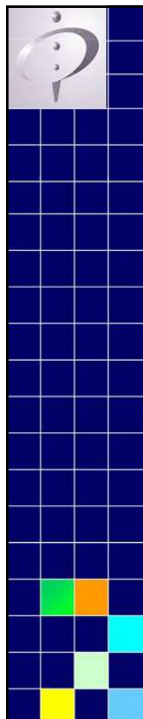




STUDY OF FORCED DEGRADATION OF SEVERAL GENERIC DRUGS

Medicines and Medical Devices Agency of Serbia (ALIMS)
Belgrade, 15th October 2010



OBJECTIVE

- **Overview of recommendations for stress studies according to EMA, ICH guidelines**
- The most common conditions for degradation studies in registration documentation, CTD format
(*Active Substance (AS) - 3.2.S.7. and Drug Product (DP) - 3.2.P.8.*)
- Compliance for forced degradation studies of AS in DMF(ASMF) between originators and generics
*Overview of Application,
Generic application (Shortcomings/Problems)*

2



Overview of recommendations for stress studies according to EMA & ICH guidelines

ICH

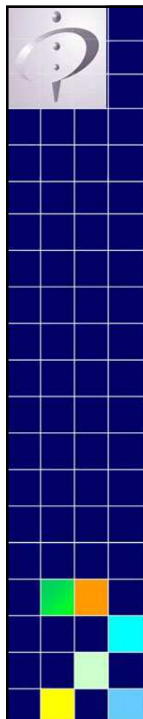
ICH Q1A (R2): Stability Testing of New Drug Substances and Products
ICH Q1B: Photostability Testing of New Drug Substances and Products
ICH Q1C: Stability Testing of New Dosage Forms
ICH Q5C: Stability Testing of Biotechnological/Biological Products
ICH Q1D: Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Products
ICH Q1E: Evaluation of Stability Data

ICH Q3A: Impurities in New Drug Substances
ICH Q3B: Impurities in New Drug Products

ICH Q6A: Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances
ICH Q6B: Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Biotechnological/Biological Products

ICH Q2(R1) - Validation of Analytical Methods – Definitions and Methodology

3



Overview of recommendations for stress studies according to EMA & ICH guidelines (2)

EMA

CPMP/ICH/ 2736/99-ICH Q1A (R2), Stability Testing of New Drug Substances and Drug Products
CPMP/ICH/279/95-ICH Q1B, Photostability Testing of New Active Substances and Medicinal Products
CPMP/ICH/ 280/95-ICH Q1C, Stability Testing: Requirements for New Dosage Forms

CPMP/ICH/ 4104/00-ICH Q1D, Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Drug Products
CPMP/ICH/ 420/02-ICH Q1E, Evaluation of Stability Data
CPMP/QWP/ 122/02 Rev. 1 corr, Stability Testing of Existing Active Ingredients and Related Finished Products

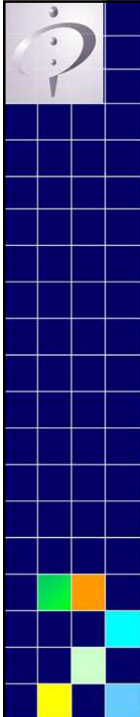
CPMP/QWP/ 609/96 Rev. 2, Declaration of Storage Conditions for Medicinal Products Particulars and Active Substances
CPMP/QWP/2934/99 In-Use Stability Testing of Human Medicinal Products
CPMP/QWP/ 159/96 Corr., Maximum Shelf-Life for Sterile Products for Human Use after first opening or following Reconstitution

CPMP/ICH/ 2737/99-ICH Q3A (R2), Impurities Testing: Impurities in New Drug Substances
CPMP/ICH/ 2738/99-ICH Q3B (R2,) Impurities in New Medicinal Products
CPMP/QWP/ 1529/04 Control of Impurities of Pharmacopoeial Substances
CPMP/SWP/5199/02, CHMP/QWP/251344/2006 , 2007, Limits of genotoxic impurities

CPMP/ICH/ 367/96-ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances

CPMP/ICH/381/95 - ICH Q2 (R1) Validation of Analytical Procedures: Text and Methodology

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Overview of recommendations for stress studies according to WHO, FDA guidelines

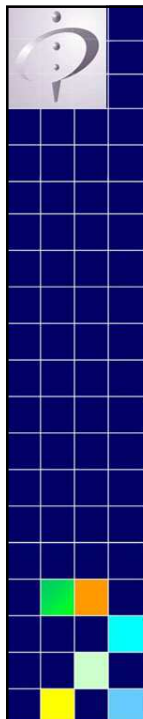
WHO

- *Stability testing of active pharmaceutical ingredients and finished pharmaceutical products, Annex 2 (WHO Technical Report Series, No. 953, 2009)*

FDA

- *Draft Guidance for Industry: Analytical Procedures and Method Validation*

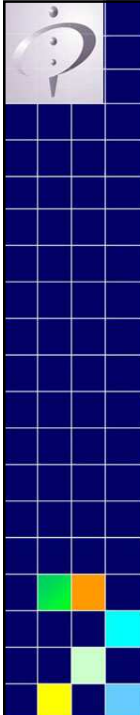
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OBJECTIVE

- Overview of recommendations for stress studies according to EMEA, ICH guidelines
- **The most common conditions for degradation studies in registration documentation, CTD format (Active Substance (AS) - 3.2.S.7. and Drug Product (DP) - 3.2.P.8.)**
- Compliance for forced degradation studies of AS in DMF(ASMF) between originators and generics
*Overview of Application,
Generic application (Shortcomings/Problems)*

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The most common conditions for degradation studies in registration documentation, CTD format

Information on the stability of the drug substance and products are an integral part of the systematic approach to stability evaluation.

The purpose (goal) of stability testing:

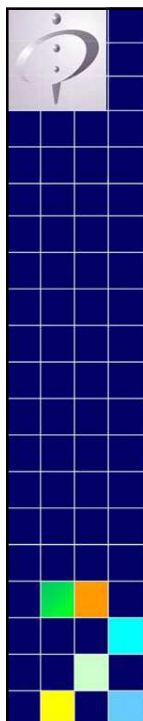
- To provide evidence on how the quality of a drug substance/drug product varies with time under the influence of a variety of environmental factors
- To establish a **re-test** period (*drug substance*) or a **shelf-life** (*drug product*) and recommended **storage conditions**

Type of stability study:

- **Stress Testing (Forced degradation)**
- Accelerated testing
- Intermediate testing
- Long term testing

ICH Q1A (R2)

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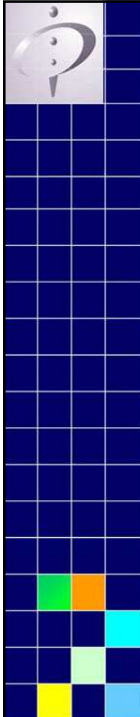
The most common conditions for degradation studies in registration documentation, CTD format (2)

Stress Testing – Active substance (AS)

3.2.S.7 (Reporting stability data in CTD)

- Studies undertaken to elucidate the intrinsic stability of the drug substance:
 - is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated testing
 - the nature of the stress testing will depend on the individual drug substance and the type of drug product involved.

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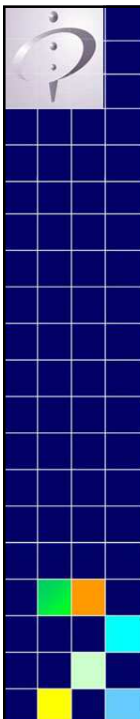
The most common conditions for degradation studies in registration documentation, CTD format (3)

Stress testing of active substance:

- can help identify the *likely degradation products*
(the possible formation of new clinical species with potential toxic side effects!)
- establishing the *degradation pathways* and *intrinsic stability* of the molecule
- *validation the stability indicating power* of the analytical procedure used

Results of stress testing are an integral part of the information provided to regulatory authorities.

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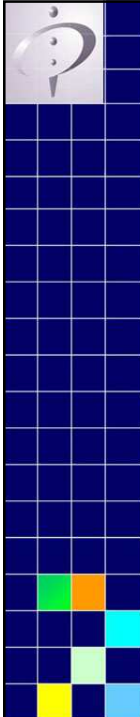
The most common conditions for degradation studies in registration documentation, CTD format (4)

Degradation products

- Generally, impurities present in the new drug substance need not be monitored or specified in the new drug product **unless they are also degradation products** (see ICH Q6A guideline on specifications) ICH Q3B (R2)
 - found only in forced degradation studies
 - found in stability studies (accelerated and long term, ICH Q3A(R2))

Impurity profile of active substance is of crucial importance for medical safety reasons...

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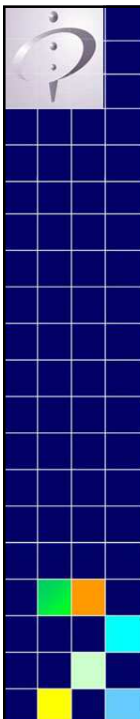


The most common conditions for degradation studies in registration documentation, CTD format (5)

Validation of analytical procedure

- Demonstration of **specificity** for the specified and unspecified degradation products
- Should include samples stored under relevant **stress conditions**: light, heat, humidity, acid/base hydrolysis and oxidation
- If analytical procedure reveals the presence of other peaks in addition to those of the degradation products (e.g., the drug substance, impurities arising from the synthesis of the drug substance, excipients and impurities arising from the excipients), these peaks should be labeled in the chromatograms and their origins discussed in the validation documentation.

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The most common conditions for degradation studies in registration documentation, CTD 3.2.S.7.

Conditions:

Stress testing of New Active Substance (one single batch)

- temperature (in 10°C increments (e.g. 50°C, 60°C))
- humidity (e.g. 75 % or greater)
- oxidation
- susceptibility of active substance to hydrolysis over wide pH range (in solution or suspension)

Photostability testing (ICH Q1B) should be an integral part of stress testing.
ICH Q1A (R2)

Stress testing of Existing Active Substance

- **described in an official pharmacopoeal monograph** – fully meets requirements, no data required
- **not described in an official pharmacopoeal monograph**
 - The relevant data published in scientific literature is acceptable
 - The relevant data published in scientific literature is NOT available- stress testing should be performed

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The most common conditions for degradation studies in registration documentation, CTD 3.2.S.7.(2)

Conditions Formal stability studies - Active substance (AS)

New Active Substance (at least 3 pilot batches)

- long-term storage conditions - 12 months stability data
- accelerated storage conditions - 6 months stability data **or**
- intermediate storage conditions - 6 months out of 12 months stability data

ICH Q1A (R2)

Existing Active Substance

Options: a) at least 2 production batches or b) 3 pilot batches

- long-term storage conditions - 6 months stability data
- accelerated storage conditions - 6 months stability data **or**
- intermediate storage conditions - 6 months out of 12 months stability data

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The most common conditions for degradation studies in registration documentation, CTD 3.2.P.8.

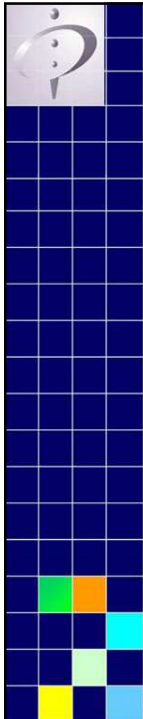
Stress testing – Drug Product (DP)

3.2.P.8. (Reporting stability data in CTD)

- Studies undertaken to assess the effect of severe conditions on the drug product.
- Such studies include *photostability testing* (see ICH Q1B) and specific testing on certain products, (e.g., metered dose inhalers, creams, emulsions, refrigerated aqueous liquid products).

ICH Q1A (R2)

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The most common conditions for degradation studies in registration documentation,CTD 3.2.P.8.(2)

Conditions Formal stability studies - Drug Product (DP)

New Active Substance (s): (at least 3 pilot batches)

- long-term storage conditions	- 12 months stability data
- accelerated storage conditions	- 6 months stability data or
- intermediate storage conditions	- 6 months out of 12 months stability data

Photostability studies (if appropriate)
ICH Q1A (R2)

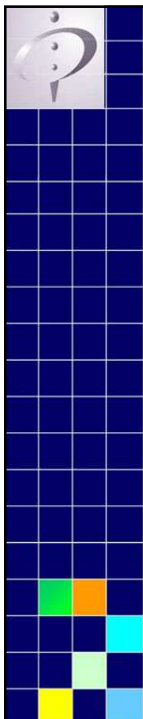
Existing Active Substance

Options: a) at least 2 pilot batches - conventional dosage forms - AS known to be stable
or b) 3 pilot batches - critical dosage forms - AS known to be unstable

- long-term storage conditions	- 6 months stability data (option a)
	- 12 months stability data (option b)
- accelerated storage conditions	- 6 months stability data or
- intermediate storage conditions	- 6 months out of 12 months stability data

Photostability studies (if appropriate)
CPMP/QWP/122/02 rev1

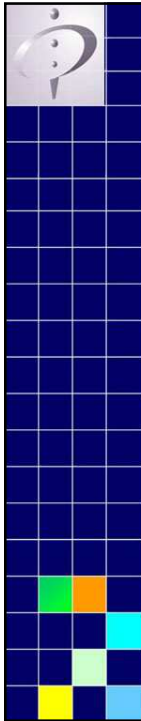
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Overview of Application,
Generic application (Shortcomings/Problems)

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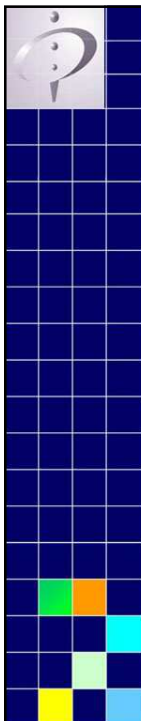


Overview of applications

PER YEAR	MARKETING AUTHORISATION, approved (Including different strengths, forms, packaging)	RENEWALS, approved (Including different strengths, forms, packaging)	VARIATIONS, approved
2005	214	139	367
2006	523	343	937
2007	487	479	1739
2008	695	525	2507
2009	679	512	4214
2010	455	138	2579

Table data refer to human drugs

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SUMMARY

Why is important to apply stress studies at generics?

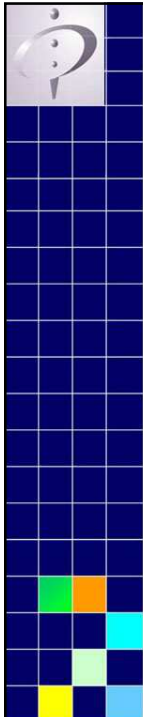
- **Active substance:**

Understanding degradation pathways and mechanism for AS :

- different starting materials
- different quality and purity of starting materials
- different synthesis pathway => different impurity profile, by-products, degradation products

Different stability of AS => possibility for arising a NEW DEGRADATION PRODUCTS (with genotoxic potential)

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SUMMARY

Why is important to apply stress studies at generics?

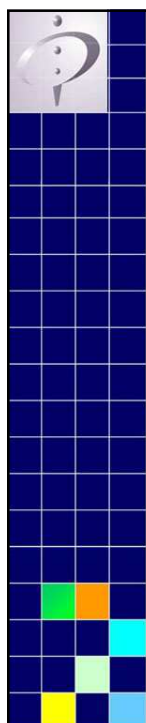
Drug Product

Understanding degradation pathways and mechanism for DP:

- *formulation of drug product - complex mixture* (one or more AS and excipients)
- qualitative composition of excipients in relation to reference product (same or different)
- drug-excipient interaction- new degradation products (chemical reactions between AS and excipients or reactions between AS and impurities in the excipients)
- choice of manufacturing process for dosage form
- choice of packaging materials (**immediate container closure system**)

Quality should be harmonized!

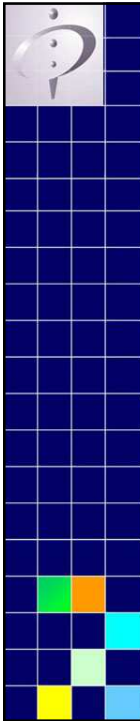
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- **M.Sc. Ph Ljiljana Vojvodic, QC spec., ALIMS,**
- **Prof. Dr Sc. Danica Agbaba, QC spec., Faculty of Pharmacy (University of Belgrade),**

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Generic Application,

Thank You for Your attention!

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