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# STABILITY STUDIES AND EXTENSION OF SHELF-LIFE:

# THE 10 COMMANDMENTS FOR INVESTIGATIONAL MEDICINAL PRODUCTS IN EU.

Sometime it is good to go back to basics, knowing that everything is not carved in stone with early phase IMPs.

This white paper does not impose mandatory commandments but presents warm recommendations. For IMPs in clinical trials we should refer to the EMA guidelines on the requirements for Quality documentation. There is one guideline for Chemicals IMPs[1] and another for Biologicals IMPs[2].
Generally we already apply them, since there are simpler and more flexible than the ICH guidelines about stability (ICHQ1 series [3,4] and ICH Q5C [5]) which apply to pre-marketing authorization or marketed medicinal products.

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References
1. EMA/CHMP/QWP/545525/2017 (2017, 20 September) Guideline on the requirements for the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials.
2. EMA/CHMP/BWP/534898/2008 rev. 1 corrigendum. (2018, November) Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials.
3. ICH Topic Q1A (R2). (2003, August) Stability Testing of new Drug Substances and Products, CPMP/ICH/2736/99.
4. ICH topic Q1E (2003, August). Evaluation of Stability Data, CPMP/ICH/420/02.
5. ICH Topic Q5C (1996, July). Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products, CPMP/ICH/138/95.

## Rule no.1: Describe in the IMPD the stability program

Stability design and extension plan must be established before starting the stability study and must be presented in the Investigational Medicinal Dossier (IMPD).

Why?
When the protocol and extension plan are accurately described in the IMPD there is no need to notify to the Authorities (substantial modification) a shelf-life extension during on-going stability.

The total duration of the clinical study should be covered by the stability study, thus the duration should be anticipated with a safety margin to avoid the necessity to submit changes.

For example, if the duration is initially planned to be 12 months in the IMPD and if it is decided after submission to continue the stability study up to 18 or 24 months to support the clinical trial, a substantial amendment will have to be sent to the Competent Authorities. However, if the initial duration is planned to be 24 months, no amendment is necessary.

## Rule no.2: Manufacture a technical batch

To manufacture a technical batch before the manufacture of the clinical batch is often worthwhile.

We are talking about IMPs, mainly in early clinical phase, with very few or no preliminary stability supportive data.

The objective is to have a technical batch (non-GMP) representative of the further clinical batch and thus predictive of its stability.

The technical batch is useful and must be recommended for the following reasons:

- It allows to present sufficient stability data to be confident in the behavior of the further clinical batch.

- The provisional extrapolated shelf-life will be claimed on the basis of technical batch stability data. Thus it reduces the risks of unexpected OOS/OOT results during stability of the clinical batch.
- No need to have produced the clinical batch at the time of submission.
- Can save therapeutic units, if a reduced plan (monitoring) is carried out on clinical batch.

## Rule no.3: Follow the ICHQ1A (ICHQ5C) stability intervals and storage conditions

Although IMPs are not strictly in the scope of ICH guidelines, the stability intervals (time points) and storage conditions described in ICHQ1A (chemical) and ICHQ5C (biological) should apply.
Storage conditions: both long-term and accelerated conditions have to be studied. Storage conditions are selected according to the expected stability of the IMP based on preliminary stab data, and stress studies / stability data on the Drug Substance which should be available. Also, a chemical product is typically expected to be more stable than a biological product.

| LONG TERM STORAGE CONDITIONS | ACCELERATED STORAGE CONDITIONS |
|---|---|
| -20°C | 5°C |
| 5°C | 25°C - 60% RH |
| 25°C - 60% RH[1] | 40°C - 75% RH |

1 If the clinical trial takes also place in a country outside climatic zone II, other long-term conditions should be applied (e.g. Brazil, zone IVb, 30°C – 75%RH)

Time points:
Long- term conditions: T0, T1M*, T3M, T6M, T9M, T12M, T18M, T24M
Accelerated conditions: T1M*, T3M, T6M
(*)T1M is not an ICHQ1A recommendation: see rule no.4

Nota:

- For biological IMP with a short expected shelf-life, 1 year or less, the testing frequency will be different according to ICHQ5C, e.g. T1M, T2M, T3M, T6M, T9M and T12M.
- Only the long term and accelerated storage conditions are presented in the table considering that intermediate storage conditions are not mandatory. However, if the IMP degradates under accelerated conditions, they could be recommended.

## Rule no.4: Add a T1 month stab point compare to ICH grid

**Why?**

Because the T1 month allows a very rapid implementation of extension plan, for the setting of a provisional shelf-life / labelling of the clinical batch at the beginning of the trial.

This is even truer for chemical IMPs where a four-fold extension is allowed up to 12 month extrapolation.

## Rule no.5: Describe the extension plan as recommended in EMA guidelines

The extension plan as recommended in the EMA guidelines is valid for IMPs stable under accelerated conditions, or showing no significant change of stability criteria under accelerated (and long-term) conditions.

## Chemical IMPs

| EXTENSION PLAN | |
|---|---|
| ACTUAL DATA | PROVISIONAL SHELF-LIFE |
| 1 month (accelerated & long-term) | 4 months (4X) |
| 3 months (accelerated & long-term) | 12 months (4X) |
| 6 months (accelerated & long-term) | 18 months (X + 12) |
| 9 months (long-term) | 21 months (X + 12) |
| 12 months (long-term) | 24 months (X + 12) |
| 18 months (long-term) | 30 months (X + 12) |
| 24 months (long-term) | 36 months (X + 12) [1] |

1 Typically, 36 months is the maximum shelf-life for an IMP

## Biological IMPs

A case-by-case basis is recommended for a safe extrapolation of biological products shelf-life.
Taking into account their low stability and long-term storage conditions at 5°C, -20°C or even lower temperature.

| EXTENSION PLAN | |
|---|---|
| ACTUAL DATA | PROVISIONAL SHELF-LIFE |
| 1 month (accelerated & long-term) | 2 months (2X) |
| 2 months (accelerated & long-term) | 4 months (2X) |
| 3 months (accelerated & long-term) | 6 months (2X) |
| 6 months (accelerated & long-term) | 12 months (2X) |
| 9 months (long-term) | 18 months (2X) |
| 12 months (long-term) | 24 months (X + 12 / 2X) |
| 18 months (long-term) | 30 months (X + 12) |
| 24 months (long-term) | 36 months (X + 12) [1] |

1 Typically, 36 months is the maximum shelf-life for an IMP

## Rule no.6: Do not extend shelf-life beyond the intended duration of the stability study

As an example: In the case of a targeted total duration of 24 months (program presented in the IMPD) an extrapolation up to 30 months using the 18 month stability point data is not allowed.

## Rule no.7: Continue the stability study up to the entire targeted duration

As an example: In the case of a targeted total duration of 24 months (program presented in the IMPD), the stability study must not be stopped at T12 month control point (24 months claimed based on extrapolation), but continued up to 18 and final 24 month points to confirm the claimed shelf-life.

## Rule no.8: Commit to inform the Competent Authorities if an unexpected issue occurs during the stability study (OOT, OOS)

That is a requirement of EMA guidelines.

This commitment has to be written in black and white in the IMPD.

## Rule no.9: Be realistic concerning the expected stability behavior of the IMP

Again: for early phase IMPs there are often little supportive stability data at the time of IMPD submission, and also at the start of the clinical trial. There is a risk when the stability protocol and extension plan are initially implemented.

The worst scenario is to be too optimistic and fall into trouble during the stability study, if the IMP appears to be much less stable as planned. With OOT & OOS results under long-term conditions.

The consequences are the following:

- Notification of a substantial modification to the Authorities (substantial amendment to the IMPD).
- Reduction of initially planned shelf-life and/or restriction on storage conditions (long-term) which may impact negatively the management of the on-going clinical study.

## Rule no.10: Evaluate reduced stability design on clinical batch for stable solid dosage forms

Monitoring (reduced design) is accepted on clinical batch, if full design has been previously conducted on technical batch for solid dosage forms (capsules / tablets / powders) exhibiting a very good stability.

As an example of reduced design:

- Storage conditions: only long-term (25°C – 60% RH)
- Stability points: T0, (T6M), T12M and T24M

The monitoring must last up to the entire duration of the clinical trial.

One advantage is to save therapeutic units for the clinical trial (and laboratory work).

## Other advices

- Do not forget the in-use stability study if requested / appropriate.

As examples: multi-doses oral solutions after first opening, freeze-dried products to be reconstituted before administration, concentrated solutions to be diluted in bulk solute for infusion.

The objective is to define a shelf-life under in-use conditions and to set a storage statement (diluted solution must be stored below X°C, away from light ...).

- Do not forget holding time study, if the bulk product is stored during a "significant period of time" before primary packaging and if stability issues are suspected.

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