Introduction to ICH
- The Quality Guidelines – An Overview -

Workshop on Implementation of ICH Q8/Q9/Q10

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The “Q-Family”

Q 1 – Stability Testing
Q 2 – Analytical Validation
Q 3 – Impurities
Q 4 – Pharmacopoeias
Q 5 – Biotechnological Products
Q 6 – Specifications
Q 7 – Good Manufacturing Practices
Q 8 – Pharmaceutical Development
Q 9 – Quality Risk Management
Q 10 – Pharmaceutical Quality System

ICH Q 1 – Stability Testing

A set of originally five guidelines (Q1A to Q1F) defining

- General aspects of stability testing (storage conditions, batch size and number, length of time...)
- Photostability
- Application to new dosage forms
- Possibilities for reduced test designs (bracketing and matrixing)

ICH Q 1 – Stability Testing

- Statistical evaluation of stability data and possibilities for extrapolation
- Storage conditions for stability testing in climatic zones III and IV (withdrawn)

ICH Q 1 A (R2) – Scope

- For new API and related medicinal products
- To provide evidence on how the quality of an API/finished product changes with time under the influence of environmental factors such as temperature, humidity and light and to establish a re-test period/shelf-life for the API/finished product

ICH Q 1 A (R2) – In a Nutshell...

- Stress testing required for API
- Long-term and accelerated testing required for API and product, where necessary intermediate testing
- Minimum of three representative batches
- Testing over a minimum of 12 months at LT and 6 months at accelerated conditions (with defined testing frequency)
- Storage conditions for the “general case”, aqueous products in semi-permeable containers, products to be stored in a refrigerator and a freezer
- Stability commitment

ICH Q 1 B – In a Nutshell...

- Describes requirements on photostability testing and defines light exposure to be applied
- To be tested on API – if not photosensitive, no further testing required
- If photosensitive, to be continued on exposed finished product and product in primary package, product in marketing package, where relevant
- Where necessary, impact of light during manufacturing process to be evaluated
- Confirmatory testing required, where applicable

ICH Q 1 C – In a Nutshell...

- Additional guidance to ICH Q1 A(R2) on new dosage forms (“line extensions”) for new substances
- Reduced requirements as regards time to be covered at LT storage conditions at time of dossier submissions

ICH Q 1 D – In a Nutshell...

- Describes possibilities to apply reduced test designs, i.e. bracketing and matrixing
- Defines situations where reduced testing can be applied without additional justification, with justification or where it is not applicable
- Bracketing: testing of extremes only
- Matrixing: testing of a different samples of factor combinations at different time points during the study
- Provides example designs

Example of Bracketing Design

Bracketing on strength and container size

Strength		50 mg			75 mg			100 mg		
Batch		1	2	3	1	2	3	1	2	3
Container size	15 ml	T	T	T				T	T	T
	100 ml									
	500 ml	T	T	T				T	T	T

Example of Matrixing Design

Two strengths, matrixing on time point

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

T: Sample tested; (T): Sample tested if full shelf life data will not be available before approval.

ICH Q 2 – Analytical Validation

A guideline defining the validation parameters needed for a variety of analytical methods and describing characteristics to be considered for the validation of analytical procedures included in a marketing authorisation dossier

ICH Q 2 – ... In a Nutshell

Defines criteria for the validation of the four most common types of analytical procedures:

- identification tests
- quantitative tests for impurities
- limit tests for the control of impurities
- quantitative tests for the active moiety in API or finished product or or other selected components in the product

ICH Q 2 – ... In a Nutshell

Defines typical analytical validation characteristics, to which tests to apply them and examples on the “how to”

- Accuracy
- Precision
  - Repeatability
  - Intermediate Precision
- Specificity
- Detection Limit
- Quantitation Limit
- Range

Typical Validation Characteristics

Validation Characteristics	Identification	Testing for Impurities		Assay
		quantitative	limit	
Accuracy	-	+	-	+
Precision				
Repeatability	-	+	-	+
Int. Precision	-	+	-	+
Specificty	+	+	+	+
Detection Limit	-	-	+	-
Quant. Limit.	-	+	-	-
Linearity	-	+	-	+
Range	-	+	-	+

ICH Q 3 – Impurities

A set of three guidelines addressing the chemistry and safety aspects of impurities, including the listing of impurities in specifications. Defines the thresholds for reporting, identification and qualification of impurities in API and finished product. Specific guideline on residual solvents

ICH Q 3 A(R) – in a Nutshell

Classifies impurities

- organic impurities
  - Starting materials
  - By-products
  - Inermediates
  - Degradation products
  - Reagents, ligants, catalysts
- Inorganic impurities
  - Reagents, liegands, catalysts
  - Heavy metals or other residual metals
  - Inorganic salts
  - Other impurities, e.g. filter aids, charcoal…
- Residual solvents

ICH Q 3 A(R) – in a Nutshell

Defines rationale for the reporting and control of impurities as well as requirements for listing impurities in specifications:

- Organic Impurities
  - Each specified identified impurity
  - Each specified unidentified impurity
  - Any unspecified impurity with acceptance criterion of NMT the identification threshold
- Residual solvents
- Inorganic impurities

ICH Q 3 A(R) – in a Nutshell

Definitions

Identified impurity:

…. impurity for which a structural characterisation has been achieved

Qualification:

….is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified.

ICH Q 3 A(R) – in a Nutshell

Definitions

Specified impurity:

… impurity that is individually listed and limited with a specific acceptance criterion in the specification. Can be either identified or unidentified.

Unidentified impurity:

… impurity for which a structural characterisation has not been achieved and that is solely defined by qualitative analytical properties, e.g. chromatographic retention time

Unspecified impurity:

… impurity that is limited by a general acceptance criterion, but not individually listed with its own specific acceptance criterion in the specification

Thresholds for Impurities in API

Maximum Daily Dose	Reporting Threshold	Identification Threshold	Qualification Threshold
≤ 2 g/day	0.05 %	0.10 % or 1.0 mg/day (whichever is lower)	0.15 % or 1.0mg/day (whichever is lower)
> 2 g/day	0.03 %	0.05 %	0.05 %

- number of decimal digits: two below 1.0 %, one above 1.0 %
- application of conventional rounding rules
- total impurities > reporting threshold

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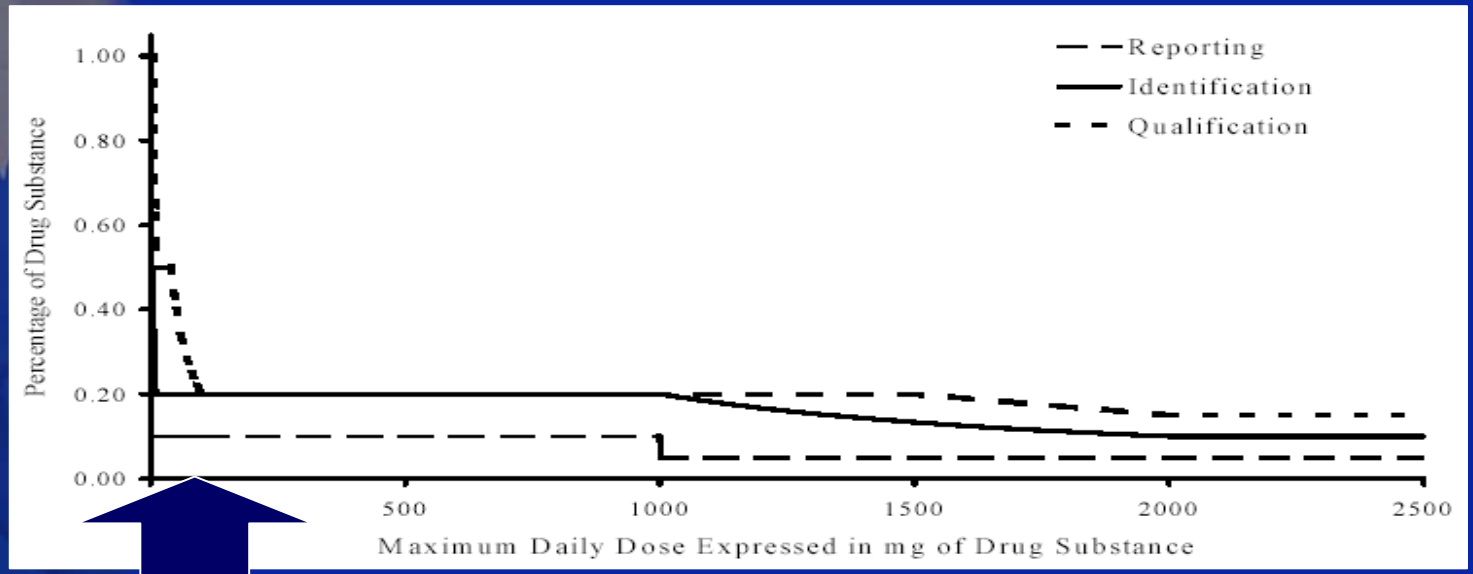
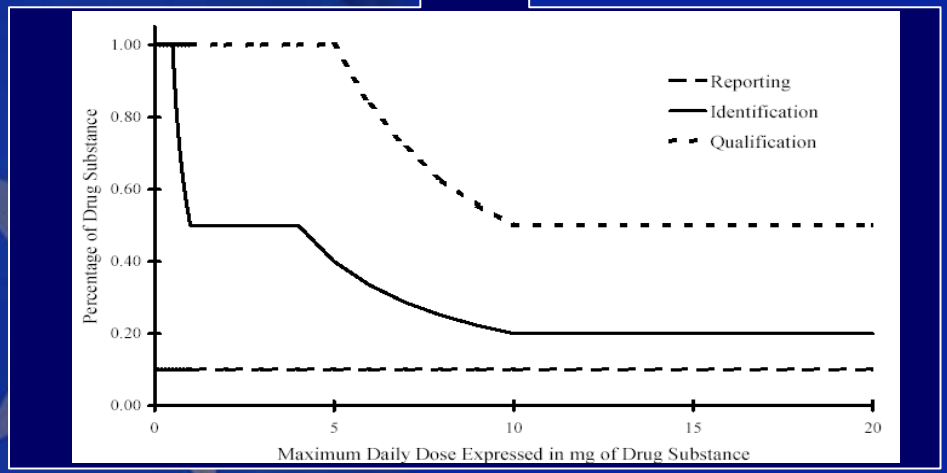
Thresholds of Impurities in Finished Products





Example 15 mg/day

Reporting threshold 0.1 %

Identification threshold 0.5%/20 µg TDI

Qualifcation threshold 0.5%/200µg TDI

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ICH Q 3 C – in a Nutshell

Recommends acceptable amounts for residual solvents in pharmaceuticals for the safety of patients, recommends use of less toxic solvents and describes levels considered to be toxicologically acceptable for some solvents. Non-exhaustive list of solvents included in the guideline as annex.

Classification of Residual Solvents

Class I

⇒ solvents to be avoided

Known human carcinogens, strongly suspected human carcinogens, and environmental hazards

Class II

⇒ solvents to be limited

Non-genotoxic animal carcinogens or possible causative agents of other irreversible toxicity. Solvents suspected of other significant but reversible toxicities

Class III

⇒ solvents with low toxic potential

Solvents with low toxic potential to man; no health-based exposure limit is needed

Classification of Residual Solvents

Class I

⇒ solvents to be avoided

Benzene, carbon tetrachloride, 1,2-dichloroethane, 1,1-dichloroethene, 1,1,1-trichloroethane

Class II

⇒ solvents to be limited

Acetonitrile, chloroform, cyclohexane, dioxane, methanol, methylbutylketone, tetrahydrofurane, toluene, ...

Class III

⇒ solvents with low toxic potential

Acetone, butanol, butyl acetate, DMSO, ethanol, ethyl acetate, ethyl ether, heptane, isopropanol, methylethyl ketone, ...

ICH Q3 C – in a Nutshell

Defines options for the definition of acceptance criteria for class 2 solvents

Option 1

⇒ tabulated limits,
calculated on the basis of a TDI of 10 g of the product

Option 2

⇒ not all individual components of a product have to comply with the tabulated limits – the total content of the solvent has to be below the permitted daily intake (PDE)

ICH Q3 C – in a Nutshell

Example for option 2

$$\text{Concentration} = \frac{1000 \times \text{PDE}}{\text{Dose}}$$

Component	Amount in Formulation	Content Acetonitril *	Daily Intake
API	0.3 g	800 ppm	0.24 mg
Excipient 1	0.9 g	400 ppm	0.36 mg
Excipient2	3.8 g	800 ppm	3.04 mg

Product	5.0 g	728 ppm	3.64 mg

* PDE: 4.1 mg/day, limit: 410 ppm

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ICH Q 4 – Pharmacopoeias

Harmonisation of 10 general methods referred to in the ICH specification guideline ICH Q 6A is undertaken by the Pharmacopoeial Discussion Group (PDG). ICH Q4 B evaluates selected pharmacopoeial texts to facilitate their recognition by regulatory authorities as interchangeable in the ICH region. Adopts specific annexes for the different texts.

ICH Q 5 – Biotechnological Products

A set of five guidelines defining requirements on various specifics for biotechnological products:

- viral safety
- Analysis of the expression construct in cells used for production of r-DNA derived protein products
- Stability testing

ICH Q 5 – Biotechnological Products

- Derivation and characterisation of cell substrates
- Comparability of biotechnological/biological products subject to changes in the manufacturing process

ICH Q 6 – Specifications

Two guidelines addressing the selection of tests and methods and setting specifications for quality control of API and finished products (chemicals and biotechnologically derived proteins and polypeptides)

ICH Q 6A – ... In a Nutshell

Intended to assist in the establishment of a single set of global specifications for API and finished product. Provides guidance on the setting and justification of acceptance criteria and the selection of test procedures.

ICH Q 6A – ... In a Nutshell

Specification:

…. A list of tests, references to analytical procedures and appropriate acceptance criteria, which are numerical limits, ranges or other criteria for the tests described. Establishes the set of criteria to be met in order to be considered “acceptable for intended use”.

… “Conformance to specification” means that the API/product will meet the acceptance criteria WHEN tested

ICH Q 6A – ... In a Nutshell

Specifications (cont.):

…. Are proposed/justified by applicant and approved by regulatory authorities as conditions of approval

…. Are one part of a total control strategy for the API/product. Other parts or this strategy include thorough product characterisation during development and adherence to GMP (!!)

… are chosen to confirm the quality… rather than to establish full characterisation, should focus on those characteristics useful in ensuring the safety and efficacy of the product.

ICH Q 6A – ... In a Nutshell

Defines general concepts, e.g.

- Periodic or skip testing
- Release vs. shelf-life acceptance criteria
- In-process tests
- Design and development considerations
- Limited data available at filing
- Parametric release
- Alternative procedures
- Pharmacopoeial tests and acceptance criteria
- Evolving technologies
- Impact of API on product specifications
- Reference standard

ICH Q 6A – ... in a Nutshell

Defines universal tests/criteria for

- **API**
- **Finished product**

Defines additional specific tests/criteria for

- **API**
- **Finished product**
  - **Solid oral dosage forms**
  - **Oral liquids**
  - **Parenteral drug products**

Universal Tests/Criteria - API

Description

Identification

⇒ specific for the substance (e.g.: IR, HPLC/UV (DAD), HPLC/MS, GC/MS)

Assay

⇒ specific / stability indicating procedure
often possible to use method that is also used for quantification of impurities (e.g. HPLC

Impurities (organic, inorganic, residual solvents)

⇒ specific /stability-indicating procedure

⇒ Decision tree # 1 on extrapolation of meaningful limits

Universal Tests/Criteria - Product

Description

Identification

⇒ specific (IR, HPLC/UV (DAD), HPLC/MS, GC/MS)

Assay

⇒ specific / stability-indicating procedure
(z.B. HPLC, which is also used for impurities quantification, where applicable, results of content uniformity test can be used)

Impurities (organic, inorganic, residual solvents)

⇒ specific /stability-indicating procedure: degradation products and impurities arising during the manufacturing process

⇒ Decision tree #2 on extrapolation of meaningful limits

Examples of Specific Tests/Criteria - API

Physicochemical properties

⇒ pH, melting point/range, refractive index ...

Particle size

⇒ API in solid or suspension drug products
Decision tree #3

Polymorphic forms

⇒ crystalline forms. Solvates, hydrates
thermal analysis (DSC, DTA), IR, microscopy, X-ray powderrdiffraction, ... For the finished product normally dissolution as surrogate parameter

⇒ Decision tree #4(1)-4(3)

Examples of Specific Tests/Criteria – Solid Oral Dosage Forms

Dissolution

⇒ in-vitro-release of active from the product.

single point-measurement for immediate release products
multiple time point sampling for extended release, two-stage testing for delayed release dosage forms

⇒Decision tree # 7 (1-3)

Disintegration

⇒ may be substituted for dissolution for rapidly dissolving prodcuts containing active which is highly soluble throughout the physiological range

ICH Q 7 – GMP for API

A guideline defining GMP requirements for the manufacture of API – based on existing regional and international (PIC/S) guidance, elaborated jointly with representatives from the generic and self-medication industry, PIC/S, Australia, India and China

ICH Q 7 - .... In a Nutshell

- Introduction
- Quality Management
- Personnel
- Buildings and Facilities
- Process Equipment
- Documentation and Records
- Materials Management
- Production and In-Process Controls

ICH Q 7 - .... In a Nutshell

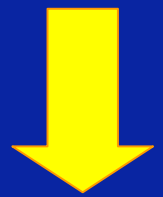
- Packaging and Identification / Labelling of APIs and Intermediates
- Storage and Distribution
- Laboratory Controls
- Validation
- Change Control
- Rejection and Re-Use of Material
- Complaints and Recalls

ICH Q 7 - .... In a Nutshell

- Agents, Brokers, Traders, Distributors, Repackers and Relabellers
- Specific Guidance for APIs manufactured by Cell Culture/Fermentation
- APIs for Clinical Trials
- Glossary

ICH M4 Q – Commont Technical Document

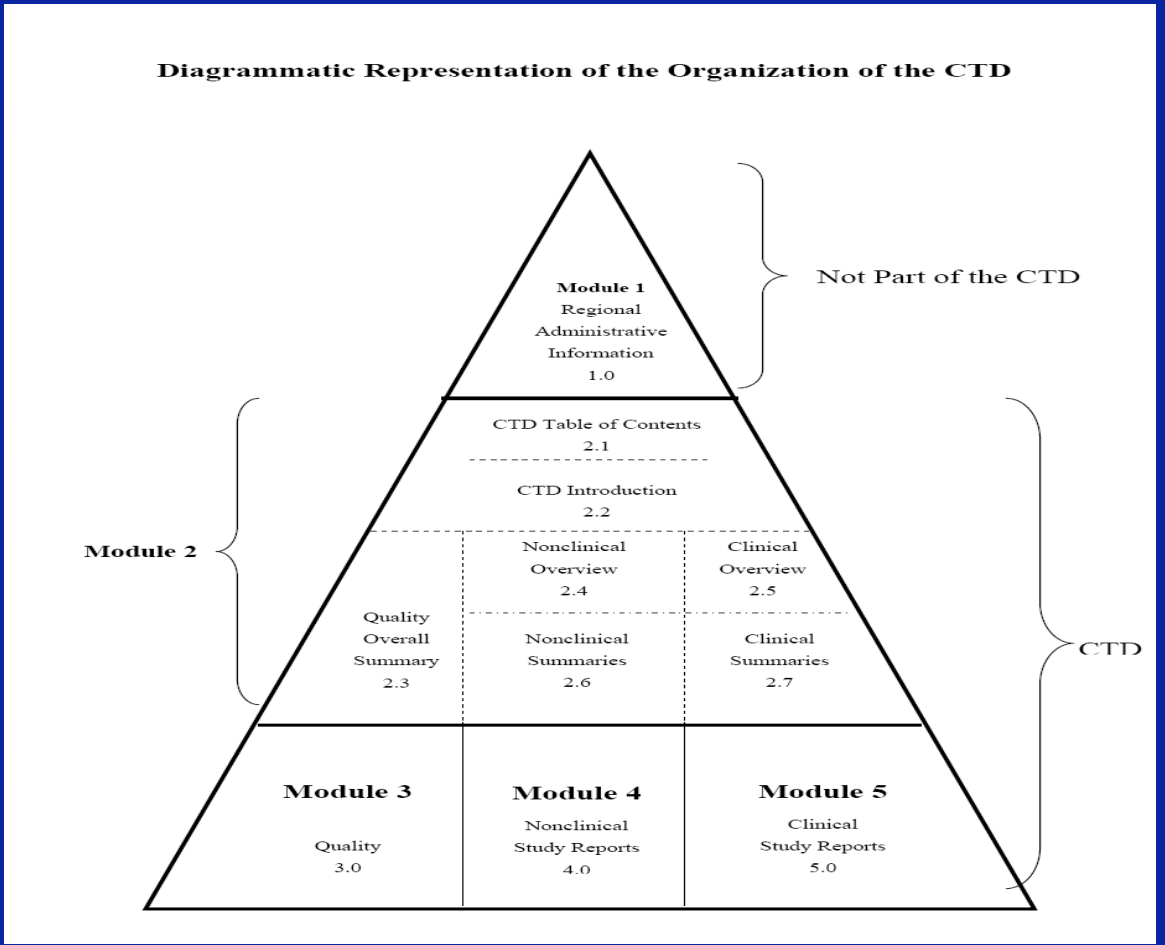
… defines a common format for the marketing authorisation application in the ICH region, BUT addresses only format/structure, not the specific requirements



CTD merely indicates the location where information has to be provided

Submission of the Dossier

Structure of the Common Technical Document (CTD)



Module 2: Overviews and summaries

2.1 CTD TOC Modules 2-5
2.2 Introduction
2.3 Quality Overall Summary
2.4 Nonclinical Overview
2.5 Clinical Overview
2.6 Nonclinical Summary
2.7 Clinical Summary

Module 3: Quality
General Structure/Drug Substance

3.2 S	**Drug Substance**
3.2 S1	General Information
3.2 S2	Manufacture
3.2 S3	Characterisation
3.2 S4	Control of Drug Substance
3.2 S5	Reference Standards or Materials
3.2 S6	Container Closure System
3.2 S7	Stability

General Structure/Drug Product

3.2 P	**Drug Product**
3.2 P1	Description and Composition of the Drug Product
3.2 P2	Pharmaceutical Development
3.2 P3	Manufacture
3.2 P4	Control of Excipients
3.2 P5	Control of Drug Product
3.2 P6	Reference Standards or Materials
3.2 P7	Container Closure System
3.2 P8	Stability

General Structure/Appendices etc.

A Appendices

A1 Facilities and Equipment

A2 Adventitous Agents Safety Evaluation

R Regional Information

C Key Literature References

Thank you!