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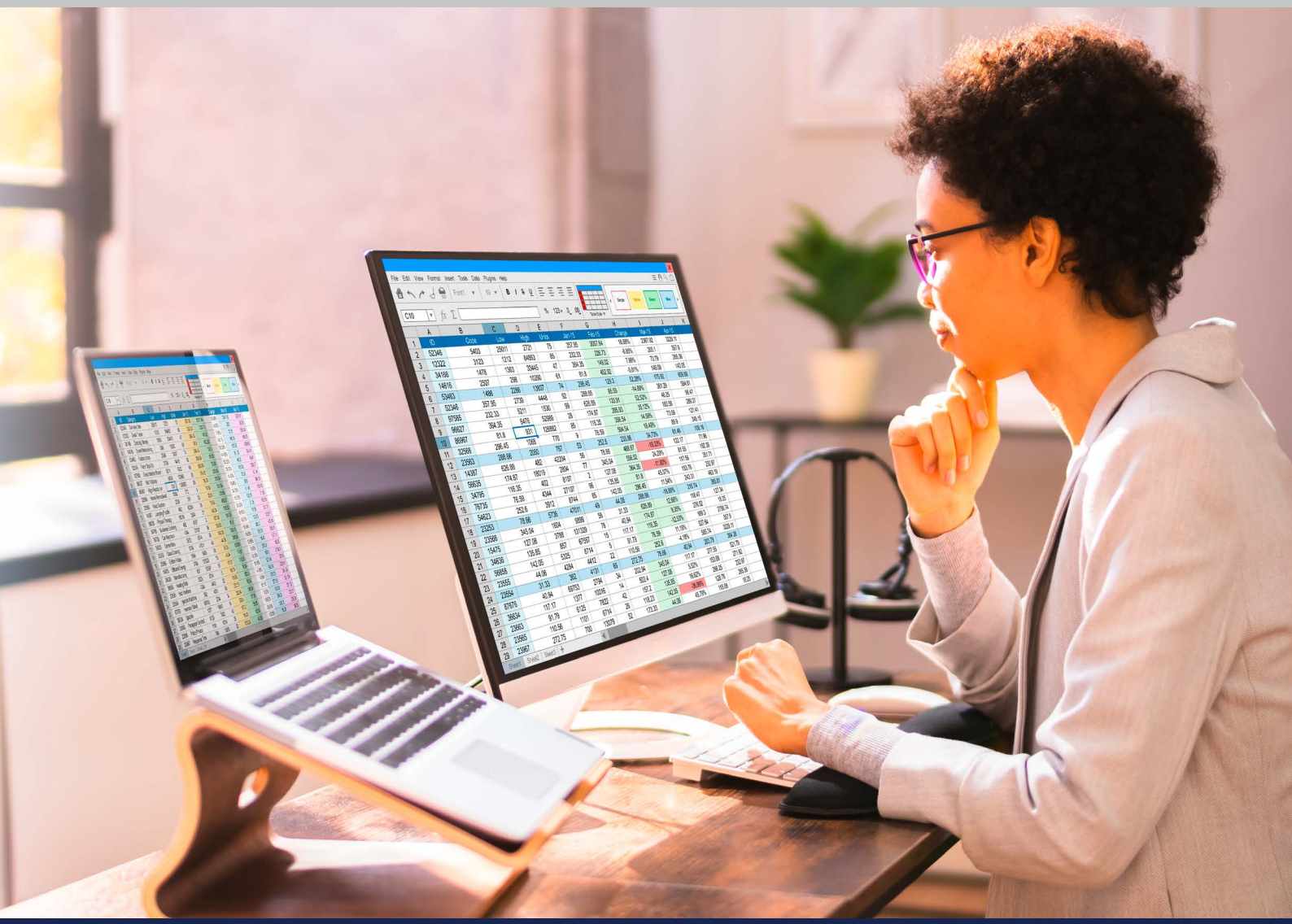

Stability Testing of Drug Products

Focus: EU and ICH Requirements

Dr Helmut Vigenschow

Dear Reader

Stay ahead of proposed regulatory changes in pharmaceutical stability testing. This „practical guide“ helps you navigate the evolving landscape of EU and ICH requirements, with special focus on the upcoming ICH Q1 draft guideline set for adoption in late 2025. Whether you‘re preparing marketing authorisation applications, managing product lifecycle changes, or ensuring compliance across different climatic zones, this resource simplifies complex regulatory concepts into actionable insights for your daily work. Essential reading for professionals seeking clarity on stability commitments and testing strategies.

About the Author

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Dr Helmut Vigenschow worked for Merckle/ratiopharm for 30 years in senior positions, including in the areas of project management, regulatory affairs, pharmaceutical development, quality assurance and quality control. He has been working as an independent consultant for several years now.

Stability Testing of Drug Products
Focus: EU and ICH Requirements

This whitepaper has been drafted to provide an overview and update on regulatory requirements related to stability testing. At present, a long list of ICH and EMA guidelines has been approved and most of them have been implemented more than 25 years ago. ICH published in May 2025 a draft guideline Q1 integrating most of the current EMA- and ICH concepts in one single guideline, which should be adopted around end of 2025.

Whereas the current ICH Q1A(R2) has two different sections for drug substances (2.1) and drug products (2.2), ICH Q1 (Draft) now states: Where “products” is mentioned by itself in this guideline, this is to be interpreted as “drug substances and drug products”.
Specific topics will be addressed in annexes to this ICH Q1.

Purpose of Stability Tests During Product Lifecycle

Studies to assess stability during the product lifecycle are performed in course of pharmaceutical development, already:

a) Development of stability-indicating analytical procedures.
This is based on information derived from stability data provided by the API manufacturer and stress tests at the drug product developer,

b) Selection of appropriate excipients
API-excipient mixtures are tested under high temperature or humidity to identify excipients which may negatively impact API stability.

c) Identification of the most stable formulation
Systematic tests of different formulation approaches under defined storage conditions are performed.

Once, a stable formulation with the intended clinical properties has been developed, pivotal real-time stability tests under conditions specified by ICH are initiated to create stability data for submission in the MA dossier.

Formulation or process changes in the commercial phase of the medicinal product, may trigger new stability tests to generate data supporting variation applications.

With a marketing authorisation application or a variation dossier, the marketing authorisation applicant or holder have to submit stability commitments to:

- continue stability tests until storage time covers the intended shelf-life
- initiate stability studies with lots of commercial batch size
- inform the regulatory authorities immediately in case of a confirmed out-of-specification (OOS) result with any of these batches

Types of Stability Studies

Formal stability studies

These are pivotal real-time (or primary), commitment, ongoing and product lifecycle stability studies, conducted under the accelerated, intermediate, or long-term storage conditions. The goal is to **establish or confirm a re-test period** (for APIs) **or a shelf life** (for drug products).

Supportive stability studies

Additionally, supportive stability studies are conducted where applicable and required. The goal is, to **support the practical use of the product**, including label claims, of a re-test period or a shelf life. Examples are: photostability studies, in-use stability tests, transport stability studies, or tests to assess short-term storage conditions.

Selection of Test Batches

The manufacturing process of batches to be included in formal stability studies should be representative for the intended commercial manufacturing process.
Any differences should be described and justified. To consider unavoidable batch-to-batch variability of the API, drug product batches included in stability batches should be manufactured by use of different API batches from each proposed API manufacturer.

Table 2: Considerations for Primary Stability Batches of Drug Substance and Drug Product

	Synthetic Chemical Entities	Biologicals
Drug Substance	• Same chemical synthetic route • Similar manufacturing process (differences justified) • At minimum, all batches manufactured at pilot scale[2] • Meet proposed registration specification • Containers constructed of the same material and type of container closure system as production batches.	• Same cell production system, if applicable • Similar manufacturing process (differences justified) • Meet proposed registration release specification • Containers constructed of the same material and type of container closure system as production batches. • Comparable to production batches (ICH Q5E)
Drug Product	• Same formulation[1] and dosage form • Minimum of 2 batches manufactured to at least pilot scale[2], other batch(es) can be smaller if justified • Same manufacturing process with equipment with the same operating principles. • Meet the proposed registration release specification • Same fill unless a reduced protocol design is applied[1] • Same container closure system as proposed for marketing	• Same formulation and dosage form • Comparable to production batches (e.g., ICH Q5E) • Meet proposed registration release specification • Same fill volume unless a reduced protocol design is applied[1] • Same container closure system as proposed for marketing.

Copied from ICH Q1 Draft

Study Design

Tests performed during pharmaceutical development

Studies conducted under **forced degradation conditions** such as elevated temperature, humidity, pH, oxidation and light are intended to deliberately degrade the sample. These studies are required to establish a degradation profile of the API and to develop stability-indicating analytical procedures. Forced degradation studies can be performed with one batch.

Studies conducted under **stress conditions** are not necessarily intended to deliberately degrade the sample. One batch is sufficient.

Photostability testing should be an important part of stress testing. Standard conditions are described in current ICH Q1B, which has been integrated to ICH Q1 (Draft).
Photostability testing is performed in two steps:

- forced degradation to evaluate the photosensitivity under extreme conditions
- confirmatory tests under realistic handling conditions for the API, only in case degradation is observed after forced degradation

Photostability testing of bulk formulations or formulations in primary packaging is only required for drug products with APIs which may degrade under realistic handling conditions.

Stability data to be included in the CTD stability section
Studies conducted under **accelerated condition**s like higher temperature and humidity are intended to increase the rate of chemical degradation and/or physical changes in the API or drug product. Accelerated testing is generally included in the formal stability program with 3 batches.

Pivotal stability tests are part of the stability program which has to be submitted with the marketing authorisation application. The pivotal stability program for drug products comprises tests of 3 batches of the same formulation under:

- „normal conditions“ and real time. Normal conditions are defined by the ICH with 25 ° and 60 % relative humidity, corresponding to mediterranean climate
- „accelerated conditions“ are defined as 40 °C and 75 % relative humidity

Intermediate storage conditions are not harmonised for all regions. This condition is either climatic zone **IVa** with 30°C and 65% relative humidity, or zone **IVb** with 30 °C and 75% relative humidity. Data obtained under storage condition IVb are required in some tropical countries like Brazil and Philipines.
3 batches of the same formulation and primary packaging must be included in pivotal stability tests.
The ICH Q1 (Draft) does not provide harmonized storage conditions, it just compiles regulatory requirements for different climatic zones and regions.

Re-test intervals
Re-testing of the stability samples should be performed in fixed intervals:

- Real time: during first year every 3 months, then every 6 or 12 months
- Accelerated: intervals could be less than 3 months depending on product stability

In case significant changes of parameters are observed at accelerated storage conditions, testing at intermediate storage conditions will be required. A minimum of 4 time points, including the initial time point is recommended.

Definition of "significant change"

- 5% change in assay from its initial value
- failure to meet the specification for degradation products
- failure to meet specification for dissolution testing
- failure to meet critical physical attributes (e.g., colour, phase separation, re-suspendability, hardness) and, when applicable, functionality tests
- failure to meet specification for pH

Product-specific tests

a) In-use stability testing

In-use stability testing should be initiated for multiple dose liquid products. The CPMP guideline on in-use stability has been integrated in the ICH Q1 (Draft) with only few clarifications. It is applicable to products intended for multiple dose applications or single dose drug products which are prepared and stored prior to administration. The test protocol should mimic the intended use of the drug product after the primary container is first breached. At least one of the batches should be at the end of its shelf life. The physical and chemical quality attributes selected for in-use stability testing should be appropriate to the individual dosage form and formulation.

b) Bottles with solid dosage forms

Some countries use special bottles which will be placed in hospitals on automated distribution equipment to prepare individual medication plans for patient. To support this process, stability tests should be performed on drug products in open and closed bottles. The MAH should define a realistic period for this specific test (e.g. 4 weeks).

c) Liquids with plastic cap

ICH Q1 (Draft) states that liquids with plastic dropper or caps should also be tested upside down.

d) Leachables and extractables

Testing for leachables and extractables must be performed for plastic primary packaging of liquid and semi-solid drug products and APIs.
The (Draft) ICH Q3E should be considered.

Interpretation of Results

ICH QE has been integrated to ICH Q1 (Draft) with the same decision tree and general approach to extrapolate from existing shorter-term data to shelf life or re-test period.
It is required that all tested parameters should comply with the proposed shelf-life specification. Up to a maximum shelf-life of 2 years, the extrapolation from stability data (X) to retest period (Y=2X) is possible if:

- data under accelerated test conditions show no change

or if data under accelerated show changes:

- long-term data backed by statistical analysis allow extrapolation

The re-test period for an API should not exceed that predicted for any single attribute tested. It is required to set extrapolated re-test periods with some safety margin, as it should be valid for future batches with release test results close to acceptance criteria.

Enhanced stability models for well-characterized molecules may be based on empirical fit of stability data to kinetic functions or incorporating prior knowledge into data evaluation. Annex 2 to ICH Q1 (Draft) describes additional recommendations on statistical tools and models to support the use of extrapolation and enhanced stability modelling approaches.

Integration of Stability Data in the CTD

Stability data generated to support formulation development will be integrated into Section 3.2.P.2 Pharmaceutical Development.

Stability data of the API are in most cases covered by the Applicants part of an ASMF/DMF and will be placed in Section 3.2.S.7.

Pivotal stability data on the drug product will be integrated in Section 3.2.P.8.

The regional part 3.2.R will contain the stability commitment in case the stability test has been conducted with pilot batches or does not cover the intended shelf-life for the product on the market. This case, the applicant must commit himself to
put the first 3 production-scale batches under real-time stability testing.
In addition, the applicant must commit himself to continue re-testing of the submission batches until end of shelf life, i.e. maximum 5 years. In any case, the competent authority must be informed immediately about any confirmed OOS result for the submission batches.

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