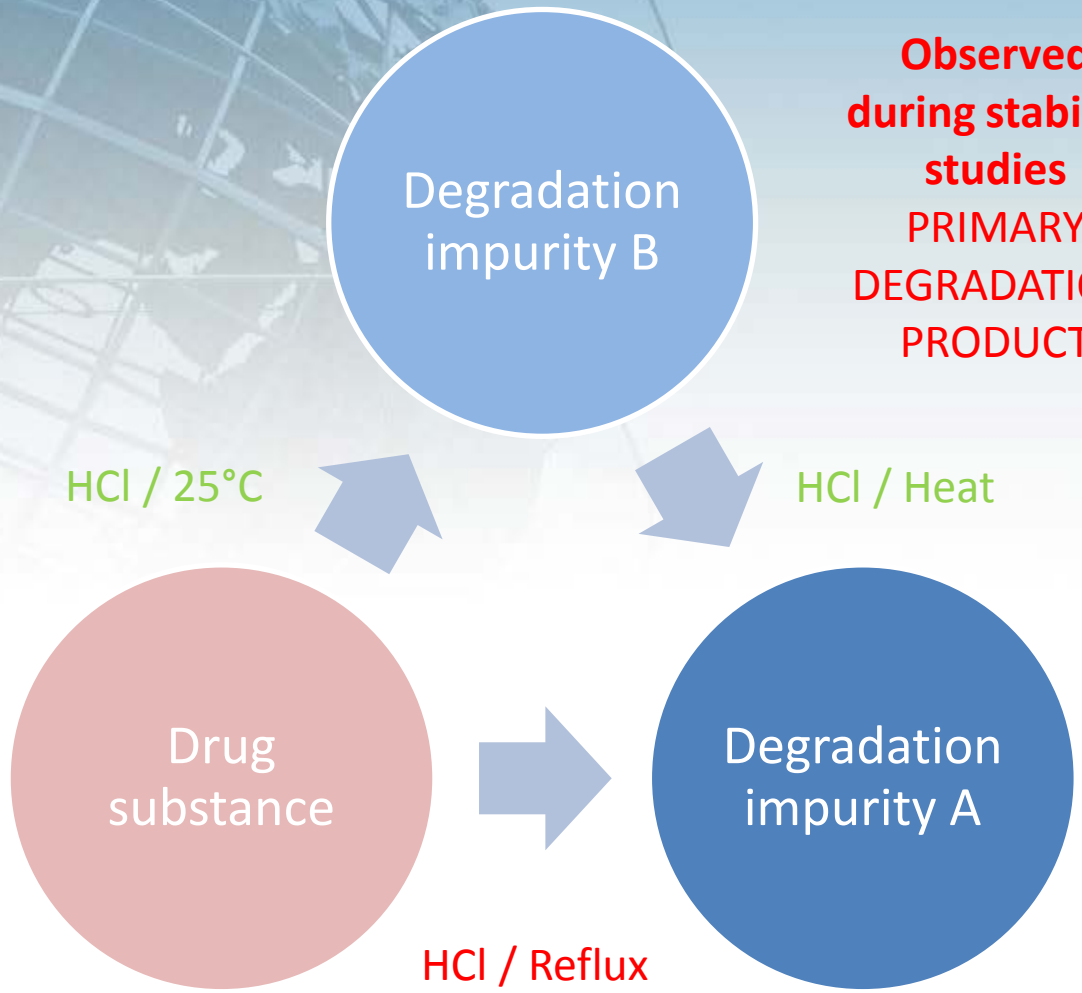
Choosing appropriate Experimental conditions

ICH guidelines do not give any guidance as to how much degradation is required in forced degradation studies.

If too little stress is applied, some degradation pathways may not be observed which would not challenge the method's ability to detect and monitor degradation products during stability testing.

If too much stress is applied then unrealistic degradation products may be observed and the resulting analytical method may be unsuitable for detecting actual degradation products formed during stability testing.

Choosing appropriate Experimental conditions



Observed during stability studies
PRIMARY DEGRADATION PRODUCT

Not observed during stability studies
SECONDARY DEGRADATION PRODUCT

Choosing appropriate Experimental conditions

Limiting the amount of degradation is scientifically sound as this should maximize chances of forming primary degradation products.

By analyzing the forced degradation samples over a number of time-points, it is possible to monitor if secondary degradation products are formed.

For the majority of drug substances and drug products, the primary degradation products are those that are likely to be observed during stability testing.

Choosing appropriate Experimental conditions

FDA perspective regarding the scientific considerations with respect to forced degradation studies.

If the substance does not show any degradation under any of the stress conditions then the Stress studies shall be repeated to obtain adequate degradation.

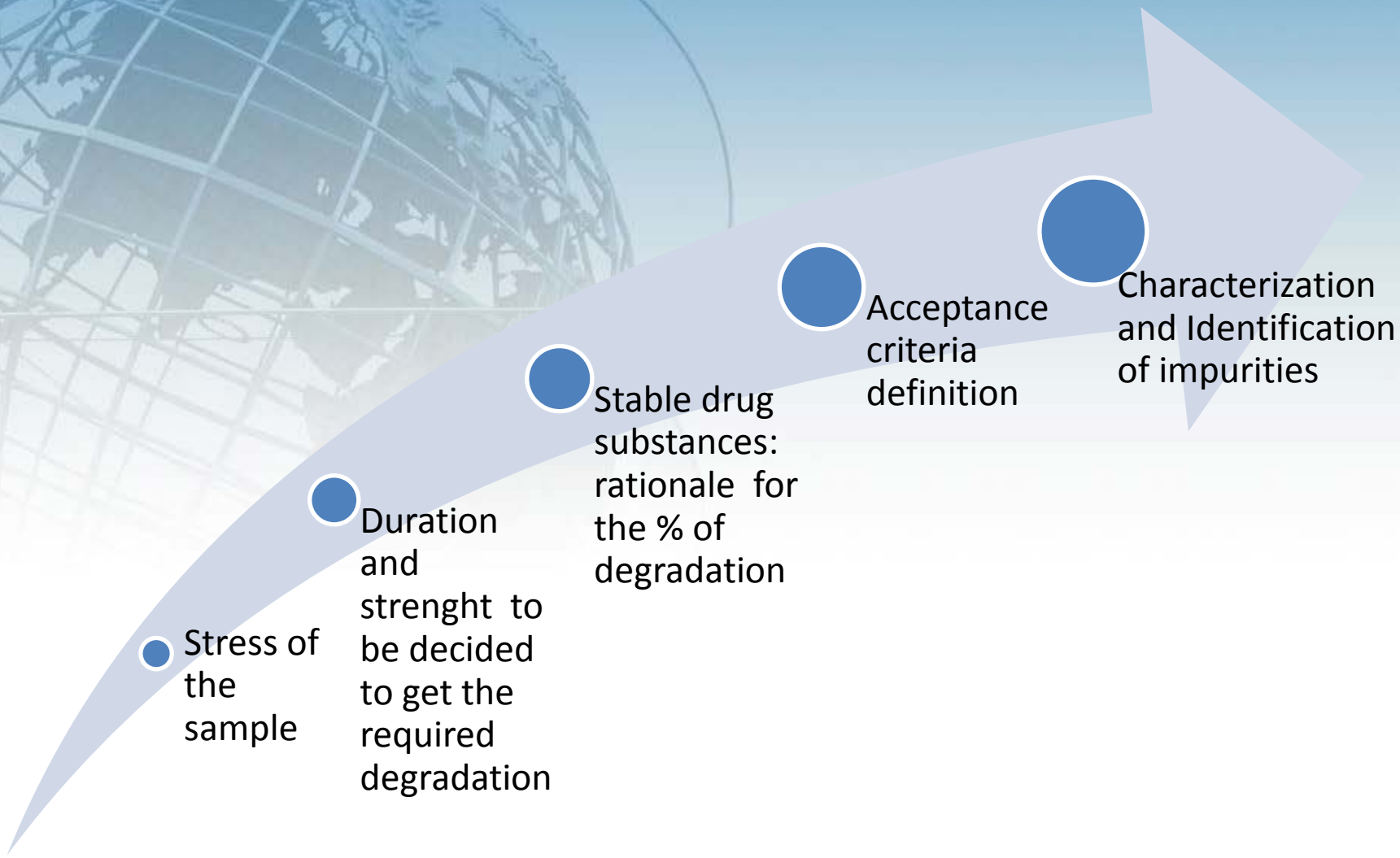
If degradation is not achievable, rationale shall be provided.

Choosing appropriate Experimental conditions

A generic approach for stress testing has been proposed to achieve purposeful degradation that is predictive of long-term and accelerated storage conditions.

- The generally recommended degradation varies between 5-20% degradation. A compound may not necessarily degrade under every single stress condition
- Although there are references in the literature that mention a wider recommended range (e.g., 10-30%), the more extreme stress conditions often provide data that are confounded with secondary degradation products.

Choosing appropriate Experimental conditions



Selection of Analytical Method

The analytical method of choice should be sensitive enough to detect impurities at low levels (i.e., 0.05% of the analyte of interest or lower), and the peak responses should fall within the range of detector's linearity.

The analytical method should be capable of capturing all the impurities formed during a formal stability study at or below ICH threshold limits

Selection of Analytical Method

Preferred method: HPLC

Stress sample preparation should mimic the sample preparation outlined in the analytical procedure as closely as possible

Chromatographic profiles of stressed samples should be compared to those of relevant blanks (containing no active) and unstressed samples to determine the origin of peaks

Selection of Analytical Method

Peak purity analysis. Peak purity is used as an aid in stability indicating method development. The spectral uniqueness of a compound is used to establish peak purity when co-eluting compounds are present.

Mass balance. Mass balance establishes adequacy of a stability indicating method though it is not achievable in all circumstances. It is performed by adding the assay value and the amounts of impurities and degradants to evaluate the closeness to 100% of the initial value (unstressed assay value) with due consideration of the margin of analytical error

Selection of Analytical Method

Degradation product identification and characterization are to be performed based on formal stability results in accordance with ICH requirements.

LC–MS, LC–NMR methods can be used in the identification and characterization of the degradation products

The identification of the impurities could add to the knowledge space of potential structural alerts for genotoxicity and the control of such impurities with tighter limits.

It should be noted that structural characterization of degradation products is necessary for those impurities that are formed during formal shelf-life stability studies and are above the qualification threshold limit.

Other considerations

Based on the fact that analytical methods reported in the Official Pharmacopoeia can be considered validated, if applied respecting the allowed adjustment of chromatographic conditions the stress testing may not be necessary for drug substances and drug products that have pharmacopeial methods.

Conclusion

Forced degradation studies provide knowledge about possible degradation pathways and degradation products of the active ingredients and help elucidate the structure of the degradants.

Degradation products generated from forced degradation studies are potential degradation products that may or may not be formed under relevant storage conditions but they assist in the developing stability indicating method.

It is better to start degradation studies earlier in the drug development process to have sufficient time to gain more information about the stability of the molecule. This information will in turn help improve the formulation manufacturing process and determine the storage conditions.

Conclusion

ICH Q3B (R2)

- **RATIONALE FOR THE REPORTING AND CONTROL OF DEGRADATION PRODUCTS**

The applicant should summarise the degradation products observed during manufacture and/or stability studies of the new drug product. This summary should be based on sound scientific appraisal of potential degradation pathways in the new drug product and impurities arising from the interaction with excipients and/or the immediate container closure system. In addition, the applicant should summarise any laboratory studies conducted to detect degradation products in the new drug product.

Thank You for Your Attention