2021 PROJECT REPORT OF FREE TEXT COMMENTS

MONITORING THE ADEQUACY OF IMPLEMENTATION AND ADHERENCE TO INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE (ICH) GUIDELINES

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CIRS Centre for Innovation in Regulatory Science

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The Centre for Innovation in Regulatory Science (CIRS) is a neutral, independent UK-based subsidiary of Clarivate plc. CIRS provides an international forum for industry, regulators, HTA and other healthcare stakeholders to meet, debate and develop regulatory and reimbursement policy through the innovative application of regulatory science and to facilitate access to pharmaceutical products. It is governed and operated by Clarivate for the sole support of its members' activities. The organisation has its own dedicated management and advisory boards, and its funding is derived from membership dues, related activities, special projects, and grants.

ICH Implementation Leads for Phase 2b Survey

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International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) - *www.ich.org; admin@ich.org*

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) is unique in bringing together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration. ICH's mission is to promote public health by achieving greater harmonisation worldwide to ensure that safe, effective, and high-quality medicines are developed and registered in the most resource-efficient manner. Since its inception in 1990, ICH has gradually evolved to respond to the increasingly global face of drug development. Since the introduction of organisational changes in October 2015, ICH, as an independent, international, non-profit organisation, has grown and now includes nineteen Members and thirty-five Observers.

Acknowledgements

Special thanks to the participating pharmaceutical companies, and the participating ICH Regulatory Members and Observers.

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EXECUTIVE SUMMARY

Background: In 2021, the ICH approached CIRS to follow up on the work done in 2018/2019, which assessed the adequacy of implementation or adherence to ICH Guidelines. In September 2021, the Phase 2b study report was published, and the anonymised free-text comments from the industry were shared with the relevant participating authorities in November.

Objectives: This report aims to analyse the industry comments to uncover Guideline-specific themes and identify the most frequent and impactful overarching trends relating to lack of implementation or adherence without identifying the participating authorities or companies. Therefore, the objectives were to 1) Provide further context to results from the Phase 2b survey (based on the 2021 report); 2) Add value on informing training associates; and 3) Inform future surveys on this topic as directed by ICH.

Method: This analysis of the free-text comments from the industry was limited to cases where there was inadequate implementation or lack of adherence only. Qualitative analysis of the industry comments was undertaken independently by two reviewers. The comments were analysed initially to generate themes and overarching trends. The comments were thematically codified according to those themes and trends.

Results:

- Across all the Guidelines and authorities, inadequate implementation or lack of adherence accounted for 6% of responses, compared to implementation not started/in process/not applicable (24%) and adequate implementation/full adherence/too early to assess adherence (70%).
- Where there was inadequate implementation or lack of adherence, 169 responses were accompanied by free text comments from 19 out of the 30 participating companies.
- The following Guidelines were assessed: Tier 1: Q1, Q7, E6(R2); Tier 2: E2A, E2B, E2D, M4; and Tier 3: E2C(R2), E2E, E2F, E3, E5(R1), E10, E11(R1), E17, M7(R1), Q2(R1), Q3A(R2), Q3B(R2), Q3C(R6), Q3D(R1), Q4B, Q5A(R1), Q5B, Q5C, Q5D, Q5E, Q6A, Q6B, Q8(R2), Q9, Q10, Q11, and Q12.
    - The Authorities which received comments were all ICH non-Standing non-Founding Regulatory Members (ANVISA, Brazil; NMPA, China; HSA, Singapore; MFDS, Republic of Korea; TFDA, Chinese Taipei; and TITCK, Turkey) and the following Observers: INVIMA, Colombia; JFDA, Jordan; and SAHPRA, South Africa. No comments were received for SFDA, Saudi Arabia as there were no instances, based on company perception, where there was inadequate implementation/lack of adherence.
- From across the 169 comments and 14 themes for Tier 1, Tier 2, and Tier 3 ICH Guidelines, the following three overarching trends were confirmed from the 2019 study and adapted to analyse 2021 study comments:
    - Additional requirements requested beyond the ICH Guideline – these varied from extra analytical tests, site-specific requirements, local language requirements, submission of special reports, and submission of raw data.
    - Local Guideline – a national/regional guideline is in place which prevents full implementation and adherence with ICH, particularly due to different definitions, concepts and terminology used or due to conflict with the current regulatory framework.
    - Implementation issue – the Guideline is not fully implemented due to the authority's interpretation being different from what is described in the ICH Guideline or the authority's system not allowing full implementation.

Conclusion: Analysis of free text comments confirmed the main findings from the Phase 2b – that generally there was strong evidence of adequate implementation or adherence to the ICH Guidelines. This analysis identified themes and trends as well as specific examples for the small proportion of cases of inadequate implementation or lack of adherence to further explain the rationale for Phase 2b results and to support training and capacity building efforts across agencies and companies. This would also aim to ensure comments add value and can be utilised to understand outliers and provide a better narrative on the responses. Finally, it would help to further increase the robustness of the results to help meet the long-term objectives of this study, which is to establish a sustainable ICH-driven mechanism to assess Guidelines over time to inform ICH stakeholders on multiple areas, such as ICH membership and training needs.

INTRODUCTION

In 2020, ICH approached the Centre for Innovation in Regulatory Science (CIRS) to undertake a follow-on study to assess the adequacy of implementation and adherence to ICH Guidelines. An online questionnaire and definitions were developed by CIRS in collaboration with ICH and the ICH Implementation Subcommittee. The survey was completed by companies (assessing all the participating authorities) and by authorities (assessing themselves only) in order to undertake a gap analysis.

The report of this study[1] has been published and endorsed by the ICH Management Committee and Assembly. All in all, the results demonstrated authorities' and companies' continued commitment and support in ICH's mission to achieve greater harmonisation worldwide and ensure that safe, effective, and high-quality medicines are developed, registered, and maintained in the most resource-efficient manner whilst meeting high standards. In addition, the study highlighted the progress made by authorities in implementing and adhering to ICH Guidelines since the 2019 assessment and the results can be used to support training needs as well as ICH-membership related activities.

In addition to the publication of the main study report, CIRS also shared with the participating authorities the anonymised comments that each received from across the industry on the Guidelines. This information has not yet been further analysed or published.

In September 2021, the Management Committee together with the ICH Implementation Leads (Junko Sato and Jerry Stewart) discussed and proposed that in addition to the already published report, CIRS should undertake a further analysis of the free text comments obtained through the 2021 survey to be able to share them with other participants and stakeholders.

The objectives are to analyse the comments and uncover themes and trends, without identifying the participating authorities or companies to provide learnings specific to the Guideline in general, or across Guidelines, focusing on cases where there was inadequate implementation or lack of adherence.

The purpose of this free text report is therefore to

1) Provide further context to results from the Phase 2b survey (based on the 2021 report).
2) Add value on informing training associates.
3) Inform future surveys on this topic as directed by ICH.

[1] 2021 PROJECT REPORT MONITORING THE ADEQUACY OF IMPLEMENTATION AND ADHERENCE TO INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE (ICH) GUIDELINES. Available at: https://admin.ich.org/sites/default/files/2021-09/ICHImplementationPublicReport_2021_0909.pdf

METHOD

For comprehensive study method, please see the 2021 full study report. This report describes an analysis of free text comments.

Scope

The analysis of the free text comments from industry participants was limited to:

1. Cases where there was inadequate implementation ('No' to question 1.2.2) or there was lack of adherence (Option 2 to question 1.3) for Tier 1 and Tier 2.
2. Or cases where there was lack of adherence (Option 2 "Even if the Guideline has been adequately implemented, it is not being applied and adhered to in practice" selected to question 1.3) for Tier 3.

For those cases an analysis of free text responses was undertaken from Question 1.2.1 (Modifications made) Questions 2.2 (Evidence) and/or Question 3 (General Comments) of the questionnaire (see Appendix 2, page 33 for the questionnaire).

The following ICH Guidelines were assessed (as part of the main study)

- **Tier 1 (only for ICH Observers)**
  - Q1 – Stability *(all subparts considered)*
  - Q7 – Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients
  - E6(R2) – Good Clinical Practice (GCP)
- **Tier 2 (only for ICH non-Standing non-Founding Regulatory Members)**
  - E2A – Clinical Safety Data Management: Definitions and Standards for Expedited Reporting
  - E2B(R3) – Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports
  - E2D – Post-approval Safety Data Management: Definitions and Standards for Expedited Reporting
  - M1 – Medical Dictionary for Regulatory Activities Terminology (MedDRA)
  - M4 – Common Technical Document (CTD)
- **Tier 3 (only for ICH non-Standing non-Founding Regulatory Members)**
  - 55 Guidelines were studied, of which 53 were unique Guidelines (where two Guidelines, E9 and S5, were included twice as E9 – E9(R1) and S5(R2)-S5(R3)) from across Q, S, E, M domains. All ICH Guidelines are listed in Appendix 3

The following organisations participated (as part of the main study)

- **10 Regulatory Authorities** from across:

ICH non-Standing non-Founding Regulatory Members
- ANVISA, Brazil
- NMPA, China
- HSA, Singapore
- MFDS, Republic of Korea
- TFDA, Chinese Taipei
- TITCK, Turkey

ICH Observers (voluntary basis)
- INVIMA, Colombia
- JFDA, Jordan
- SAHPRA, South Africa
- SFDA, Saudi Arabia (since June 2021 SFDA, Saudi Arabia is an ICH Member)

- **30 Major Pharmaceutical Companies** (assessing all the participating authorities) provided a response in total out of 40 invited from across PhRMA, EFPIA, JPMA, BIO and IGBA companies

Analysis

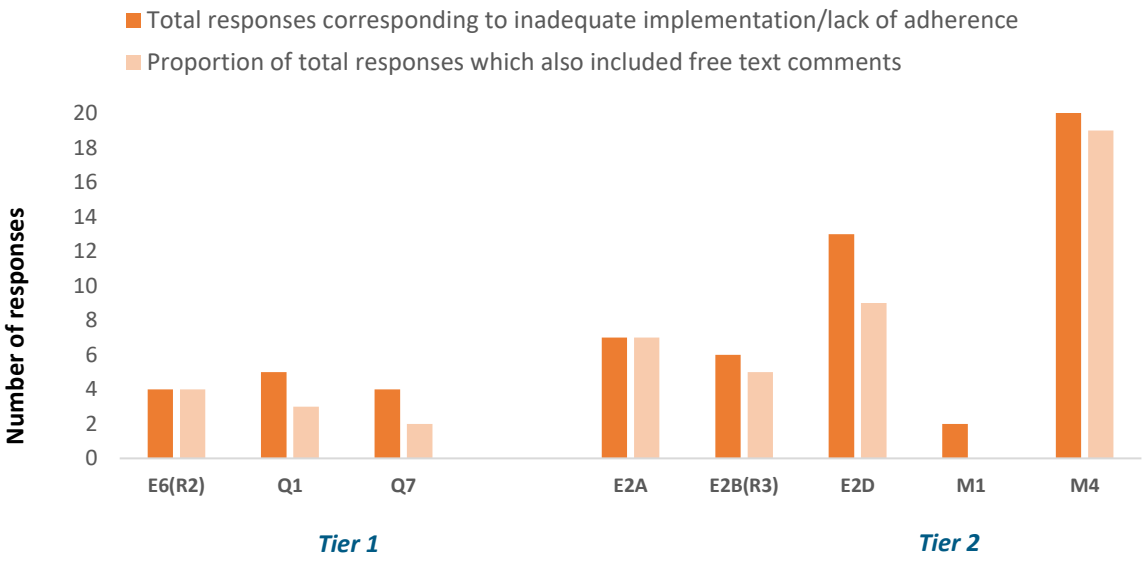
Qualitative analysis of free text comments was undertaken independently by two reviewers. The comments were analysed initially to generate themes and overarching trends that could be used to compare to the 2019 results. The comments were thematically codified according to those themes and trends. For each theme, 2-3 verbatim examples were identified.

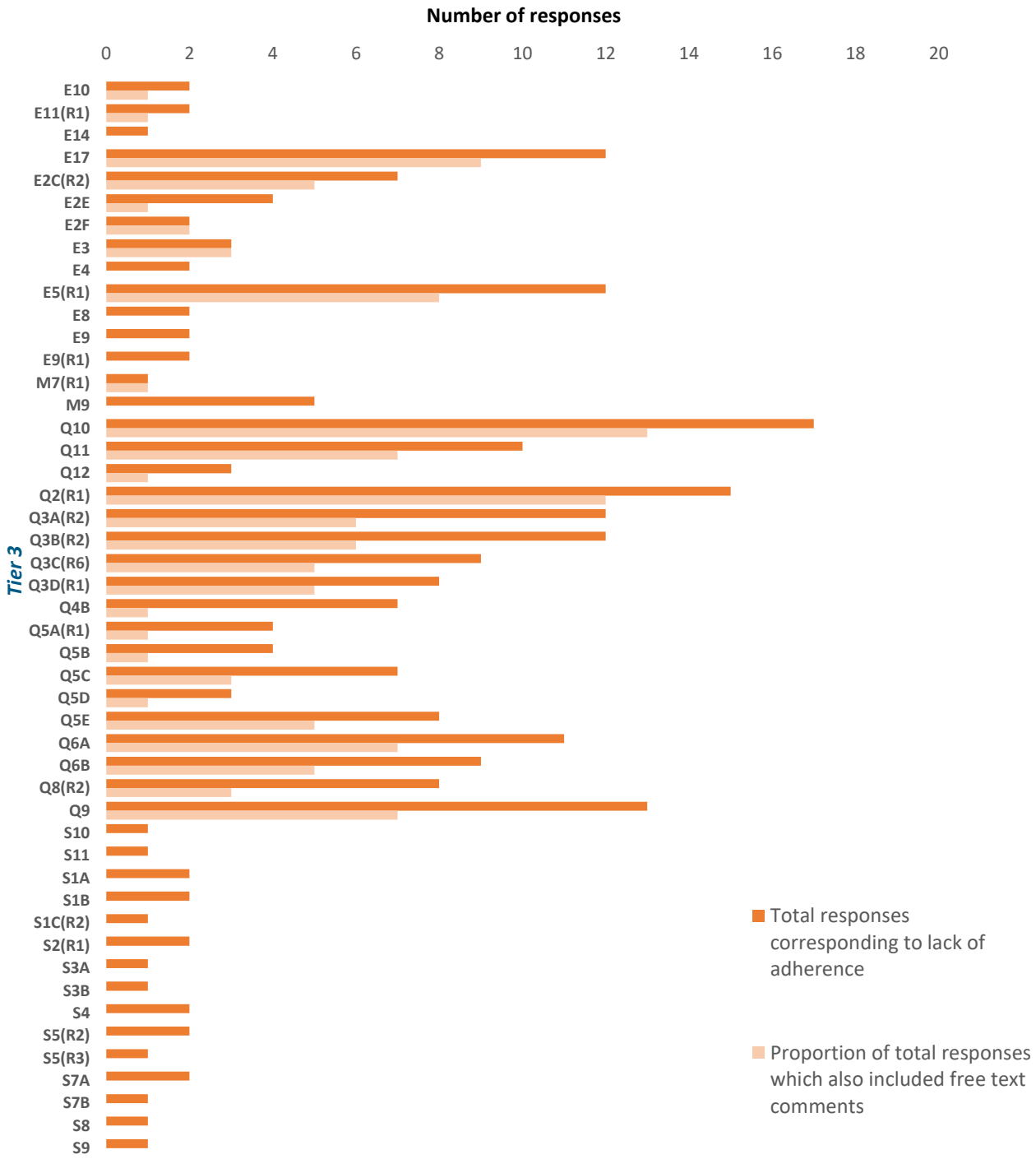
RESULTS PART 1: OVERALL TRENDS ACROSS ICH GUIDELINES

A. Respondent's rate

- Across all the authorities and ICH Guidelines, there was a total of 302 (6%) responses from companies suggesting inadequate implementation or lack of adherence
- 1084 (24%) responses where companies selected implementation not started, in process or not applicable
- 3206 (70%) responses suggested that Guideline is adequately implemented and either there is full adherence or too early to assess. For more details, please see the published full study report.

- Across all the authorities, out of the 302 responses corresponding to inadequate implementation or lack of adherence, 169 of the responses were accompanied by free text comments, whereas 133 were not. This varied by Guideline (Tier 1 and 2 on this page; see next page for Tier 3):

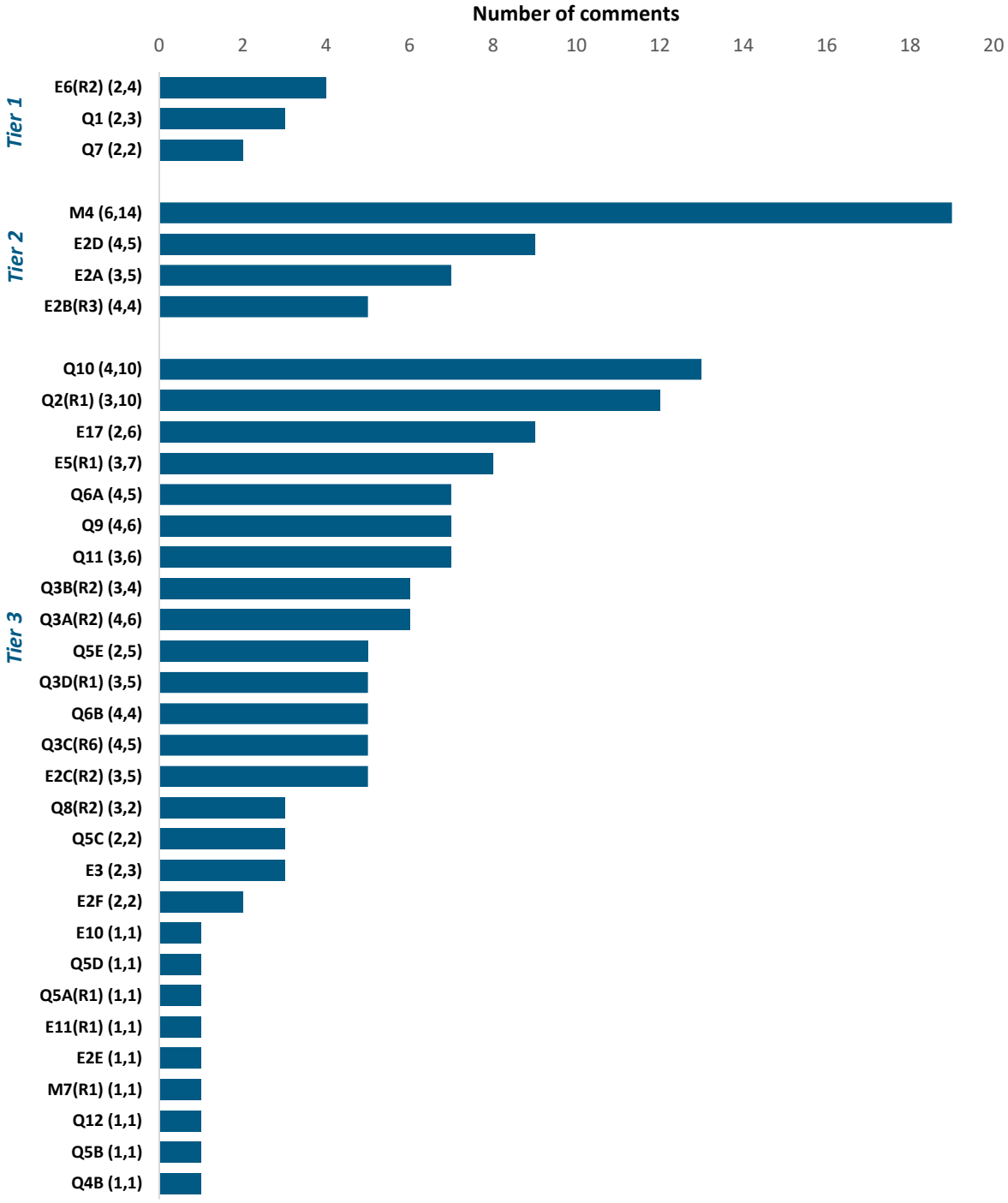




- For the 169 free text comments, these were provided by 19 out of 30 companies participating in the study on 9 Regulatory Authorities (ANVISA, Brazil; HSA, Singapore; INVIMA, Colombia; JFDA, Jordan; MFDS, Republic of Korea; NMPA, China; SAHPRA, South Africa; TFDA, Chinese Taipei; and TITCK, Turkey).
- No comments were received for SFDA, Saudi Arabia as there were no instances, based on company perception, where there was inadequate implementation/lack of adherence.

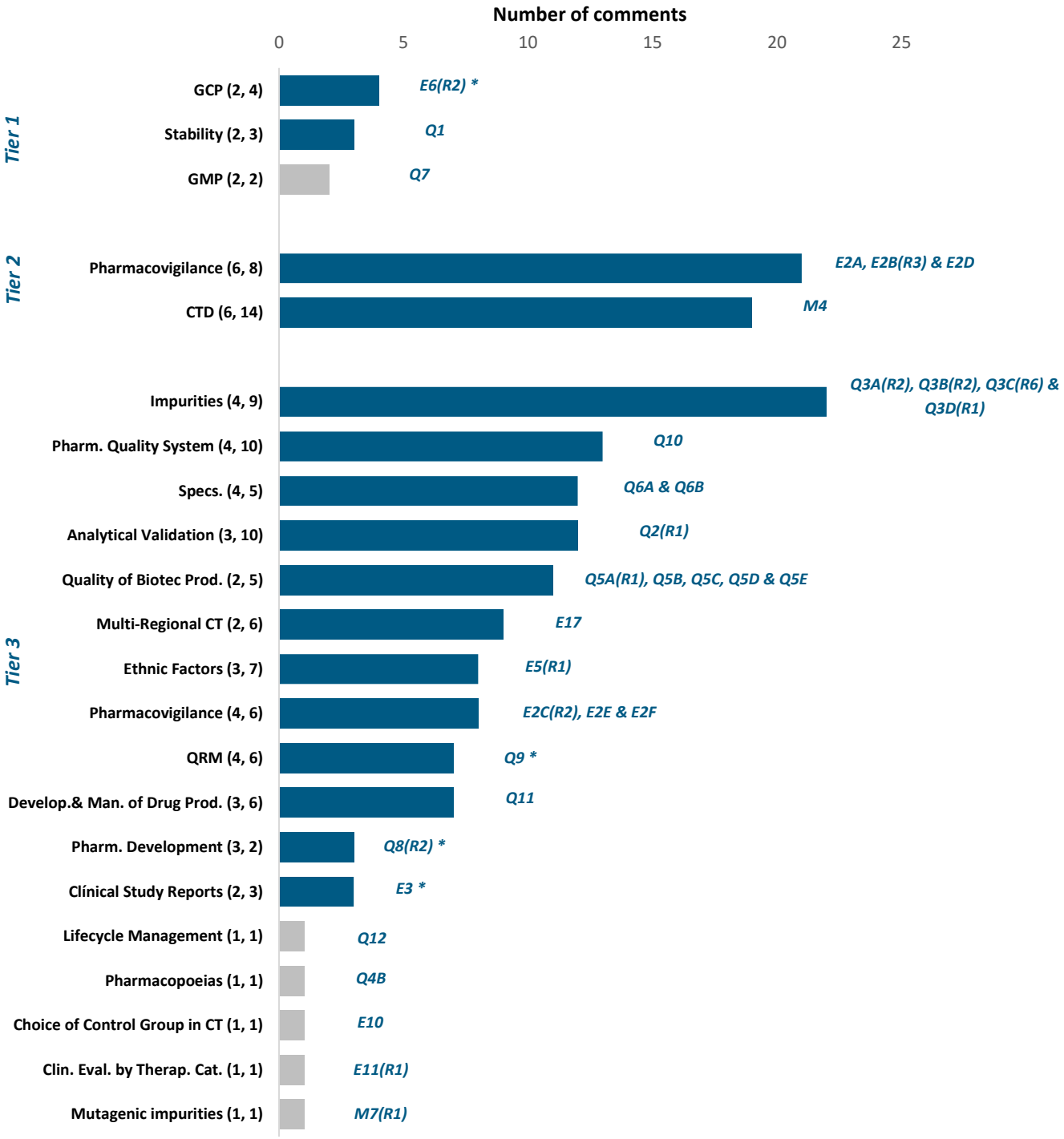
B. Number of comments received per Guideline

- Most comments were received for ICH Guideline M4 (19 comments from 14 companies on 6 Regulatory Authorities), followed by Q10 (13 comments from 10 companies on 4 Regulatory Authorities), and Q2(R1) (12 comments from 10 companies on 3 Regulatory Authorities).



NOTE: On the y-axis (n1) = number of authorities (n2) = number of companies;

Guidelines were subsequently combined to increase the dataset for the thematic analysis of comments



*NOTE: On the y-axis (n1) = number of authorities (n2) = number of companies; The Guidelines/Group of Guidelines that didn't receive at least three free-text comments by three different companies were coloured in grey and excluded from the thematic analysis to avoid company specific issues and to ensure the results are anonymous and representative. In addition, * refers to other Guidelines that were excluded from the results as a result of no trend being identified following the analysis.*

C. Number of comments received for each Guideline/Guidelines group according to the number of companies vs. authorities

- For M4, 19 comments were received from 14 companies across six ICH Regulatory Members.
- Impurities ICH Guidelines (Q3A(R2), Q3B(R2), Q3C(R6) & Q3D(R1)) received 22 comments from nine companies across four ICH Regulatory Members.
- Pharmacovigilance ICH Guidelines (E2A, E2B(R3) & E2D) received 21 comments from eight companies across six ICH Regulatory Members.
- In general, comments were received from multiple companies across several authorities, thereby enabling identification of overarching trends for specific Guidelines.

D. Overarching trends and themes identified

The following three key themes, identified in the 2019 analysis of free text comments, were utilised in the review of the comments, to identify if the same themes are relevant for the 2021 analysis, and whether additional ones could be identified:

- **Additional requirements requested beyond the ICH Guideline** – these varied from extra analytical tests, site-specific requirements, local language requirements, submission of special reports, and submission of raw data.
- **Local Guideline** – a national/regional guideline is in place which prevents full implementation and adherence with ICH, particularly due to different definitions, concepts and terminology used or due to conflict with the current regulatory framework.
- **Implementation issue** – the Guideline is not fully implemented due to the authority's interpretation being different from what is described in the ICH Guideline or the authority's system not allowing full implementation.

SUMMARY OF COMMON THEMES IDENTIFIED ACROSS THE COMMENTS REGARDING INADEQUATE IMPLEMENTATION/LACK OF ADHERENCE TO ICH TIER 1, TIER 2, AND TIER 3 GUIDELINES AS WELL AS THE CORRESPONDING BROADER TRENDS ACROSS ALL THE THEMES – FOR GUIDELINE/GUIDELINES GROUP -SPECIFIC ANALYSIS SEE PAGES 14-2

Tier	Involved Guideline(s)	Guideline topic	Page no. for analysis	Frequency*	No. of authorities	No. of comp.	Theme	Broader trend
Tier 1	Q1	Stability	14	3	2	3	**1. Incorporates additional requirements** (e.g., extra analytical analysis and site-specific requirements for imported products)	Additional requirement
Tier 2	E2A, E2B(R3), and E2D	Pharmacovigilance	14	16	5	7	**1. Incorporates additional requirements for reporting beyond those defined in the ICH Guideline** (e.g., expedited submission of: SUSARs to investigators; SUSARs for non-interventional PAC studies; positive control medicine case; unrelated adverse events (other than ADR); lack of efficacy reports, regardless of whether it is serious or not, and mandatory local language reporting)	Additional requirement
				6	3	4	**2. Does not include all relevant elements, concepts, and principles of the ICH Guidelines** (e.g., local regulation limits legal applicant only to submit SUSARs; MedDRA coding not implemented; no classification of source of ICSR (e.g., solicited/unsolicited); no guidance regarding the prioritisation of follow-up activities)	Local guideline
				4	2	4	**3. Implementation still in process or incomplete, or issues with adherence** (e.g., more training is required; and implementation not yet effective)	Implementation issue
Tier 2	M4	Common Technical Document	16	18	6	13	**1. Different local or regional CTD format or nomenclature followed to incorporate additional requirements**	Local guideline
				10	2	10	**2. Lack of adequate electronic system that facilitates the migration to CTD format****	Implementation issue
Tier 3	Q3A(R2), Q3B(R2), Q3C(R6), and Q3D(R1)	Impurities	17	12	4	6	**1. Incorporates additional analytical requirements/acceptance criteria beyond those defined in the ICH Guidelines** (e.g., drug substance impurities' documentation per each manufacturing site; unnecessary stress testing; use of stricter conversion factor to set impurity acceptance criterion; and inclusion of drug substance process impurities within drug product impurities specification) **	Additional requirement

Tier	Involved Guideline(s)	Guideline topic	Page no. for analysis	Frequency*	No. of authorities	No. of comp.	Theme	Broader trend
				3	2	3	**2. A national/regional guideline is in place which prevents full implementation and adherence with ICH, particularly due to different definitions, concepts and terminology used or due to conflict with the current regulatory framework**	Implementation issue
Tier 3	Q10	Pharmaceutical Quality System	19	10	2	9	**1. Authority's interpretation differs from what is described in the ICH Guideline** (e.g., manufacturing areas sharing between medicinal products for human use and medicinal veterinary products)	Implementation issue
Tier 3	Q6A, and Q6B	Specifications	20	9	4	4	**1. Local/regional guidelines conflict with ICH Guideline either by incorporating additional requirements or not including all relevant aspects** (e.g., release specification and shelf-life specification are not clearly divided, and additional requirements based on especially European pharmacopoeia)	Local guideline
				3	2	3	**2. Implementation of Guideline in progress or implementation issue - either an element of the ICH Guideline in general or the specific Guideline revision** (e.g., ICH Q4B not implemented thereby preventing implementation of Q6A)	Implementation issue
Tier 3	Q2(R1)	Validation of Analytical Procedures	21	12	3	10	**1. Incorporates additional analytical/acceptance criteria requirements beyond those defined in the ICH Guidelines** (e.g., additional requirements for linearity, robustness, selectivity, reference standard and compendial test; and requisition of raw data for all validation experiments)	Additional requirement
Tier 3	Q5A(R1), Q5B, Q5C, Q5D, and Q5E	Quality of Biotechnological Products	23	7	2	3	**1. Does not include all relevant elements, concepts, and principles of the ICH Guidelines** (e.g., not incorporated into relevant regulations; different scope of applications; and multiple manufacturing sites are banned/restricted for imported biologics)	Implementation issue
				6	2	4	**2. Incorporates additional requirements beyond those defined in the ICH Guidelines** (e.g., full stability studies for combination products with devices even when the device does not impact in drug product quality; and comparability data of biological products for investigational medicinal products)	Additional requirement
Tier 3	E17	General principles for planning and	25	6	2	6	**1. Incorporates additional requirements beyond those defined in the ICH Guidelines** (e.g., mandatory	Additional requirement

Tier	Involved Guideline(s)	Guideline topic	Page no. for analysis	Frequency*	No. of authorities	No. of comp.	Theme	Broader trend
		design of Multi-Regional Clinical Trials					representation of the country's population in the study; sample size considerations vary from TA to TA)	
				4	2	3	**2. Interpretation differs from the ICH Guideline** (e.g., gaps between ICH and local guidelines; discussion about definition of region)	Implementation issue
Tier 3	E5(R1)	Ethnic Factors in the Acceptability of Foreign Clinical Data	26	6	3	6	**1. Local/regional guidelines conflict with ICH Guideline either by incorporating additional requirements or not including all relevant aspects** (e.g., mandatory representation of the country's population in the study)	Local guideline
Tier 3	E2C(R2), E2E, and E2F	Pharmacovigilance	27	6	3	4	**1. Incorporates additional requirements for reporting beyond those defined in the ICH Guideline** (e.g., additional information within PBRER, and DSUR)	Additional requirement
Tier 3	Q11	Development and Manufacture of Drug Substances	28	6	2	5	**1. Local/regional guidelines conflict with ICH Guideline either by incorporating additional requirements or not including all relevant aspects** (e.g., detailed information above starting material)	Local guideline
				3	2	3	**2. Does not include all relevant elements, concepts, and principles of the ICH Guidelines** (e.g., design space concept is currently not endorsed; and real time release test has not been accepted)	Implementation issue
Tier 3	E3	Structure and Content of Clinical Study Reports	29	3	2	3	**1. Local/regional guidelines conflict with ICH Guideline either by incorporating additional requirements or not including all relevant aspects** (e.g., statistical analysis report is still requested as part of clinical safety report; request of additional analysis and reports)	Local guideline

*NOTE: *: Frequency is described as the total number of times that a theme was mentioned among all comments for a specific ICH Guideline; **: Points out when a new theme was discovered compared with themes mentioned in the 2019 report*

RESULTS PART 2: TRENDS FOR SPECIFIC TIER 1, TIER 2, AND TIER 3 GUIDELINES

A. Tier 1 – ICH Guideline Q1 – Stability (all subparts considered)

a) Context based on results from 2021 Report

Based on the 2021 full study report, there was general agreement for the company and authority perception regarding the adequate implementation and adherence to this Guideline by Observers. This section summarises themes identified from free text responses from companies to explain the rationale for this (in addition to what the 2021 full study report outlined based on responses from the multiple-choice question 2).

b) Responder Characteristics

Comments were received from **three** different companies regarding **two** ICH Observers. The table below shows common themes across the companies following the analysis.

c) Analysis of themes

Common themes identified across the comments regarding inadequate implementation/lack of adherence to ICH Guideline Q1

Theme	Frequency*	Number of authorities	Number of companies
1. Incorporates additional requirements (e.g., extra analytical analysis and site-specific requirements for imported products)	3	2	3

*NOTE: *: Frequency is described as the total number of times that a theme was mentioned among all comments for a specific ICH Guideline; **: Points out when a new theme was discovered compared with themes mentioned in the 2019 report*

Example of verbatim comments/evidence corresponding to the theme

Theme 1: Incorporates additional requirements (e.g., extra analytical analysis and site-specific requirements for imported products)

- **Example 1:** *"Additional Chromatograms Request. No Stability data requested for API."*
- ***Example 2:*** *"For imported products the Authority follows ICH guidelines but for local products the Authority it has less restrictive guidelines"*

B. Tier 2 – Pharmacovigilance ICH Guidelines E2A, E2B(R3), and E2D

- **E2A –** Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.
- **E2B(R3) –** Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports.
- **E2D –** Post-approval Safety Data Management: Definitions and Standards for Expedited Reporting.

a) Context based on results from 2021 Report

Based on the 2021 full study report, there was general agreement for the company and authority perception regarding the adequate implementation and adherence to these Guidelines by ICH Regulatory Members. This section summarises themes identified from free text responses from companies to explain the rationale for

this (in addition to what the 2021 full study report outlined based on responses from the multiple-choice question 2).

b) Responder Characteristics

Comments were received from **eight** different companies regarding **six** ICH Regulatory Members. The table below shows common themes across the companies following the analysis.

c) Analysis of themes

Common themes identified across the comments regarding inadequate implementation/lack of adherence to Pharmacovigilance ICH Guidelines – ICH E2A, E2B(R3), and E2D

Theme	Frequency*	Number of authorities	Number of companies
1. Incorporates additional requirements for reporting beyond those defined in the ICH Guideline (e.g., expedited submission of: SUSARs[2] to investigators; SUSARs for non-interventional PAC studies; positive control medicine case; unrelated adverse events (other than ADR[3]); lack of efficacy reports, regardless of whether it is serious or not, and mandatory local language reporting)	16	5	7
2. Does not include all relevant elements, concepts, and principles of the ICH Guidelines (e.g., local regulation limits legal applicant only to submit SUSARs; MedDRA coding not implemented; no classification of source of ICSR (e.g., solicited/unsolicited); no guidance regarding the prioritisation of follow-up activities)	6	3	4
3. Implementation still in process or incomplete, or issues with adherence (e.g., more training is required; and implementation not yet effective)	4	2	4

*NOTE: *: Frequency is described as the total number of times that a theme was mentioned among all comments for a specific ICH Guideline; **: Points out when a new theme was discovered compared with themes mentioned in the 2019 report*

Example of verbatim comments/evidence corresponding to the theme – ICH E2A, E2B(R3), and E2D

Theme 1: Incorporates additional requirements for reporting beyond those defined in the ICH Guideline (e.g., expedited submission of: SUSARs to investigators; SUSARs for non-interventional PAC studies; positive control medicine case; unrelated adverse events (other than ADR); lack of efficacy reports, regardless of whether it is serious or not, and mandatory local language reporting)

- **Example 1:** *"Regulation requires sponsor to forward SUSARs to investigators within the same timeline (7 or 15 days) …"*
- **Example 2:** *"Expedited SUSAR Reporting is required for non-interventional PAC studies."*

[2] SUSAR: Suspected Unexpected Serious Adverse Reaction
[3] ADR: Adverse Drug Reaction

- ***Example 3:*** *Lack of efficacy cases must be submitted to the Health Authority in 15 days. It is not applicable in ICH..."*

Theme 2: Does not include all relevant elements, concepts, and principles of the ICH Guidelines (e.g., local regulation limits legal applicant only to submit SUSARs; MedDRA coding not implemented; no classification of source of ICSR (e.g., solicited/unsolicited); no guidance regarding the prioritisation of follow-up activities)

- **Example 1:** *"… 2) Local regulation limits legal applicant only to submit SUSARs; If the sponsor is not a legal applicant for CTA, the sponsor could not submit SUSARs to the Authority."*
- **Example 2:** *"… As MedDRA is not implemented, we need to modify all MedDRA coding …"*
- ***Example 3:*** *"… 2. No guidance regarding the prioritisation of follow-up activities"*

Theme 3: Implementation still in process or incomplete, or issues with adherence (e.g., more training is required; and implementation not yet effective)

- **Example 1:** *"More training is welcome to industry for helping industry and the Authority has the same understanding at the same page"*
- **Example 2:** *"Review based on mandation for CT requirement only, post-marketing requirements not effective until 2022"*

C. Tier 2 – ICH Guideline M4 – Common Technical Document

a) Context based on results from 2021 Report

Based on the 2021 full study report, there was general agreement for the company and authority perception regarding the adequate implementation and adherence to this Guideline by ICH Regulatory Members. This section summarises themes identified from free text responses from companies to explain the rationale for this (in addition to what the 2021 full study report outlined based on responses from the multiple-choice question 2).

b) Responder Characteristics

Comments were received from **14** companies regarding **six** ICH Regulatory Members. The table below shows common themes across the companies following the analysis.

c) Analysis of themes

Common themes identified across the comments regarding inadequate implementation/lack of adherence to Guideline – ICH M4

Theme	Frequency*	Number of authorities	Number of companies
1. Different local or regional CTD format or nomenclature followed to incorporate additional requirements	18	6	13
2. Lack of adequate electronic system that facilitates the migration to CTD format**	10	2	10

*NOTE: *: Frequency is described as the total number of times that a theme was mentioned among all comments for a specific ICH Guideline; **: Points out when a new theme was discovered compared with themes mentioned in the 2019 report*

Example of verbatim comments/evidence corresponding to each theme – ICH M4

Theme 1: Different local or regional CTD format or nomenclature followed to incorporate additional requirements.

- **Example 1***: "The already implemented local regulation requires many country-specific documents, where the content and structure's CTD is substantially changed to accommodate the local requirements. This scenario complicates regulatory convergence on having a standard package among ICH members. In addition, the local guideline defined that some country-specific documents should be presented in specific CTD sections instead of the Regional Section. This represents a high impact for the multinational companies that receive a standard CTD package. For this situation, the regulatory convergence in terms of requirements could minimise or solve the problem..."*

Theme 2: Lack of adequate electronic system that facilitates the migration to CTD format

- **Example 1:** *"The Authority has developed their own system for CTD, but it conflicts with eCTD which is commonly used in the world. The Authority should update regulations and their system to implement this ICH guideline."*
- **Example 2:** *"...The other pain point is the absence of an electronic submission option. Currently a lot of applications can be done electronically. But due to the lack of an electronic system implemented, if the company adopts CTD format, the submissions should be done in a physical way (paper-based + electronic media as pen drive)."*

D. Tier 3 – Impurities ICH Guidelines Q3A(R2), Q3B(R2), Q3C(R6), and Q3D(R1)

- **Q3A(R2)** – Impurities in New Drug Substances.
- **Q3B(R2)** – Impurities in New Drug Products.
- **Q3C(R6)** – Maintenance of the Guideline for Residual Solvents
- **Q3D(R1)** – Guideline for Elemental Impurities

a) Context based on results from 2021 Report

Based on the 2021 full study report, there was general agreement for the company and authority perception regarding the adherence to these Guidelines by ICH Regulatory Members. This section summarises themes identified from free text responses from companies to explain the rationale for lack of adherence (in addition to what the 2021 full study report outlined based on responses from the multiple-choice question 2).

b) Responder Characteristics

Comments were received from **nine** different companies regarding **four** ICH Regulatory Members. The table below shows common themes across the companies following the analysis.

c) Analysis of themes

Common themes identified across the comments regarding lack of adherence to the Impurities ICH Guidelines Q3A(R2), Q3B(R2), Q3C(R6), and Q3D(R1)

Theme	Frequency*	Number of authorities	Number of companies
1. Incorporates additional analytical requirements/acceptance criteria beyond those defined in the ICH Guidelines (e.g., drug substance impurities' documentation per each manufacturing site; unnecessary stress testing; use of stricter conversion factor to set impurity acceptance criterion; and inclusion of drug substance process impurities within drug product impurities specification) **	12	4	6
2. A national/regional guideline is in place which prevents full implementation and adherence with ICH, particularly due to different definitions, concepts and terminology used or due to conflict with the current regulatory framework	3	2	3

*NOTE: *: Frequency is described as the total number of times that a theme was mentioned among all comments for a specific ICH Guideline; **: Points out when a new theme was discovered compared with themes mentioned in the 2019 report*

Example of verbatim comments/evidence corresponding to each theme – ICH Q3A(R2), Q3B(R2), Q3C(R6), and Q3D(R1)

Theme 1: Incorporates additional analytical requirements/acceptance criteria beyond those defined in the ICH Guidelines. (e.g., drug substance impurities' documentation per each manufacturing site; unnecessary stress testing; use of stricter conversion factor to set impurity acceptance criterion; and inclusion of drug substance process impurities within drug product impurities specification)

- **Example 1:** *"If the manufacturing sites are more than 2 for Drug substance, every document is required per sites including characterisation. It is challenging as the company generates only one core document for the substance regardless of manufacturing sites."*
- ***Example 2:*** *"When setting acceptance criterion of related substance based on NOAEL of animals, the Authority asks to apply the conversion factor shown in FDA guideline on estimating the maximum safety starting dose in initial clinical trials for therapeutics in adult healthy."*
- ***Example 3:*** *"Companies must produce a theoretical report for their products, investigation and previewing the possible Degradation Products and, after that, an experimental step is required, a full forced degradation study and investigation at stability batches, in order to prove that the theoretical preview is secure and consistent and the adopted control strategy is adequate to control the product, even if any degradation occurs"*
- ***Example 4:*** *"… the Authority requires applicants to include drug substance process impurities in the drug product specification when approving import drug specification"*

Theme 2: A national/regional guideline is in place which prevents full implementation and adherence with ICH, particularly due to different definitions, concepts and terminology used or due to conflict with the current regulatory framework

- **Example 1:** *"There is conflict with local guideline. The agency has formally implemented the ICH guideline but its adherence to the guideline or interpretation is inconsistent as it often asks for additional information or data that are outside that intended by the ICH guideline."*

E. Tier 3 – ICH Guideline Q10 – Pharmaceutical Quality System

a) Context based on results from 2021 Report

Based on the 2021 full study report, there was general agreement for the company and authority perception regarding the adherence to this Guideline by Regulatory Members. This section summarises themes identified from free text responses from companies to explain the rationale for lack of adherence (in addition to what the 2021 full study report outlined based on responses from the multiple-choice question 2).

b) Responder Characteristics

Comments were received from **10** companies regarding **four** ICH Regulatory Members. The table below shows common themes across the companies following the analysis.

c) Analysis of themes

Common themes identified across the comments regarding lack of adherence to ICH Guideline Q10

Theme	Frequency*	Number of authorities	Number of companies
1. Authority's interpretation differs from what is described in the ICH Guideline (e.g., manufacturing areas sharing between medicinal products for human use and medicinal veterinary products)	10	2	9

*NOTE: *: Frequency is described as the total number of times that a theme was mentioned among all comments for a specific ICH Guideline; **: Points out when a new theme was discovered compared with themes mentioned in the 2019 report*

Example of verbatim comments/evidence corresponding to each theme – ICH Guideline Q10

Theme 1: Authority interpretation differs from what is described in the ICH Guideline (e.g., manufacturing areas sharing between medicinal products for human use and medicinal veterinary products)

- **Example 1***: "FAQ's local regulation brings some interpretations that differ from ICH guideline and PICs regulations. As an example, we can point out the sharing of manufacturing areas between medicinal products and veterinary products, which is allowed by ICH and PICs, independently if the veterinary product is approved for human use or not. Despite that, the Authority is using a local regulation that closes possibilities of sharing a manufacturing line between Human Drugs and Veterinarian Drugs not approved for human use, even though there is a risk assessment evaluation (under ICH Guideline Q9) and cleaning validation of the equipment and facilities, which mitigate the risk of cross contamination.*

If there is no agreement between the Health Authority and the Companies, this can negatively impact the registration and maintenance of medicinal products and access for patients to new therapies."

F. Tier 3 – Specifications ICH Guidelines Q6A, and Q6B

- **Q6A** – Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances**.**
- **Q6B** – Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products.

a) Context based on results from 2021 Report

Based on the 2021 full study report, there was general agreement for the company and authority perception regarding the adherence to this Guideline by Regulatory Members. This section summarises themes identified from free text responses from companies to explain the rationale for lack of adherence (in addition to what the 2021 full study report outlined based on responses from the multiple-choice question 2).

b) Responder Characteristics

Comments were received from **five** companies regarding **four** ICH Regulatory Members. The table below shows common themes across the companies following the analysis.

c) Analysis of themes

Common themes identified across the comments regarding lack of adherence to the Specifications ICH Guidelines Q6A, and Q6B

Theme	Frequency*	Number of authorities	Number of companies
1. Local/regional guidelines conflict with ICH Guideline either by incorporating additional requirements or not including all relevant aspects (e.g., release specification and shelf-life specification are not clearly divided, and additional requirements based on especially European pharmacopoeia)	9	4	4
2. Implementation of Guideline in progress or implementation issue - either an element of the ICH Guideline in general or the specific Guideline revision (e.g., ICH Q4B not implemented thereby preventing implementation of Q6A)	3	2	3

*NOTE: *: Frequency is described as the total number of times that a theme was mentioned among all comments for a specific ICH Guideline; **: Points out when a new theme was discovered compared with themes mentioned in the 2019 report*

Example of verbatim comments/evidence corresponding to the theme – ICH Guidelines Q6A, and Q6B

Theme 1: Local/regional guidelines conflict with ICH Guideline either by incorporating additional requirements or not including all relevant aspects (e.g., release specification and shelf-life specification are not clearly divided, and additional requirements based on especially European pharmacopoeia)

- **Example 1***: "In the specification, release specification and shelf-life specification are clearly divided."*

- **Example 2***: "The Authority may ask for additional requirements based on especially European pharmacopoeia and the others."*

Theme 2: Implementation of Guideline in progress or implementation issue - either an element of the ICH Guideline in general or the specific Guideline revision (e.g., ICH Q4B not implemented thereby preventing implementation of Q6A)

- **Example 1***: "The Q6A guideline relies in part on the harmonisation of key pharmacopeial texts. The Authority needs to implement ICH Q4B to full implement Q6A."*
- **Example 2***: "…Certain test methods, e.g., water content, microbial limit, dissolution, in local pharmacopeia are not deemed interchangeable with USP, EP, or JP under Q4B..."*

G. Tier 3 – ICH Guideline Q2(R1) – Validation of Analytical Procedures: Text and Methodology

a) Context based on results from 2021 Report

Based on the 2021 full study report, there was general agreement for the company and authority perception regarding the adherence to this Guideline by Regulatory Members. This section summarises themes identified from free text responses from companies to explain the rationale for lack of adherence (in addition to what the 2021 full study report outlined based on responses from the multiple-choice question 2).

b) Responder Characteristics

Comments were received from **10** companies regarding **three** ICH Regulatory Members. The table below shows common themes across the companies following the analysis.

c) Analysis of themes

Common themes identified across the comments regarding lack of adherence to ICH Guideline Q2(R1)

Theme	Frequency*	Number of authorities	Number of companies
1. Incorporates additional analytical/acceptance criteria requirements beyond those defined in the ICH Guidelines (e.g., additional requirements for linearity, robustness, selectivity, reference standard and compendial test; and requisition of raw data for all validation experiments)	12	3	10

*NOTE: *: Frequency is described as the total number of times that a theme was mentioned among all comments for a specific ICH Guideline; **: Points out when a new theme was discovered compared with themes mentioned in the 2019 report*

Example of verbatim comments/evidence corresponding to the theme – ICH Guideline Q2(R1)

Theme 1: Incorporates additional analytical/acceptance criteria requirements beyond those defined in the ICH Guidelines. (e.g., additional requirements for linearity, robustness, selectivity, reference standard and compendial test; and requisition of raw data for all validation experiments)

- **Example 1***: "...These additional requests do not allow companies to use the same validation report used for other countries for country submissions, due these specificities: (1) Reference standard: the national resolution requests a reference standard characterisation report, with a lot of information. ICH does not detail which information needs to be evaluated/presented; (2) Linearity: the national resolution exceeds that recommended by the ICH regarding statistical analysis, discriminating exactly the tests and statistical methods to be used. In addition, stock solution must be done in triplicate & assessment of homoscedasticity; (3) Robustness: present recovery and DPR; (4) Selectivity: peak purity graphs (0.99); (5) Compendial test: It's also required verification of compendial analytical methods; LD: ruined signal 2:1. Authority enforces to industry retroactive harmonisation to current validation requirements for mature products and methods approved and in use. This might occur during a variation assessment. Besides that, since national regulation is in force, companies noticed interpretation varies by submission/ review division/ reviewer"*

- **Example 2***: "…Also, the regulatory authority is in its practice adding requirements beyond what is provided in the ICH guideline. Followings are examples; - raw data for all of validation experiments; - for unidentified impurities, validation is required; - actual test result is excessively required (e.g., all values of S/N ratio)"*

H. Tier 3 – Quality of Biotechnological Products ICH Guidelines Q5A(R1), Q5B, Q5C, Q5D, and Q5E

- **Q5A(R1)** – Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin.
- **Q5B** – Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products.
- **Q5C** – Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products.
- **Q5D** – Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products.
- **Q5E** – Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process.

a) Context based on results from 2021 Report

Based on the 2021 full study report, there was general agreement for the company and authority perception regarding the adherence to this Guideline by Regulatory Members. This section summarises themes identified from free text responses from companies to explain the rationale for lack of adherence (in addition to what the 2021 full study report outlined based on responses from the multiple-choice question 2).

b) Responder Characteristics

Comments were received from **five** companies regarding **two** ICH Regulatory Members. The table below shows common themes across the companies following the analysis.

c) Analysis of themes

Common themes identified across the comments regarding lack of adherence to the Quality of Biotechnological Products ICH Guidelines Q5A(R1), Q5B, Q5C, Q5D, and Q5E

Theme	Frequency*	Number of authorities	Number of companies
1. Does not include all relevant elements, concepts, and principles of the ICH Guidelines (e.g., not incorporated into relevant regulations; different scope of applications; and multiple manufacturing sites are banned/restricted for imported biologics)	7	2	3
2. Incorporates additional requirements beyond those defined in the ICH Guidelines (e.g., full stability studies for combination products with devices even when the device does not impact in drug product quality; and comparability data of biological products for investigational medicinal products)	6	2	4

*NOTE: *: Frequency is described as the total number of times that a theme was mentioned among all comments for a specific ICH Guideline; **: Points out when a new theme was discovered compared with themes mentioned in the 2019 report*

Example of verbatim comments/evidence corresponding to the theme – ICH Guidelines Q5A(R1), Q5B, Q5C, Q5D, and Q5E

Theme 1: Does not include all relevant elements, concepts, and principles of the ICH Guidelines (e.g., not incorporated into relevant regulations; different scope of applications; and multiple manufacturing sites are banned/restricted for imported biologics)

- **Example 1***: "The guideline has been translated and distributed but has not been incorporated into relevant regulations and so not being applied in practice."*
- **Example 2***: "…The scope of application is different: the Authority's guidelines are used for clinical application and production, and the ICH guidelines are only for the production and marketing phase…"*
- **Example 3***: "Adhere to the requirements but only somewhat as despite of comparability exercise and data the concept of multiple manufacturing sites are banned/restricted for imported biologics."*

Theme 2: Incorporates additional requirements beyond those defined in the ICH Guidelines (e.g., full stability studies for combination products with devices even when the device does not impact in drug product quality; and comparability data of biological products for investigational medicinal products)

- **Example 1***: "Guideline is implemented but the Authority requests excessive data such as the following cases: combination products with device (even though the device does not impact DP quality, full DP stability for Prefilled Pen itself for 3 lots is required), forced degradation study (requests raw data and 3 lot comparison data before/after change)."*
- **Example 2***: "The Authority requires too much information regarding comparability data of biological products even for investigational medicinal products. Sometimes they ask the lab notes for each test."*

I. Tier 3 – ICH Guideline E17 - General principles for planning and design of Multi-Regional Clinical Trials

a) Context based on results from 2021 Report

Based on the 2021 full study report, there was general agreement for the company and authority perception regarding the adherence to this Guideline by Regulatory Members. This section summarises themes identified from free text responses from companies to explain the rationale for lack of adherence (in addition to what the 2021 full study report outlined based on responses from the multiple-choice question 2).

b) Responder Characteristics

Comments were received from **six** companies regarding **two** ICH Regulatory Members. The table below shows common themes across the companies following the analysis.

c) Analysis of themes

Common themes identified across the comments regarding lack of adherence to ICH Guideline E17

Theme	Frequency*	Number of authorities	Number of companies
1. Incorporates additional requirements beyond those defined in the ICH Guidelines (e.g., mandatory representation of the country's population in the study; sample size considerations vary from TA to TA)	6	2	6
2. Interpretation differs from the ICH Guideline (e.g., gaps between ICH and local guidelines; discussion about definition of region)	4	2	3

*NOTE: *: Frequency is described as the total number of times that a theme was mentioned among all comments for a specific ICH Guideline; **: Points out when a new theme was discovered compared with themes mentioned in the 2019 report*

Example of verbatim comments/evidence corresponding to the theme – ICH Guideline E17

Theme 1: Incorporates additional requirements beyond those defined in the ICH Guidelines (e.g., mandatory representation of the country's population in the study; sample size considerations vary from TA to TA)

- **Example 1***: "The pooling of clinical trial subjects with similar intrinsic and extrinsic factors is key and important element of this guideline. Despite a slight improvement it seems to be a challenge for the Authority as they continue to require country's subjects in clinical trials. The only exception is oncology drugs and other drugs for life threatening diseases meeting an unmet medical need for treatment in the submission country. Acceptance of data from other Region populations including submission country's people living abroad are not sufficient in most cases. The pooling of clinical trial subjects with similar intrinsic and extrinsic factors is a very crucial principle in this guideline so the Authority will hopefully adapt this concept more in the future."*

- **Example 2***: "The requirement regarding domestic sample size consideration varies from TA to TA"*

Theme 2: Interpretation differs from the ICH Guideline (e.g., gaps between ICH and local guidelines; discussion about definition of region)

- **Example 1:** "Gap in interpretation and implementation between ICH and local guidelines."
- **Example 2:** "It is still under discussion about the definition of region. So far, the country is regarded as "region", requiring the bridging data comparing domestic vs foreign when using MRCT"

J. Tier 3 – ICH Guideline E5(R1) – Ethnic Factors in the Acceptability of Foreign Clinical Data

a) Context based on results from 2021 Report

Based on the 2021 full study report, there was general agreement for the company and authority perception regarding the adherence to this Guideline by Regulatory Members. This section summarises themes identified from free text responses from companies to explain the rationale for lack of adherence (in addition to what the 2021 full study report outlined based on responses from the multiple-choice question 2).

b) Responder Characteristics

Comments were received from **seven** companies regarding **three** ICH Regulatory Members. The table below shows common themes across the companies following the analysis.

c) Analysis of themes

Common themes identified across the comments regarding lack of adherence to ICH Guideline E5(R1)

Theme	Frequency*	Number of authorities	Number of companies
1. Local/regional guidelines conflict with ICH Guideline either by incorporating additional requirements or not including all relevant aspects (e.g., mandatory representation of the country's population in the study)	6	3	6

*NOTE: *: Frequency is described as the total number of times that a theme was mentioned among all comments for a specific ICH Guideline; **: Points out when a new theme was discovered compared with themes mentioned in the 2019 report*

Example of verbatim comments/evidence corresponding to the theme – ICH Guideline E5(R1)

Theme 1: Local/regional guidelines conflict with ICH Guideline either by incorporating additional requirements or not including all relevant aspects (e.g., mandatory representation of the country's population in the study)

- **Example 1***: "The local guideline is mainly based on ICH guideline. However, local guideline is much more detailed and requires specific requirements. (e.g., local guideline defines only the country as one region, so bridging data is interpreted as country's population vs population outside the country)"*

- **Example 2***: "Authorities still insist on having local population data"*

K. Tier 3 – Pharmacovigilance ICH Guidelines E2C(R2), E2E, and E2F

- **E2C(R2)** – Periodic Benefit-Risk Evaluation Report
- **E2E** – Pharmacovigilance Planning
- **E2F** – Development Safety Update Report.

a) Context based on results from 2021 Report

Based on the 2021 full study report, there was general agreement for the company and authority perception regarding the adherence to these Guidelines by ICH Regulatory Members. This section summarises themes identified from free text responses from companies to explain the rationale for lack of adherence (in addition to what the 2021 full study report outlined based on responses from the multiple-choice question 2).

b) Responder Characteristics

Comments were received from **six** different companies regarding **four** ICH Regulatory Members. The table below shows common themes across the companies following the analysis.

c) Analysis of themes

Common themes identified across the comments regarding lack of adherence to Pharmacovigilance ICH Guidelines – ICH E2C(R2), E2E, and E2F

Theme	Frequency*	Number of authorities	Number of companies
1. Incorporates additional requirements for reporting beyond those defined in the ICH Guideline. (e.g., additional information within PBRER, and DSUR)	6	3	4

*NOTE: *: Frequency is described as the total number of times that a theme was mentioned among all comments for a specific ICH Guideline; **: Points out when a new theme was discovered compared with themes mentioned in the 2019 report*

Example of verbatim comments/evidence corresponding to the theme – ICH E2C(R2), E2E, and E2F

Theme 1: Incorporates additional requirements for reporting beyond those defined in the ICH Guideline. (e.g., additional information within PBRER, and DSUR)

- **Example 1:** *"The Authority is requiring the following additional information: 1) similar to a line listing, 2) field specific forms in local language, and 3) signing of a declaration that all the content is valid"*
- **Example 2:** *"DSUR requirements exceed those laid out in ICH E2F, specifically: a. Domestic list of deaths (instead of Global list where country of occurrence is already indicated), including a country specific study identifier; b. Domestic list of study/treatment drop-outs (instead of Global list where country of occurrence is already indicated), including a country specific study identifier; c. List of NON-safety changes submitted to the CTA during the DSUR period (e.g., protocol changes, new clinical, non-clinical, and pharmaceutical changes/findings). This requirement deviates from ICH E2 concept as information*

is not related to safety; d. non-clinical studies planned during the next period; and e. Translation into the local language of full DSUR (except line listings) required"

L. Tier 3 – ICH Guideline Q11 – Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)

a) Context based on results from 2021 Report

Based on the 2021 full study report, there was general agreement for the company and authority perception regarding the adherence to this Guideline by Regulatory Members. This section summarises themes identified from free text responses from companies to explain the rationale for lack of adherence (in addition to what the 2021 full study report outlined based on responses from the multiple-choice question 2).

b) Responder Characteristics

Comments were received from **six** companies regarding **three** ICH Regulatory Members. The table below shows common themes across the companies following the analysis.

c) Analysis of themes

Common themes identified across the comments regarding lack of adherence to ICH Guideline Q11

Theme	Frequency*	Number of authorities	Number of companies
1. Local/regional guidelines conflict with ICH Guideline either by incorporating additional requirements or not including all relevant aspects (e.g., detailed information above starting material)	6	2	5
2. Does not include all relevant elements, concepts, and principles of the ICH Guidelines (e.g., design space concept is currently not endorsed; and real time release test has not been accepted)	3	2	3

*NOTE: *: Frequency is described as the total number of times that a theme was mentioned among all comments for a specific ICH Guideline; **: Points out when a new theme was discovered compared with themes mentioned in the 2019 report*

Example of verbatim comments/evidence corresponding to the theme – ICH Guideline Q11

Theme 1: Local/regional guidelines conflict with ICH Guideline either by incorporating additional requirements or not including all relevant aspects (e.g., detailed information above starting material)

- **Example 1***: "DMF registration is required for NCEs DS of chemical products. The Authority sometimes requests too much detailed level of information above starting material (manufacturers, manufacturing process flow chart (including solvent used and metal catalyst), test method validation summary table and CoAs etc.)"*

Theme 2: Does not include all relevant elements, concepts, and principles of the ICH Guidelines (e.g., design space concept is currently not endorsed; and real time release test has not been accepted)

- **Example 1***: "Design space concept is currently not endorsed, but the Authority has plans to allow this in the future."*
- **Example 2***: "Real Time Release Test has not been accepted. So far, typical final test result is requested."*

M. Tier 3 – ICH Guideline E3 – Structure and Content of Clinical Study Reports

a) Context based on results from 2021 Report

Based on the 2021 full study report, there was general agreement for the company and authority perception regarding the adherence to this Guideline by Regulatory Members. This section summarises themes identified from free text responses from companies to explain the rationale for lack of adherence (in addition to what the 2021 full study report outlined based on responses from the multiple-choice question 2).

b) Responder Characteristics

Comments were received from **three** companies regarding **two** ICH Regulatory Members. The table below shows common themes across the companies following the analysis.

c) Analysis of themes

Common themes identified across the comments regarding lack of adherence to ICH Guideline E3

Theme	Frequency*	Number of authorities	Number of companies
1. Local/regional guidelines conflict with ICH Guideline either by incorporating additional requirements or not including all relevant aspects (e.g., statistical analysis report is still requested as part of clinical safety report; request of additional analysis and reports)	3	2	3

*NOTE: *: Frequency is described as the total number of times that a theme was mentioned among all comments for a specific ICH Guideline; **: Points out when a new theme was discovered compared with themes mentioned in the 2019 report*

Example of verbatim comments/evidence corresponding to the theme – ICH Guideline E3

Theme 1: Local/regional guidelines conflict with ICH Guideline either by incorporating additional requirements or not including all relevant aspects (e.g., statistical analysis report is still requested as part of clinical safety report; request of additional analysis and reports)

- **Example 1***: "In recent cases, a country specific document, Statistical Analysis Report (SAR) is still requested as part of CSR."*

CONCLUSION

In addition to the 2021 full study report, this report summarises an analysis of industry free text comments, in cases where the response suggested inadequate implementation or lack of adherence to an ICH Guideline by the Authorities. The analysis identified themes and trends as well as specific examples for the small proportion of cases of inadequate implementation or lack of adherence. The main outcomes of this report based on the objectives were:

1) Provide further context to results from the Phase 2b survey (based on the 2021 report):

The analysis of industry free text comments confirmed three overarching trends as the root causes for inadequate implementation or lack of adherence which accounted for 6% of the responses:

a) Additional requirements requested beyond the ICH Guideline – these varied from extra analytical tests, site-specific requirements, local language requirements, submission of special reports, and submission of raw data.
b) Local Guideline – a national/regional guideline is in place which prevents full implementation and adherence with ICH, particularly due to different definitions, concepts and terminology used or due to conflict with the current regulatory framework.
c) Implementation issue – the Guideline is not fully implemented due to the authority's interpretation being different from what is described in the ICH Guideline or the authority's system not allowing full implementation.

2) Add value on informing ICH training

Two out of three companies submitted free-text comments (169 responses from 19 companies on 9 authorities). ICH M4 received the largest number of comments individually, whereas Pharmacovigilance ICH Guidelines (E2A, E2B(R3), and E2D) received the largest number of comments as group. Nevertheless, the findings from this report highlighted differences in interpretation of a Guideline and its implementations status, based on the above identified themes.

These findings could be subsequently assessed by ICH Training Subcommittee and the training associates to determine if there are specific issues that need to be addressed or some general themes that need to be clarified as part of training. In addition, it could be utilised by the authorities to ensure that local guidelines are being aligned with ICH Guidelines and that any divergences from ICH are justified and are clear to stakeholders. Whereas the aim of this study was to analyse comments and identify themes, the arbitration whether these comments are justified was outside the scope of this study. Nevertheless, this could be addressed by ICH as well as the authorities as they have already received consolidated comments relevant to their jurisdiction.

3) Inform future surveys on this topic as directed by ICH

These finding can be used to further explain divergences in Phase 2b responses as well as to inform future studies. In addition, enhancements to the survey approach, such as a verification step, could be used to facilitate alignment in how the survey is completed. This would also aim to ensure comments add value and can be utilised to understand outliers and provide a better narrative on the responses. Finally, it would help to further increase the robustness of the results to help meet the long-term objectives of this study, which is to establish a sustainable ICH-driven mechanism to assess Guidelines over time to inform ICH stakeholders on multiple areas, such as ICH membership and training needs.

The outcomes described in this study:

1. Have given the industry and the authorities, an opportunity to review the collective free text entries, uncover meaningful divergences, and differentiate them from organisational or unique outliers
2. Can be used to support training efforts and capacity building initiatives by identifying challenges within specific Guidelines and across Guidelines regarding their implementation and adherence
3. Have outlined common trends that can be used to build tailored case studies among training groups and EWGs

APPENDIX 1 – DEFINITIONS

Definitions of terms in the context of the implementation of ICH Guidelines

Term	Definition	Comments
Not (yet) implemented	The process for the implementation of an ICH Guideline has not yet started.	a) No guideline exists or b) national/ regional Guideline deviating from ICH Guideline or national/regional Guideline exists but the process for replacement or amendments for alignment with the ICH Guideline has not started yet.
In the process of implementation	The process for the implementation of the ICH Guideline has started and has reached a specified milestone. The process is monitored by the regulatory agency and the progress is reported to the ICH MC/Assembly on a regular basis.	The process can have different starting points: a) no national/regional guideline exists; the ICH Guideline defines new requirements and b) a national/regional guideline is in the process of development or c) a national/regional guideline exists and is replaced by or is amended to be in line with the ICH Guideline. Generic processes for a) non-electronic and b) electronic guidelines will be defined outlining the milestones that should be followed.
Implemented	The process of implementation is completed. This step is identical to step 5 of the ICH process.	This term refers to the self-declaration of the regulator regarding the conclusion of the implementation process. Usually, the regulator publishes the final Guideline.
Adequately implemented	All relevant elements, concepts and principles of the ICH Guideline are followed. This is done preferably by referring to/implementing the original ICH Guideline text and/or translating the original Guideline text. This may include in justified cases implementation of the Guideline in a way that may incorporate additional information beyond those defined in the ICH Guideline in circumstances when the Guideline is too high-level and does not provide sufficient guidance.	Minimal elements, concepts and principles will be defined and included in the survey to assess the degree of implementation. Additional information to the ICH Guideline should only be included in order to provide clarity and facilitate implementation by industry but should not increase regulatory burden. Deviations or additional information to help clarify concepts should be communicated (with the justification) to the ICH Management Committee for transparency and possibly assessment.
Not adequately implemented	The ICH Guideline has been implemented in a modified way that a) incorporates additional requirements beyond those defined in the ICH Guideline without objective justification in cases where clear guidance is provided, or b) does not include all relevant elements, concepts and principles of the ICH Guideline and	Lack of adequate implementation means that the ICH Guideline has not been adequately implemented following an assessment of the regulatory or administrative measure that incorporates the ICH Guideline into the regulatory framework. There may be varying degrees of inadequate implementation and this assessment can only be

Term	Definition	Comments
	does not provide any objective justification for omitting some requirements in the Guideline or c) requires application of the Guideline for a smaller range of products than outlined in the ICH Guideline.	done on a case-by-case basis. Examples could be taken from the Industry Survey to illustrate this range. It should be noted that according to the Assembly RoP (v. 4.0), deviation from the Guideline, in exceptional cases, may be accepted if objectively justified.
Adherence[4]	In its practice, the regulatory authority consistently adheres to (applies) all identified relevant elements, concepts, and principles of the ICH Guideline over time.	Once an ICH Guideline has been (adequately) implemented by a regulatory authority, experience is gathered on how the regulator applies the Guideline in practice. Adherence leads to a stable regulatory environment and to increased sustainability. Adherence may be assessed in regular intervals.
Lack of adherence	Even if the Guideline has been adequately implemented, it is not being applied and adhered to in practice.	The regulatory authority does not in practice require industry to adhere to the Guideline or does not follow the Guideline when assessing the applications, e.g., is in its practice adding requirements beyond what is provided in the (implemented) ICH Guideline.
Confirmed implementation / adherence	Both the implementation of and adherence to the ICH Guideline have been assessed by an independent third party and have been found to be adequate by the Assembly/the MC (see above).	The assessment should be done in two-steps: first assessment of a) adequate implementation and then b) adherence to the ICH Guideline. The implementation should not be considered confirmed even in case of adherence if there is no adequate implementation of the ICH Guideline (i.e., where the regulatory authority in practice accepts submissions that comply with the requirements in the ICH Guideline despite not having adequately implemented it).
Not applicable	The implementation of a specific ICH Guideline is not applicable in a country/region. An appropriate justification is provided.	Example: A country may not have its own Pharmacopeia but references internationally recognised Pharmacopoeias. Hence, the ICH Q4B Guideline is not applicable (and does not need to be implemented).

[4] Adherence at this point in time is defined as application of the ICH Guideline by the regulator's view. At a later stage, consideration will be given to the aspect of adherence to the Guideline requirements by industry's view.

APPENDIX 2 – STUDY TOOL

Questionnaire

This document outlines the questions that will be listed as part of the online data collection tool (DCT).

The below questions will be used for each Guideline and Authority for respondents from both companies and authorities (note that where specified, certain questions are applicable to companies only).

Companies will have to answer the following general questions:

Question 1i (Companies only): Please specify your company type, which refers to what countries/regions the company is submitting drug applications to:

- ☐ Local country only
- ☐ Single region
- ☐ Multi-regional
- ☐ Global

Question 1ii (Companies only): Please specify your company's focus for drug development:

- ☐ Innovative medicines
- ☐ Generic medicines
- ☐ Both

All questions will be available for Tier 1 and Tier 2 Guidelines whereas Tier 3 Guidelines, an abbreviated questionnaire will be utilised based on questions highlighted in gray. This questionnaire has also been slightly adapted from the questionnaire used in the 2019 study, and the changes are marked with track changes.

Question 1a (for Companies only)

What is your company's experience about this Guideline for the selected Authority? Select one (most recent and relevant). (Additional text to display as 'hover box' for company's experience: "Please specify your company's experience relating to the Guideline/authority before answering Questions 2-4. If 'no experience' selected, scroll down to Question 3. If multiple options apply, select one that is most relevant, noting that responses in the subsequent Questions 2-4 should relate to your company's general experience, and not only to the single submission/experience selected. Additional comments and/or divergences can be captured through comment boxes, for example Question 3.")

- ☐ From a past regulatory submission

1.1.a. If yes, give a year of the most recent submission Text box 'yyyy' format

- ☐ Through ongoing regulatory intelligence input/local affiliate opinion
- ☐ Being used to prepare for an upcoming submission
- ☐ Through interactions and exchanges with the Authority
- ☐ No experience

If 'no experience', respondent redirected to Question 3. If other responses selected, respondent asked to answer Question 1.

Question 1 (for Companies and Authorities)

1.1. Please provide your organisation's view on the implementation status for the selected Guideline. Select one.

- ☐ Not implemented - The process for the implementation of an ICH Guideline has not yet started. (Additional text to display as a 'hover box' for 'not implemented': "a) No guideline exists or b) national/ regional Guideline deviating from ICH Guideline or national/regional Guideline exists but the process for replacement or amendments for alignment with the ICH Guideline has not started yet.")

- ☐ In the process of implementation - The process for the implementation of the ICH Guideline has started and has reached a specified milestone. (Additional text to display as a 'hover box' for 'in the process of implementation': "The process can have different starting points: a) no national/regional guideline exists; the ICH Guideline defines new requirements and b) a national/regional guideline is in the process of development or c) a national/regional guideline exists and is replaced by or is amended to be in line with the ICH Guideline. Generic processes for a) non-electronic and b) electronic guidelines will be defined outlining the milestones that should be followed.")
- ☐ Implemented - The process of implementation is completed. (Additional text to display as a 'hover box' based for 'implemented': "This term refers to the self-declaration of the regulator regarding the conclusion of the implementation process. Usually, the regulator publishes the final Guideline. This could relate to both adequate or inadequate implementation of the Guideline. The adequacy of implementation will be queried in the next question.")
- ☐ Not Applicable - The implementation of a specific ICH Guideline is not applicable in this country/region. An appropriate justification is provided. (Additional text to display as a 'hover box' for 'not applicable': "Example: A country may not have its own Pharmacopeia but references internationally recognised Pharmacopoeias. Hence, the ICH Q4B Guideline is not applicable (and does not need to be implemented).")

If 'Not applicable' selected in Question 1.1, respondent redirected to Question 1.1.1, and then Question 3. If 'not implemented' or 'in the process of implementation' selected in Question 1.1, respondent redirected to Question 3. If 'implemented', respondent asked to answer Question 1.2.

1.1.1 If 'not applicable', please comment

(Free text comment);

1.2. Please indicate which statement best characterises your organisation's view of the implementation of the ICH Guideline? Select one.

- ☐ An unmodified ICH guideline has been implemented, where all relevant elements, concepts and principles of the ICH Guideline are followed. This is done preferably by referring to/implementing the original ICH Guideline text and/or translating the original guideline text.
- ☐ Some modifications have been made to the original ICH guideline either by adding or altering certain elements, concepts, or principles

If 'An unmodified ICH…' to Question 1.2, respondent redirected to Question 1.3.

If 'Some modification' to Question 1.2, respondent redirected to 1.2.1

1.2.1. Please specify what modifications were made (either by indicating the section of the Guideline, inserting the wording, or outlining the area concerned).

- ☐ (Free text comment);

1.2.2. Are these modifications objectively justified by the Authority? (Additional text to display as a 'hover box' for 'objectively justified': "This may include in justified cases implementation of the Guideline in a way that may incorporate additional information beyond those defined in the ICH Guideline in circumstances when the Guideline is too high-level and does not provide sufficient guidance. Additional information to the ICH guideline should only be included in order to provide clarity and facilitate implementation by industry, but should not increase regulatory burden.")

- ☐ Yes
- ☐ No

If 'No' to Question 1.2.2, respondent redirected to Question 2.

If 'Yes' to Question 1.2.2, respondent asked to answer Question 1.3 (i.e., only if Guideline is 'adequately' implemented will the respondent answer the question on adherence)

1.3. Please provide your organisation's view on the adherence status for the selected Guideline. Select one.

- ☐ In its practice, the regulatory Authority consistently adheres to (applies) all identified relevant elements, concepts, and principles of the ICH Guideline over time (Additional text to display as a 'hover box' for 'consistently adheres (applies) ': "Once an ICH Guideline has been (adequately) implemented by a regulatory authority, experience is gathered on how the regulator applies the Guideline in practice. Adherence leads to a stable regulatory environment and to increased sustainability. Adherence may be assessed in regular intervals.")
- ☐ Even if the Guideline has been adequately implemented, it is not being applied and adhered to in practice (Additional text to display as a 'hover box' for 'not being applied and adhered to ': "The regulatory authority does not in practice require industry to adhere to the guideline or does not follow the guideline when assessing the applications; e.g. is in its practice adding requirements beyond what is provided in the (implemented) ICH guideline.")
- ☐ The regulatory Authority has only recently implemented the Guideline therefore it is too early to assess the adherence to the Guideline due to limited experience

If 'Even if the guideline has been adequately implemented, it is not being applied and adhered (…)' to Question 1.3, respondent asked to answer Question 2. Otherwise, respondents redirected to Question 3.

Question 2 (for Companies and Authorities)

2.1. Please provide the rationale for your selection by specifying the appropriate root cause(s) listed below. Select all that apply.

If 'not adequately implemented' is specified in Question 1.2, the following will be displayed:

- ☐ Incorporates additional requirements beyond those defined in the ICH Guideline without objective justification in cases where clear guidance is provided
- ☐ Does not include all relevant elements, concepts and principles of the ICH Guideline and does not provide any objective justification for omitting some requirements in the Guideline
- ☐ Requires application of the Guideline for a smaller range of products than outlined in the ICH Guideline
- ☐ Other

If 'other', please specify

(Free text comment)

If 'lack of adherence' is specified in Question 1.3, the above will be displayed, as well as the below (i.e., all 9 options)

- ☐ Other local guidelines conflict with the ICH Guideline and prevent full adherence to the Guideline
- ☐ Agency process or capacity issues (agency does not have an internal process and/or resources to implement the Guideline)
- ☐ There is a general lack of understanding of the elements of the ICH Guideline by technical reviewers (the underlying regulatory science is not understood)
- ☐ Inconsistent application of the Guideline, e.g. adherence and interpretation varies by submission/review division/reviewer
- ☐ The agency does not in practice require industry to adhere to the Guideline

2.2 Please provide specific evidence or examples that substantiate your root cause choice(s), (OPTIONAL)

(Free text comment)

Question 3 (for Companies and Authorities- OPTIONAL)

Please provide any other comments you would like to make in regard to the implementation and adherence of the Guideline.

(Free text comment)

Question 4 (for Companies and Authorities)

Please provide the following respondent information

4.1. Name

(Free text comment)

4.2. Department

(Free text comment)

4.3. *(Company only question)* Location of respondent. Select one.

- ☐ Head office
- ☐ Local/regional office

Completion tickbox: Respondent tick 'complete' if section completed. This will enable tracking of response rate in a summary table for each organisation.

APPENDIX 3 – LIST OF GUIDELINES

Quality Guidelines

Q1 – Stability (NOTE: this Guideline should be considered as a whole, but as it is made up of sub parts, these should be taken into consideration when answering and can be referred to using comment boxes)
Q2(R1) – Validation of Analytical Procedures: Text and Methodology
Q3A(R2) – Impurities in New Drug Substances
Q3B(R2) – Impurities in New Drug Products
Q3C(R6) – Maintenance of the Guideline for Residual Solvents
Q3D(R1) – Guideline for Elemental Impurities
Q4B – Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions
Q5A(R1) – Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin
Q5B – Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products
Q5C – Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products
Q5D – Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products
Q5E – Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process
Q6A – Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances
Q6B – Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products
Q7 – Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients
Q8(R2) – Pharmaceutical Development
Q9 – Quality Risk Management
Q10 – Pharmaceutical Quality System
Q11 – Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)
Q12 – Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

Safety Guidelines

S1A – Need for Carcinogenicity Studies of Pharmaceuticals
S1B – Testing for Carcinogenicity of Pharmaceuticals
S1C(R2) – Dose Selection for Carcinogenicity Studies of Pharmaceuticals
S2(R1) – Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use
S3A – Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies
S3B – Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies
S4 – Duration of Chronic Toxicity Testing in Animals (Rodent and Non-Rodent Toxicity Testing)
S5(R2) – Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility
S5(R3) – Revision of S5 Guideline on Detection of Toxicity to Reproduction for Human Pharmaceuticals
S6(R1) – Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals
S7A – Safety Pharmacology Studies for Human Pharmaceuticals
S7B – The Non-Clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals
S8 – Immunotoxicity Studies for Human Pharmaceuticals
S9 – Nonclinical Evaluation for Anticancer Pharmaceuticals
S10 – Photosafety Evaluation of Pharmaceuticals
S11 – Nonclinical Safety Testing in Support of Development of Paediatric Medicines

Efficacy Guidelines

E1 – The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions
E2A – Clinical Safety Data Management: Definitions and Standards for Expedited Reporting
E2B(R3) – Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports
E2C(R2) – Periodic Benefit-Risk Evaluation Report
E2D – Post-approval Safety Data Management: Definitions and Standards for Expedited Reporting
E2E – Pharmacovigilance Planning
E2F – Development Safety Update Report
E3 – Structure and Content of Clinical Study Reports
E4 – Dose-Response Information to Support Drug Registration
E5(R1) – Ethnic Factors in the Acceptability of Foreign Clinical Data
E6(R2) – Good Clinical Practice
E7 – Studies in Support of Special Populations: Geriatrics
E8 – General Considerations for Clinical Trials
E9 – Statistical Principles for Clinical Trials
E9(R1) – Addendum: Statistical Principles for Clinical Trials
E10 – Choice of Control Group and Related Issues in Clinical Trials
E11(R1) – Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population
E14 – The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs
E15 – Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories
E16 – Biomarkers Related to Drug or Biotechnology Product Development: Context, Structure and Format of Qualification Submissions
E17 - General principles for planning and design of Multi-Regional Clinical Trials
E18 – Genomic Sampling and Management of Genomic Data

Multidisciplinary Guidelines

M1 – Medical Dictionary for Regulatory Activities Terminology
M3(R2) – Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals
M4 – Common Technical Document
M7(R1) – Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk
M9 – Biopharmaceutics Classification System-based Biowaivers

MONITORING THE ADEQUACY OF IMPLEMENTATION AND ADHERENCE TO INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE (ICH) GUIDELINES

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