EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

ICH Q5C

Stability testing of Biotechnological / Biological products

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EMA guidance on Stability

ICH Q5C

- **Introduction**
- Scope
- Selection of Batches
- Stability indicating profile
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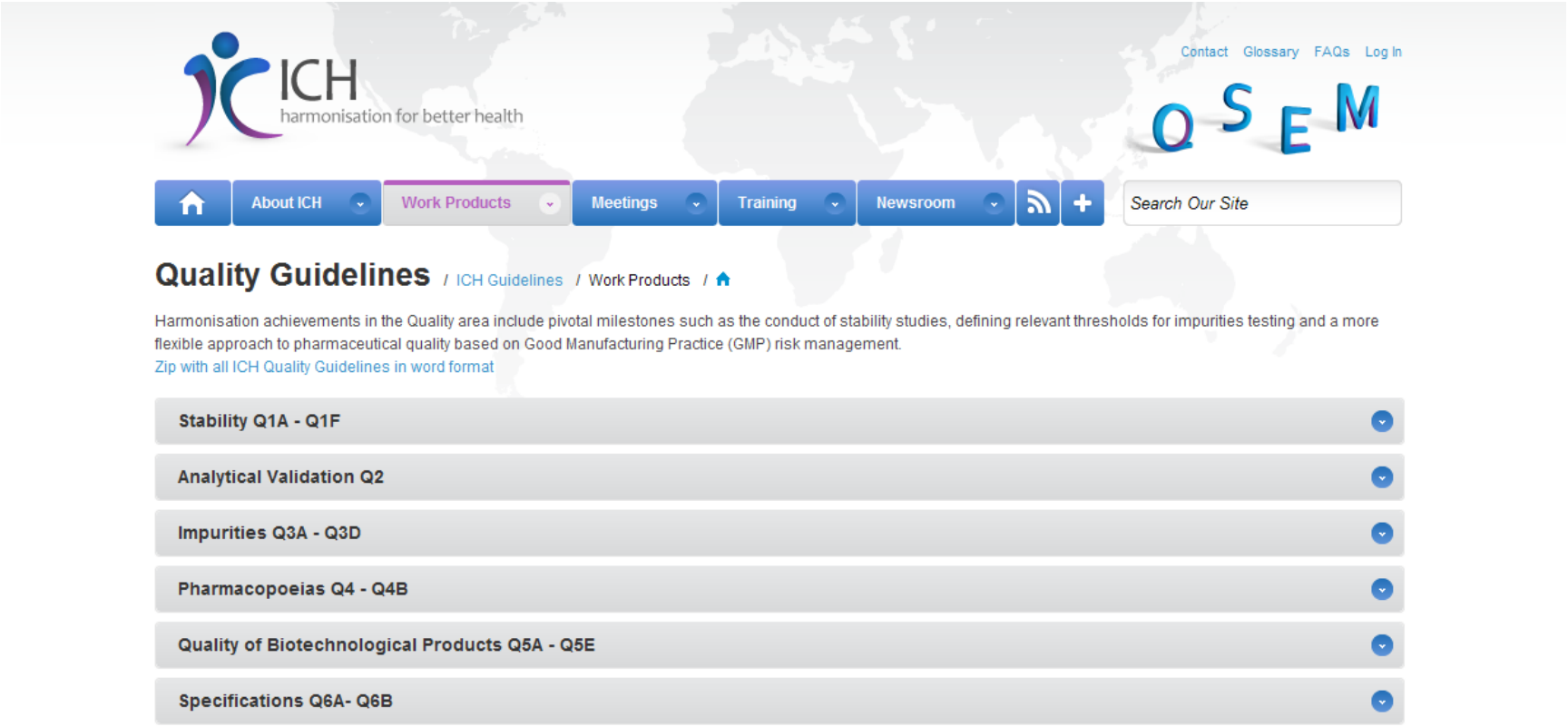
- Labelling

EMA guidance on Stability

ICH Stability guidelines

ICH website: www.ich.org



ICH guidelines on stability

- **Q1A - Stability testing for new drug substances and products (R2 - 2003)**
  - PARENT GUIDELINE.

    Defines the stability data package for registration of a new molecular entity as drug substance/drug product.
- **Q1B – Stability testing of new drug substances and products (1996)**
  - Recommendations on photostability testing
- **Q1C – Stability testing for new dosage forms (1996)**
  - Recommendations on new dosage forms for authorised medicinal products

ICH guidelines on stability (II)

- **Q1D – Bracketing and matrixing designs for Stability testing for new drugs substance and products (2002)**
  - Specific principles for the bracketing and matrixing in the study designs.
- **Q1E – Evaluation of Stability data (2003)**
  - Recommendations how to establish shelf life or retest period based on stability studies performed.

ICH/EMA guidelines on stability

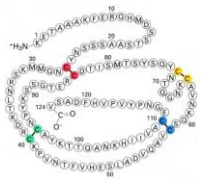
- ICH guidance on biologicals
  - Q5C: Stability testing of biotechnological/ biological products
    - Main reference for biological medicinal substances/products
  - Q1: some principles defined in Q1 guidelines are also applicable
- EMA guidance on stability
  - CPMP/QWP/609/96: Declaration of storage conditions
  - CPMP/QWP/2934/99: In-use stability testing
  - CPMP/QWP/159/96: Maximum shelf-life for sterile products after first opening or following reconstitution

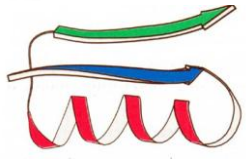
EU definition of Biological substance

In EU, a biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control. (Dir 2001/83/EC)

Why ICH specific guidance for biologicals? (I)

- Biological substances are complex molecules



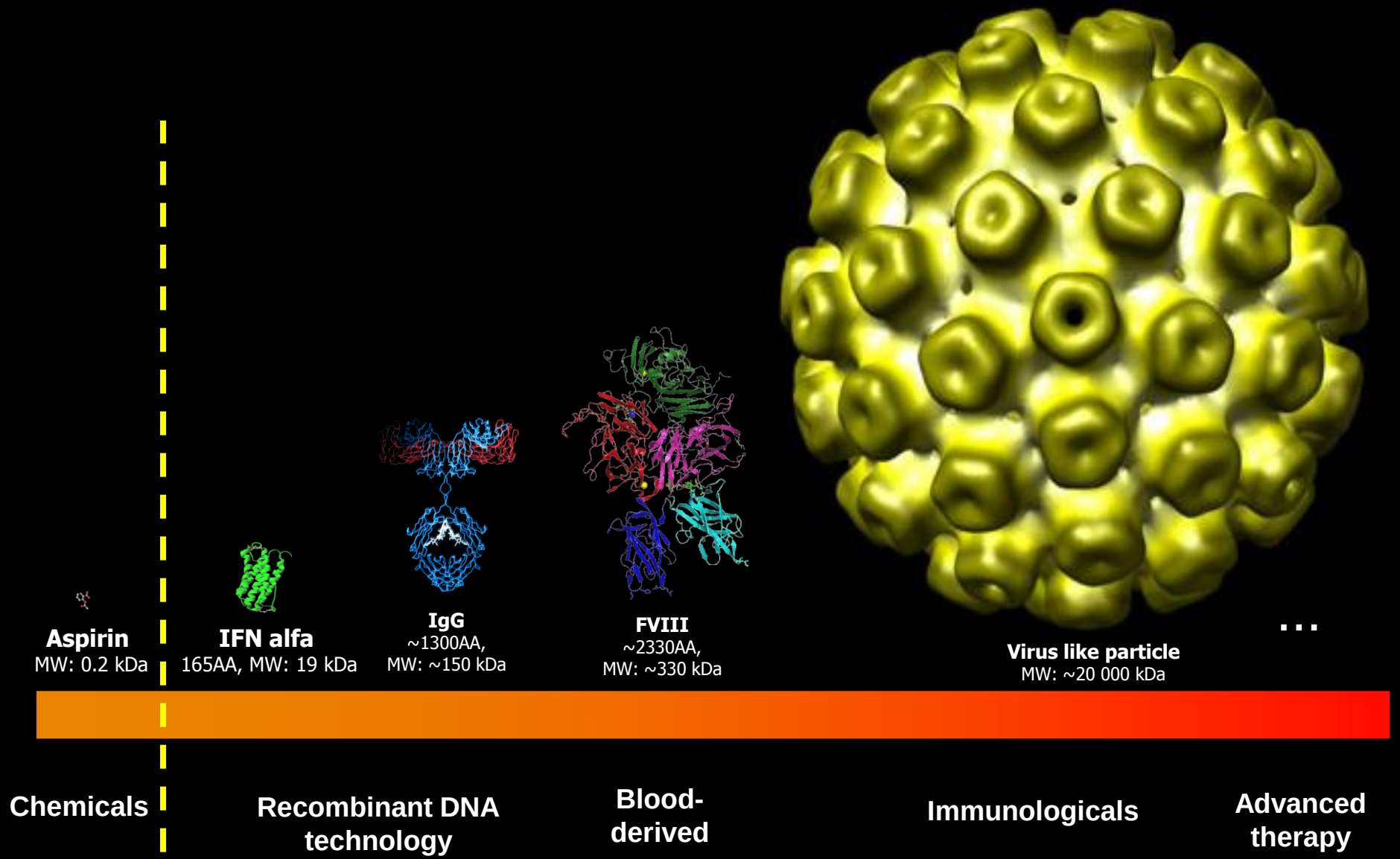


  - Primary structure: amino acid sequence of polypeptide chain
  - Secondary structure: α-helix, β-sheet - stabilised by hydrogen bonds
  - Tertiary structure: 3D structure of a single molecule folded

    into compact globule, stabilized by non-specific hydrophobic

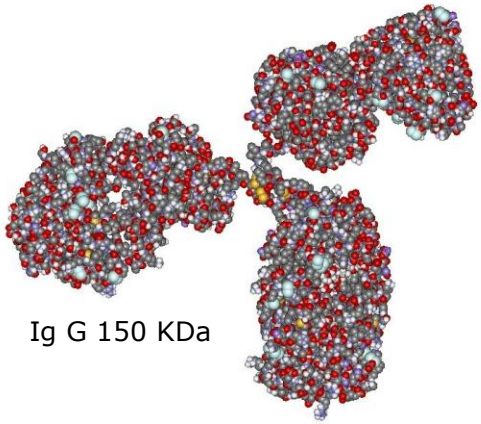
    interactions and specific interactions (salt bridges, H bonds, -S-S- bonds)
  - Quaternary: assembly of several polypeptide chains: non covalent interactions -S-S- bonds

Spectrum of complexity



Source: Dr Kowid Ho (Afssaps, France)

Protein instability


Ig G 150 KDa

Most common:

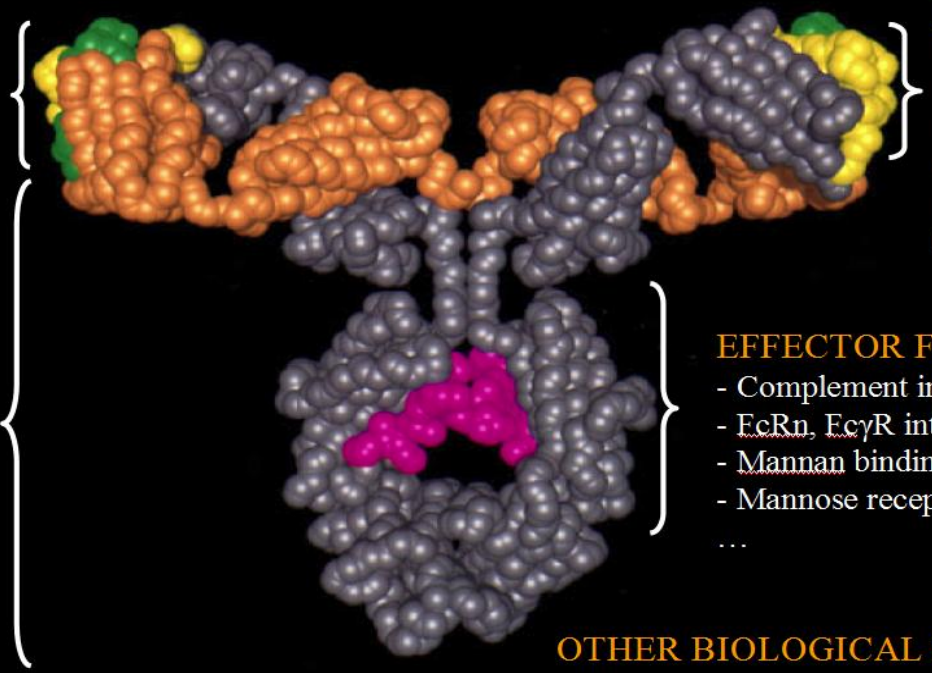
- Deamidation – hydrolysis of Asn and Gln side chain amides
- Oxidation – of Met, His, Cys, Tyr amnd Trp residues
- Denaturation - loss of 3-D structure
- Aggregation –association of monomers or native multimers covalent or non covalent
- Glycoproteins – most common instability of glycosylation hydrolysis of sialic acid residues.

Monoclonal antibody

PHYSICOCHEMICAL CHARACTERISTICS

VARIABLE REGION
- Deamidation
- Oxidation
- N-term Pyro-Glu
- Glycosylation
- Glycation
…

CONSTANT REGION
- Deamidation
- Oxidation
- Acetylation
- Glycation
- Glycosylation (fucosylation, sialylation, galactosylation, mannosylation…)
- C-term Lys
- Di-sulfide bond shuffling/ cleavage
- Fragmentation/clipping
…



BIOLOGICAL CHARACTERISTICS

BINDING
- Affinity
- Avidity
- Immunoreactivity / crossreactivity
- Unintentional reactivity
…

EFFECTOR FUNCTION
- Complement interaction
- FcRn, FcγR interaction
- Mannan binding ligand interaction
- Mannose receptor interaction
…

OTHER BIOLOGICAL PROPERTIES
- PK properties
- Epitope / Immunogenicity
- Modulatory region (Tregitope …)
…

Why specific guidance for Biologicals? (II)

- Maintenance of biological activity dependent on non-covalent, covalent interactions,
- Products particularly sensitive to environmental factors: temperature, oxidation, light, ionic content, shear,

STRINGENT CONDITIONS FOR STORAGE are usually necessary

Why ICH specific guidance for Biologicals? (III)

- The evaluation of stability may necessitate **complex analytical methodologies**
- Physicochemical tests alone are insufficient to characterize the product sufficiently to permit prediction of the biological activity

- Physicochemical
- Biochemical methods
- Immunochemical
- assay for biological activity

→

- analysis of molecular entity
- quantitative detection of degradation products

ICH Q5C

- Introduction
- **Scope**
- Selection of Batches
- Stability indicating profile
- Storage conditions
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EMA guidance on Stability

Scope of ICH Q5C

ICH Q5C was published as an Annex to the Tripartite ICH Guideline for Stability of new Drug substance and Products.

ICH Q5C intends to give **guidance** to applicants regarding the *type of stability studies* to be provided in support of *marketing authorisation applications* for **biological medicinal products**.

Medicinal products covered by ICH Q5C

ICH Q5C applies to **well characterised proteins and polypeptides** isolated or manufactured by rDNA technology.

COVERS:

- cytokines (IFN, IL, CSF, TNF)
- EPO
- plasminogen activators
- blood products
- growth hormones
- insulins
- monoclonal antibodies
- vaccines

DOES NOT COVER:

- antibiotics
- allergenic extracts
- heparins
- vitamins
- whole blood
- cellular/ blood components

ICH Q5C - General Principles

The applicant should:

- develop data to support the claimed shelf life
- consider any external condition affecting potency, purity and quality
- Primary data to support the requested shelf life should be based on **long–term, real time, real condition stability studies**. The design of the long-term stability program is critical
- Retest period not appropriate for biotech/biologicals

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Batch selection for a Marketing authorisation

Stability data for Drug substance

- At least **3 batches representative** of the manufacturing scale of production
- "Representative" data:
  - Representative of the quality of batches used in pre-clinical and clinical studies
  - Representative manufacturing process and storage conditions
  - Representative containers

Batch selection for a Marketing authorisation

Stability data for Drug substance (II)

- If shelf life claimed:
  - > 6 months: minimum **6 months data** at the time of submission
  - < 6 months: submission data discussed on a case-by-case basis

Batch selection for a Marketing authorisation

Stability data for Drug substance (III)

- At the time of Marketing Authorisation application, data from pilot-plant scale batches may be submitted
  - Pilot scale batches should be produced and stored in conditions representative of commercial scale
  - Pilot scale batches should use the same container/closure system
- A commitment to place the first 3 manufacturing scale commercial batches in a stability program after approval

Batch selection for a Marketing authorisation

Stability data for Intermediates

- May be critical to the production of finished product
- Hold time / storage step should be identified
- Generate in-house data and process limits should be defined
  - Appropriate validation and/or stability study should be performed
    - Usually documented in section:
      - on process validation when hold time / short storage (CTD 3.2.S.2.5 or 3.2.P.3.5)
      - on stability when significant storage period (CTD 3.2.S.7 or 3.2.P.8)

Batch selection for a Marketing authorisation

Stability data for Drug Product (DP)

- At least **3 batches** of the final container product, representative of manufacture scale
- DP batches should be derived from different batches of Drug substance
- If shelf life claimed:
  - > 6 months: minimum 6 months data at the time of submission
  - < 6 months: submission data discussed on a case-by-case basis

Batch selection for a Marketing authorisation

Stability data for Drug Product (II)

- Shelf life should be derived from representative **real time / real conditions data**. Data can be provided during the review and evaluation process.
- "Representative" data:
  - Representative of the quality of batches used in pre-clinical and clinical studies
  - Representative manufacturing process and storage conditions
  - Use final containers

Batch selection for a Marketing authorisation

Stability data for Drug Product (III)

- Shelf life will be based upon real time / real storage conditions data submitted for review
- Pilot scale batches may be submitted, with a commitment to place the first 3 manufacturing scale batches in long term stability program.

Sample selection

Full study design

Samples for every combination, all factors included in the design of the stability programme are tested at all time points

Reduced study design*

Samples for every combination of all design factors are NOT tested at all time points.

- Reduced design should be justified scientifically. Type and level of justification depends on available supporting data.
- Potential risk of establishing shorter shelf life due to more limited data.

*Q1D Bracketing and matrixing designs for stability testing.

Matrixing and Bracketing

Matrixing and Bracketing* study designs can be applied to the testing of new drug substances and products.

Bracketing

- Only samples on the extremes of certain design factors are tested at all time points
- Stability of any intermediate levels is represented by the stability of the extremes
- Bracketing is generally not applicable for drug substance

*Q1D Bracketing and matrixing designs for stability testing.

Bracketing (II)

- Can be applied to studies with multiple strengths of identical or closely related formulations
- Only samples on the extremes of certain design factors (e.g. strength, container size, fill) are tested at all time points.
- In certain cases, needs to be demonstrated that the extremes are representative.
- Bracketing can be applied to studies with the same container closure system whether either the fill volume and/or the container size change.

Bracketing (III)

Strengths

- Applicable without justification with multiple strengths with identical or closely related formulations.
- Applicable with justification to studies with multiple strengths where relative amounts of DS and excipients change in a formulation.
- Justification means that corresponding supportive data on the drug product are available (e.g. stability profiles of different strengths in clinical or development batches)
- Not applicable if different excipients are used among strengths.

Bracketing (IV)

Container closure size and /or fills

- Applicable without justification with same container closure system where either size or fill varies.
- If both container and fill vary, largest or smaller container may not represent the extremes of all packaging.
- Extremes should be selected comparing various characteristics (e.g. surface are to volume ratio, head space to volume ratio).

Example of a bracketing design

A medicinal product containing: pancreatic lipase

Strengths: 3,000, 5,000, 10,000, 15,000 Eur. Ph Units of lipase enzymatic activity.

Pharmaceutical form: HPMC Capsule shell containing enteric coated minitablets (same excipients proportions, manufacturing formula and batch size)

Packaged in type II amber glass bottles containing desiccants closed with a polypropylene screw cap containing 12, 50 and 150 capsules

			Strenghts												
			3,000 U. (minitablets)			**5,000 U.** (minitablets)			**10,000 U.** (minitablets)			**15,000 U.** (minitablets)			Desiccant amount
Batches			1	2	3	1	2	3	1	2	3	1	2	3	
Bottle volume	**30 ml**	12 units	**x**	**x**	**x**							**x**	**x**	**x**	**1 g**
	100 ml	50 units													**2,5 g**
	200 ml	100 units	**x**	**x**	**x**							**x**	**x**	**x**	**5 g**

Matrixing

- Matrixing is the design of a stability study schedule such that:
  - a selected subset of total number of possible samples for all factor combinations is tested at a specific time point.
  - at a subsequent time point, another subset of samples for all factor combinations is tested.
- Each subset of samples represents the stability of all samples at a given time point. Differences in the samples should be identified as:
  - covering different batches,
  - different strengths
  - different sizes of same container closure system.

Matrixing (II)

- A matrix design should be balanced such that each combination of factor is tested to the same extent over the duration of the studies
- Initial and final point values should be included in all samples
- All samples should be tested at the last time point before submission of application.
- Should retain the ability to detect stability differences within / among factors.

Matrixing example - timepoints

Examples of a matrixing in a long term stability study for one storage condition:

-One half reduction eliminates one in every two time points

-One third design eliminates one in very three time points

"One-Half Reduction"

Time point (months)			0	3	6	9	12	18	24	36
Strength	S1	Batch 1	T	T		T	T		T	T
		Batch 2	T	T		T	T	T		T
		Batch 3	T		T		T	T		T
	S2	Batch 1	T		T		T		T	T
		Batch 2	T	T		T	T	T		T
		Batch 3	T		T		T		T	T

Key: T = Sample tested

"One-Third Reduction"

Time point (months)			0	3	6	9	12	18	24	36
Strength	S1	Batch 1	T	T		T	T		T	T
		Batch 2	T	T	T		T	T		T
		Batch 3	T		T	T	T	T	T	T
	S2	Batch 1	T		T	T	T	T	T	T
		Batch 2	T	T		T	T		T	T
		Batch 3	T	T	T		T	T		T

Key: T = Sample tested

These examples reduce the number of tested time points in 32% and 18% respectively.

			Total time points		
Strengths	Container size	Batches	Extended	1/2 design	2/3 design
2	1	6	48	33 (68%)	38 (82%)

Matrixing example – timepoints + factors

3a Matrixing on Time Points

Strength	S1			S2			S3		
Container size	A	B	C	A	B	C	A	B	C
Batch 1	T1	T2	T3	T2	T3	T1	T3	T1	T2
Batch 2	T2	T3	T1	T3	T1	T2	T1	T2	T3
Batch 3	T3	T1	T2	T1	T2	T3	T2	T3	T1

3b Matrixing on Time Points and Factors

Strength	S1			S2			S3		
Container size	A	B	C	A	B	C	A	B	C
Batch 1	T1	T2		T2		T1		T1	T2
Batch 2		T3	T1	T3	T1		T1		T3
Batch 3	T3		T2		T2	T3	T2	T3	

Key:

Time-point (months)	0	3	6	9	12	18	24	36
T1	T		T	T	T	T	T	T
T2	T	T		T	T		T	T
T3	T	T	T		T	T		T

Medicinal product with:
- 3 strengths
- 3 containers
- 8 timepoints

tested in one storage condition

Full programme: 216 tests

Matrix on:
- timepoints: 171 tests (79%)
- factors + timepoints: 114 tests (53%)

ICH Q5C

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EMA guidance on Stability

ICH Q5C – Stability indicating profile

- there is no single stability indicating assay
- should be product-specific
- should allow the detection of any changes in purity, identity and potency
- methods validated at the time of submission

5.1 Protocol

- a detailed protocol for stability of DS and DP to support the shelf life and storage conditions
- necessary information to demonstrate the stability of the biotechnological / biological product through shelf life
- the design is critical for the successful establishment of shelf life

5.2 Potency

- is the specific ability or capacity of a product to achieve its intended effect (activity)
- based on the quantitative measurement of an attribute
- the attribute is indicative of the clinical effect
- compared to a reference material (calibrated versus an internal, national or international reference material)
- potency assays should be part of the stability studies

Potency (II)

- should be presented as units of biological activity calibrated versus
  - International reference standard (e.g. WHO) (if available), or
  - Nationally recognised reference standard, or
  - in-house reference standard

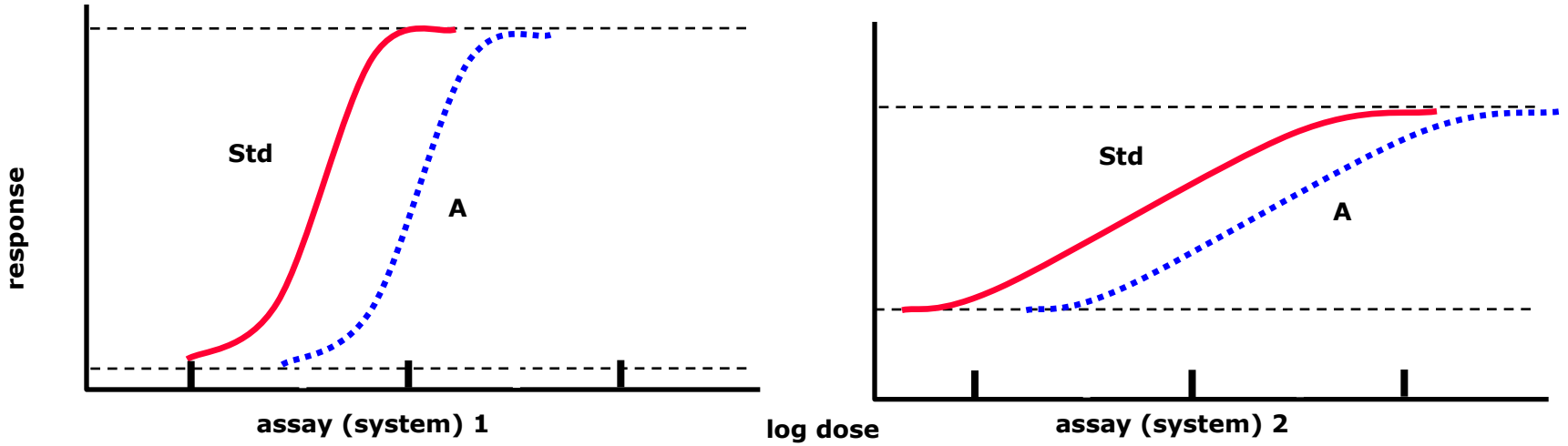
Potency assay

What characteristics should a potency assay have?

- stability indicating
- specific – likely impurities should not interfere
- activity of an unknown sample is measured relative to that of a reference standard of a similar material

Potency assay (II)

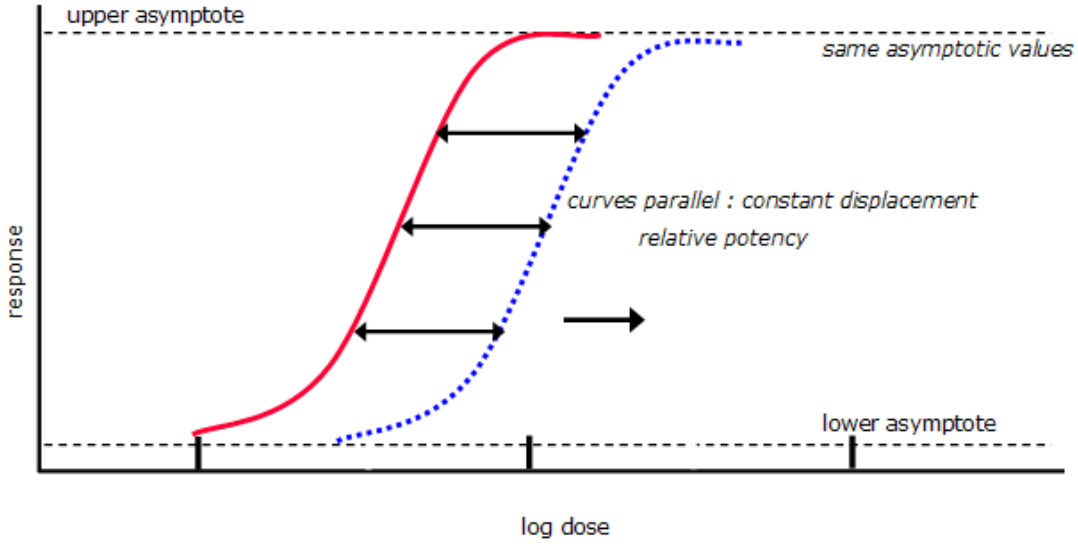
- Differences in the assay system should affect the test and reference preparations to the same extent



- Statistical analysis of results of biological assays and tests (Eur. Ph. General texts 5.3)

Potency assay - Functional similarity

- Functional similarity of the reference standard and sample is a fundamental condition for assay validity
- Displacement between the cures along concentration axis is constant and is a measure of the relative potency



Degradation products

Degradation products can interact with the performance of the bioassay

- If degradation products may not be functionally similar to original, no relative potency can be calculated: change of activity can be noted
- If degradation product is functionally similar to original, measured relative potency may not reflect degree of degradation

Degradation products - Example

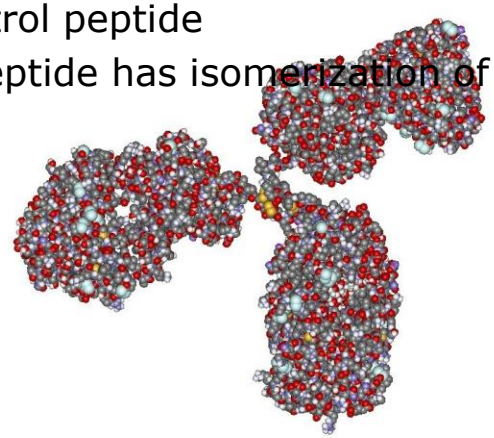
Bioassay alerts to degradation, then physicochemical analysis reveals nature of change

Rehder et al Biochemistry 2008, 47, 2518-2530

- Monoclonal antibody anti-EGFR, indication colorectal cancer

- When stored under certain conditions (increase Temp, decreased pH) decreased *in vitro* potency.

- Not due to aggregation or proteolysis, no change in molecular mass
- RP-HPLC: increased peak preceding light chain (LC) peak. Both LC & Pre-LC peak MW = 23641
- Peptide maps: additional early eluting peptide, same MW as control peptide
- Sequence analysis + Asp-N enzymatic digestion: early eluting peptide has isomerization of Asp-92
- Potency decreases with increase in iso-Asp at position 92



Potency assays: Limitation in stability studies

- Potency measurement may be complex to interpret – nature of change and percentage of degradation products
- Formulation may interfere with bioassay
- Changes need to be identified by some form of physicochemical assay
- Change in potency may alert to degradation not detected by other techniques

5.3: Purity and molecular characterisation

- Purity is a relative term, difficult to determine and method-dependent
- Stability studies: Test for purity should focus on methods for determination of degradation products.
- More than one method, purity value is method dependent
- In stability, purity tests should focus on determination of degradation products
- Limits of acceptable degradation should be derived from the analytical profiles of batches of the drug substance used in preclinical and clinical studies.

Purity and molecular characterisation (II)

- The use of relevant physicochemical, biochemical and immunochemical method to determine:
  - comprehensive characterisation (e.g. molecular size, charge hidrophobicity)
  - degradation changes (e.g. deamidation, oxidation, sulfoxidation, aggregation, fragmentation) during storage

Purity and molecular characterisation (III)

- when significative quantitative or qualitative changes in degradation products during long tem, accelerated or stress studies:
  - consider potential hazard
  - need to characterize and quantify degradation products within the long term studies
- Acceptable limits proposed and justified based on pre-clinical clinical batch studies.

5.4 Other products characteristics

Other characteristics should also be monitored for the drug product in the final container:

- **visual appearance (e.g. colour/opacity of solutions/suspensions)**
- **visible /subvisible particulates in solution / after reconstitution**
- **pH**
- **moisture levels (powders or lyophilised pdts.)**
- **sterility or alternative tests (at least initially or end of shelf life)**
- **additives (e. g. preservatives) that may degrade during storage**
- **container/closure**

Example of stability indicating profile of a recombinant protein

Non-glycosylated recombinant protein (150-180 aa)

Formulated with acetate and polysorbate 80

Overview of Analytical Test Procedures	
Parameter	**Test Method**
Appearance and Description	
Colour	–
Clarity	–
Identity	
Distribution in polyacrylamide gel acc. to protein molecular mass	SDS-PAGE
Distribution in chromatographic column acc. to protein hydrophobic properties	RP-HPLC
Purity/Impurities	
Purity and product-related impurities	RP-HPLC IE-HPLC
Dimers	SE-HPLC
Higher Molecular Weight Species other than Dimers (HMWs)	
Bacterial endotoxins content	Gel-clot method

Parameter	Test Method
Content/Potency	
Protein concentration	SE-HPLC
Potency	cell proliferation assay
Other tests	
pH	–
Particulate contamination: visible particles	–
Particulate contamination: sub-visible particles	–
Sterility	–
Acetate	Capillary Zone Electrophoresis (CZE)
Polysorbate 80	Spectrophotometry
Extractable volume	–

Examples of stability indicating tests profile of vaccine

Non-adjuvanted flu vaccine

split virion

Test	Time Points (Months)						
	0	3	6	9	12	18	24
Appearance	✓	✓	✓	✓	✓	✓	✓
HA Content	✓	✓	✓	✓	✓	✓	✓
Sterility	✓	NT	NT	NT	✓	✓	✓
Endotoxin	✓	NT	NT	NT	✓	✓	✓

NT, Not tested.

Surface bacterial antigen vaccine

Stability Protocol Testing Requirements

Assay	Time Points
Appearance	Initial, 3, 6, 9, 12, 18, 24 months
Antigenicity	Initial, 3, 6, 9, 12, 18, 24 months
Endotoxin	Initial, 12, 24 months
pH	Initial, 3, 6, 9, 12, 18, 24 months
Protein – Total	Initial, 3, 6, 9, 12, 18, 24 months
Sterility	Initial, 12, 24 months

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Humidity

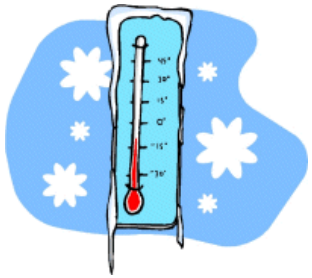
- Products are generally distributed in containers protecting against humidity. If demonstrated that container (& storage conditions) provide sufficient protection against high and low humidity, relative humidities can be omitted.
- if humidity protecting containers are not used,

appropriate data should be provided.

ICH Q5C Storage conditions - continues

TEMPERATURE

- most biologicals need precisely defined storage temperatures
- real time / real temperature studies are confined to the proposed storage temperature.



LIGHT

- case by case basis

Accelerated and Stress conditions

- Shelf life established based on **real time / real temperature data**

Accelerated studies

- supportive to establish shelf life
- can provide information on post development changes, validation of stability indicating tests
- generate help to elucidate the degradation profile
- testing conditions are normally one station higher than real storage conditions

Accelerated and Stress conditions (II)

Stress studies

- Representative accidental exposures to other conditions
- Determination of best product-stability indicators
- Can reveal patterns of degradation

Accelerated and Stress conditions (III)

- Conditions should be carefully selected on a case-by-case basis
- ICH Q1A recommends the following accelerated conditions related to the long term studies. ICH Q1A addresses climatic zones I and II.

Long term	Accelerated	Stress
≤-20°±5°C	+5°±3°C and/or +25±2°C/60%RH	temperature, pH, light, oxidation, shaking, freeze/thaw ...
+5°±3°C	+25±2°C/60%RH	
+25±2°C/60%RH or +30±2°C/65%RH	+40±2°C/75%RH	

Container/closure

- interactions may occur between product and container/closure
- data to be supplied for all different container/closure combinations
- where lack of interactions cannot be excluded -> determine the effect of the closure to be determined (horizontal, upright studies)

Additional stability studies

- In use stability for multidose presentations
  - requirement to demonstrate that the protein retains its full potency, purity and quality taking into account the repeated insertions and withdrawals
  - should be included in labelling
- Stability after reconstitution of freeze-dried
  - analysis of maximum storage period after reconstitution
  - inclusion in the labelling

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Protocol testing frequency

- Shelf life biologicals can vary
- ICH Guidance is based on a 0.5-5 years shelf life for most biologicals.
- The recommended intervals for long term studies in pre-licensing:

Shelf life	Testing frequency or real time studies	Testing points (months)
≤ 1 year	-Monthly for the first 3 months -3 months interval thereafter	0, 1, 2, 3, 6,9 and 12
> 1 year	-every 3 months during first year -every six months during second year -annually thereafter	0, 3 ,6 , 9 , 12, 18, 24, 36, 48...

- Post approval, if adequate stability is demonstrated, the applicant can propose a protocol suppressing some timepoints

ICH Q5C

- Introduction
- Scope
- Selection of Batches
- Stability indicating profile
- Storage conditions
- Testing frequency
- **Specifications**
- Labelling

EMA guidance on Stability

Specifications

- Should consider losses of activity, physicochemical changes, degradation during storage.
- No specific guidance on product classes.
- Includes stability indicating parameter
- Limits of acceptable degradation: justified taking into account levels observed in materials used in non-clinical / clinical studies
- Shelf-life specification acceptable, where appropriately justified (EU)
- All test parameters may not be required at all timepoints

ICH Q5C

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EMA guidance on Stability

Guidance

- ICH Q5C:
  - Specific recommendations should be stated (e.g. do not freeze)
  - Protection against light, humidity should appear on containers, packages and/or package inserts.
- EMA guidance on declaration of storage conditions in product information (CPMP/QWP/609/96/Rev 2)
  - Storage conditions should be be included in Summary of product characteristics (SPC), Package leaflet (PL), and product labelling.
  - Should be based on the demonstrated stability characteristics of the product
  - Terms ‘room temperature’ or ‘ambient conditions’ unacceptable

ICH Q5C

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EMA guidance on Stability

Information on Stability guidelines

-EMA website:

www.ema.europa.eu

home/regulatory

/human medicines

/scientific guidelines

EMA Stability guidelines

- Guideline on Stability testing: Stability testing of Existing active substances and related finished products (CPMP/QWP/122/02 rev 1 corr.)
- Stability Testing for Applications for Variations to a Marketing Authorisation (CPMP/QWP/576/96/rev 1.)
- Guideline on declaration of storage conditions: a) in the product information of medicinal products b) for active substances (CPMP/QWP/609/96 rev 2)
- Note for guidance on in-use stability testing of human medicinal products (CPMP/QWP/2934/99)

EMA Stability guidelines (II)

- Maximum Shelf-Life for Sterile Products for Human Use after first opening or following Reconstitution (CPMP/QWP/159/96 Corr.)

- Requirements for Quality documentation concerning investigational biological medicinal products in clinical Trials (EMA /CHMP/BWP/534898/2008) DRAFT

EMA Guidance storage conditions / labelling

- EMA guidance on declaration of storage conditions in product information (CPMP/QWP/609/96/Rev 2)
  - Storage conditions should be be included in Summary of product characteristics (SPC), Package leaflet (PL), and product labelling.
  - Should be based on the demonstrated stability characteristics of the product
  - Terms ‘room temperature’ or ‘ambient conditions’ unacceptable

EMA Guidance storage conditions / labelling

- Storage conditions statements in product information

Stability demonstration		Storage statement	Additional statement*
Long term	Accelerated (6 months)		
+25±2°C/60%RH or +30±2°C/65%RH	+40±2°C/75%RH	No special storage conditions	Do not refrigerate or freeze
+25±2°C/60%RH or +30±2°C/65%RH	-	Do not store above +30°C or +25°C	Do not refrigerate or freeze
+5±3°C	-	Store at +2-+8°C	Do not freeze
<0°C	-	Store at –XX°C	-

* where relevant

EMA Guideline on in-use stability testing (I)

•Attempts to define a framework for batch selection, test design, test storage conditions, test parameters and test procedures,... to be undertaken to define an in-use shelf life

BATCHES

•Minimum of two representative batches (at least pilot scale) should be tested.

•At lest one batch should be chosen at end of shelf life.

•If more than one container/strength, it should be tested in the at the final point.

EMA Guideline on in-use stability testing (II)

TEST DESIGN

- Simulate the use in practice considering filling volume, dilution/reconstitution
- Sampling should be done under normal conditions of use
- The appropriate physical, chemical and microbial properties susceptible to change should be monitored.
- If possible testing at initial, intermediate points and end of in-use shelf life on remaining content.

LABELLING

- In-use shelf life should be stated in the label and if space allows there should be space for the user to write the date of opening
- In use shelf life to be included in SPC, leaflet and outer carton text.

EMA Guideline on administration of sterile products (I)

Maximum shelf life for sterile products after first opening or following reconstitution (CHMP/QWP/159/96 corr)

- This guidance relates to the time between opening the product and administration to the patient,
- Difficult to predict how the opening, dilution, reconstitution and storage conditions are performed by the user
- Maintenance of the quality of the product that is administered to the patient is users responsibility
- Appropriate information to be included in the product information (SPC, PL, label)

EMA Guideline on administration of sterile products (II)

- Unpreserved sterile products

General

Chemical and physical in-use stability has been demonstrated for x hours/days at y °C.

From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbial contamination, the product should be used immediately.

If not used immediately, in-use storage times and conditions are the responsibility of the user.

Specific text for Preparations for Infusion or Injection

Chemical and physical in-use stability has been demonstrated for x hours/days at y °C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless reconstitution / dilution (etc) has taken place in controlled and validated aseptic conditions

EMA Guideline on administration of sterile products (III)

- Aqueous preserved sterile products or non-aqueous preparations

Chemical and physical in use stability has been demonstrated for x hours/days at y °C.

From a microbiological point of view, once opened, the product may be stored for a maximum of z days at t °C. Other in-use storage times and conditions are the responsibility of the user.

Example of storage conditions in PI

Example Herceptin (trastuzumab)

- Herceptin 150 mg powder for concentrate for solution for infusion
- Vial presentation containing L-histidine, thehalose dihydrate, polisorbate 20

SPC:

6.3 Shelf life

4 years

After reconstitution with water for injections the reconstituted solution is physically and chemically stable for 48 hours at 2°C – 8°C. Any remaining reconstituted solution should be discarded.

Solutions of Herceptin for infusion are physically and chemically stable in polyvinylchloride, polyethylene or polypropylene bags containing sodium chloride 9 mg/ml (0.9%) solution for injection for 24 hours at temperatures not exceeding 30°C.

From a microbiological point of view, the reconstituted solution and Herceptin infusion solution should be used immediately. The product is not intended to be stored after reconstitution and dilution unless this has taken place under controlled and validated aseptic conditions. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Package leaflet:

The following information is intended for medical or healthcare professionals only

Always keep this medicine in the closed original pack at a temperature of 2ºC – 8 ºC in a refrigerator.
A vial of Herceptin reconstituted with water for injections (not supplied) is stable for 48 hours at 2ºC – 8 ºC after reconstitution and must not be frozen.

Guideline on the Requirements for Quality Documentation Concerning Biological Investigational Medicinal Products in Clinical Trials

Draft

STABILITY

- Stability protocol should follow IC Q5C
- 1 Batch representative of material used in clinical trials. Same container.
- Accelerated and stress studies are recommended.
- For Phase III the applicant should have a comprehensive understanding of the stability profile of the Active substance.
- Shelf life based on long term real time / real condition. However extension of shelf life beyond this period may be acceptable, if supported by relevant data, including accelerated studies.
- Maximum extension not exceed two fold and should not be more that 12 months beyond the long term real conditions data.

Thank you for your attention

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