Workshop - Mercoledì 10 giugno

SIMPOSIO AFI

Risk-based thinking come vera intelligenza per il mondo farmaceutico

Moderatori

Piero Iamartino
AFI

Paolo Mazzoni
PTM Consulting

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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

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

Benedetta Vietti
Professional Consultant – PTM Consulting

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Contents

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 requirments 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 biologicals ○ 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 shellf 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

Stability focused on registration

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

Alternative approaches are encouraged, with appropriate justification

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

Stability and Product Lifecycle

STABILITY STUDIES DURING A PRODUCT LIFECYCLE

Development

- Stress Testing Q1A
- Photostability Q1B
- Intermediates
- Freeze-thaw
- Packaging compatibility
- Formulation
- Clinincal trials
- Transport
- In use

Submission

- Formal studies Q1A, Q1D, Q1E, Q1F, Q5C
- Accelerated
- Long Term
- New dosage forms Q1C
- Commitment batches Q1A, Q1D, Q1E, Q1F, Q5C

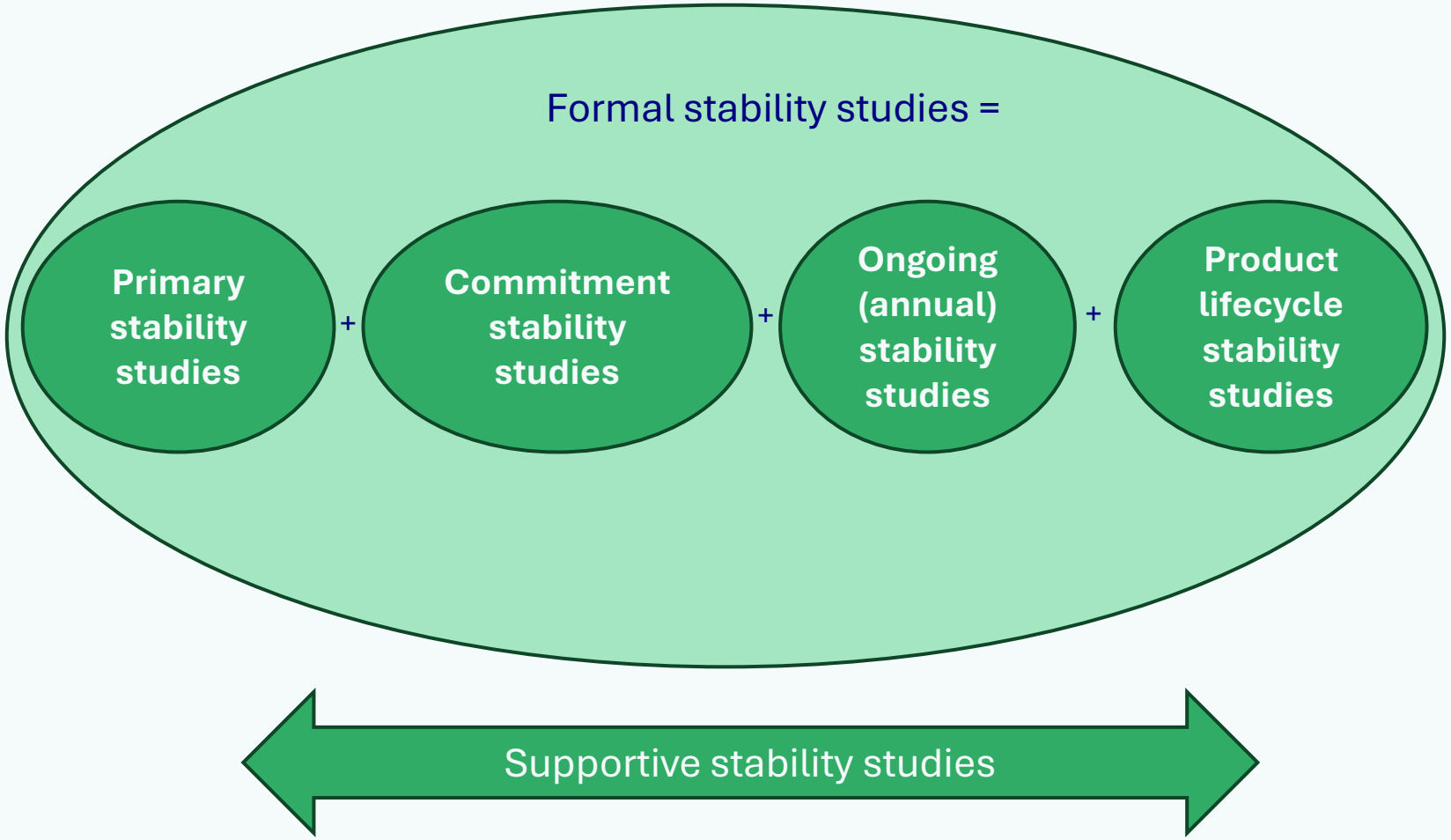
Post- approval

- Follow up
- Change Management

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

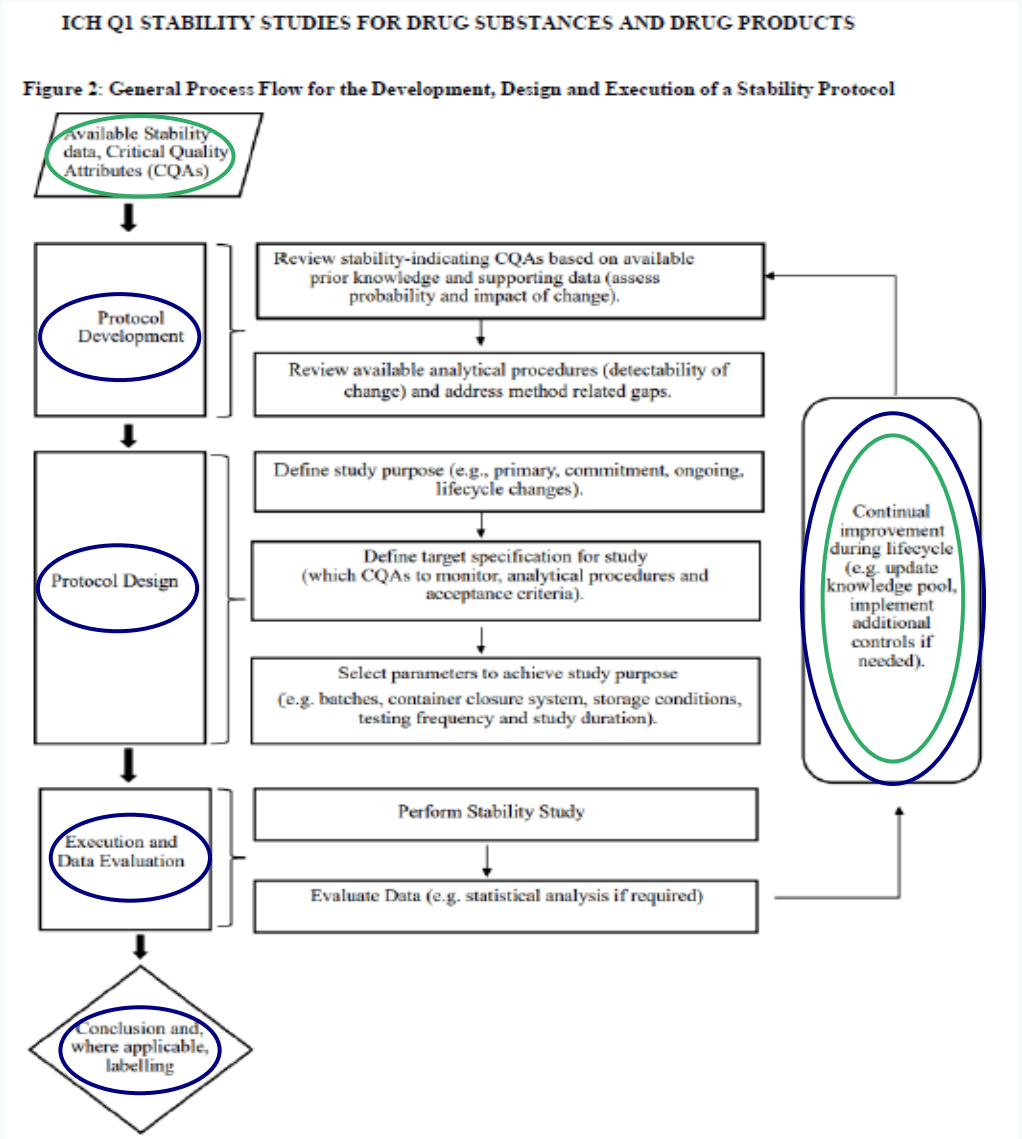
Quality Risk Management in Stability

What can degradate/change?	Which is the probability of occurrence/severity of the consequence?	How can we design a stability study to control the Risk?
HAZARD IDENTIFICATION	RISK ANALYSIS	RISK CONTROL

*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)



Product Knowledge - Process Understanding

Quality Attributes

ICH Q8 – ICH Q9

Identification of CQAs

stressed /forced degradation studies (sections 2.1 – 2.2)

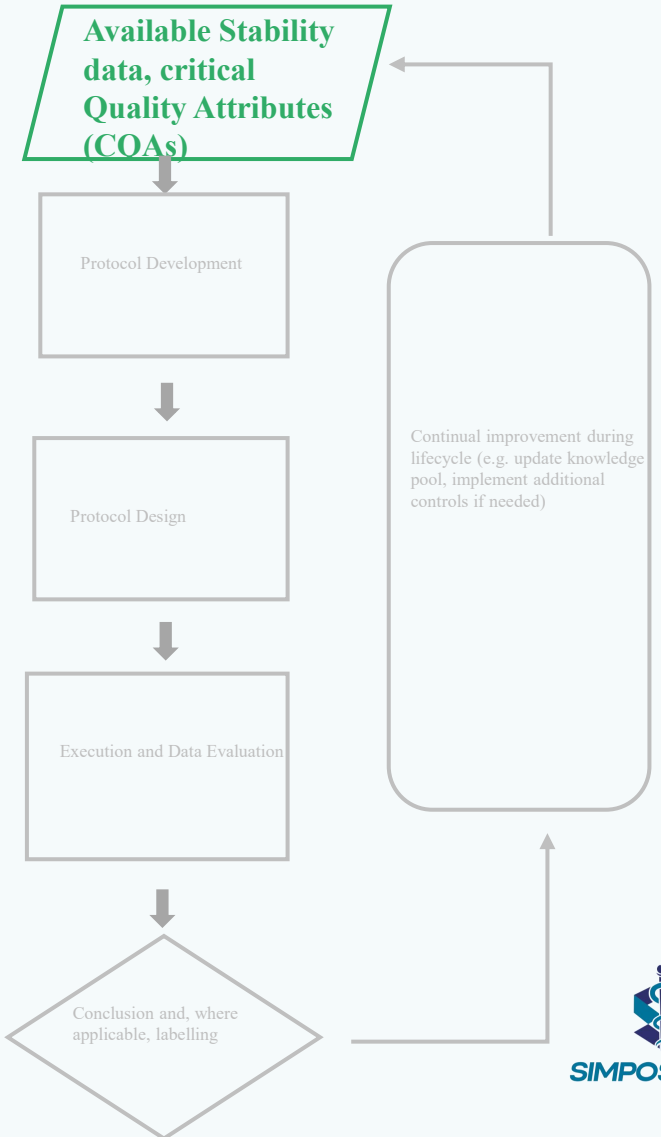
Which stress tests?

Which parameters?

What does data mean?

- Identification of Stability Indicating Parameters
- Process – product relations
- Validation of the analytical methods (ICH Q2/14)

Support the design of a formal stability study



QRM in Protocol Development e Protocol Design

PRE-REQUISITES

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

STRUCTURED RISK ASSESSMENT considering:

PRODUCT
- API degradation profile (oxidation, hydrolisis, photodegradation)
- Sensitiveness to: T°C, RH, O_2, light
- Formulation

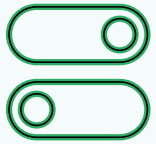
PROCESS
- Process variability (CPP)
- Impurities (API, excipients, SUS…)

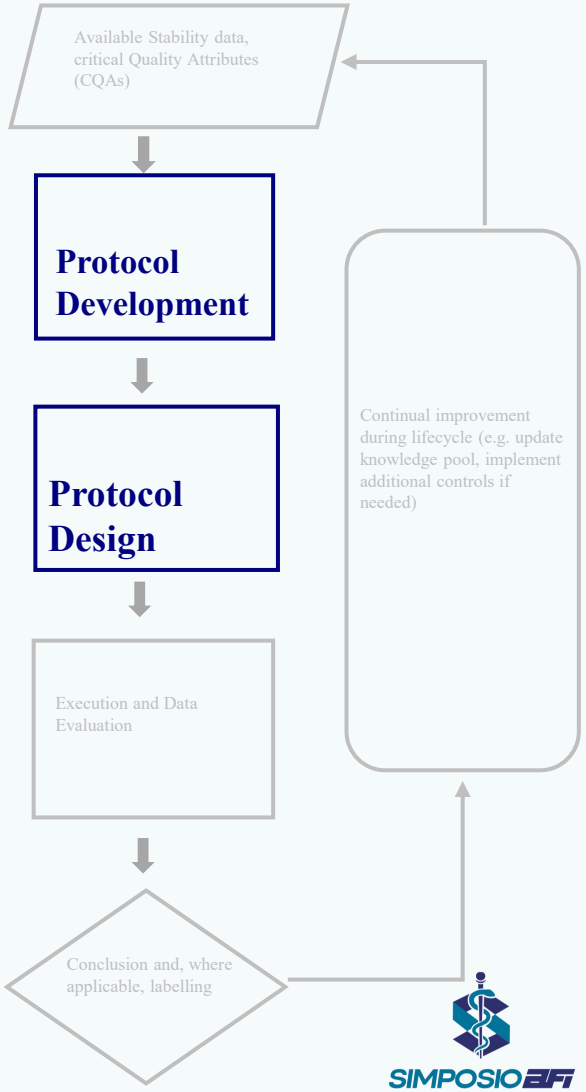
CCS
- RH/ O_2 permeability
- Container/content interactions

DISTRIBUTION
- Target climatic zones
- Supply chain
- In-Use stability

RISK BASED STABILITY STUDY DESIGN:

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





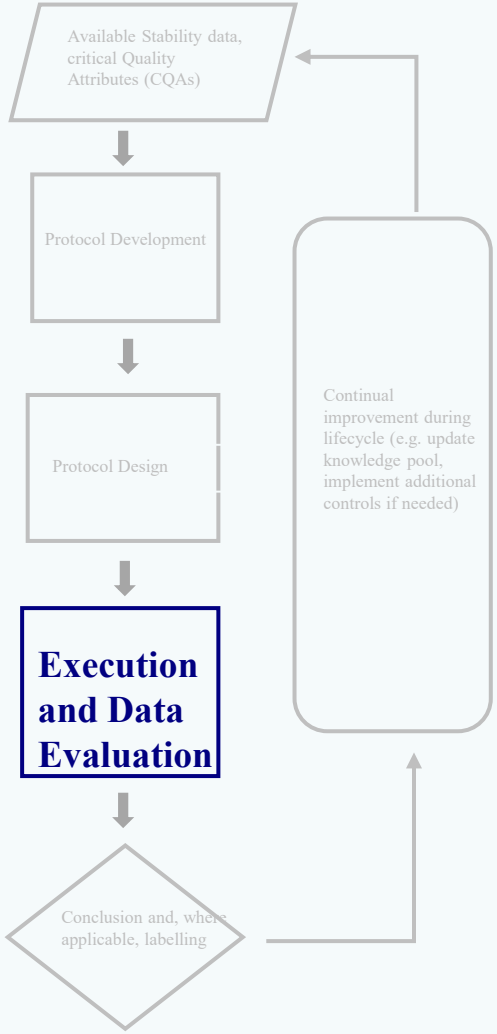
Stability Protocol Execution and Data Evaluation

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

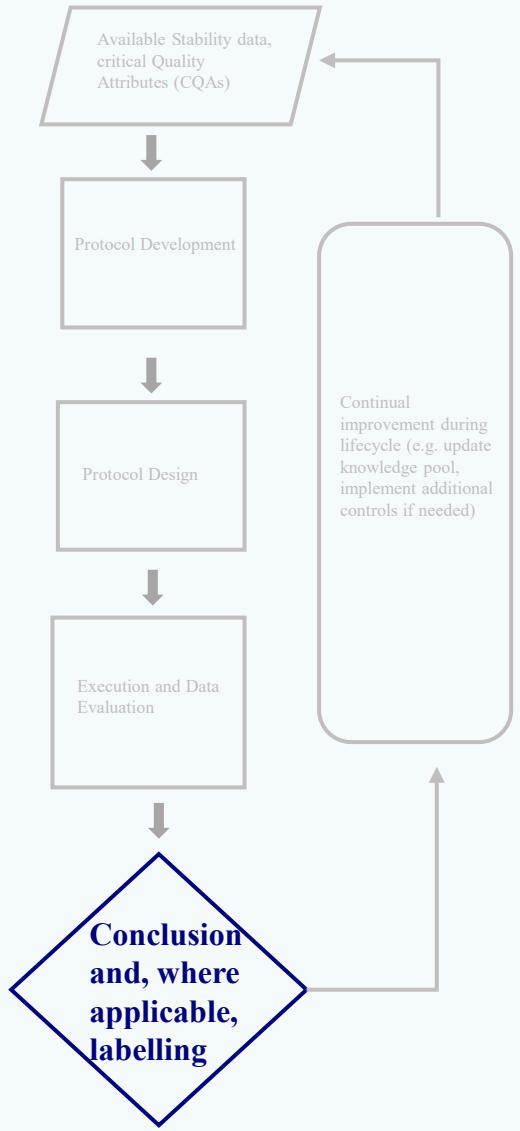
- after stability study completion
- after supply chain definition

WHAT

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

PRE-REQUISITES

- Known degradation patways
- Demonstrated robustness of mathemathical models
- Significant data available



Product Knowledge – Process Understanding in Product Lifecycle

ON-GOING / LIFECYCLE STBILITY STUDIES

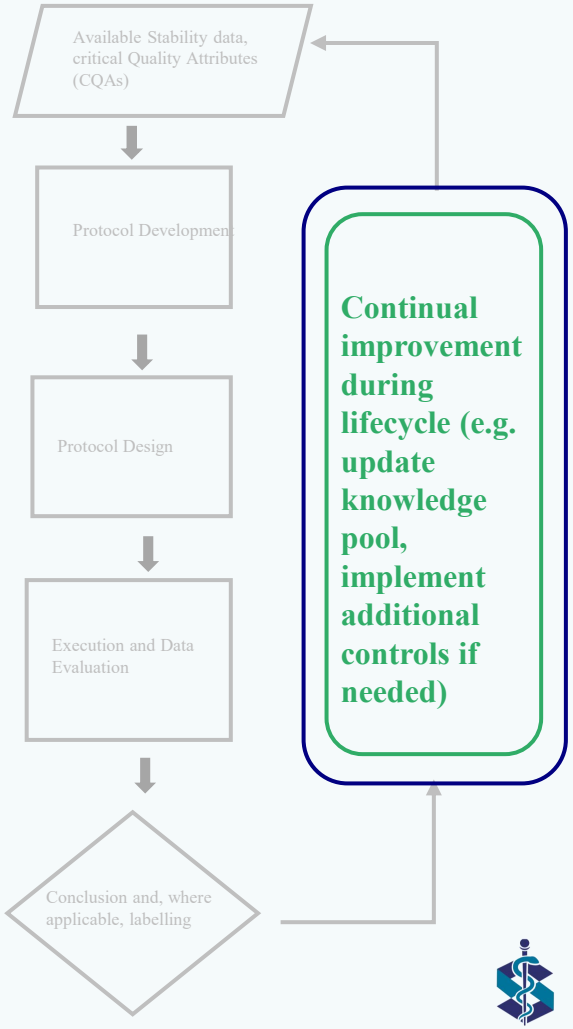
- Identify the impact of variations/changes in manufacturing process
- Predict OOS
- Confirm assumptions on shelf life predictions through commercial batches data

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

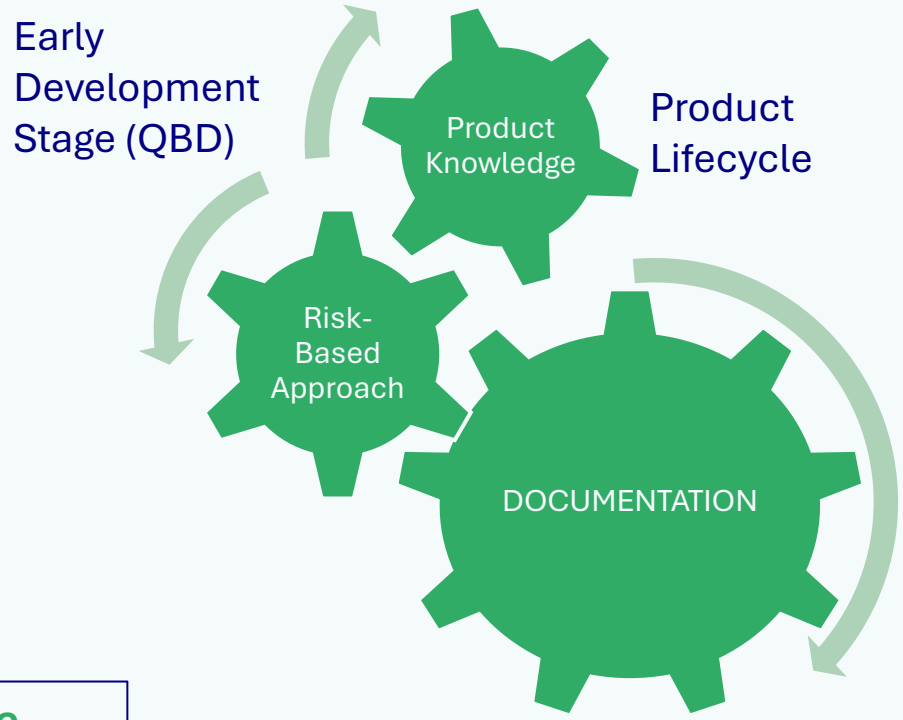
Development: KM and QRM support **Strategic design**

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

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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?

info@ptm-consulting.com | +39 0522 472812

Via Roma, 24 – 42049 S. Ilario d’Enza (RE) Italia

ptm-consulting.com

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