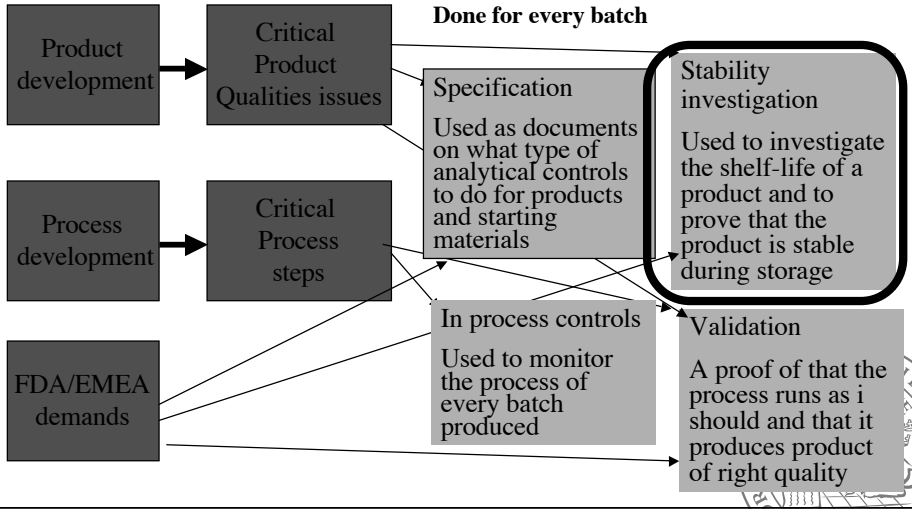
Stability testing

Aulton

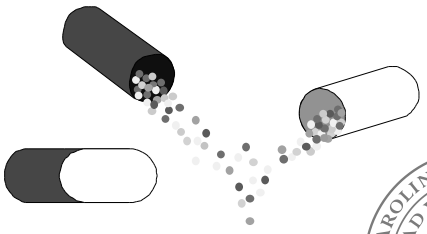
Chapter 7

Specification, stability, inprocess controls and validation

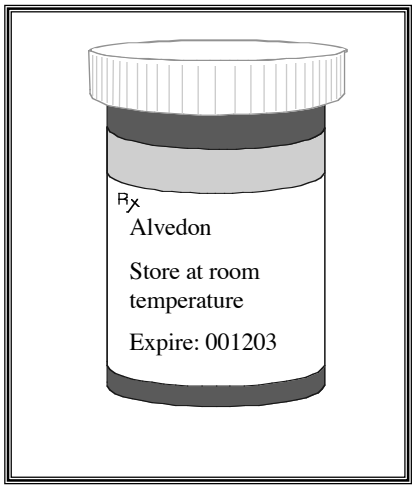


What are stability investigations?

All medicinal products decompose over time. Stability testing investigates this decomposition

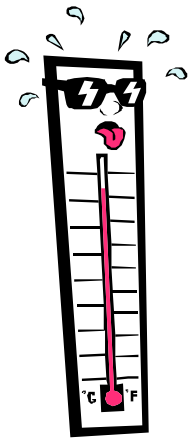


When and why?



- **Pre-formulation**
  - **Investigating the stability of the drug substance**
- **Development**
  - **Ensuring stability during tox and clinical tests**
  - **Drug optimisation**
  - **Determinating the shelf-life and conducting formal studies for the filling of the product**
- **Changes in the product or production**
  - **Ensuring that the quality of the product is unaffected**

Accelerated testing



Why

- To obtain information faster
- To obtain information to cover transport and storage conditions(refrigerated products)

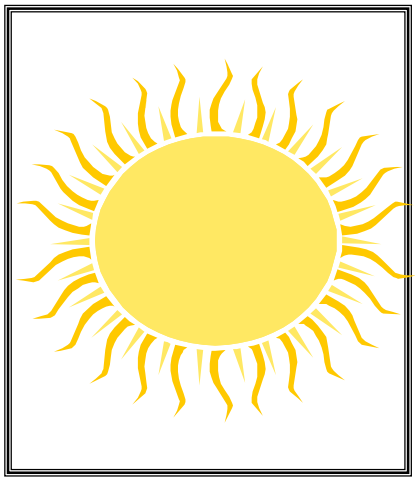
How

- Store samples at higher temperatures or humidity levell

Problems

- Low predictability if the reaction pattern is different at high temperatures and humidity levels.

Light tests



Why

- To obtain information on photo-degradation for choice of packaging

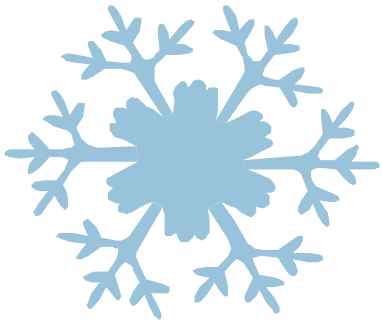
How

- Test one batch during development and employ one confirmatory test
- Expose the sample to artificial daylight at normal storage temperature
- The exposure time selected should be justified

Problems

- How to avoid heating the sample during testing

Freeze-thaw tests



Why

- To ensure that freezing does not alter the sample, for example due to crystallisation
- Important for ensuring transport stability

How

- Let the sample go through a number of freeze thaw cycles.

Problems

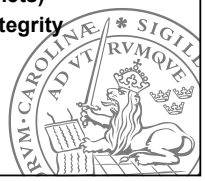
- No standard procedures availble

ICH Guidelines

- Q1A(R2); Stability Testing of New Drug Substances and Products
- Q1B;Stability Testing : Photostability Testing of New Drug Substances and Products
- Q1C; Stability Testing for New Dosage Forms
- Q1D; Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products
- Q1E Evaluation of Stability Data
- Q1F: Stability Data Package for Registration Applications in Climatic Zones III and IV

ICH Guidelines what to test

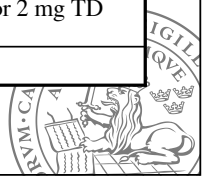
- **Test conditions**
  - **Long term**
  - **Accelerated**
  - **Photostability testing should be conducted on at least one primary batch of the drug product if appropriate.**
  - **Freeze stability**
- **To tests for**
  - **Chemical stability**
    - **Content (>95 of label)**
    - **Total impurities (<5%)**
    - **Known impurities**
    - **Unknown (<0,1%-1%)**
    - **Uniformity of content**
  - **Physical**
    - **Dissolution**
    - **Particle size**
    - **Hardness (tablets)**
  - **Microbiological integrity**



limits for impurities

- **Reporting limits**
  - **Daily dose <1mg , 0,1%**
  - **Daily dose <1 mg , 0,05%**
- **Identification threshold: a limit above (>) which a degradation product should be identified**

Maximum Daily Dose1	Threshold (what ever comes first)
< 1 mg	1.0% or 5 g TDI
1 mg - 10 mg	0.5% or 20 g TDI
>10 mg - 2 g	0.2% or 2 mg TD
> 2 g	0.10%



Special consideration for biotechnology products

- **Assays of biological activity should be part of the pivotal stability studies.**
- **Physical chemical characterisation, immune assays, etc. should be included**
- **Where possible, batches of the final container product included in stability testing should be derived from different batches of bulk material.**
- **the expiration dating should be based on real-time/real-temperature data.**

Formal stability testing

Product tested

- **The final product in its primary package.**

Batches tested

- **At least 3**
- **At least 2 batches of 3 produced in a pilot scale**
- **The 3 first production batches should always be placed on stability**

Analytical methods

- **Validated**

Test conditions

- **Normal storage temperature**
- **(Intermediate)**
- **Accelerated**

Test frequency

- **Year 1: 3 month intervals**
- **Year 2: 6 month intervals**
- **Year ≥ 3: yearly**

Test duration

- **Long term: 12 months beyond shelf life, no less than 12 months**
- **Accelerated and intermediate: 6 months**

Special issues concerning bio-molecules

- **Stability**
  - **On the whole, there is no single stability-indicating assay or parameter that profiles the stability, the manufacturer should propose a stability-indicating profile that provides assurance that changes in the identity, purity, and potency of the product will be detected**
  - **Assays for biological activity, where applicable, should be part of the pivotal stability studies.**
  - **For the purpose of stability testing, tests for purity should focus on methods for determination of degradation products.**

Test temperatures

- **Storage at room temperature**

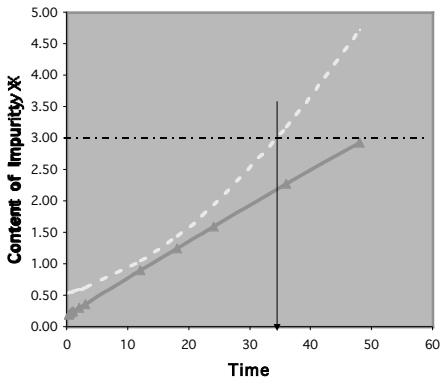
	Study Storage condition
Long-term	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH
Intermediate	30°C ± 2°C/65% RH ± 5% RH
Accelerated	40°C ± 2°C/75% RH ± 5% RH

- **Refrigerated storage**

	Study Storage condition
Long-term	5°C ± 3°C
Accelerated	25°C ± 2°C/60% RH ± 5% RH

- **For drug products intended for storage in a freezer, the shelf life should be based on the real time data obtained at the long-term storage condition.**

The prediction of shelf life



- **Determine the test parameters that change over time**
- **Determine when 95% of a one sided confidence interval intersect the specification limits**
- **If batches are similar, the data from all batches can be pooled.**
- **In other cases, shelf life is determinated by the worst case**
- **Note that not all changes are linear.**

Kinetic of chemical degradation

The reaction rate is often dependent upon the concentration of reactants

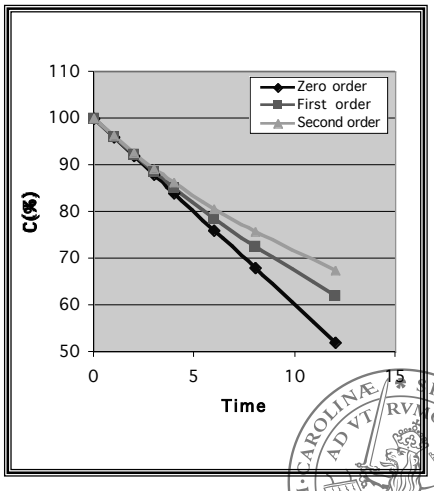
$$\frac{dC}{dt} \propto f(C) \quad \int_{C_0}^{C_t} \frac{1}{f(C)} = kt$$

- **Zero order**

  $f(C) = k$
- **First order**

  $f(C) = kC$
- **Second order**

  $f(C) = kC^2 \; f(C) = kC_aC_b$



Arrhenius equation

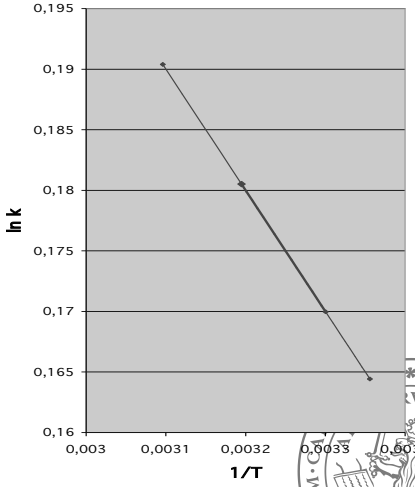
$$k = A * e^{-E_a / RT}$$

Use

- **To evaluate the degradation constant from accelerated data**

Risk

- **Incorrect for complex degradation profiles**



Evaluation in reality

- **Most parameters are found to be not shelf life determining simply by looking on the results**
- **If there is no strong evidence against it, zero order kinetics is assumed**
- **The shelf life is not always investigated in follow up stability investigations**

When to test existing products

When there is a risk that a change could affect the drug product

- **A change in the excipients**
- **A change in the primary packing material**
- **A change in the manufacturing process**
- **An increased in the batch size**

Annual tests of every sold product (US requirements)

- **Package of all sizes**
- **Only at the prescribed storage temperature**
- **Failure: Authorities have to be notified and the product be withdrawn from the market**

How to reduce the amount of work required

Matrixing

To reduce the number of samples analysed at any given time. Have to show that the predictability of the model works.

Time	A	B	C	D
3	x	x	x	x
6	-	x	-	x
9	x	-	x	-
12	-	x	-	x
24	x	x	x	x

Bracketing

To investigate only the extremes and assume a linear behaviour of parameters in between.

Example

Only investigate the smallest and the largest pack size for an oral formulation.

Terms to know from today's lecture

- **Shelf-life the time during which the product is safe to use**
- **Formal stability study. a stability study used to determinate shelf-life**
- **Matrixing and Bracketing ways of reducing the amount of work during a stability study**
- **ICH International Committee of Harmonisation (Common guidelines for Japan, the US and Europe)**

Seminar stability investigation

Design a stability study

- In groups of four discuss what should be included in a design of a stability study
- Individually design the study for the formulation you have obtained
- Present your design for the other member of your group and discuss in the group each others studies.

Estimation of stability

- In group of four discuss how two calculate the shelf-life for the formulations
- Calculate shelf-life for one of the three disintegrant
- Discuss in what way this study does differ from a formal study.