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

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ICH harmonisation for better health

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.

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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 eighteen Members and thirty-three Observers.

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

Report date: 09 September 2021 Version 1.4
With editorial changes added on 07 January 2022

EXECUTIVE SUMMARY

Background: This study was built on the previous 2018/2019 assessment[1] where ICH selected the Centre for Innovation in Regulatory Science (CIRS) to collaborate on the development and the conduct of this project.

Objectives: This study aimed to monitor the adequacy of implementation and adherence to ICH Guidelines by regulatory authorities. The objectives were:

- To assist the Management Committee in determining whether ICH non-Standing non-Founding Regulatory Members would meet the eligibility criteria for the ICH Management Committee (MC) elections in June 2021
- To allow participating Observers interested in future ICH Membership to reference the survey findings to confirm their eligibility.

Method: An online questionnaire and definitions developed in 2018 and updated in 2019 by CIRS in collaboration with ICH were adapted for the purpose of this study. The questionnaire was completed in January-March 2021 by companies (assessing all the participating authorities) and authorities (assessing themselves only).

This questionnaire focused on assessing implementation and adherence to ICH Guidelines by ICH non-Standing, non-Founding Regulatory Members (ANVISA, Brazil; NMPA, China; HSA, Singapore; MFDS, Republic of Korea; TFDA, Chinese Taipei and TITCK, Turkey) for Tier 2 and 3 Guidelines. The study was also open to ICH Observers on a voluntary basis, where INVIMA, Colombia; JFDA, Jordan; SAHPRA, South Africa and SFDA, Saudi Arabia participated in the study for Tier 1 ICH Guidelines.

Assessment of implementation/ adherence across 63[2] ICH Guidelines

10 ICH Regulatory Members/ Observers undertook a self-assessment

30 international pharmaceutical companies provided a perception across the authorities to facilitate a gap analysis

Results: The results demonstrate that in general, there is a strong level of implementation and adherence across the agencies studied, as well as alignment between the perception of the companies and the self-declaration of authorities studied. **10 regulatory authorities** (100% response rate) and **30 pharmaceutical companies** (75% response rate) participated in the 2021 study to undertake gap analysis, indicating strong interest and support for this initiative.

Implementation

- ICH non-Standing non-Founding Regulatory Members:
  - **Tier 2:** Two authorities implemented all of the Tier 2 Guidelines, while all of the authorities implemented the E2D and M4 Guidelines, followed by E2A (five out of six). Compared with 2019[1] report, results indicated an increase in implementation and adherence across most of the Tier 2 Guidelines
  - **Tier 3:** Five out of the six Regulatory Members implemented >70% of the Tier 3 Guidelines
- ICH Observers:
  - **Tier 1**: Two out of the four ICH Observers implemented all three of the Tier 1 Guidelines

Adherence: Across all the authorities, where implementation was confirmed, there was a good level of adherence to the ICH Guidelines, or it was too early to assess.

Conclusion: The results demonstrate 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 highlights progress made by authorities in implementing and adhering to ICH Guidelines since the 2019 assessment and the results will be used to support training needs as well as ICH-membership related activities.

[1] https://admin.ich.org/sites/default/files/inline-files/ICHImplementationReportOutline_v1.4_2019_1101_0.pdf

[2] 63 Guidelines where 61 are unique given that E9 and S5 were included twice as E9 – E9(R1) and S5(R2)-S5(R3)

BACKGROUND AND OBJECTIVES

In the ICH Assembly Rules of Procedure, it is stated that there should be a process for the Assembly to monitor the progress of international harmonisation and coordinate efforts to provide the current state of play of the implementation and adherence to the ICH Guidelines.

On behalf of ICH, the ICH Founding Industry Members agreed that a pilot study, Phase 1, would be conducted in 2017 to obtain feedback from companies on their perspective and perception of implementing the ICH Guidelines. An independent third party (CIRS) developed and led a proof-of-concept survey of PhRMA/EFPIA/JPMA company members on their perspective and perception of the implementation status of Tier 1 and 2 ICH Guidelines. The Phase 1 study results demonstrated that a survey could be undertaken across companies, where the response rate was excellent, indicating strong interest in the project.

In 2018, ICH approached CIRS to undertake a follow-on study to assess the adequacy of implementation and adherence to ICH Guidelines. The aim of this phase of the project, namely Phase 2a, was to build on the outcomes and lessons learned from Phase 1. CIRS developed an online questionnaire and definitions in collaboration with ICH and the ICH Implementation Subcommittee. The survey was completed by companies (assessing all the participating authorities) and authorities (assessing themselves only) to undertake a gap analysis. The report of this study has been published and endorsed by the ICH Management Committee (MC)[1]. In addition, CIRS prepared a report for ICH to analyse the study's free-text comments further to support ICH work, including training efforts.

At the ICH 2019 Meeting in Singapore, the ICH MC, together with the ICH Implementation Co-Leads (Jerry Stewart and Junko Sato), discussed and proposed that a follow-on survey should be conducted in 2020/2021. The remit of the study described in this report, here referred to as Phase 2b, was principally to assist the Management Committee in their elections. Data collection, data cleaning, and analysis occurred from January to March 2021, followed by delivering a tailored report to each authority and an overall draft report to the MC in April. After the draft report was delivered, the results were presented in May and June to the ICH MC and Assembly respectively.

Goals and Objectives

This study aimed to monitor the adequacy of implementation and adherence to ICH Guidelines by regulatory authorities, continuing the assessment initiated in 2019.

The objectives were:

- To assist the Management Committee in determining whether ICH non-Standing non-Founding Regulatory Members would meet the eligibility criteria for the MC elections in June 2021
- To allow participating Observers interested in future ICH Membership to reference the survey findings to confirm their eligibility.

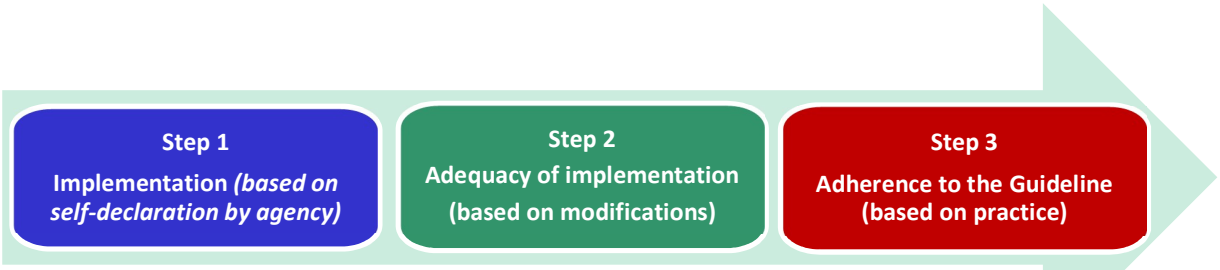
The long-term objectives would be to establish a sustainable ICH-driven mechanism to assess implementation and adherence to the ICH Guidelines over time to inform ICH stakeholders on multiple areas as specified in the goals and, therefore, to fulfil the ICH mission.

[1] https://admin.ich.org/sites/default/files/inline-files/ICHImplementationReportOutline_v1.4_2019_1101_0.pdf

SCOPE AND METHOD

CIRS adapted the study questionnaire and the online data collection tool (DCT) developed in collaboration with ICH as part of the 2019 Phase 2a study[1]. The study utilised the same definitions for 'implementation' and 'adherence' developed jointly by ICH and the ICH Implementation Subcommittee as part of the 2017 Phase 1 study (see Appendix 1). The questionnaire was completed between January and March 2021 by companies (assessing all the participating authorities) and authorities (assessing themselves only) to undertake a gap analysis.

Three sequential concepts were used to evaluate the implementation/ adherence status using the developed questionnaire:



Implementation
The process of implementation is completed. This term refers to the self-declaration of the regulator regarding the conclusion of the implementation process. Usually, the regulator publishes the final guideline.
- **Question 1 in survey**

Adequate implementation
ICH Guideline implemented by authority without modifications or modifications are justified (do not increase regulatory burden)
- **Question 1.2 and 1.2.2**

Adherence
The regulatory authority consistently adheres to (applies) all identified relevant elements, concepts, and principles of the ICH Guideline in practice
- **Question 1.3**

In addition, where there was inadequate implementation or lack of adherence, respondents were asked to provide the rationale, including specific evidence and examples.

It should be noted that for Tier 1 and 2 ICH Guidelines, participants were asked to complete the entire questionnaire (assessing Step 1, 2, 3 and the rationale) while for Tier 3, recognising a large workload needed to complete the questionnaire for 53 Guidelines, participants were only asked questions related to implementation status and adherence status (Step 1 and 3). To provide consistency in the results among Tier 1, 2 and 3, only results from Step 1 (implementation) and Step 3 (adherence) are presented in this report. However, the complete set of results, including Step 2 for Tier 1 and 2 Guidelines, as well as unaggregated results, were shared with the participating organisations and presented to the ICH.

	Step 1: implementation	Step 2: Adequacy of implementation	Step 3: Adherence	Rationale: lack of implementation /adherence
What was assessed through questionnaire and shared with participants for the different Guidelines:				
Tier 1 Guidelines	X	X	X	X
Tier 2 Guidelines	X	X	X	X
Tier 3 Guidelines	X		X	
What is presented in this report (all Guidelines) to provide consistency	X		X	X (adherence only as example)

[1] https://admin.ich.org/sites/default/files/inline-files/ICHImplementationReportOutline_v1.4_2019_1101_0.pdf

The following ICH Guidelines were assessed:

- 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 4

The following organisations participated in undertaking a gap analysis:

- 10 regulatory authorities (assessing themselves only):

ICH non-Standing non-Founding Regulatory Members	**ICH Observers (voluntary basis)**
- ANVISA, Brazil - NMPA, China - HSA, Singapore - MFDS, Republic of Korea - TFDA, Chinese Taipei - TITCK, Turkey	- INVIMA, Colombia - JFDA, Jordan - SAHPRA, South Africa - SFDA, Saudi Arabia

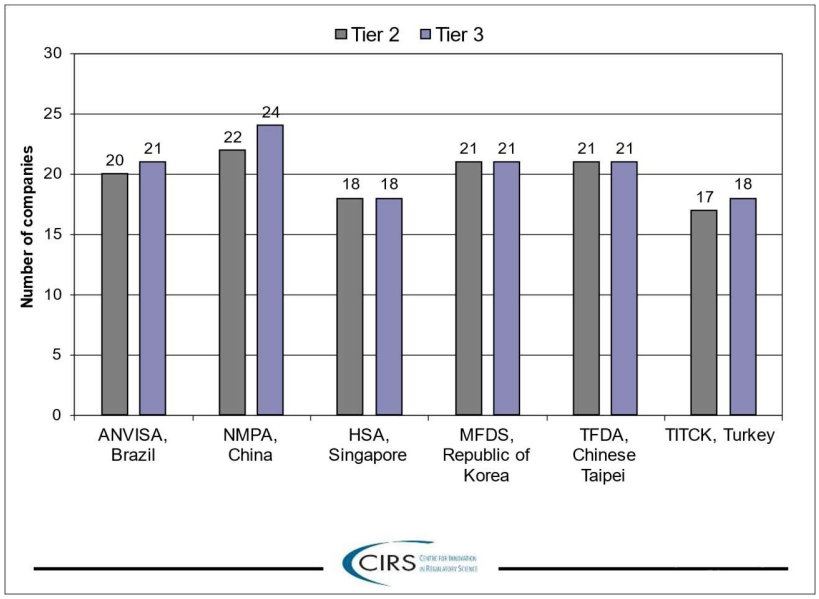
- 30 Major Pharmaceutical Companies (assessing all the participating authorities) provided a response in total out of 40 invited from across PhRMA, EFPIA, JPMA, BIO and IGBA companies.

RESULTS PART 1: ICH REGULATORY MEMBERS (TIER 2 & TIER 3)

Characteristics of participating companies

Key Messages

- 30 companies participated out of 40 invited companies (75% response rate)
- There was a good level of experience among the participating pharmaceutical companies regarding implementation of Tier 2 and Tier 3 ICH Guidelines by ICH non-Standing non-Founding Regulatory Members
- 27 out of the 30 participating companies had experience with at least one authority and at least one Guideline (Tier 2 or 3).

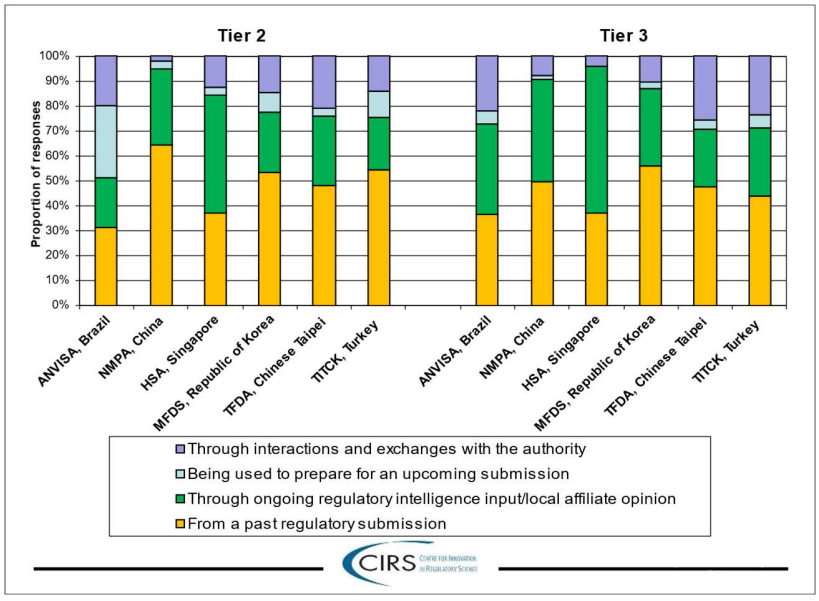


Method: Question 1i (see Appendix 1)

Companies' Experiences with ICH non-Standing non-Founding Regulatory Members: Participating companies were asked for their most recent/relevant experience regarding a Guideline for a selected authority.

Key Messages

- In general, the most recent/relevant experiences for companies were from a past regulatory submission or by ongoing regulatory intelligence input/local affiliate opinion
- Where companies indicated that they had experience from a past regulatory submission, 91% of them were submitted in 2019 or later.

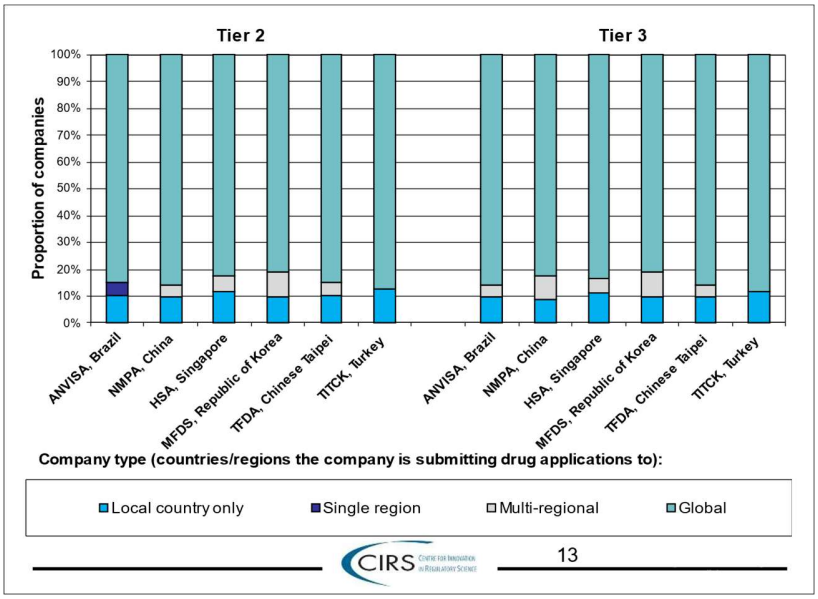


Method: Question 1a (see Appendix 2)

Company type: Companies were asked to specify their company type based on the countries/regions where they submitted drug applications.

Key Messages

- More than 80% of companies were global, and this varied little according to authority or Guideline.

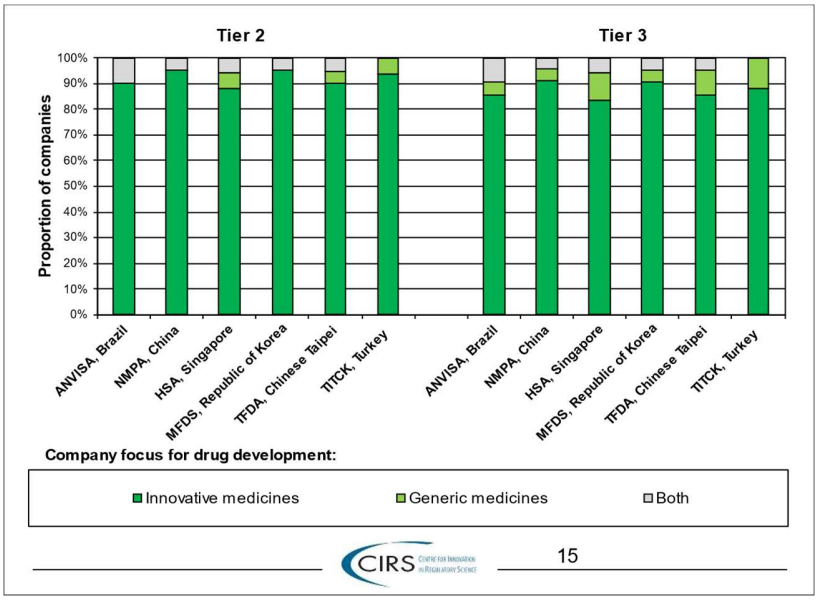


Method: Question 1i (see Appendix 2)

Company Focus: Companies were also asked to specify their focus for drug development, i.e. innovative and/or generic medicines.

Key Messages

- 90% of surveyed companies were innovative companies.



Method: Question 1ii (see Appendix 2)

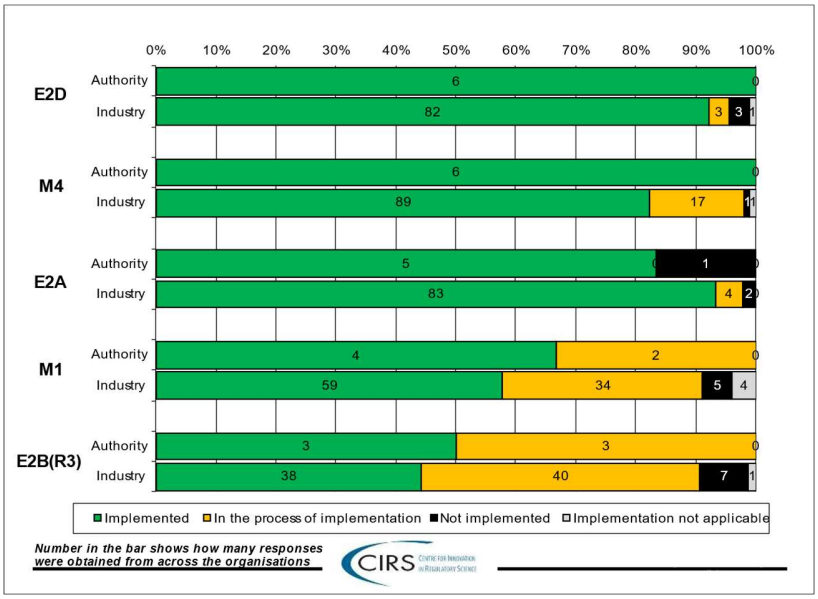
RESULTS PART 1.1: TIER 2 GUIDELINES

Implementation status: Authorities and companies were asked about their views on the implementation status for the selected Tier 2 Guidelines. The first bar in the graph below corresponds to the self-declaration by the authorities (aggregated results across the six ICH non-Standing non-Founding Regulatory Members), and the second bar shows the number of responses across the companies. The ICH Guidelines were firstly ordered in descending order based on the percentage of answers that authorities marked as 'Implemented' in question 1, and secondly based on the responses from companies.

Key Messages

- Most of the Guidelines were seen as implemented or in the process of implementation
- Company perception of implementation status was generally aligned with agency self-declaration
- E2A, E2D and M4 had the highest proportion of 'implemented' responses
- For E2B(R3) and M1, the response was mixed between 'implemented' and 'in the process of implementation'.

Method: Question 1 (See Appendix 2)

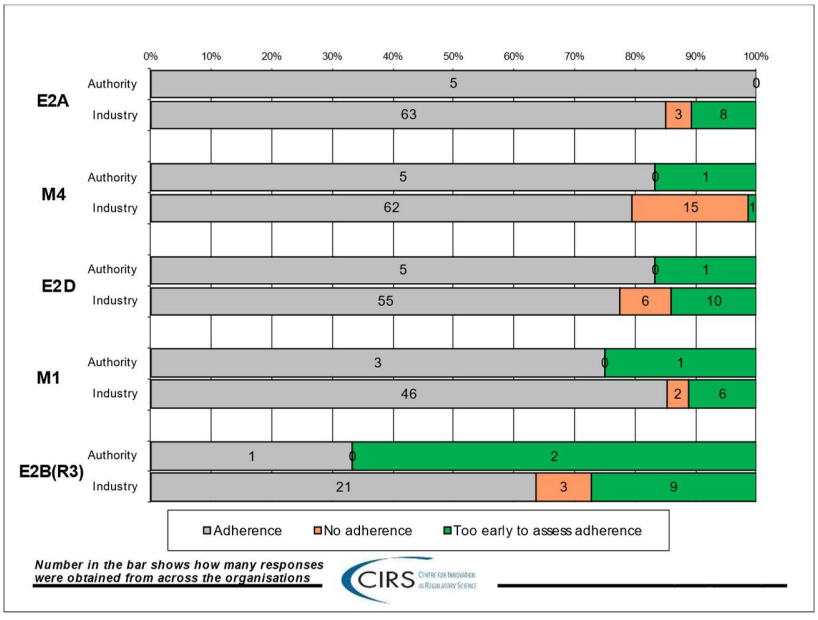


Adherence status: Organisations that confirmed that a Tier 2 Guideline had been adequately implemented (unmodified or modified with justification) were asked to provide views on the adherence status. Adherence relates to whether, in practice, the authority applies all identified relevant elements, concepts, and principles of the ICH Guideline over time. The ICH Guidelines were firstly ordered in descending order based on the percentage of answers that authorities marked as 'adherence' in question 1.3, and secondly based on the responses from companies.

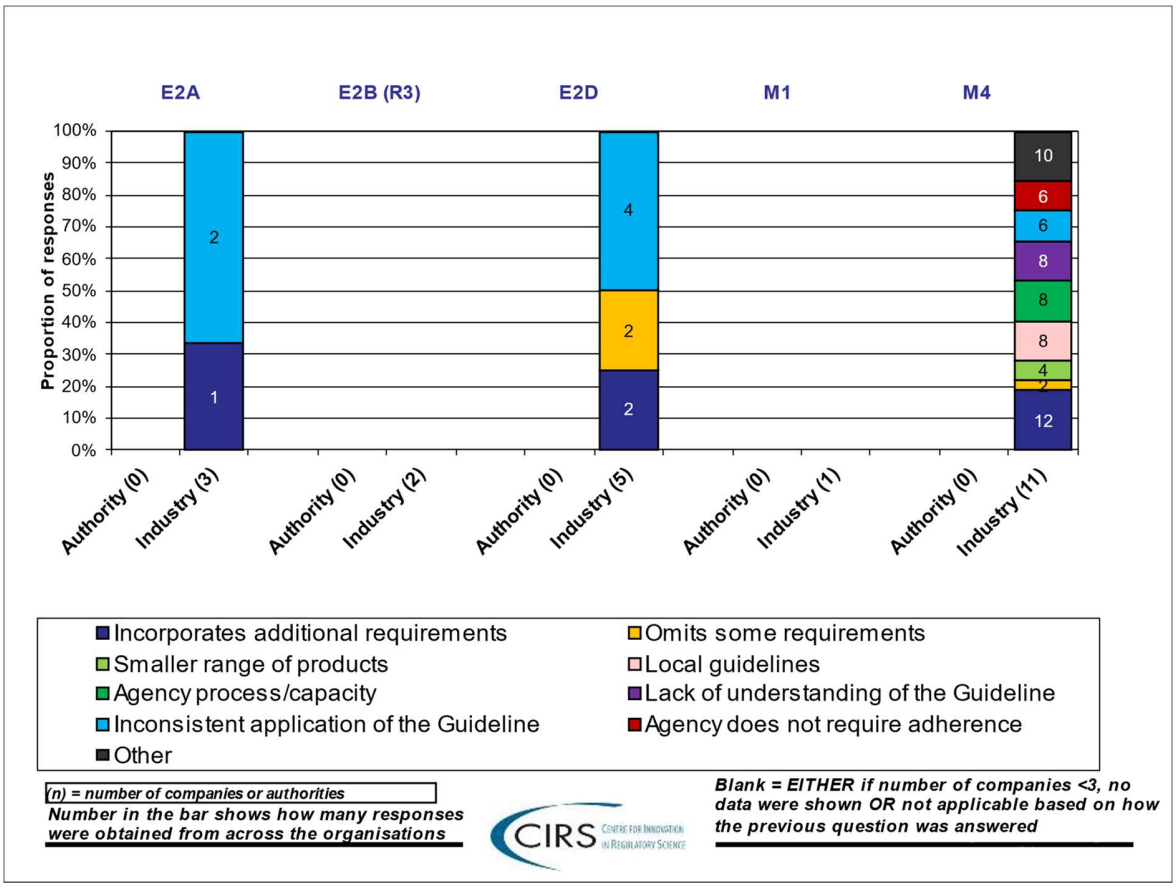
Key Messages

- Where implementation was confirmed, the perceived level of adherence to the Guidelines was high or too early to assess, particularly for E2B(R3) Guideline
- In general, company perception and agency self-declaration was aligned.

Method: Question 1.3 (See Appendix 2)



Rationale for lack of adherence: The graph below outlines the rationale for selecting a "lack of adherence" response for selected Guidelines.



Method: Question 2 (See Appendix 2)

Key Messages

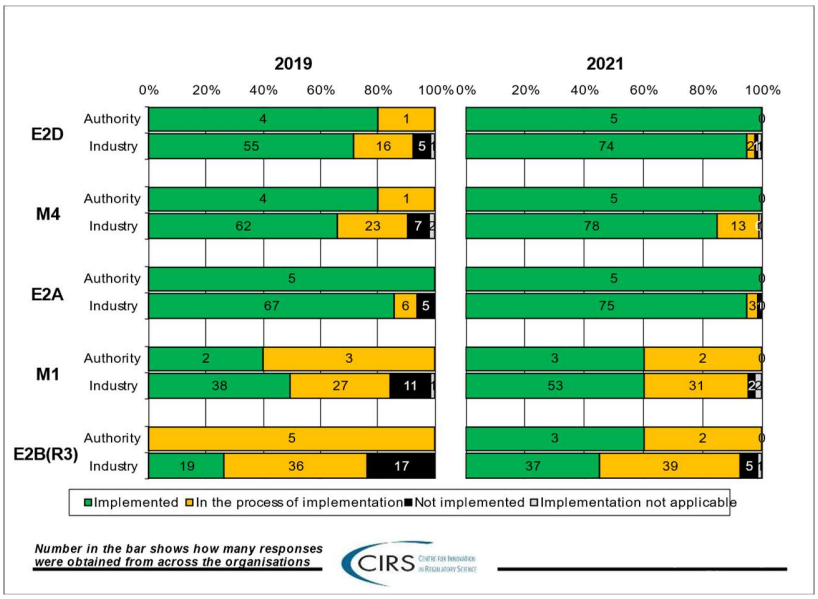
- As no authorities declared 'lack of adherence' response for Tier 2 Guidelines, the results below only show rationale from companies, aggregated across all the authorities studied
- However, it should be noted that the number of companies that perceived lack of adherence, and subsequently provided the rationale, was low (three, five and eleven companies for E2A, E2D and M4 Guidelines, respectively)
- The most common reasons among E2A, E2D and M4 Guidelines based on company perception was that authorities incorporate additional requirements or apply them inconsistently
- M4 Guideline received the largest number of responses with varied reasons for lack of adherence.

Comparison to 2019 Survey Results[1]

The following graphs compare the 2019[1] and 2021 surveys' results regarding implementation and adherence of Tier 2 Guidelines from included ICH non-Standing non-Founding Regulatory Members (except for TITCK, Turkey, who was an Observer at the time)

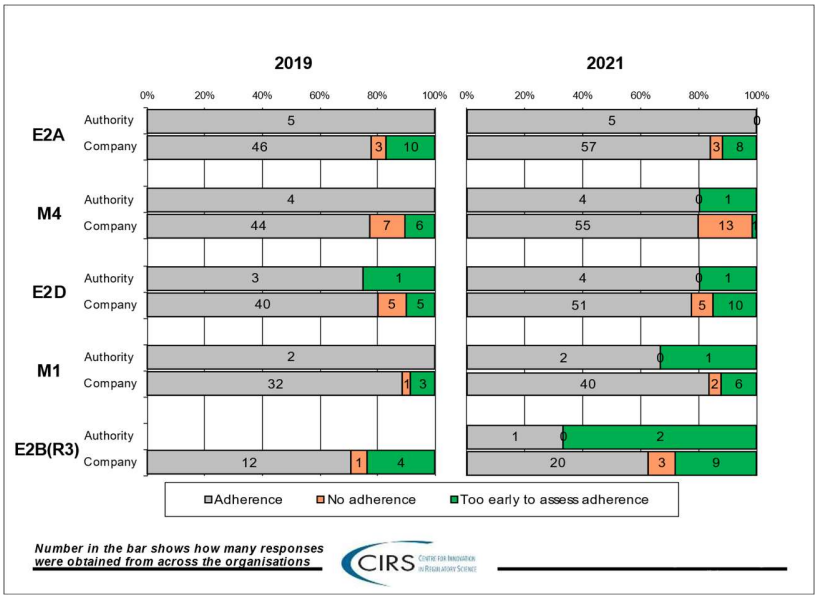
Key Messages for implementation progress

- In only two years, the number of authorities that declared implementation of E2B(R3) Guideline have increased by three
- The implementation of E2D, M4, and M1 Guidelines have progressed in one authority compared with 2019 results
- In general, based on the industry perception, there was also an increased level of Guideline implementation by the authorities compared to two years ago.



Key Messages for adherence progress

- Where implementation was confirmed, the perceived level of adherence to the Guidelines was high
- There was an increase in adherence based on the authorities' declaration and industry perception, compared to the 2019 study e.g. for E2D
- For a number of Guidelines and authorities where implementation occurred recently, it was too early to assess adherence e.g. E2B(R3).



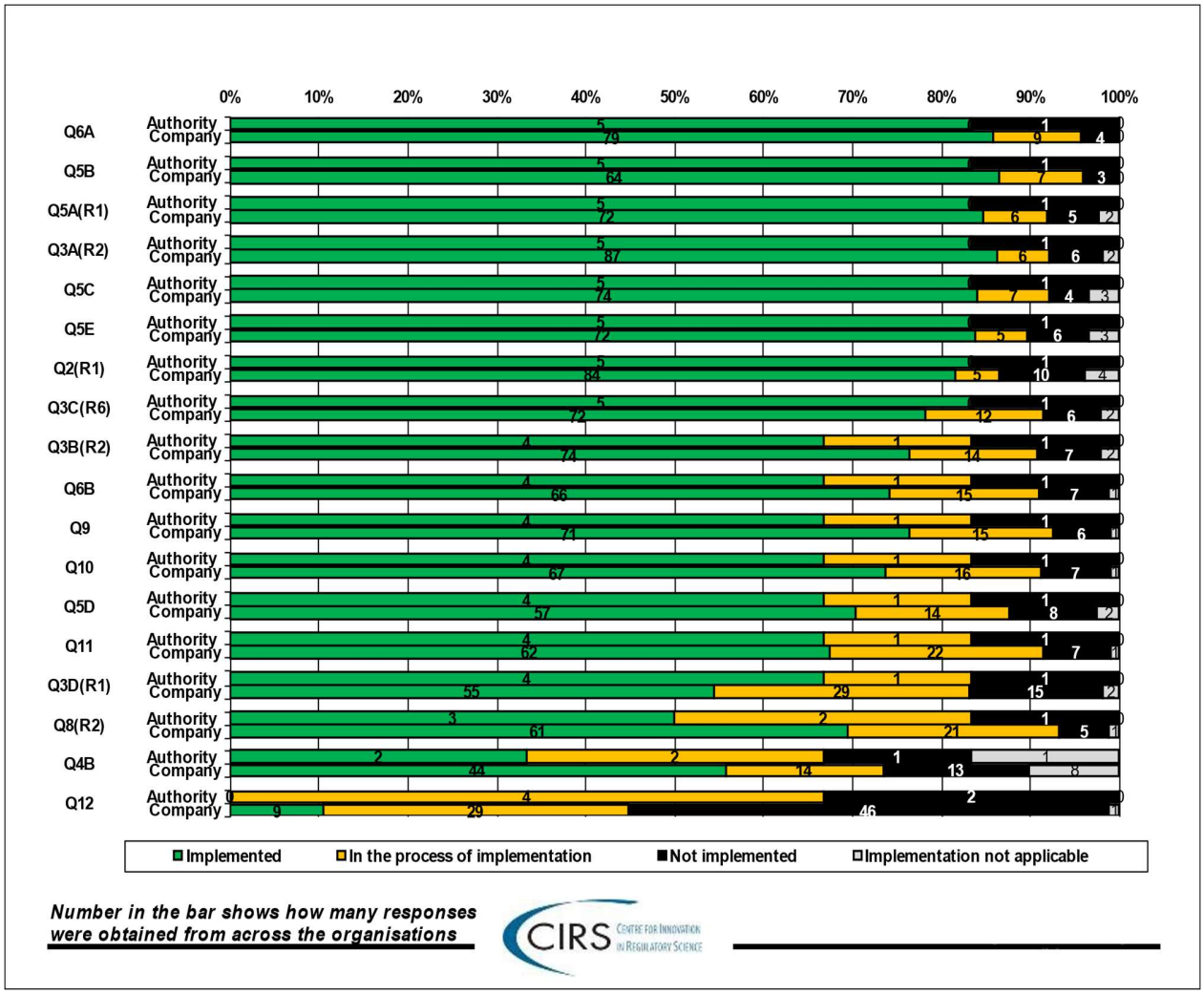
[1] https://admin.ich.org/sites/default/files/inline-files/ICHImplementationReportOutline_v1.4_2019_1101_0.pdf

RESULTS PART 1.2: TIER 3 GUIDELINES

Implementation status: Authorities and companies were asked about their views on the implementation status for the selected Tier 3 Guidelines. The first bar in the graph below corresponds to the self-declaration by the authorities (aggregated results across the six ICH non-Standing non-Founding Regulatory Members), and the second bar shows the number of responses across the companies. The ICH Guidelines were firstly ordered in descending order based on the percentage of answers that authorities marked as 'Implemented' in question 1, and secondly based on the responses from companies.

Key Messages for Quality Guidelines

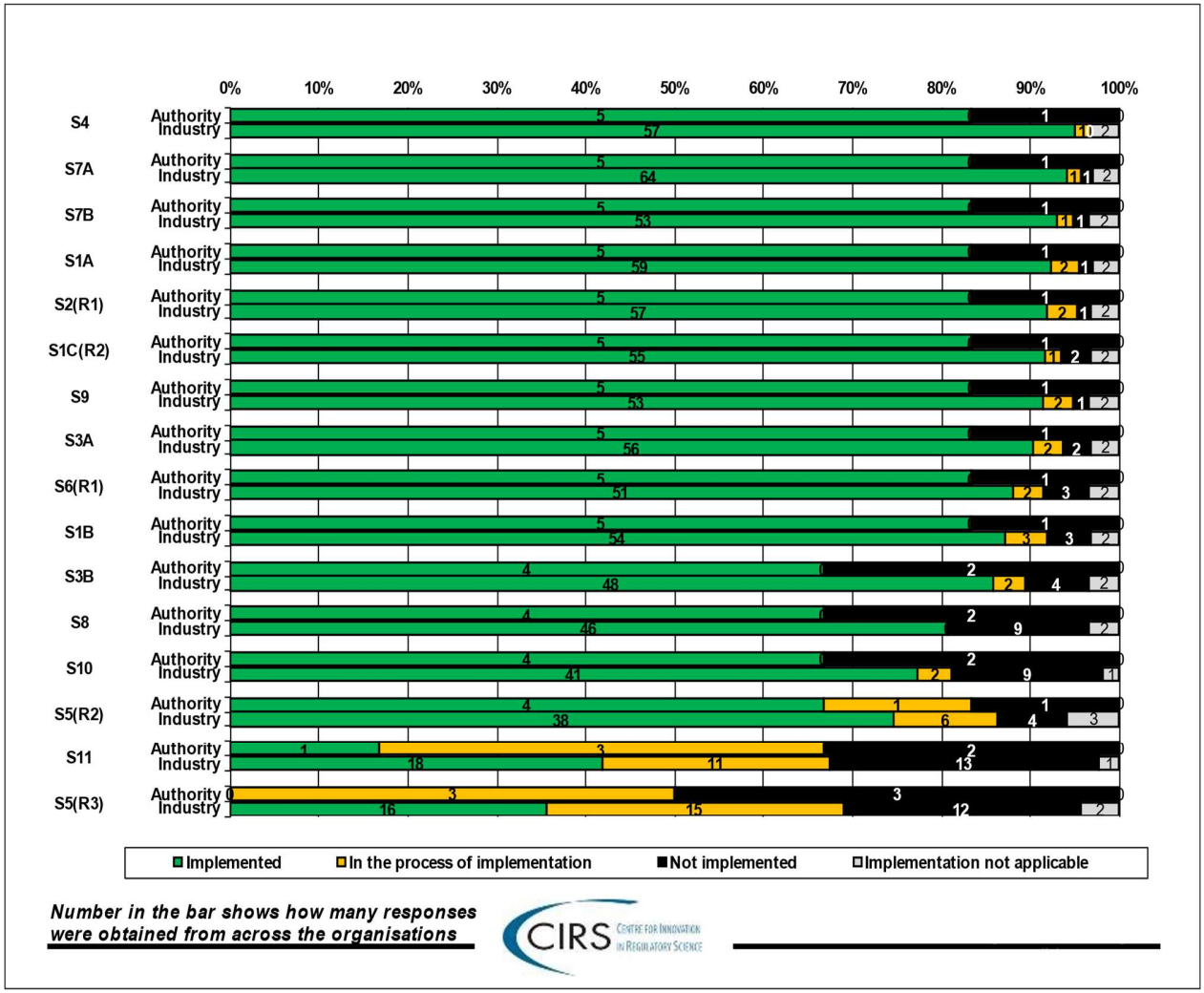
- Generally, the self-declaration of the ICH Regulatory Members on the implementation of the Quality ICH Guidelines was aligned with companies' implementation perceptions
- The aggregated results demonstrate that, in general, the Guidelines were perceived as implemented
- A number of the Guidelines, particularly Q12, are still seen to be in the process of being implemented or not implemented.



Method: Question 1 (See Appendix 2)

Key Messages for Safety Guidelines

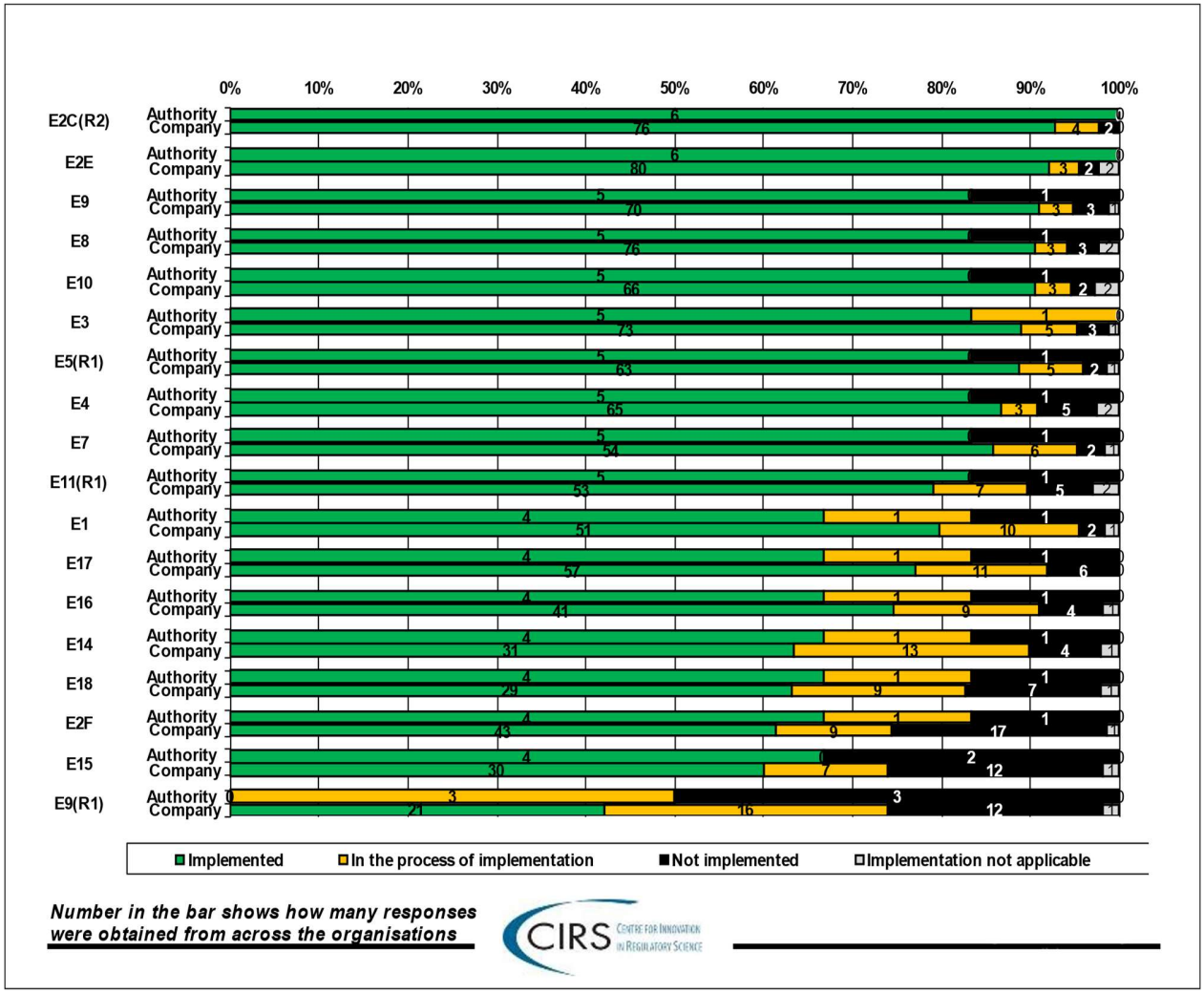
- The aggregated results across the stakeholders demonstrate that, in general, the Safety Guidelines were perceived as implemented
- A few of the Guidelines, particularly S11 and S5(R3), are still seen to be in the process of being implemented or not implemented.



Method: Question 1 (See Appendix 2)

Key Messages for Efficacy Guidelines

- Most of the Efficacy Guidelines were perceived by companies and self-declared by authorities as implemented
- A number of the Guidelines, particularly E9(R1), are seen to be in the process of being implemented or not implemented.

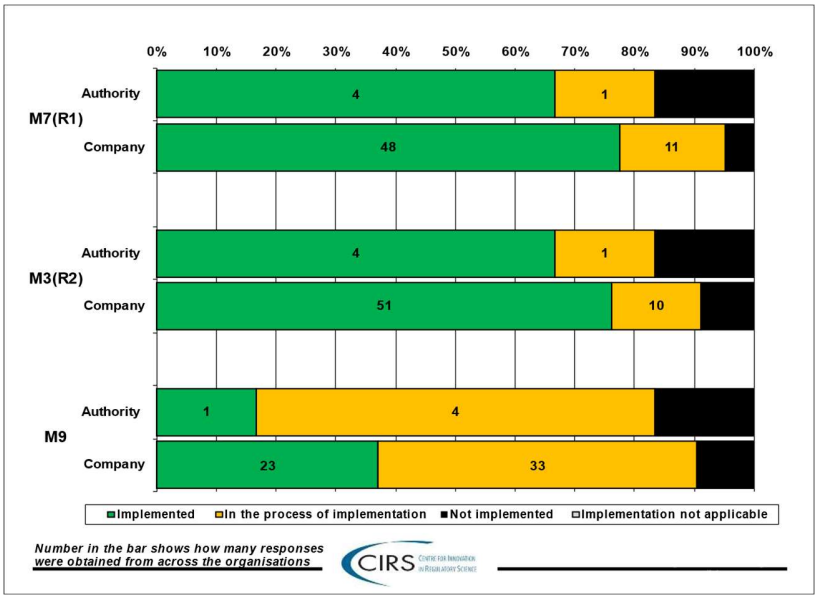


Method: Question 1 (See Appendix 2)

Key Messages for Multidisciplinary Guidelines

- M7(R1) and M3(R2) Guidelines were considered as implemented by the majority of companies and declared by authorities
- M9 Guideline was considered as mainly in the process of implementation.

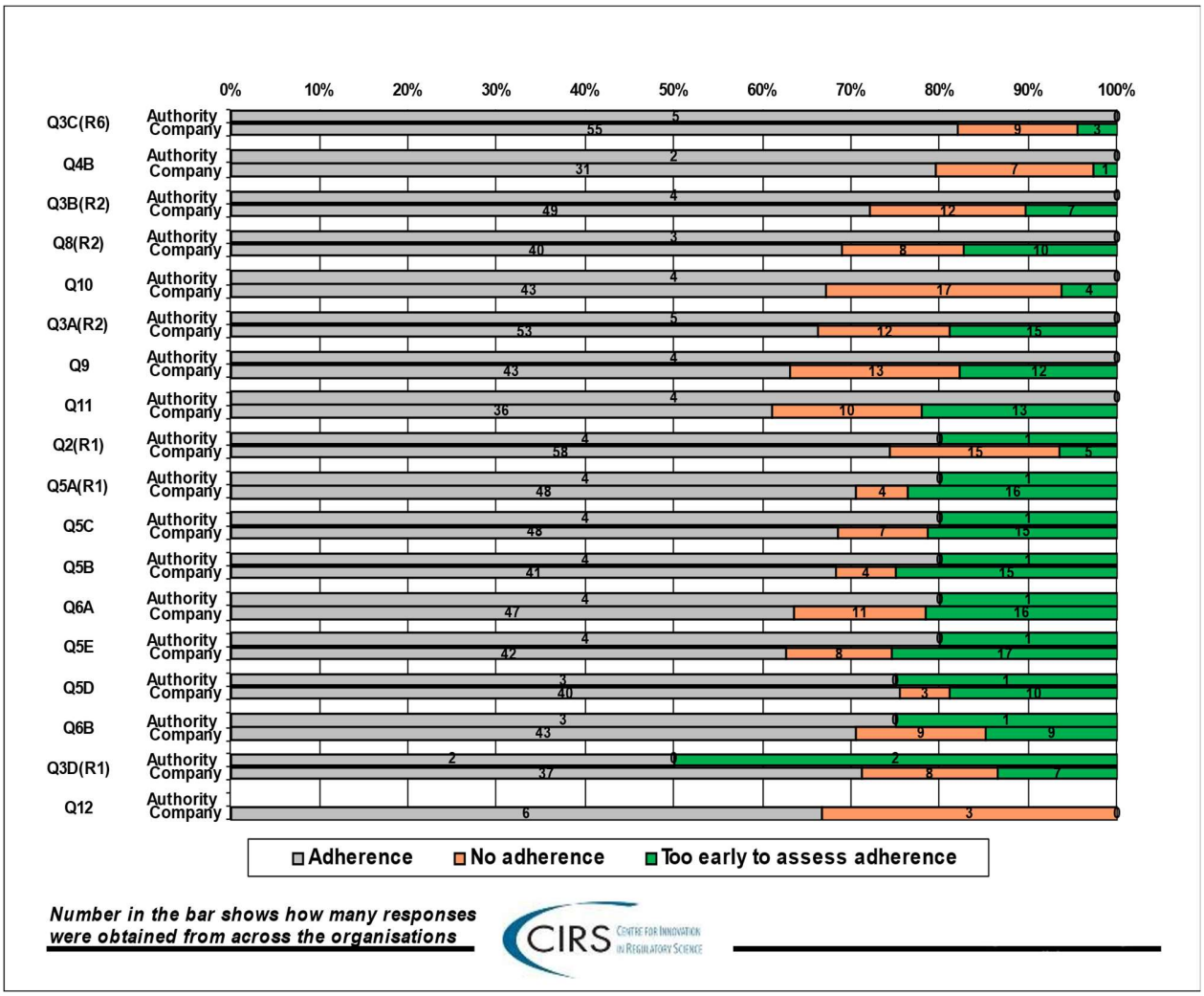
Method: Question 1 (See Appendix 2)



Adherence status: Organisations were asked to provide views on the adherence status. Adherence relates to whether, in practice, the authority applies all identified relevant elements, concepts, and principles of the ICH Guideline over time. The ICH Guidelines were firstly ordered in descending order based on the percentage of answers that authorities marked as 'adherence' in question 1.3, and secondly based on the responses from companies.

Key Messages for Quality Guidelines

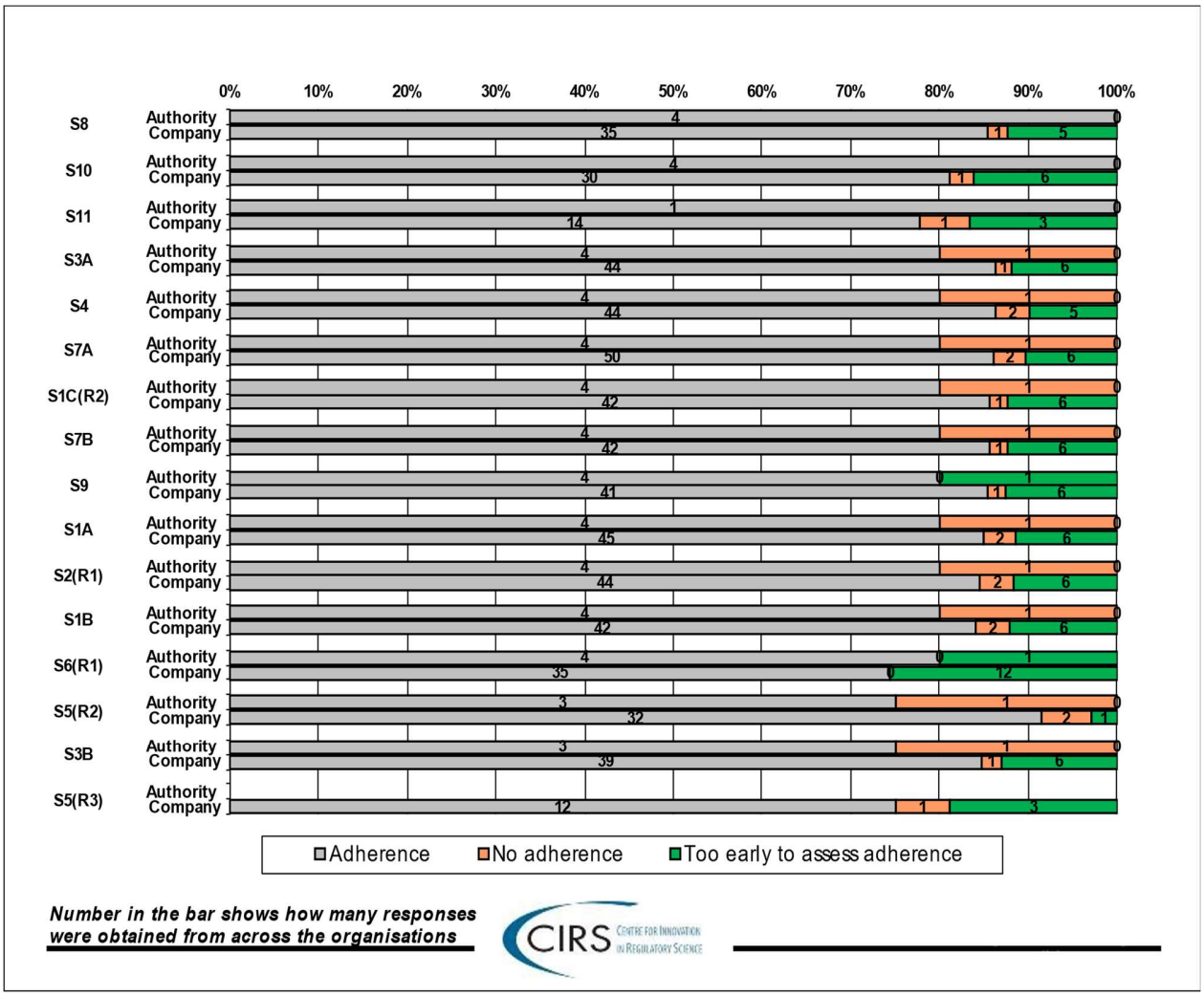
- For those Quality ICH Guidelines that were confirmed as implemented, there was generally a strong level of adherence based on agency self-declaration and company perception
- For Q12, no responses were received from authorities regarding adherence status, as no authority declared it as implemented (see page 12) however, four authorities confirmed they are in the process of Implementing.



Method: Question 1.3 (See Appendix 2)

Key Messages for Safety Guidelines

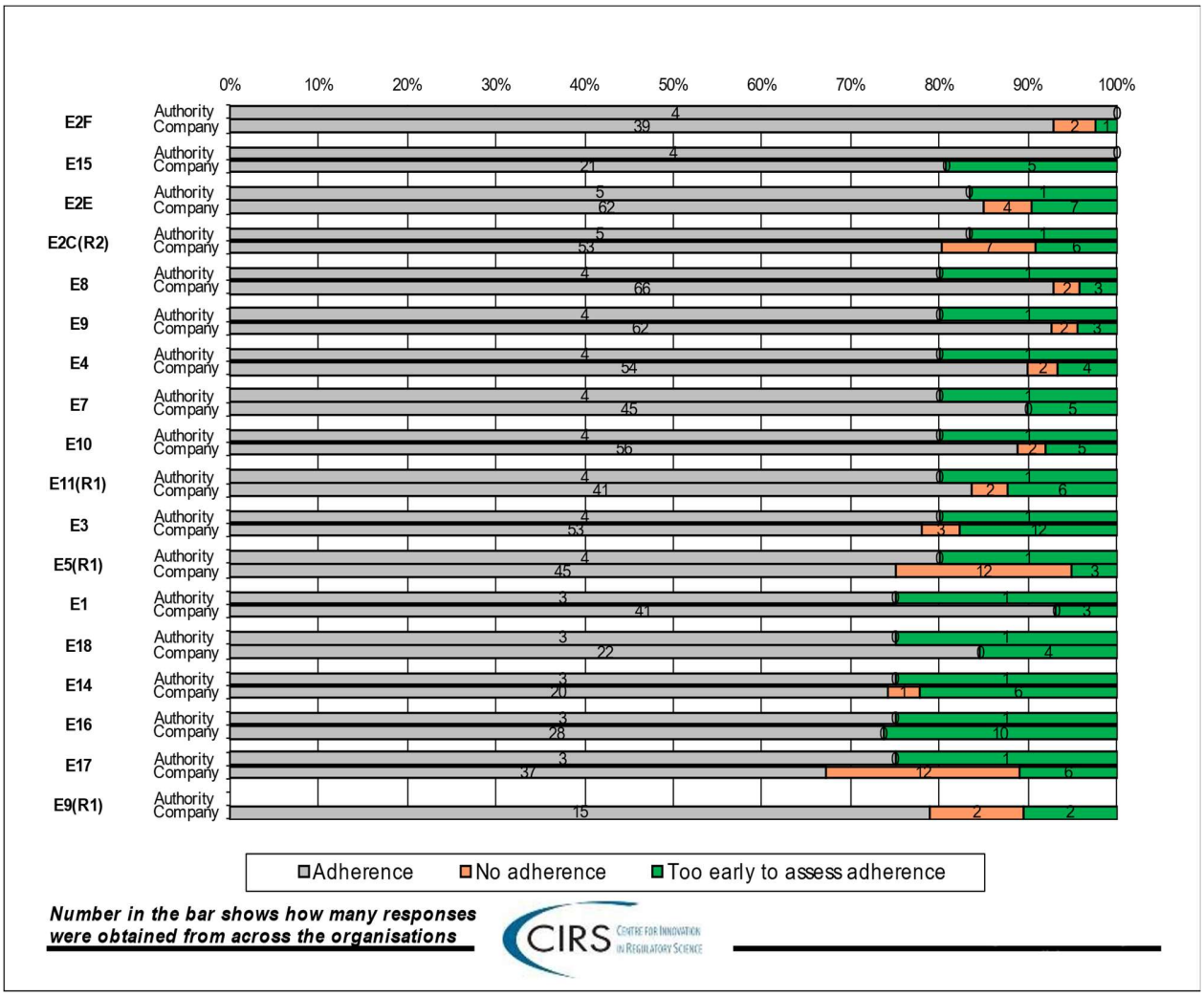
- Based on the companies and authorities' responses, there was a good level of adherence to the implemented Safety Guidelines
- For S5(R3), no responses were received from authorities regarding adherence status, as no authority declared it as implemented (see page 13) however, three authorities confirmed they are in the process of Implementing.



Method: Question 1.3 (See Appendix 2)

Key Messages for Efficacy Guidelines

- Based on agencies self-declaration and companies' perception, in general Efficacy Guidelines were seen as adhered to by most of the authorities
- For E9(R1), no responses were received from authorities regarding adherence status, as no authority declared it as implemented (see page 14) however three authorities confirmed they are in the process of Implementing.

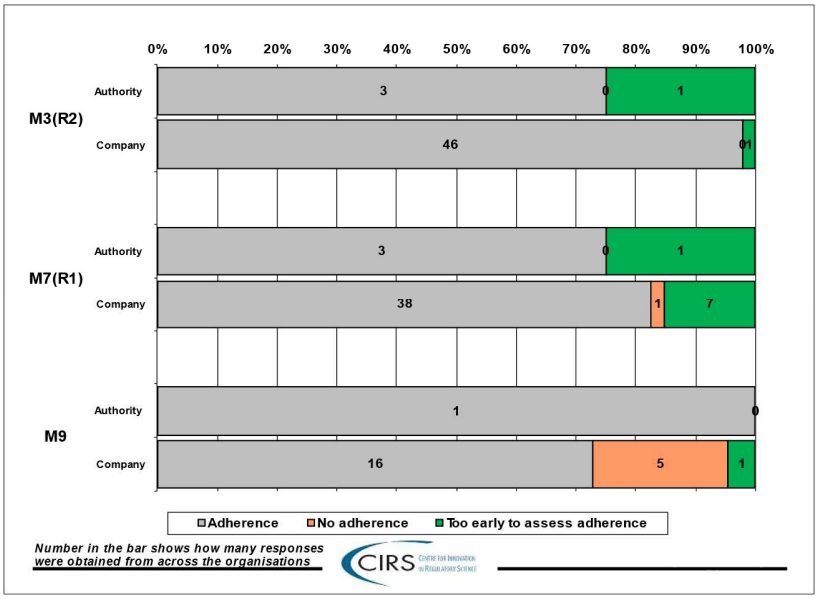


Method: Question 1.3 (See Appendix 2)

Key Messages for Multidisciplinary Guidelines

- Based on agencies self-declaration, there was adherence to M3(R2) and M7(R1) Guidelines by three out of the six authorities; this was generally consistent with the industry perception.

Method: Question 1.3 (See Appendix 2)

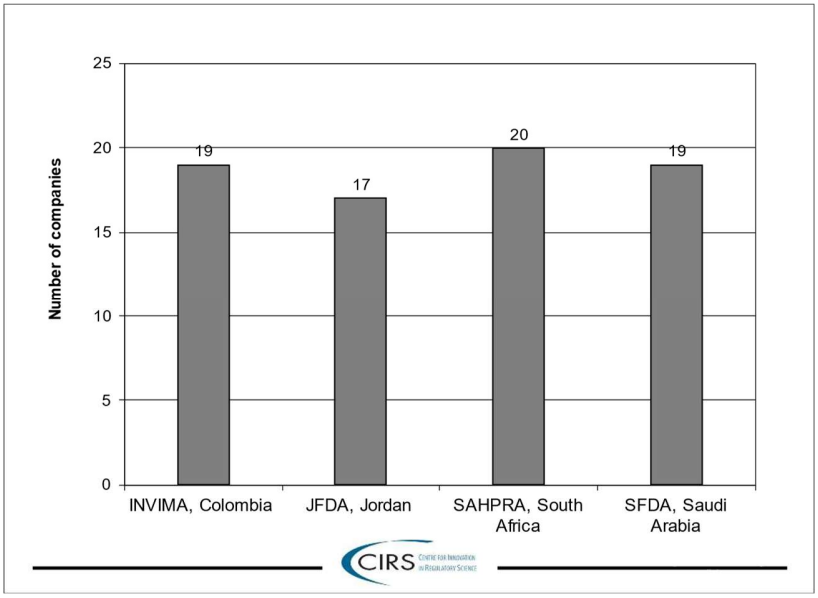


RESULTS PART 2: ICH REGULATORY OBSERVERS (TIER 1)

General overview of participating companies

Key Messages

- The majority of participating companies had experiences across the studied ICH Observers.

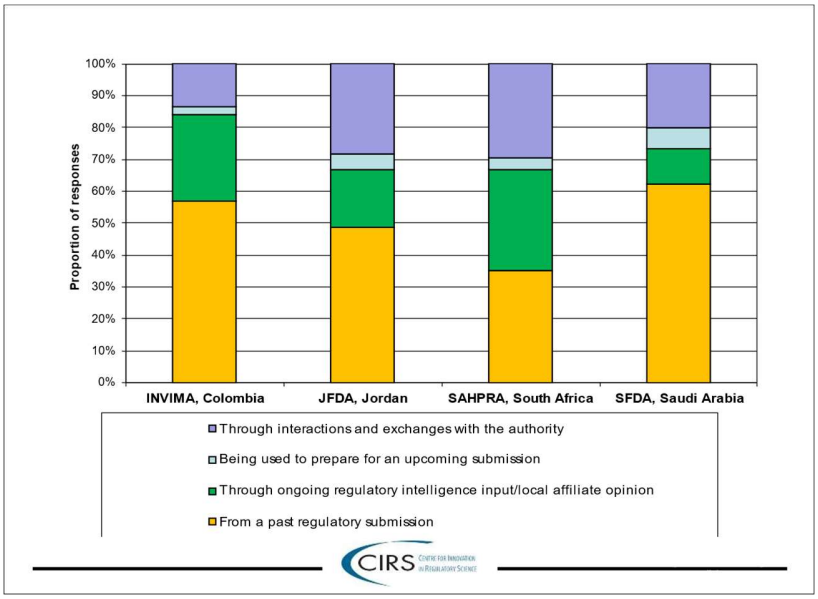


Method: Question 1i (see Appendix 2)

Companies' Experiences with ICH Observers: Participating companies were asked for their most recent/relevant experience regarding a Guideline for a selected authority.

Key Messages

- The most recent/relevant experience from companies regarding the studied ICH Observers were from a past regulatory submission
- Where companies indicated that they had experience from a past regulatory submission, 93% of them were submitted in 2019 or later.

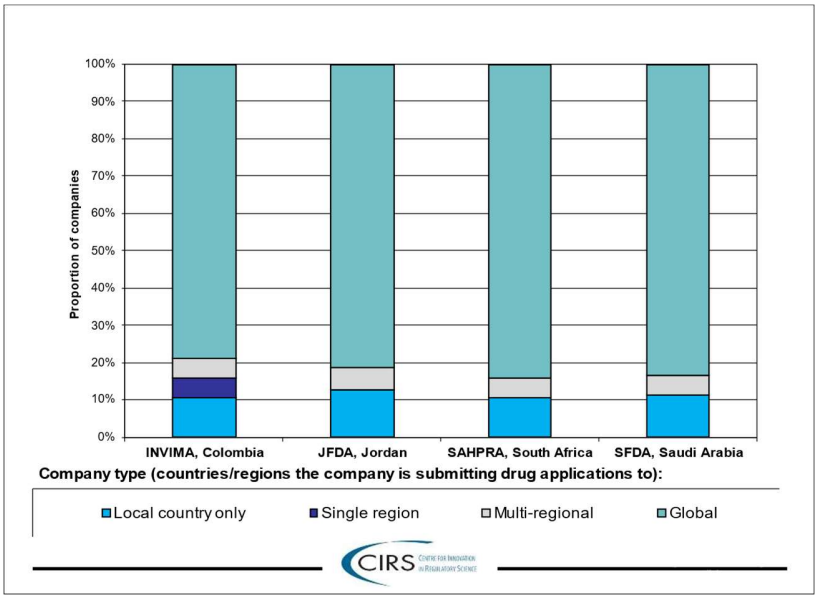


Method: Question 1a (see Appendix 2)

Company type: Companies were asked to specify their company type based on the countries/regions where they submitted drug applications.

Key Messages

- More than 80% of companies were global, and this was consistent across the different authorities.

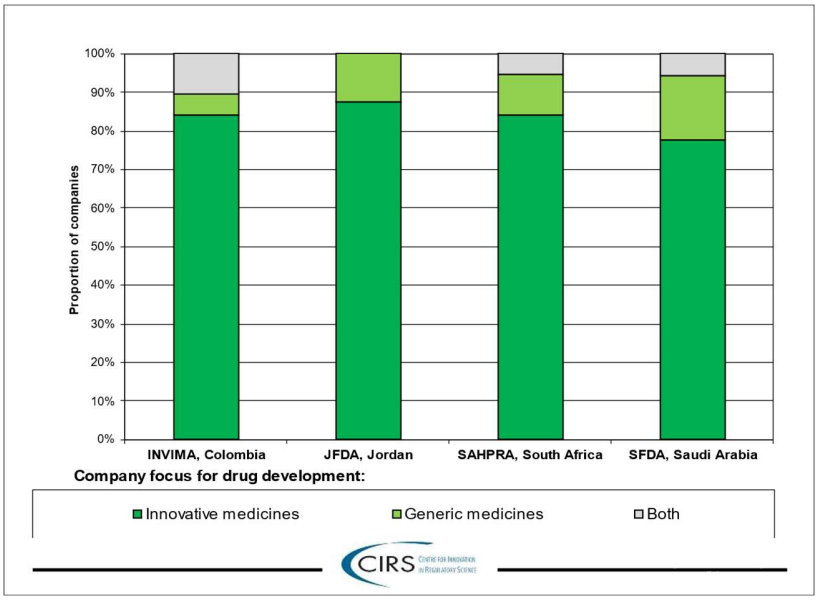


Method: Question 1i (see Appendix 2)

Company Focus: Companies were also asked to specify their focus for drug development, i.e. innovative and/or generic medicines.

Key Messages

- Approximately 80% of companies are focused on innovative medicines.

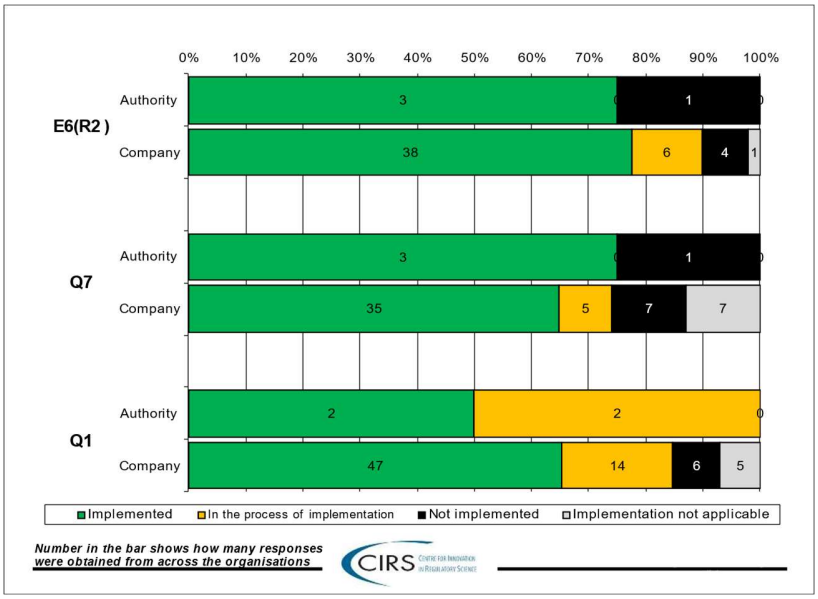


Method: Question 1ii (see Appendix 2)

Implementation status: Authorities and companies were asked about their views on the Tier 1 Guidelines' implementation status. The first bar in the graph below corresponds to the self-declaration by the authorities (aggregated results across the six ICH Observers), and the second bar shows the number of responses across the companies. The ICH Guidelines were firstly ordered in descending order based on the percentage of answers that authorities marked as 'Implemented' in question 1, and secondly based the responses from companies.

Key Messages

- E6(R2), Q7 and Q1 Guidelines were declared as implemented by three of the authorities; this was generally aligned with the views of the industry
- Q1 Guideline was declared as implemented by two authorities while it is in the process of implementation by other two

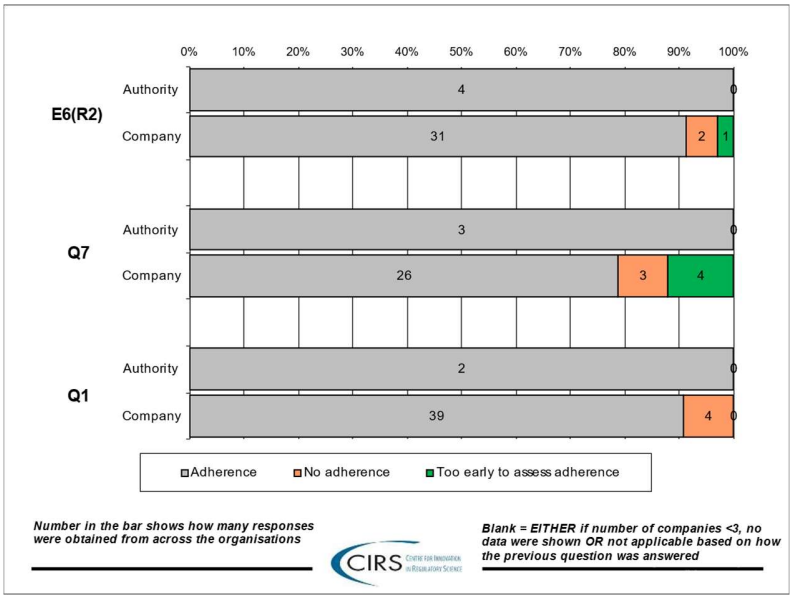


Method: Question 1 (See Appendix 2)

Adherence status: Organisations that confirmed that a Guideline had been adequately implemented (unmodified or modified with justification) were asked to provide views on the adherence status. Adherence relates to whether, in practice, the authority applies all identified relevant elements, concepts and principles of the ICH Guideline over time. The ICH Guidelines were firstly ordered in descending order based on the percentage of answers that authorities marked as 'adherence' in question 1.3, and secondly based on the responses from companies.

Key Messages

- For those Guidelines that were implemented, there was generally a strong level of adherence.

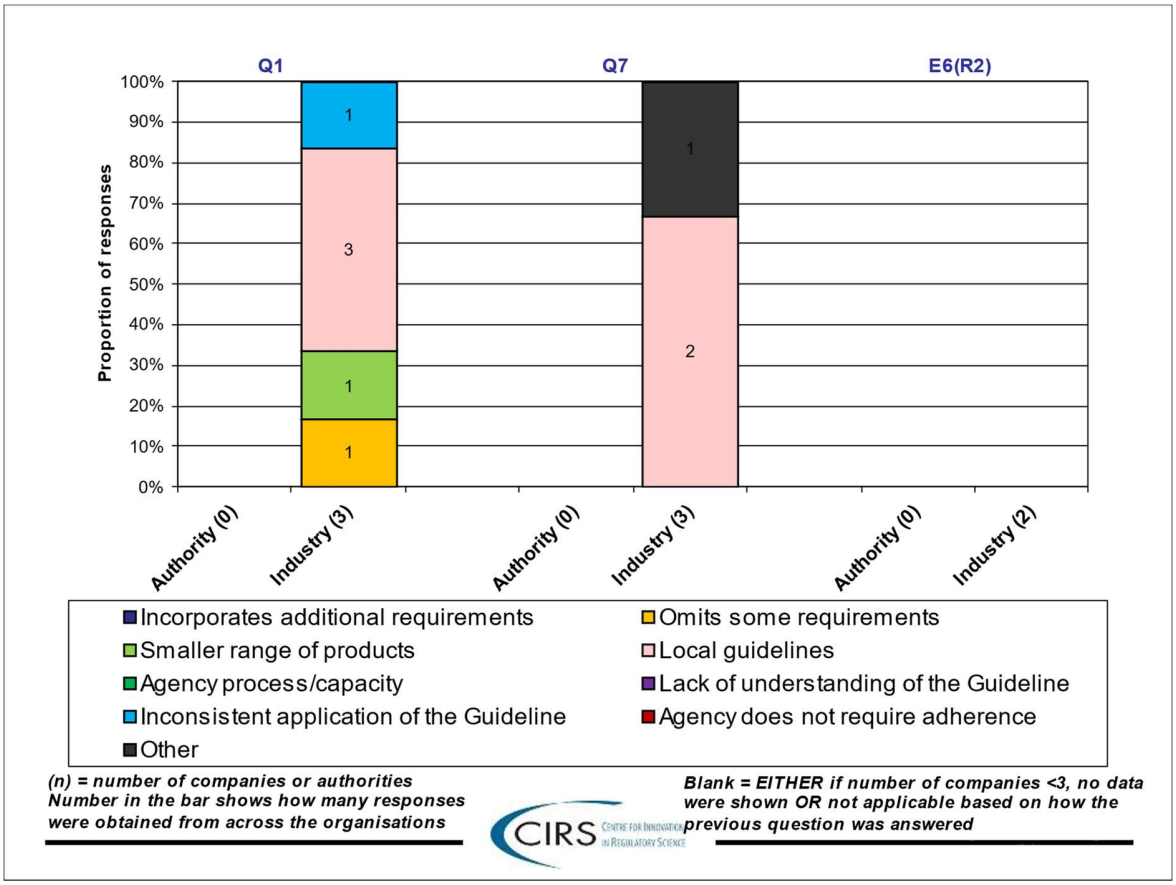


Method: Question 1.3 (See Appendix 2)

Rationale for lack of adherence: The graph below outlines the rationale for selecting a "lack of adherence" response for selected Guidelines.

Key Messages

- As no authorities declared 'lack of adherence' response for Tier 1 Guidelines, the results below only show rationale from companies, aggregated across all the authorities studied
- However, it should be noted that the number of companies that perceived that there is a lack of adherence, and subsequently provided the rationale, was low (three companies for Q1 and Q7 only)
- The most mentioned rationale for lack of adherence was that other local guidelines conflict with the Guideline and prevent full adherence to the ICH Guideline.



Method: Question 2 (See Appendix 2)

RESULTS PART 3.1: SUMMARY TABLES - IMPLEMENTATION STATUS

Aiming to compare and find agreement among authorities' self-declaration and companies' perception, an assessment was undertaken to summarise the consensus implementation status of the ICH Guidelines among the authorities for all Tiers. The following tables show the result of this assessment, and the method used for developing it is described in Appendix 3.

A. Implementation of Tier 2 Guidelines by ICH Regulatory Members

Guideline/ authority	E2D	M4	E2A	M1	E2B(R3)
% of authorities where the Guideline was implemented (no. of authorities out of 6)	100% (6)	100% (6)	83% (5)	33% (2)	17% (1)

Method: Question 1 (See Appendix 2 and Appendix 3)

Key Messages

- Two authorities implemented all of the Tier 2 Guidelines
- All of the authorities implemented the E2D and M4 Guidelines, followed by E2A (five out of six) based on agreement between authority self-declaration and majority industry perception.

B. Implementation of Tier 3 Guidelines by ICH Regulatory Members

Key Messages for Implementation of all Tier 3 Guidelines by ICH Regulatory Members

- Five out of the six authorities implemented >70% of the Tier 3 Guidelines (data not shown but were shared with participants). The results for the Tier 3 Guideline were organised below according to the topic:

a) Quality Guidelines

Guideline/ authority	Q6A	Q5B	Q5A(R1)	Q3A(R2)	Q5C	Q5E	Q2(R1)	Q3C(R6)	Q3B(R2)	Q6B	Q9	Q10	Q5D	Q11	Q8(R2)	Q3D(R1)	Q4B	Q12
% of authorities where the Guideline was implemented (no. of authorities out of 6)	83% (5)	83% (5)	83% (5)	83% (5)	83% (5)	83% (5)	67% (4)	67% (4)	67% (4)	67% (4)	67% (4)	67% (4)	67% (4)	67% (4)	50% (3)	33% (2)	33% (2)	0% (0)

Method: Question 1 (See Appendix 2 and Appendix 3)

Key Messages for Quality Guidelines

- Four out of the six authorities implemented more than 14 out of the 18 (87%) Quality Guidelines.

b) Safety Guidelines

Guideline/ authority	S4	S7A	S7B	S1A	S2(R1)	S1C(R2)	S9	S3A	S6(R1)	S1B	S3B	S8	S10	S5(R2)	S11
% of authorities where the Guideline was implemented (no. of authorities out of 6)	83% (5)	83% (5)	83% (5)	83% (5)	83% (5)	83% (5)	83% (5)	83% (5)	83% (5)	83% (5)	67% (4)	67% (4)	67% (4)	50% (3)	17% (1)

Note: Guideline S5(R3) excluded from '% of authorities where the Guideline was implemented since S5(R2) was included

Method: Question 1 (See Appendix 2 and Appendix 3)

Key Messages for Safety Guidelines

- Four out of the six authorities implemented more than 13 out of the 15 (87%) Safety Guidelines.

c) Efficacy Guidelines

Guideline/ authority	E2C(R2)	E2E	E9	E8	E10	E3	E5(R1)	E4	E7	E11(R1)	E1	E17	E16	E14	E18	E2F	E15
% of authorities where the Guideline was implemented (no. of authorities out of 6)	100% (6)	100% (6)	83% (5)	83% (5)	83% (5)	83% (5)	83% (5)	83% (5)	83% (5)	67% (4)	67% (4)	67% (4)	67% (4)	50% (3)	50% (3)	50% (3)	50% (3)

Note: Guideline E9(R1) excluded from '% of Guidelines implemented across the six authorities' in the final column as E9 was included

Method: Question 1 (See Appendix 2 and Appendix 3)

Key Messages for Efficacy Guidelines

- E2C(R2) and E2E Guidelines were considered as implemented by all the authorities
- Four out of the six authorities implemented more than 13 out of the 17 (76%) Efficacy Guidelines.

d) Multidisciplinary Guidelines

Guideline/ authority	M3(R2)	M7(R1)	M9
% of authorities where the Guideline was implemented (no. of authorities out of 6)	67% (4)	67% (4)	17% (1)

Method: Question 1 (See Appendix 2 and Appendix 3)

Key Messages for Multidisciplinary Guidelines

- M3(R2) and M7(R1) were implemented by four out of the six authorities.

C. Implementation of Tier 1 Guidelines for ICH Observers

Guideline/ authority	E6(R2)	Q7	Q1
% of authorities where the Guideline was implemented (no. of authorities out of 4)	100% (4)	75% (3)	50% (2)

Method: Question 1 (See Appendix 2 and Appendix 3)

Key Messages

- The four ICH Observers studied implemented the E6(R2) Guideline
- Results showed that two authorities implemented all Tier 1 Guidelines.

RESULTS PART 3.2: ADHERENCE STATUS

Aiming to compare and find agreement among authorities' self-declaration and companies' perception, an assessment was undertaken to summarise the consensus adherence status of the ICH Guidelines among the authorities for all Tiers. The following tables show the result of this assessment, and the method used for developing it is described in Appendix 3.

A. Adherence to Tier 2 Guidelines by ICH Regulatory Members

Guideline/ authority	Adherence category	E2D	M4	E2A	M1	E2B(R3)
% of authorities where the Guideline was adhered to (no. of authorities out of 6)	Adherence	83% (5)	83% (5)	67% (4)	33% (2)	0% (0)
	No adherence	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)
	Too early to assess adherence	17% (1)	17% (1)	0% (0)	0% (0)	17% (1)

Note: Each column does not add up to 100% because there was no consensus response for some Guidelines/authorities, or Guidelines were not implemented by the authority

Method: Question 1.3 (See Appendix 2 and Appendix 3)

Key Messages

- E2D and M4 Guidelines were considered as adhered to, in addition to being implemented, by five of the authorities based on agreement between authority self-declaration and the majority industry perception
- E2A Guideline was considered as adhered to by four authorities
- Where there was no adherence this was largely due to the fact that implementation occurred recently and it is too early to assess adherence i.e. E2D, M4 and E2B(R3) for one authority each.

B. Adherence to Tier 3 Guidelines by ICH Regulatory Members

Key Messages for adherence of Tier 3 Guidelines by ICH Regulatory Members

- Across all six Regulatory Members, adherence to the Tier 3 Guidelines ranged from 2%-92%; where adherence was low, this was due to the Guideline being not implemented or only recently
- Three out of the six Regulatory Members adhered to >70% of the Tier 3 Guidelines (data not shown but was shared with participants). The results for the Tier 3 Guidelines were organised below according to the topic:

a) Quality Guidelines

Guideline/ authority	Adherence category	Q3C(R6)	Q10	Q2(R1)	Q3A(R2)	Q3B(R2)	Q5A(R1)	Q5B	Q5C	Q5D	Q5E	Q6B	Q8(R2)	Q9	Q4B	Q6A	Q11	Q3D(R1)	Q12
% of authorities where the Guideline was adhered to (no. of authorities out of 6)	Adherence	67% (4)	50% (3)	50% (3)	50% (3)	50% (3)	50% (3)	50% (3)	50% (3)	50% (3)	50% (3)	50% (3)	50% (3)	50% (3)	33% (2)	33% (2)	33% (2)	17% (1)	0% (0)
	No adherence	0% (0)	17% (1)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)
	Too early to assess adherence	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	17% (1)	17% (1)	17% (1)	17% (1)	17% (1)	17% (1)	0% (0)	17% (1)	0% (0)	33% (2)	17% (1)	0% (0)	0% (0)

Note: Each column does not add up to 100% because there was no consensus response for some Guidelines/authorities, or Guidelines were not implemented by the authority

Method: Question 1.3 (See Appendix 2 and Appendix 3)

Key Messages for Quality Guidelines

- Most of the Quality Guidelines were considered as adhered to by three or more authorities
- Where there was no adherence this was largely due to the fact that implementation occurred recently and it was too early to assess adherence e.g. Q6A for two authorities

b) Safety Guidelines

Guideline/ authority	Adherence category	S1A	S1B	S2(R1)	S3A	S4	S7A	S9	S1C(R2)	S3B	S6(R1)	S7B	S8	S10	S5(R2)	S11
% of authorities where the Guideline was adhered to (no. of authorities out of 6)	Adherence	67% (4)	67% (4)	67% (4)	67% (4)	67% (4)	67% (4)	67% (4)	50% (3)	50% (3)	50% (3)	50% (3)	50% (3)	50% (3)	33% (2)	17% (1)
	No Adherence	17% (1)	17% (1)	17% (1)	17% (1)	17% (1)	17% (1)	0% (0)	17% (1)	17% (1)	0% (0)	17% (1)	0% (0)	0% (0)	17% (1)	0% (0)
	Too early to assess adherence	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	17% (1)	0% (0)	0% (0)	17% (1)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)

Note: Each column does not add up to 100% because there was no consensus response for some Guidelines/authorities, or Guidelines were not implemented by the authority

Method: Question 1.3 (See Appendix 2 and Appendix 3)

Key Messages for Safety Guidelines

- Most of the Safety Guidelines were considered as adhered to by three or more authorities

c) Efficacy Guidelines

Guideline/ authority	Adherence category	E2C(R2)	E2E	E3	E7	E8	E9	E10	E1	E2F	E4	E5(R1)	E11(R1)	E17	E14	E15	E16	E18
% of authorities where the Guideline was adhered to (number of authorities out of 6)	Adherence	83% (5)	83% (5)	67% (4)	67% (4)	67% (4)	67% (4)	67% (4)	50% (3)	50% (3)	50% (3)	50% (3)	50% (3)	33% (2)	33% (2)	33% (2)	33% (2)	33% (2)
	No Adherence	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	17% (1)	0% (0)	0% (0)	0% (0)	0% (0)
	Too early to assess adherence	17% (1)	17% (1)	17% (1)	17% (1)	17% (1)	17% (1)	17% (1)	17% (1)	0% (0)	17% (1)	17% (1)	17% (1)	17% (1)	17% (1)	0% (0)	17% (1)	17% (1)

Note: Each column does not add up to 100% because there was no consensus response for some Guidelines/authorities, or Guidelines were not implemented by the authority

Method: Question 1.3 (See Appendix 2 and Appendix 3)

Key Messages for Efficacy Guidelines

- Most of the Efficacy Guidelines were considered as adhered to by three or more authorities

d) Multidisciplinary Guidelines

Guideline/ authority	Adherence category	M3(R2)	M7(R1)	M9
% of authorities where the Guideline was adhered to (number of authorities out of 6)	Adherence	50% (3)	50% (3)	17% (1)
	No Adherence	0% (0)	0% (0)	0% (0)
	Too early to assess adherence	17% (1)	17% (1)	0% (0)

Note: Each column does not add up to 100% because there was no consensus response for some Guidelines/authorities, or Guidelines were not implemented by the authority Method: Question 1.3 (See Appendix 2 and Appendix 3)

Key Messages for Multidisciplinary Guidelines

- M3(R2) and M7(R1) Guidelines were considered as adhered to by three authorities, while one Authority was shown to adhere to M9.

Adherence of Tier 1 Guidelines by ICH Observers

Guideline/ authority	Adherence category	E6(R2)	Q7	Q1
% of authorities where the Guideline was adhered to (number of authorities out of 6)	Adherence	100% (4)	75% (3)	50% (2)
	No Adherence	0% (0)	0% (0)	0% (0)
	Too early to assess adherence	0% (0)	0% (0)	0% (0)

Note: Each column does not add up to 100% because there was no consensus response for some Guidelines/authorities, or Guidelines were not implemented by the authority Method: Question 1.3 (See Appendix 2 and Appendix 3)

Key Messages

- All ICH Observers have implemented the E6(R2) Guideline, while only two have implemented all Guidelines.

CONCLUSION

The results of Phase 2b project show evidence of a strong level of implementation and adherence to the ICH Guidelines by the participating 6 ICH non-Standing non-Founding Regulatory Members and the 4 ICH Observers with a good alignment between the perception of the participating 30 pharmaceutical companies and the self-declaration from the assessed authorities.

ICH non-Standing non-Founding Regulatory Members: Tier 2 Guidelines were implemented and adhered to by most of the ICH non-Standing non-Founding Regulatory Members. By comparing results from 2019, in general, the guideline implementation increased in the last two years. For Tier 3 Guidelines there is evidence that most of the Guidelines in this Tier are implemented and adhered to by the authorities, or that they are in the process of implementation

ICH Observers - Tier 1 Guidelines: Results showed that two ICH Observers implemented and adhered to all Tier 1 Guidelines.

Overall, the results demonstrate 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. These could be used to support decisions related to ICH membership applications, the transparent communication of Guideline implementation status, and more targeted approaches to ICH training activity, as well as future revisions of ICH Guidelines.

APPENDIX 1 – DEFINITIONS OF TERMS IN THE CONTEXT OF THE IMPLEMENTATION AND ADHERENCE 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	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.

Term	Definition	Comments
	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 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.	There may be varying degrees of inadequate implementation and this assessment can only be 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[1]	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).

[1] 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.

Question 1a (for Companies only)

What is your company's experience in regard to 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 – METHOD OF ANALYSIS

Summary – Implementation status' Method

To consider that a Guideline was implemented in a specific agency, the answers to Question 1 were analysed using the following inclusion criteria:

1. The Guideline should be considered as implemented by at least 60% of the companies that responded to Question 1
2. At least three companies are in consensus
3. The regulatory agency declared that the Guideline was implemented

Once the Guidelines were categorised as implemented for each authority, the **% of authorities where the Guideline was implemented, was calculated** dividing the number of authorities with Guideline implemented by the authorities' total number

Summary – Adherence status' Method

An assessment utilising the following three categories was undertaken to summarise the implementation and adherence status of the agency for the Guidelines assessed

Category 1: Guideline implemented AND adhered to	Category 2a: Guideline implemented BUT no adherence	Category 2b: Guideline implemented BUT too early to assess adherence

The method is as follows:

- **Implementation:** For both categories 1, 2a and 2b the first criterion is that the response to Question 1 on implementation was 'implemented' for BOTH the authority and based on a majority response from all companies (here assumed as >60% responses e.g. 6/10 companies)
- **Adherence:** The difference in categories is response to Question 1.3 on adherence, where:
  - Category 1: both authority and company majority response (>60%) is 'adherence'
  - Category 2a and 2b: a number of combinations are possible (see table below):

		Company majority response to Question 1.3 (>%60)		
		Adherence	No adherence	Too early to assess
Authority response to Question 1.3	Adherence	Category 1	Category 2a	Category 2b
	No adherence	Category 2a	Category 2a	Category 2b
	Too early to assess	Category 2b	Category 2b	Category 2b

NOTE: number of companies stating 'implemented' AND 'adherence' must be ≥ 3 to be included in analysis

Once the Guidelines were categorised based on their adherence status, the **% of authorities where the Guideline was adhered to** was calculated with the number of authorities that have adhered the Guideline divided by total number of authorities

APPENDIX 4 – 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

Report date: 09 September 2021
With editorial changes added on 07 January 2022
Version 1.4