

Workshop - Mercoledì 10 giugno

Risk-based thinking come vera intelligenza per il mondo farmaceutico

Moderatori

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AFI

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PTM Consulting



SIMPOSIO EFT



Informed decisions
for better process

Workshop schedule

10:10 – 10:40

La nuova era dell'intelligenza del rischio

10:40 - 11:10

Nuova ICH Q1: Product Intelligence per un approccio innovativo alla stabilità

11:10 – 11:35

ICH Q3E: approccio risk-based integrato per la valutazione di E&L

11:35 – 12:00

Il dato come bussola: l'analisi statistica a supporto del rischio

12:00 – 12:25

Dalla teoria alla pratica: dalla gestione dello studio di stabilità all'analisi dei dati

12:25 – 12:30

Conclusione dei lavori



Informed decisions
for better process

New ICH Q1: Product Intelligence for an Innovative Approach to Stability

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Professional Consultant – PTM Consulting



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Contents

#1 – ICH Q1 Draft Guideline: situation and main changes

#2 – Stability and Product Lifecycle

#3 – Product Intelligence: Knowledge Management and Risk-Based Approach at the core of the new ICH Q1

#4 – Conclusions and take-home messages



ICH Q1 Draft Guideline: situation and main changes

Status of the project



Main changes (I/II)

TOPIC	NEW ICH Q1 (draft 2025)	CURRENT SITUATION (ICH Q1A-F AND Q5C)
SCOPE	○ Drug substances and drug products (already on market) ○ Small molecules and biopharm (including vaccines) ○ Biotech & ATMP (cell & gene therapy): Annex 3 ○ Combination products ○ Oligonucleotides, polysaccharides, polypeptides ○ Semi-synthetic drug substances and fermentation-derived drug substances	○ NME (New Molecular Entities) (Q1A R2)/new dosage forms (Q1C) ○ Focus on small molecules ○ Biotech: Q5C ○ ATMP not in scope
STRUCTURE	○ Consolidated document divided into 18 sections (from development to lifecycle) + 3 Annexes (bracketing/matrixing, stability modelling, ATMP)	○ Fragmented documentation: ○ Bracketing/matrixing (Q1D) ○ Statistical evaluation (Q1E) ○ Photostability: Q1B
REFERENCE STANDARDS/MATERIALS ADJUVANTS NOVEL EXCIPIENTS	○ New sections about stability data to support in use period	○ Not in scope of Q1A-F ○ Mentioned in Q5C
IN USE – SHORT TERM	○ Dedicated sections – clear definitions	○ Partially covered by Q1A (R2) ○ Requirements defined at regional level (EMA/FDA)

Main changes (II/II)

TOPIC	NEW ICH Q1 (draft 2025)	CURRENT SITUATION (ICH Q1A-F AND Q5C)
DATA EVALUATION	Predictive Role of statistical modelling with focus on scientific justification	Described in ICH Q1E (traditional statistical analysis for shelf life definition)
PHOTOSTABILITY	- Integrated in the process with updated requirements for new packaging systems - Related to design, Container Closure System and label claim	Q1B as a stand-alone guideline
CLIMATIC ZONES	Extended to all climatic zones with harmonization of Zones III and IV	Previously in the withdrawn Q1F in June 2006, definition of storage conditions in Climatic Zones III and IV left to the respective regions and WHO.
HOLDING TIMES	Specific requirements for processing holding times for intermediates and bulk	GMP management

Overview of Public Consultation comments (I/II)

TOPIC	% OF TOTAL COMMENTS	EXAMPLES	% OF CRITICAL COMMENTS (TOT 92)
BATCH REQUIREMENTS (PRIMARY VS PRODUCTION)	18%	○ Number of batches, definitions, more stringent requirements for biologics and vaccines ○ Poor sustainability for ATMP (low volume drugs) ○ More stringent requirement than the current ones (Q1A/Q5C).	16%
DEFINITION, TERMINOLOGY AND GLOSSARY	15%	○ Inconsistent use of key terminology “products”, “synthetics”, “biologics”, “primary batch”, “definition of “significant change” ○ Lack of adequate glossary	12%
STANDARD APPROACH VS ENHANCED APPROACH, FLEXIBILITY RISK-BASED	12%	○ Confusion about enhanced approach for biologics ○ How to document alternative approaches ○ Lack of definition, examples not exhaustive ○ No link of development/stress studies to enhanced modelling, no clear differences between enhanced and predictive models (if any)	8%
TESTING FREQUENCY	10%	○ Monthly testing for the first 3 months for products with shelf life ≤12 months: not supported by ICH Q1A(R2). ○ Requirement of annual sterility (CCIT) non aligned with current Q5C	13%

Overview of Public Consultation comments (II/II)

TOPIC	% OF TOTAL COMMENTS	EXAMPLES	% OF CRITICAL COMMENTS (TOT 92)
STRESS STUDIES/FORCED DEGRADATION	8%	○ Differences between stress and forced degradation, ○ Lack of definition of target degradation levels ○ Confusing requirement for ATMP	5%
PACKAGING / CONTAINER CLOSURE SYSTEM (CCS)	8%	○ Expectations for justification of use of different sizes ○ Extractable/leachables not mentioned (implied in «compatibility») ○ Slight differences in primary packaging (e.g. child-resistant packaging cases) not included in justification approach	-
DRUG-DEVICE COMBINATION PRODUCTS	5%	○ When to include administration-dependent parameters in stability studies when they are the same as CQAs ○ Make more clear the boundaries of this guideline wrt design verification studies (ref. ISO 13485:2016) for functional performance characteristics of the device constituent alone, where the drug does not chemically influence performance	10%
STATISTICS, MODELLING AND EXTRAPOLATION	5%	○ Requirement to use tolerance intervals in mixed models → considered technically incorrect ○ Requirement of ≥5 batches for mixed models → considered overly demanding ○ Extrapolation for biologics: too many limitations	15%
ATMP AND SPECIAL CASES	4%	○ Need for more detail on cell-based products, mRNA, non-cryopreserved products, very short shelf lives ○ Guidance considered not exhaustive for mRNA, ATMP, adjuvants	7%
PHOTOSTABILITY	4%	○ Differences between confirmatory and forced photodegradation studies ○ Clarify the scope of the flow chart (development, post approval changes, or both) ○ Batches to be used for confirmatory photostability studies ○ Clarify decision making process for use of Option 1/2/3 ○ Clarify definitions “e.g. “cool white”)	-

CORE CHANGES

Highly prescriptive and rigid requirements

Alternative approaches are encouraged, with appropriate justification

Science & risk based principles through product lifecycle (ICH Q8-10 and Q12)



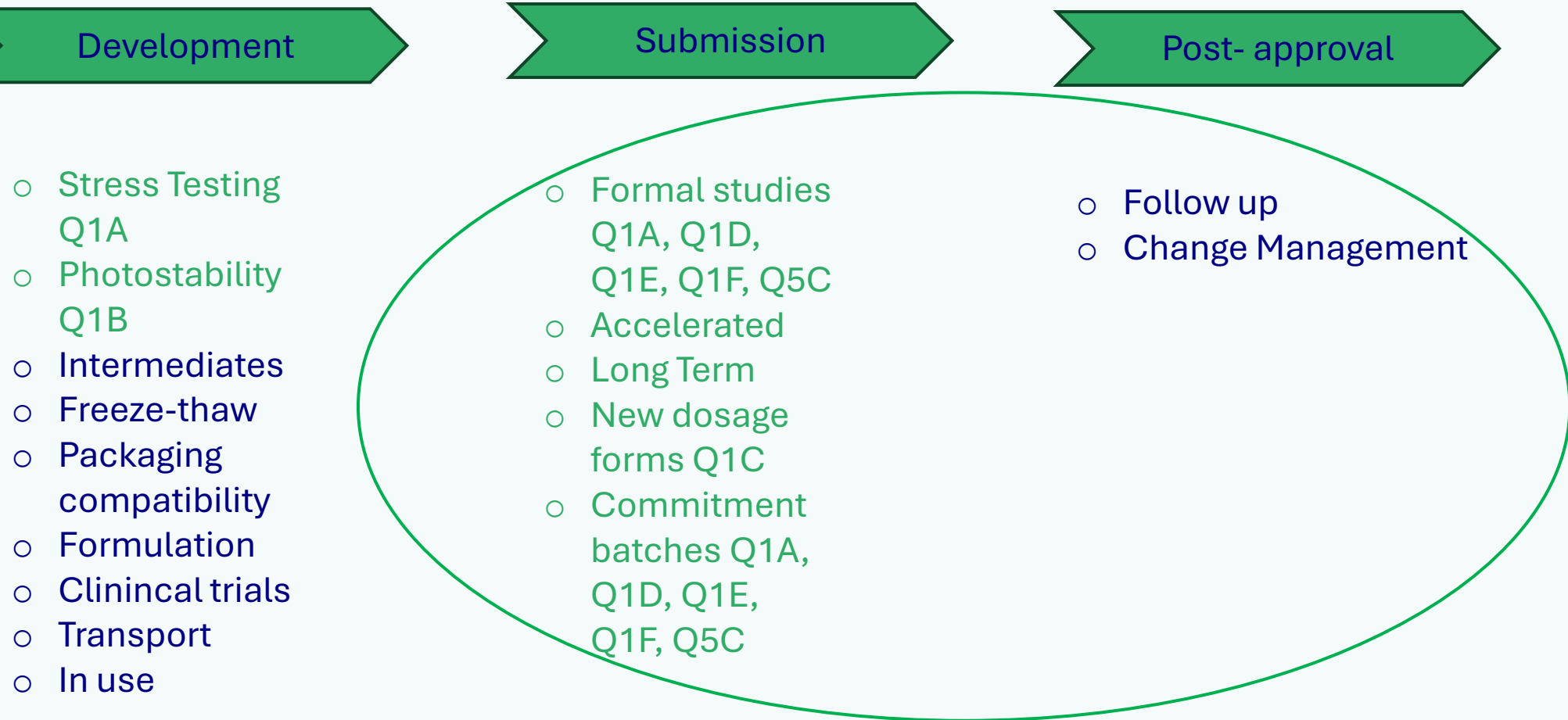
Stability focused on registration

Registration + post approval Lifecycle (focus on control strategy & change management)



Stability and Product Lifecycle

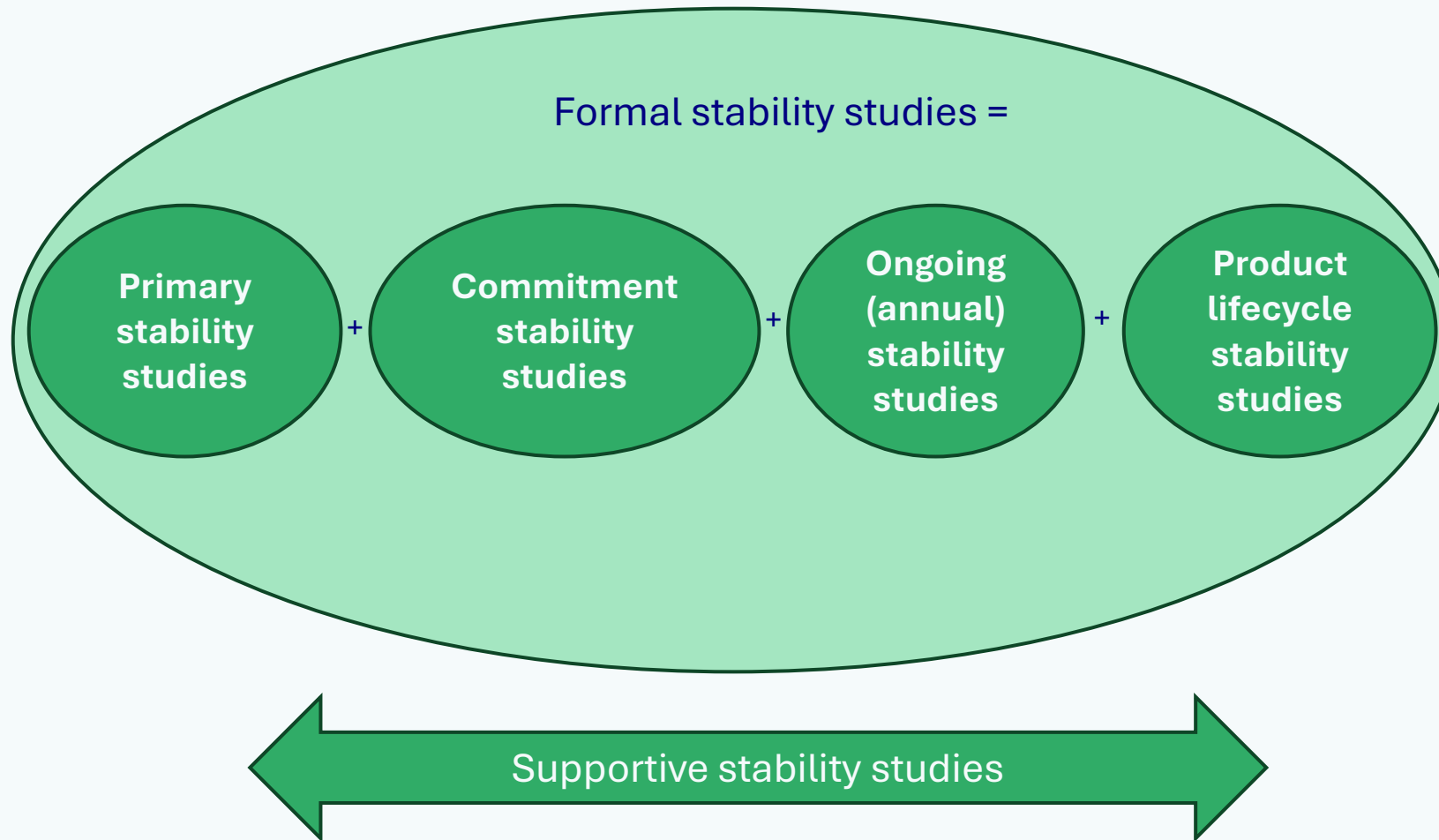
STABILITY STUDIES DURING A PRODUCT LIFECYCLE

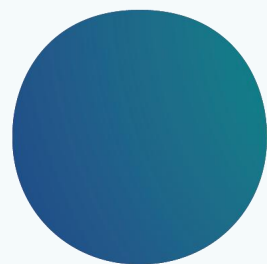


DESCRIBED in ICH Q1A-F/Q5C

NOT DESCRIBED in ICH Q1A-F /Q5C

FORMAL STABILITY STUDIES

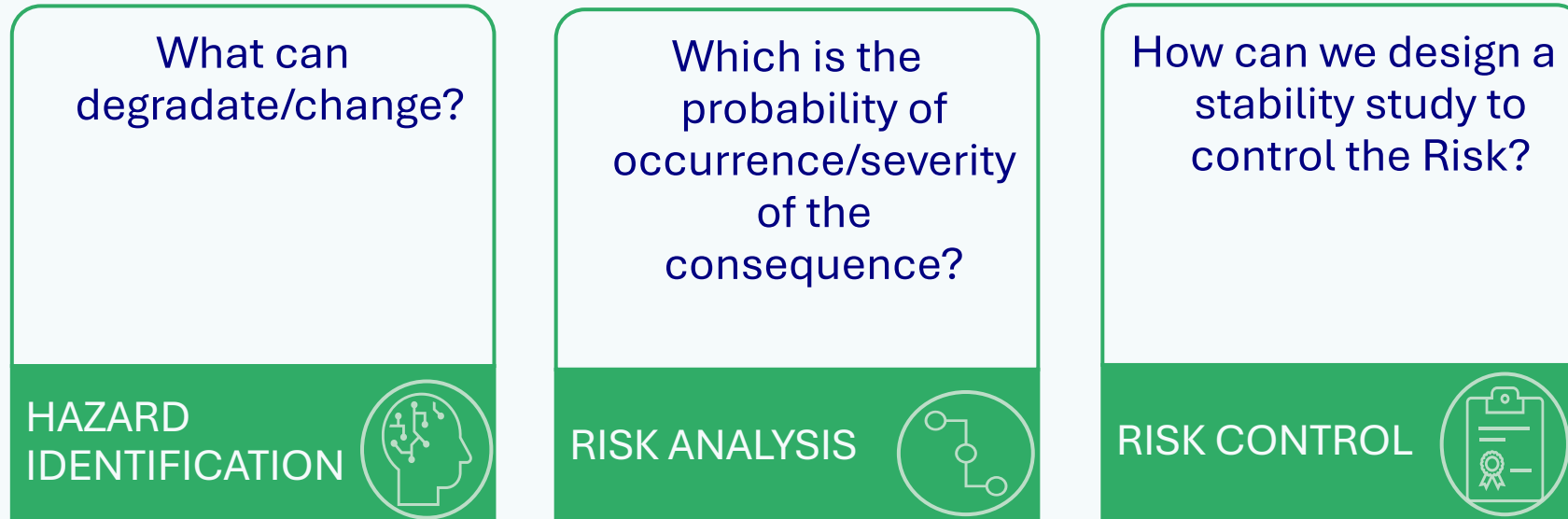




Product Intelligence

Knowledge Management and Risk-Based Approach at the core of the new ICH Q1

Quality Risk Management in Stability



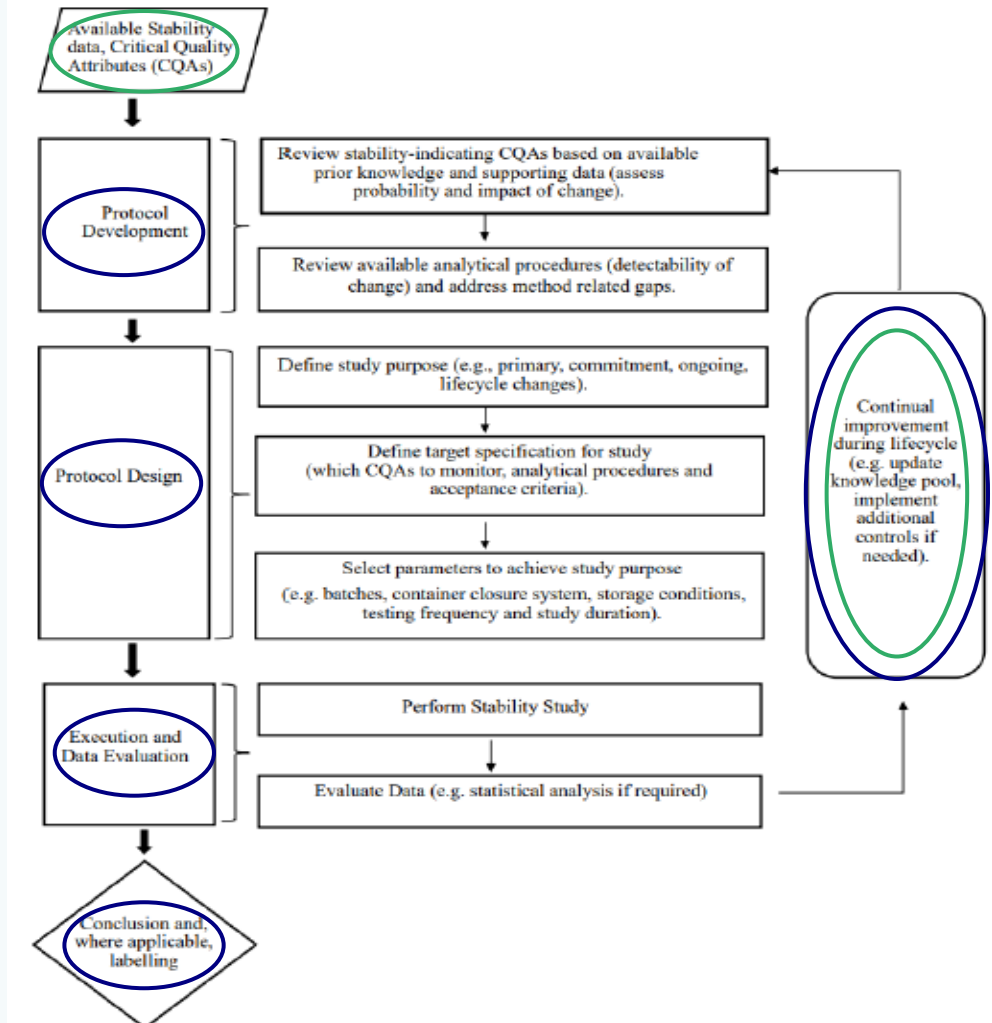
*QRM in Stability means the opportunity to conduct **PRODUCT SPECIFIC** stability protocols based on the output of the Risk assessment.*

Product Intelligence: Knowledge and Quality Risk Management through Product Lifecycle

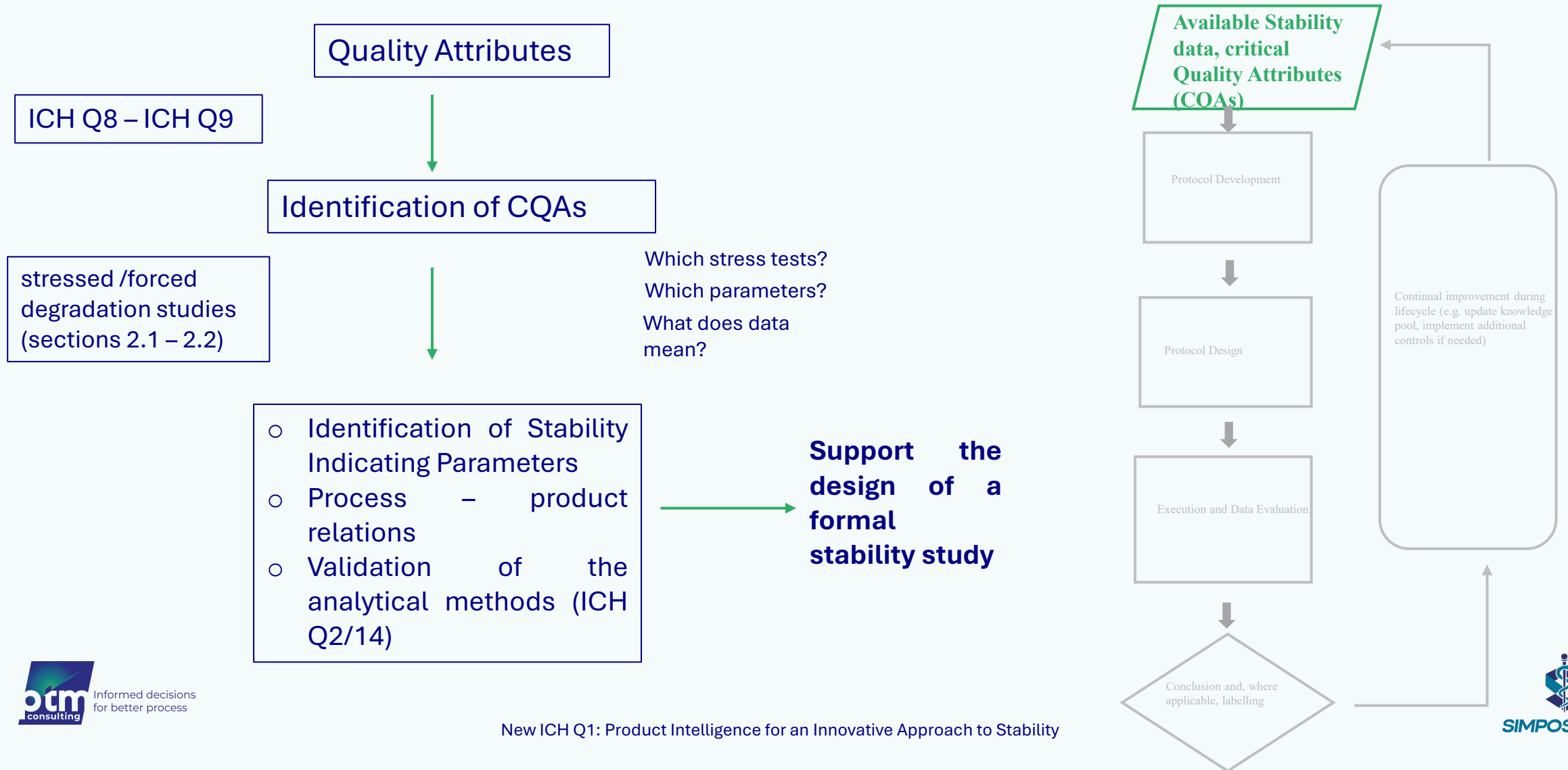
- Current ICH: list of technical activities
- ICH Q1: flexible approach sustained by appropriate tools and objective methodology
- Synergic Combination (Continuous Improvement during Product Lifecycle)

ICH Q1 STABILITY STUDIES FOR DRUG SUBSTANCES AND DRUG PRODUCTS

Figure 2: General Process Flow for the Development, Design and Execution of a Stability Protocol



Product Knowledge - Process Understanding

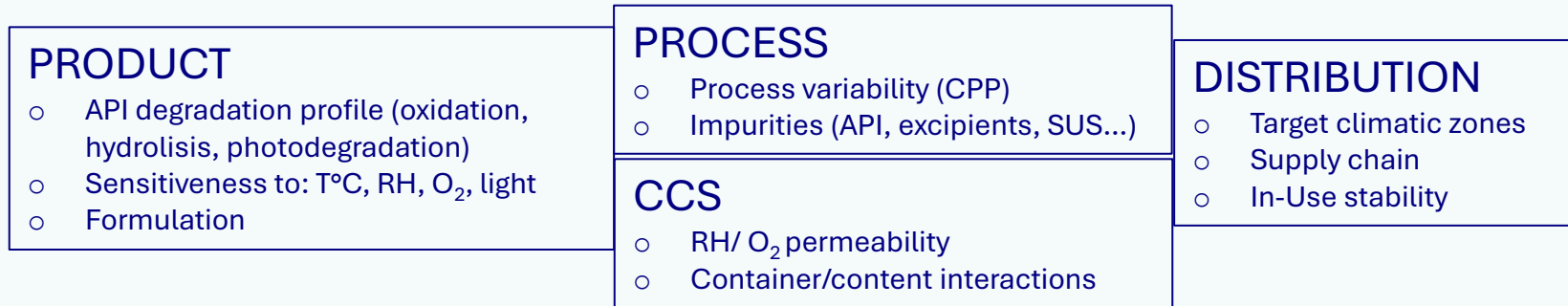


QRM in Protocol Development e Protocol Design

PRE-REQUISITES

- CQA and Stability Indicating Parameters identified
- Relevant Analytical methods Validated

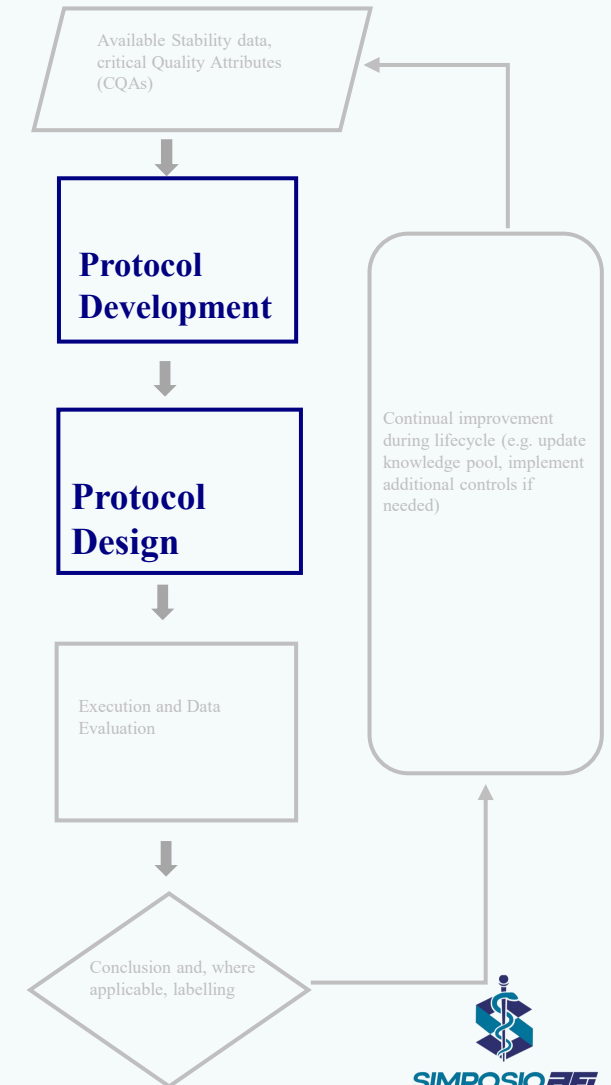
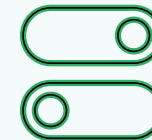
STRUCTURED RISK ASSESSMENT considering:



RISK BASED STABILITY STUDY DESIGN:



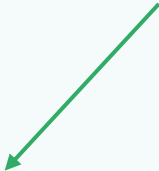
- Selection of the stability conditions
- Number of batches (based on variability)
- Testing frequency
- Testing based on stability indicating parameters



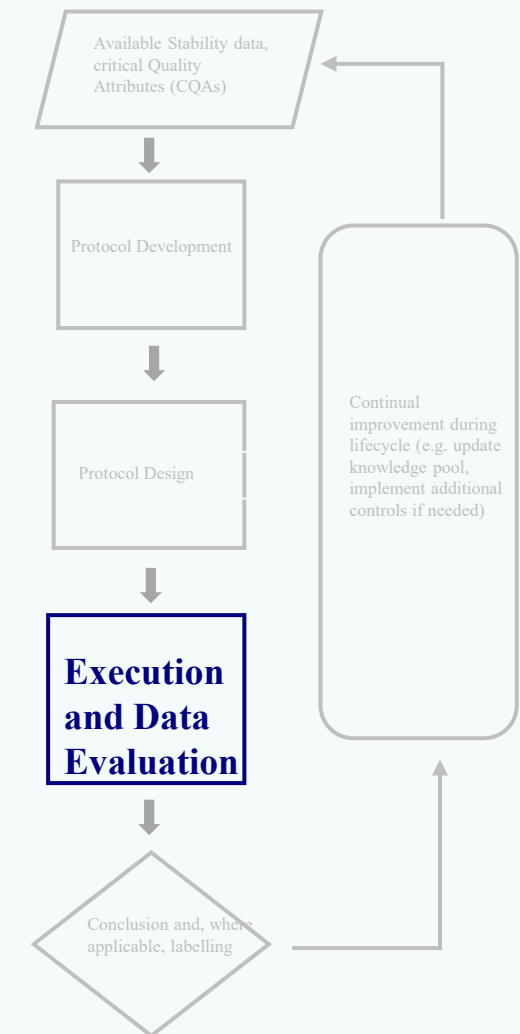
Stability Protocol Execution and Data Evaluation

Shelf life/retest period definitions based on:

- Available data
- Level of uncertainty (risk-based extrapolation)


HIGH BUSINESS RISK:
conservative approach


LOW BUSINESS RISK + SCIENTIFIC KNOWLEDGE:
Enhanced predictive approach (ASAP studies)



QRM in labelling

WHEN

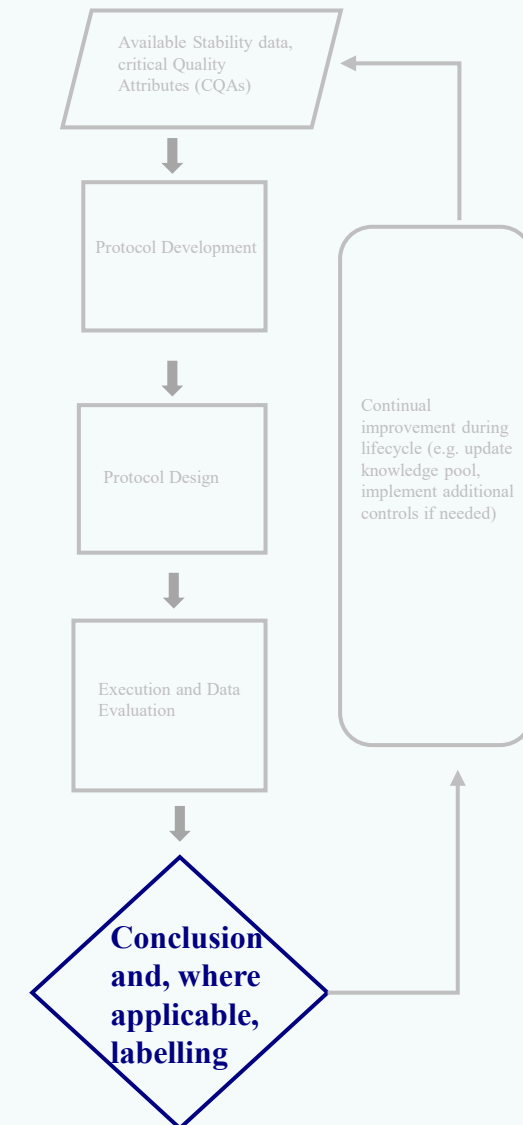
- after stability study completion
- after supply chain definition

WHAT

- assessment of the risk and impact of product handling, transport, storage excursion

PRE-REQUISITES

- Known degradation pathways
- Demonstrated robustness of mathematical models
- Significant data available



Product Knowledge – Process Understanding in Product Lifecycle

ON-GOING / LIFECYCLE STABILITY STUDIES

- Identify the impact of variations/changes in manufacturing process
- Predict OOS
- Confirm assumptions on shelf life predictions through commercial batches data

RISK – BASED APPROACH

BATCH SELECTION

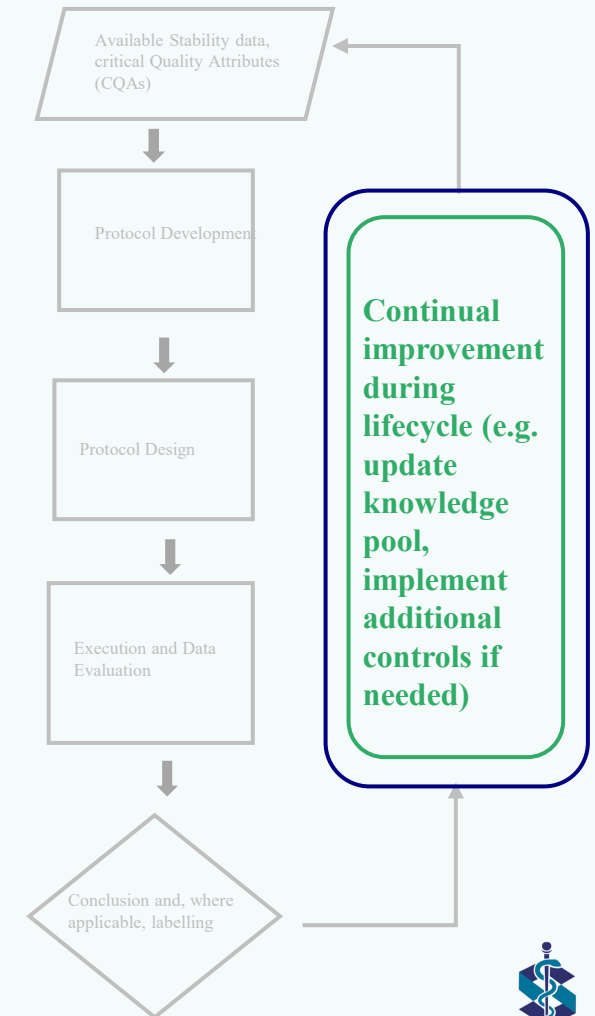
- Change control
- Process deviations
- Complaints

TESTING FREQUENCY

- Historical data evaluations
- OOS/OOT review



- CAPAs
- Re-design of the studies
- Shelf-life re-evaluations





Conclusions and take-home messages

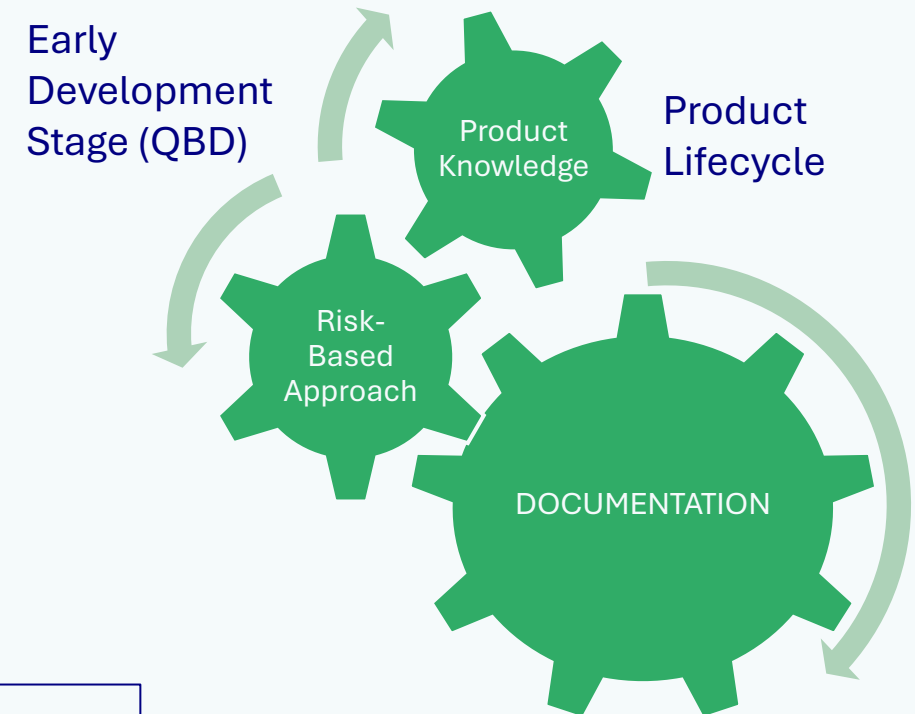
New ICH Q1 and Product Intelligence: from passive and standard to proactive and customized approach

Development: KM and QRM support **Strategic design**
On-going: KM and QRM drive **Process Improvement**

Predictive roles of statistical modelling

Shorter submission times: availability for patients and competitive advantage

Greater *flexibility* while maintaining *regulatory confidence*



Thanks for listening

New ICH Q1: Product Intelligence for an Innovative Approach to Stability

Knowledge Management and Risk-Based Approach at the core of the new ICH Q1



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Any questions?

Do you need any information?

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