2024 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)

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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 twenty-three Members and thirty-five Observers.

Acknowledgements

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

Report date: 1 October 2024 Version 1

EXECUTIVE SUMMARY

Background: This study aimed to monitor the adequacy of implementation and adherence to ICH Guidelines by regulatory authorities – continuing the assessment initiated in 2019 and repeated in 2021.[1]

Objectives: This study aimed to monitor the adequacy of implementation and adherence to ICH Guidelines by regulatory authorities. The main 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 2024
- To allow participating Observers interested in future ICH Membership to reference the survey findings to confirm their eligibility
- To identify regulatory training and capacity building needs

Method: An online questionnaire and definitions developed by CIRS in collaboration with ICH were utilised. The questionnaire was completed in January-April 2024 by companies (assessing all the authorities) and authorities (assessing themselves). It assessed implementation and adherence to ICH Guidelines by all the ICH Non-Founding, Non-Standing Regulatory Members[2] for Tier 2 and 3 Guidelines; ICH Founding and Standing Regulatory Members[3] for selected new Tier 3 Guidelines; and ICH Observers on a voluntary basis for Tier 1 ICH Guidelines, where results for ANMAT, Argentina; SAHPRA, South Africa and NAFDAC, Nigeria were included in this report.[4]

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. **19 regulatory authorities** (100% response rate) and **26 pharmaceutical companies** (70% response rate) participated in the 2024 study to undertake gap analysis, indicating strong interest and support for this initiative.

Assessment of implementation and adherence across 64 ICH Guidelines

19 authorities undertook a self-assessment

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

Non-Founding, Non-Standing Regulatory Members: Results for 2024 indicate that:

- For Tier 2 Guidelines: Implementation and adherence for Tier 2 Guidelines ranged from 40-100% across the ten authorities. Nine out of 10 authorities implemented and adhere to ≥80% of Tier 2 Guidelines. Some challenges for implementation and adherence were highlighted, particularly for M4, as well as E2B(R3), E2D and M1.
- For Tier 3 Guidelines: Implementation and adherence for Tier 3 Guidelines ranged from 5-95% across the ten Authorities. Seven out of ten authorities implemented and adhere to ≥50% of Tier 3 Guidelines. Guidelines with least implementation and adherence across the authorities included: Q4B, Q12, Q13; S1B(R1); E8(R1), E15, E16, E19 and, and M10.

The results also demonstrate progress made by authorities in implementing ICH Guidelines since the 2019 and 2021 assessment:

- For Tier 2 Guidelines: implementation and adherence increased from 47% in 2019, to 64% in 2021 and 73% in 2024. This was driven by an increase in implementation of E2B(R3) and M1.
- For Tier 3 Guidelines: the increase was from 70% in 2021 to 79% in 2024 (not studied in 2019). This was driven by an increase in implementation and adherence by ANVISA, Brazil; NMPA, China, and TITCK, Türkiye, which is now similar to the other Regulatory Members.

Founding and Standing Regulatory Members: The results show for the selected Tier 3 Guidelines that implementation ranged from 86-100%, whereas adherence ranged from 28-86% across the five Authorities. Guidelines with least implementation and adherence across the authorities were E19, M10, Q13 and S1B(R1).

Observers: The results show that implementation and adherence ranged from 33-100% across the three Authorities.

[1] https://www.ich.org/page/ich-guideline-implementation

[2] ANVISA, Brazil; COFEPRIS, Mexico; EDA, Egypt; HSA, Singapore; MFDS, Republic of Korea; MHRA, UK; NMPA, China; SFDA, Saudi Arabia; TFDA, Chinese Taipei; TITCK, Türkiye

[3] EC, Europe; FDA, United States; Health Canada, Canada; MHLW/PMDA, Japan; Swissmedic, Switzerland

[4] Results were excluded for CECMED, Cuba due to insufficient volume of industry data

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 and 2021 assessments and the results will be used to support training needs as well as ICH-membership related activities.

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.

This study was built on the previous 2019 and 2021 studies where ICH selected the Centre for Innovation in Regulatory Science (CIRS) to collaborate on the development and the conduct this project, including the design the study questionnaire and the online data collection tool (DCT). The report of these studies has been published[5] and endorsed by the ICH Management Committee (MC).

Goals and Objectives

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

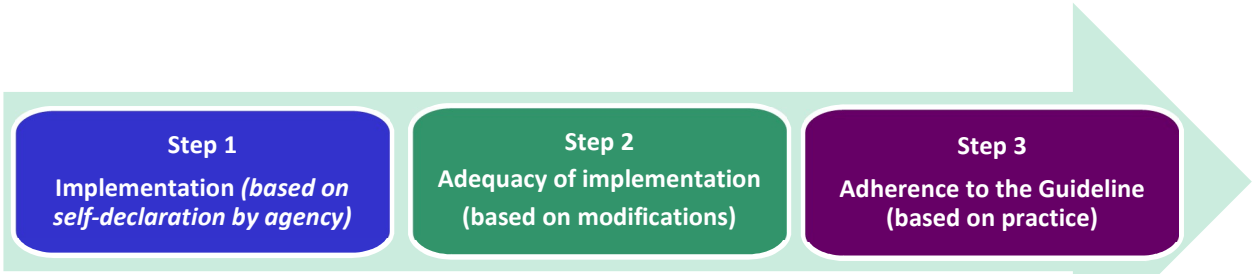
- To assist the Management Committee in determining whether ICH Non-Founding, Non-Standing Regulatory Members would meet the eligibility criteria for the ICH MC elections in June 2024
- To allow participating Observers interested in future ICH Membership to reference the survey findings to confirm their eligibility
- To provide ICH Members and Observers with additional data for internal considerations
- To identify regulatory training and capacity building needs
- To inform related industry and agency initiatives
- To compare the results with previous studies in 2019 and 2021 survey to identify progress towards harmonisation

[5] https://www.ich.org/page/ich-guideline-implementation

SCOPE AND METHOD

CIRS utilised the same questionnaire and definitions developed jointly by ICH and the ICH Implementation Subcommittee as part of the previous studies (see Appendix 1). The questionnaire was completed between January and March 2024 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 and 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 56 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.

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-Founding, Non-Standing 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
  - 56 Guidelines were studied, from across Q, S, E, M domains and are listed in Appendix 4
  - All those Guidelines were studied for Non-Founding, Non-Standing Regulatory Members;
  - A subset of 7 selected new Guidelines[6] were studied for Founding and Standing Regulatory Members

[6] E8(R1); E19; M10; Q3C(R8); Q3D(R2); Q13; S1B(R1)

The following organisations participated:

- 19 Regulatory authorities (assessing themselves only):

  Founding and Standing Regulatory Members
  - EC, Europe
  - FDA, United States
  - Health Canada, Canada
  - MHLW/PMDA, Japan
  - Swissmedic, Switzerland

  Non-Founding, Non-Standing Regulatory Members
  - ANVISA, Brazil
  - COFEPRIS, Mexico
  - EDA, Egypt
  - HSA, Singapore
  - MFDS, Republic of Korea
  - MHRA, UK
  - NMPA, China
  - SFDA, Saudi Arabia
  - TFDA, Chinese Taipei
  - TITCK, Türkiye

  Regulatory Observers
  - ANMAT, Argentina
  - CECMED, Cuba[7]
  - NAFDAC, Nigeria
  - SAHPRA, South Africa

- 26 Major Pharmaceutical Companies (assessing all the participating authorities) provided a response in total out of 37 representing the following associations – EFPIA, IGBA, JPMA, PhRMA, and BIO. In addition, the Global Self-Care Federation participated in the survey consolidating responses into a single submission on behalf of its members.

[7] Results were excluded for CECMED, Cuba due to insufficient volume of industry data

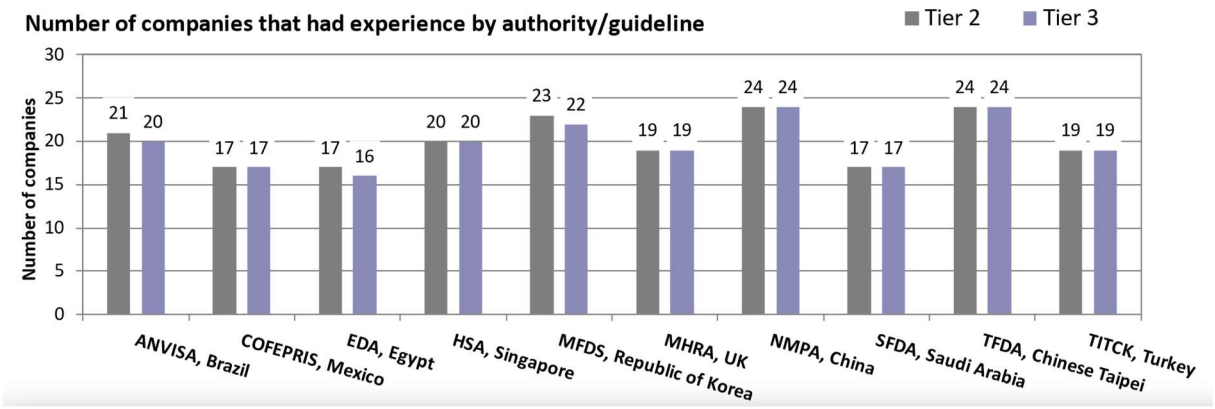
RESULTS PART 1: ICH NON-FOUNDING, NON-STANDING REGULATORY MEMBERS

Characteristics of participating companies

Key Messages

- 25 companies participated out of 37 invited companies (68% 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-Founding, Non-Standing Regulatory Members

Method: Question 1i (see Appendix 2)

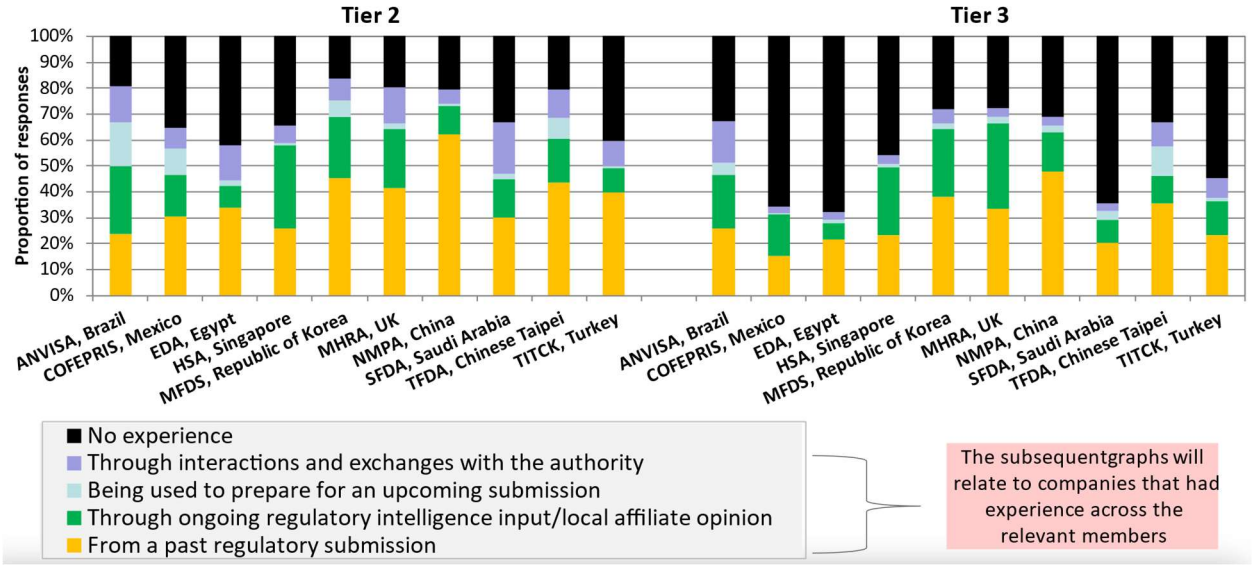


Companies' Experiences with ICH Non-Founding, Non-Standing Regulatory Members: Participating companies were asked for their most recent/relevant experience regarding a Guideline for a selected authority.

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, 75% of them were submitted in 2022 or later

Method: Question 1a (see Appendix 2)

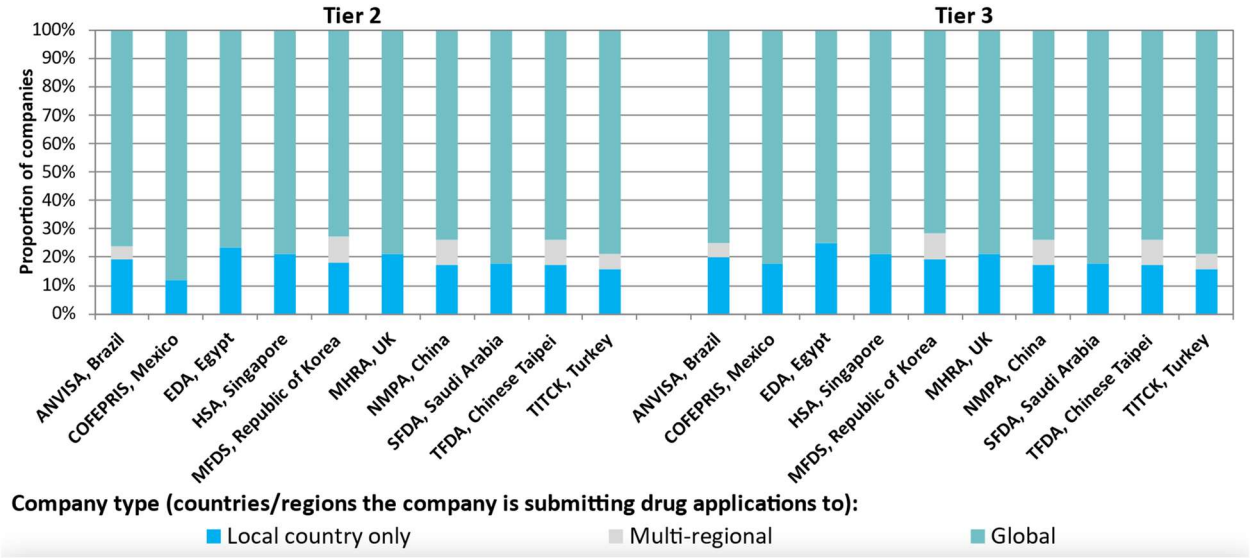


Company type: Companies were asked to specify their company type based on the countries/regions where they submitted drug applications.

Key Messages

- The majority of companies were global

Method: Question 1i (see Appendix 2)

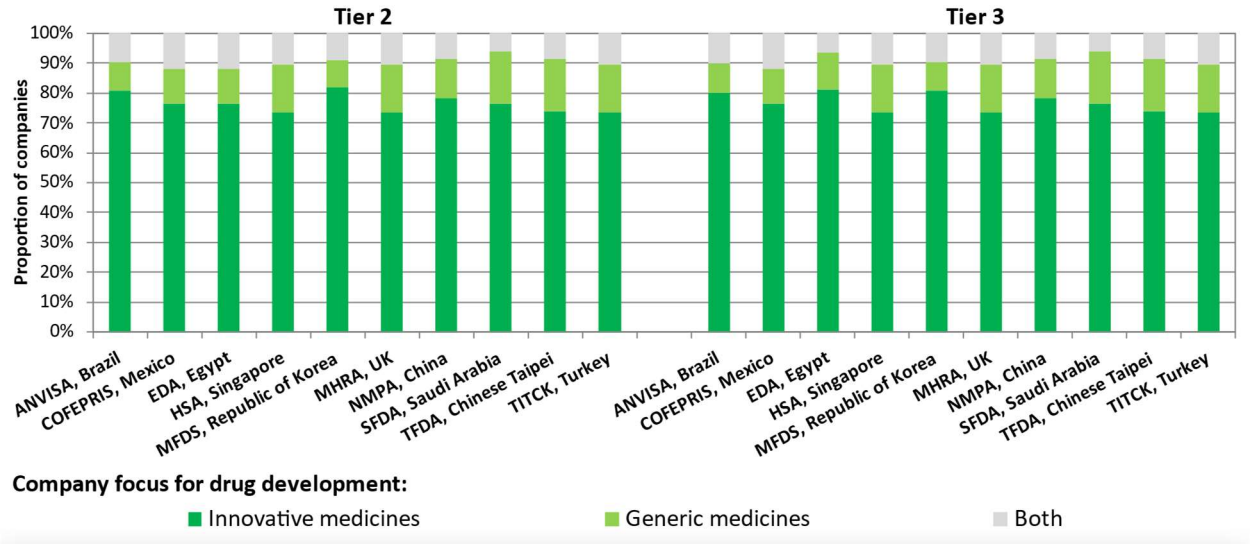


Company Focus: Companies were also asked to specify their focus for drug development, i.e. innovative and/or generic medicines

Key Messages

- The majority 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 ICH Non-Founding, Non-Standing Regulatory Members), and the second bar shows the number of responses across the companies.

Key Messages

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

Method: Question 1 (See Appendix 2)

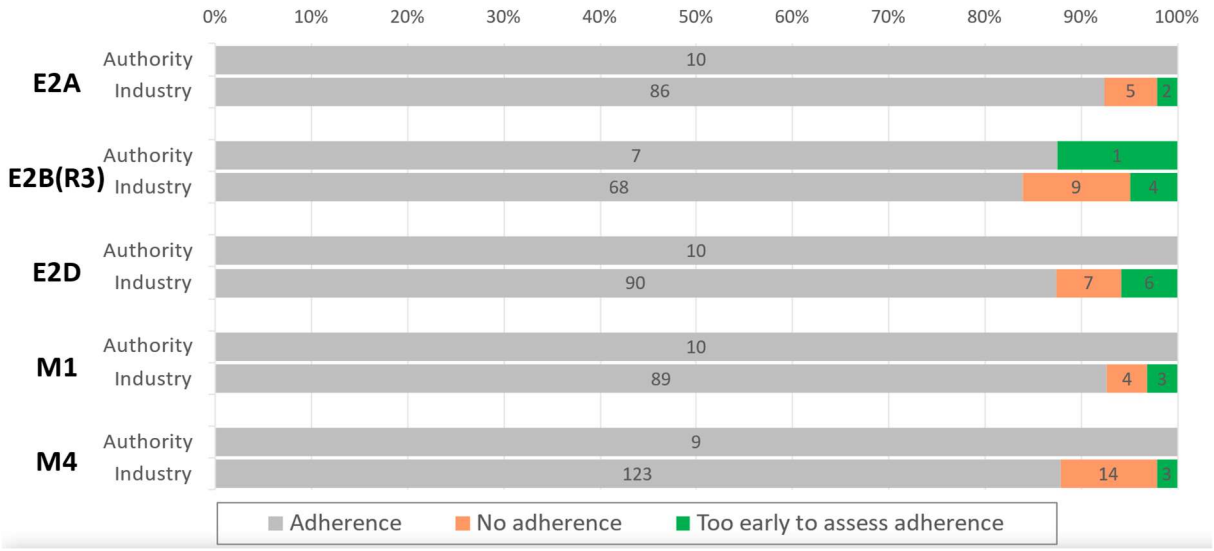
Number in the bar shows how many responses were obtained from across the organisations

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.

Key Messages

- Where implementation was confirmed, the perceived level of adherence to the Guidelines was high
- All authorities confirmed adherence to the Guidelines, except for one authority for E2B(R3), where this was too early to assess; company perception and authority declaration were generally aligned

Method: Question 1.3 (See Appendix 2)



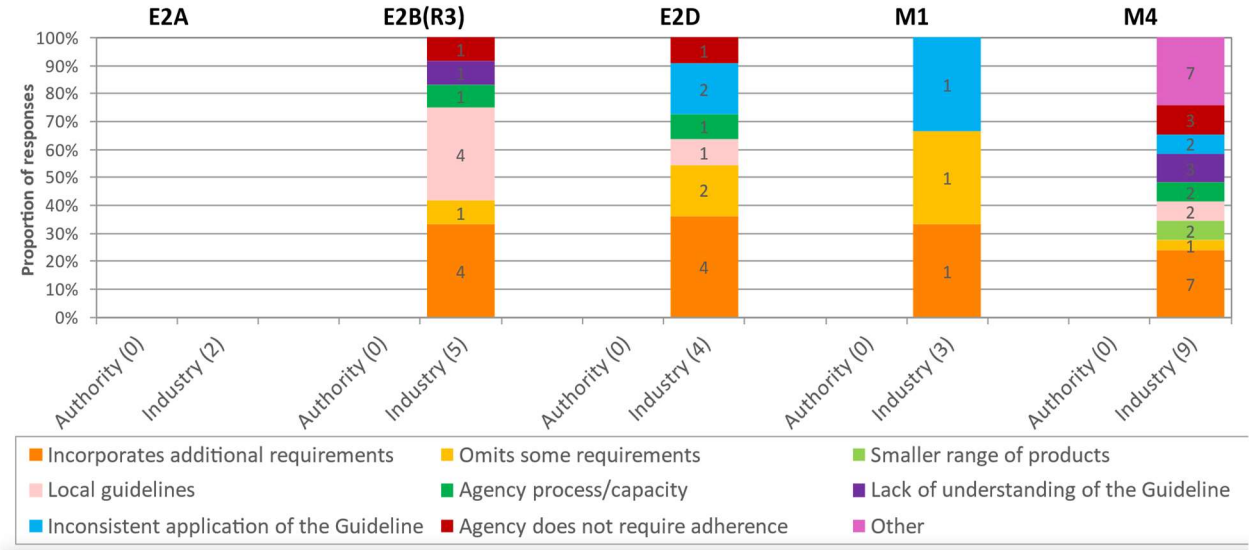
Number in the bar shows how many responses were obtained from across the organisations

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 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 (nine, five, four, three and companies for M4, E2B(R3), E2D, and M1 Guidelines, respectively)
- The most common reasons among the above 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

Method: Question 2 (See Appendix 2)



(n) = number of companies or authorities

Number in the bar shows how many responses were obtained from across the organisations

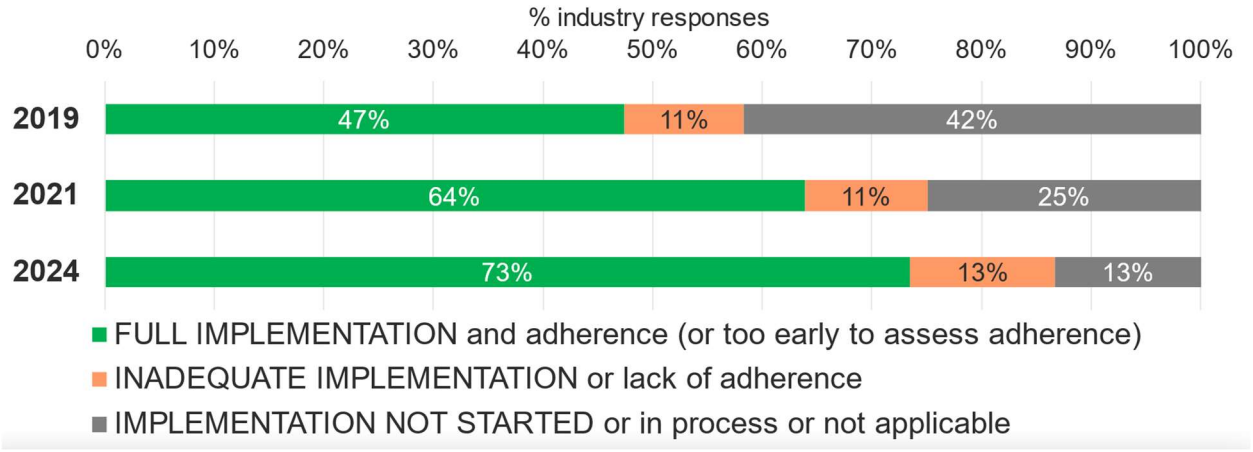
Blank = EITHER if number of companies <3, no data were shown OR not applicable based on how the previous question was answered

Comparison to Previous Survey Results

Results from this study, based on the industry perception, were compared to the 2019 and 2021[8] results for Tier 2 Guidelines using a consistent cohort of authorities (ICH Non-Founding, Non-Standing Regulatory Members) and companies which were included in all three studies.[9]

Key Messages

- Based on industry perception, implementation and adherence increased from 47% in 2019, to 64% in 2021 and 73% in 2024 for ICH Non-Founding, Non-Standing Regulatory Members
- This was driven by an increase in implementation of E2B(R3) and M1
- The shift occurred primarily from 'implementation not started (or in the process or not applicable)' to 'full implementation (or adherence or too early to assess adherence)'; 'inadequate implementation' remained low at 11% in 2019 and 2021 and 13% in 2024



[8] https://www.ich.org/page/ich-guideline-implementation

[9] Guidelines: E2A, E2B, E2D, M1 and M4; Companies: data from 15 companies
Authorities: ANVISA, Brazil; NMPA, China; HSA, Singapore; MFDS, Republic of Korea; TFDA, Chinese Taipei; TITCK, Türkiye

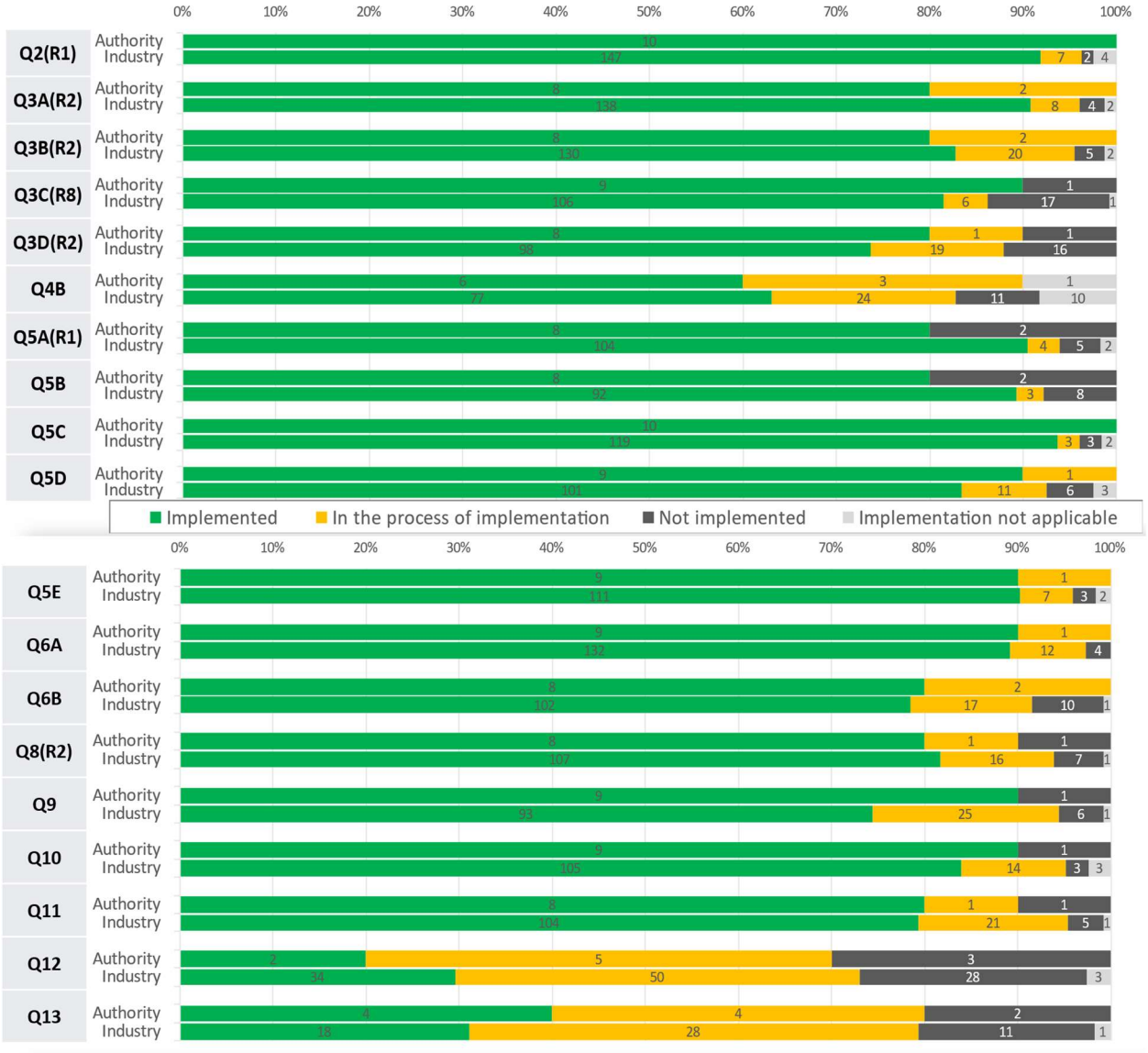
RESULTS PART 1.2: TIER 3 GUIDELINES

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 ten ICH Non-Founding, Non-Standing Regulatory Members), and the second bar shows the number of responses across the 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 Q4B, Q12 and Q13 and, are still seen to be in the process of being implemented or not implemented

Method: Question 1 (See Appendix 2)



Number in the bar shows how many responses were obtained from across the organisations

Key Messages for Safety Guidelines

- The aggregated results across the stakeholders demonstrate that, in general, the Safety Guidelines were perceived as implemented
- For S1B(R1), the response was mixed between 'implemented' and 'in the process of implementation'

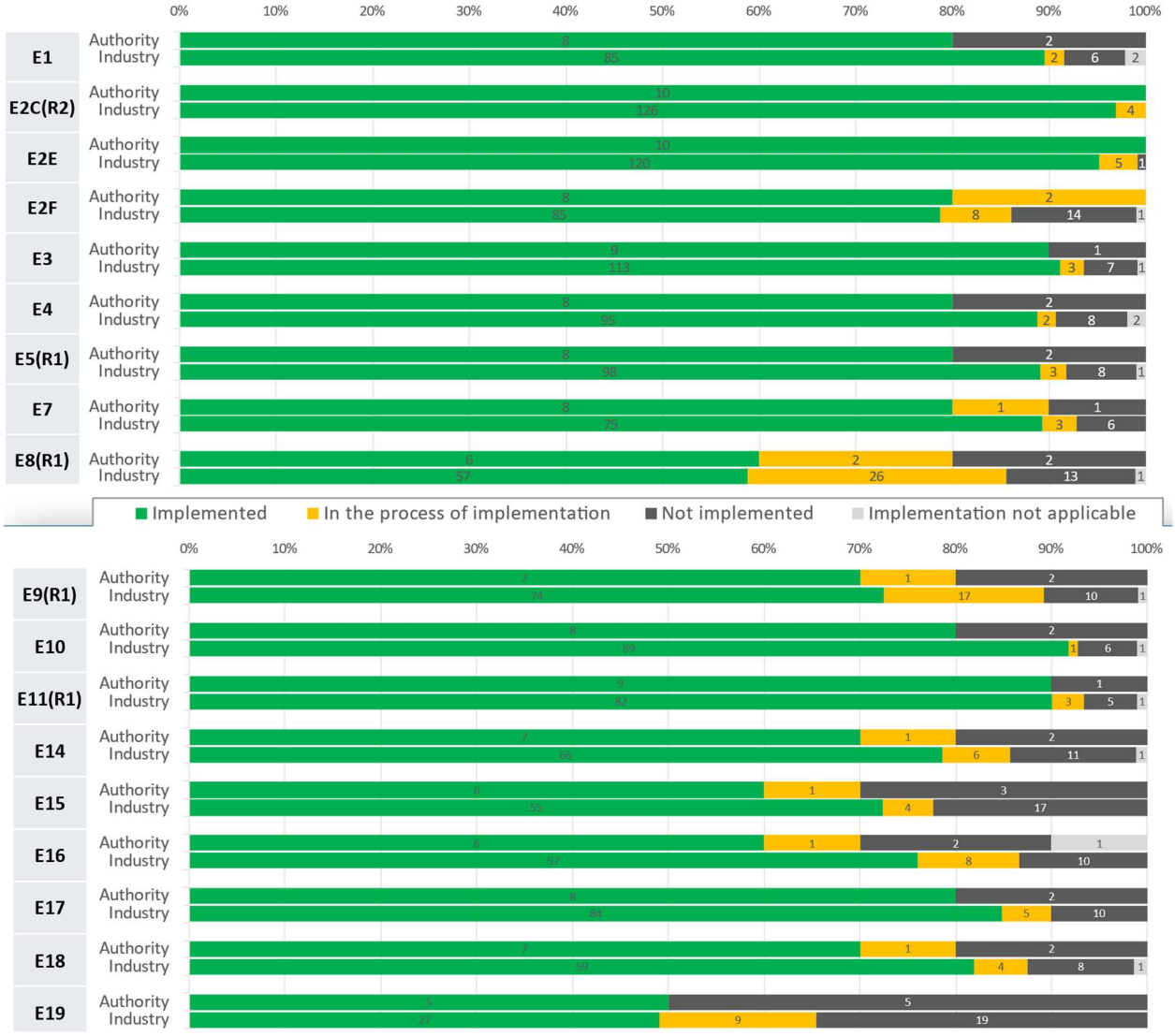
Method: Question 1 (See Appendix 2)

Number in the bar shows how many responses were obtained from across the organisations

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 E8(R1), E15, E16, E19 are seen to be in the process of being implemented or not implemented

Method: Question 1 (See Appendix 2)

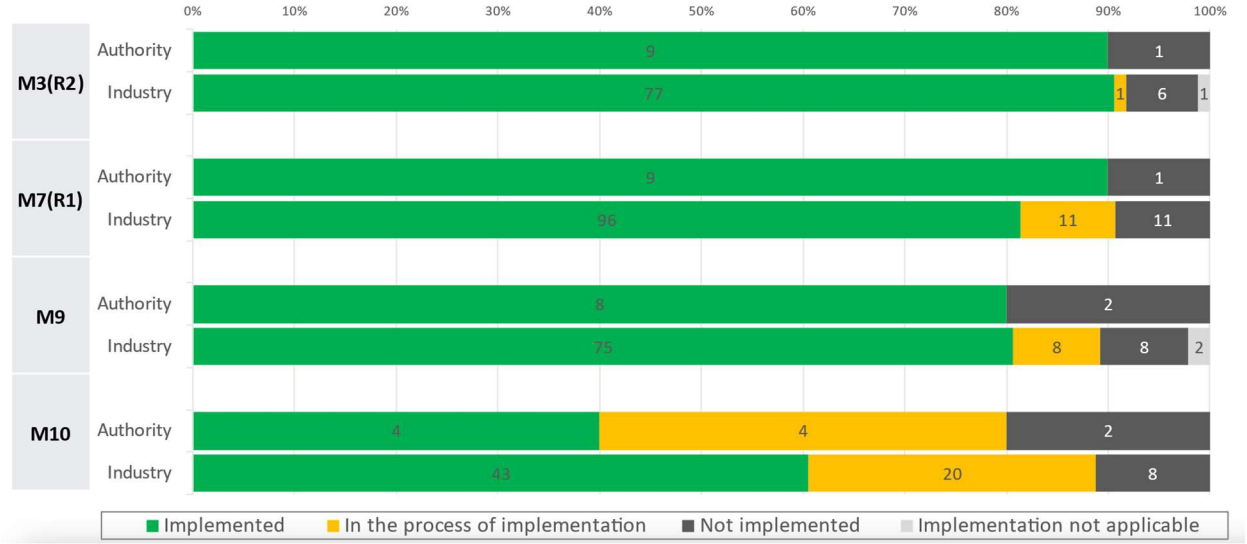


Number in the bar shows how many responses were obtained from across the organisations

Key Messages for Multidisciplinary Guidelines

- M3(R2), M7(R1) and M9 Guidelines were generally perceived by companies and self-declared by authorities as implemented
- M10 Guideline was considered as mixed, either implemented or in the process of implementation

Method: Question 1 (See Appendix 2)



Number in the bar shows how many responses were obtained from across the organisations

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.

Key Message for Quality, Safety, Efficacy and Multidisciplinary Guidelines

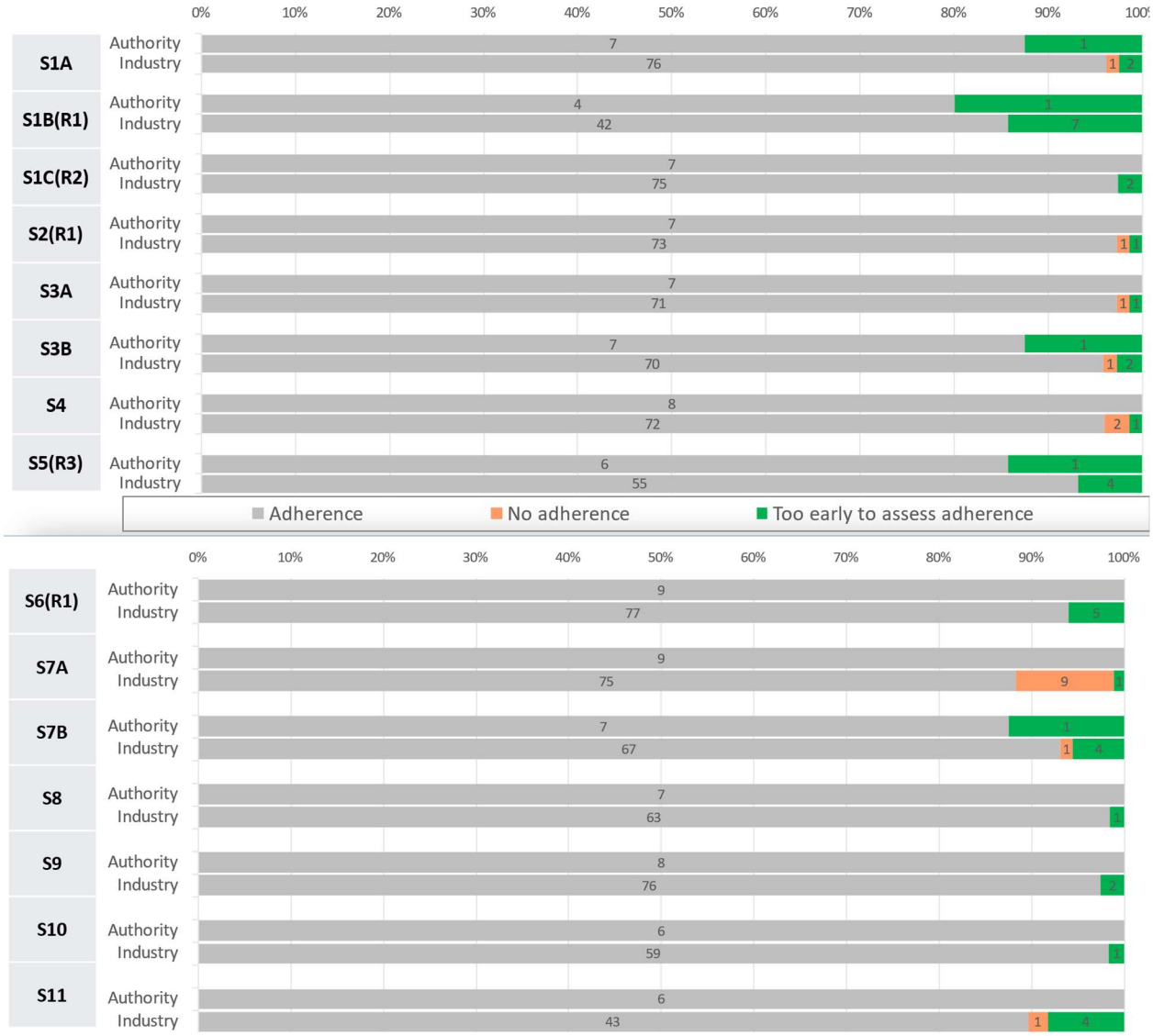
- For those ICH Guidelines that were confirmed as implemented, there was generally a strong level of adherence based on agency self-declaration and company perception

Method: Question 1.3 (See Appendix 2)

Quality Guidelines

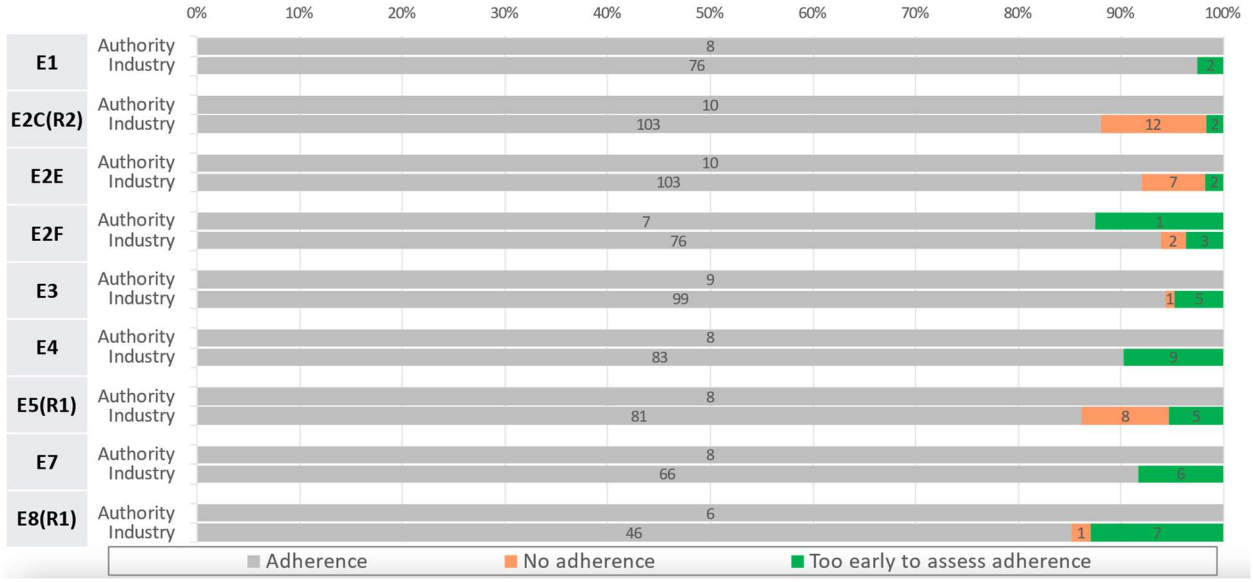
Number in the bar shows how many responses were obtained from across the organisations

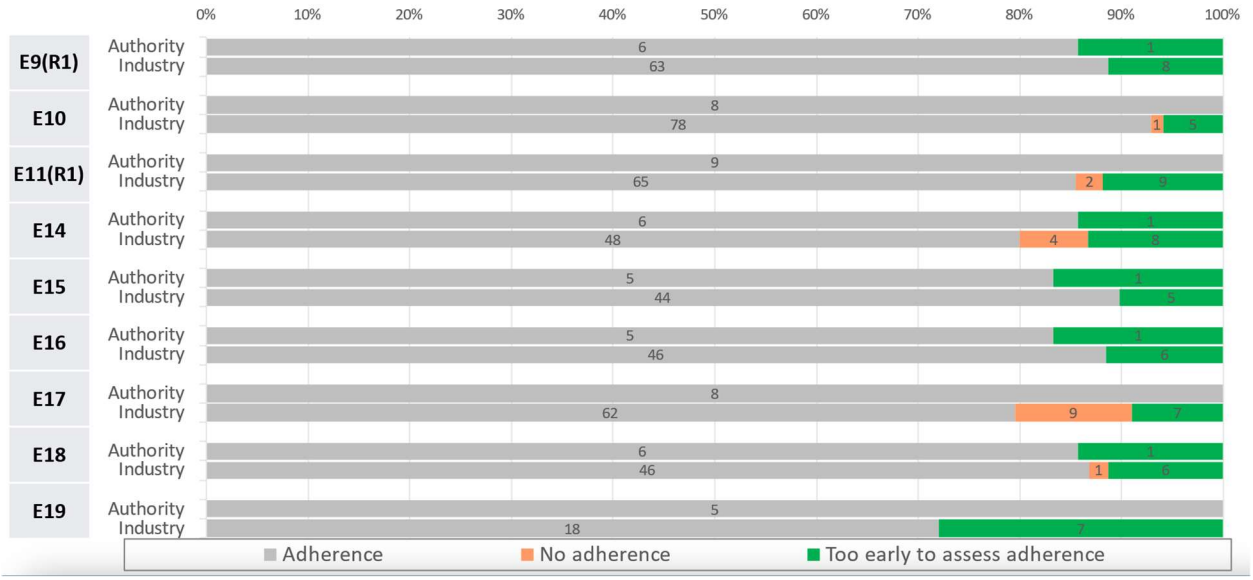
Safety Guidelines



Number in the bar shows how many responses were obtained from across the organisations

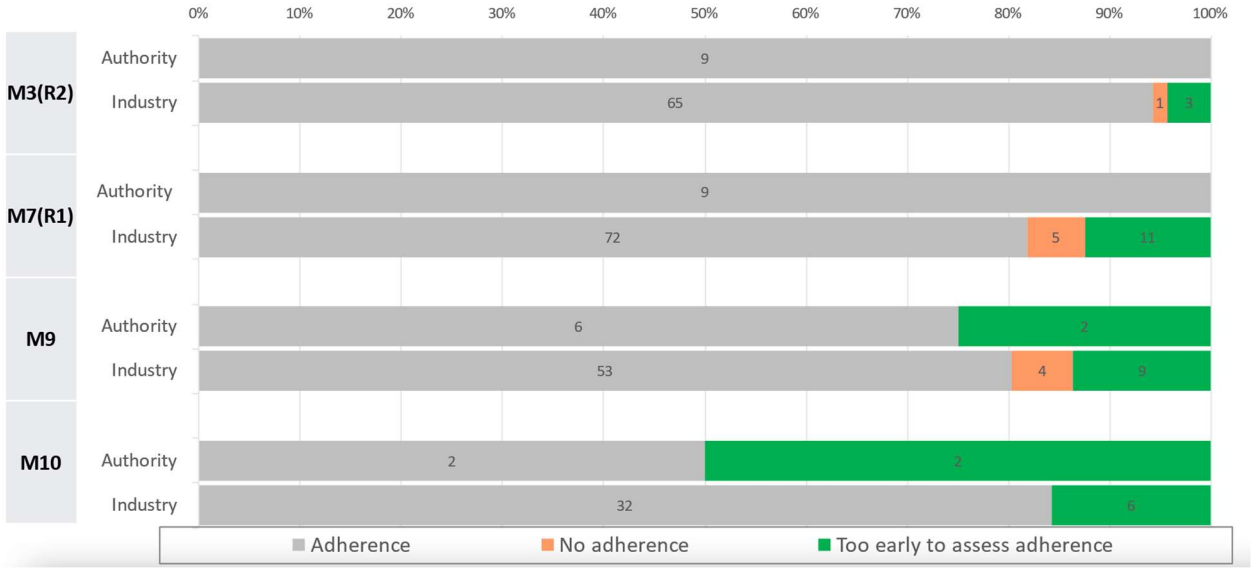
Efficacy Guidelines





Number in the bar shows how many responses were obtained from across the organisations

Multidisciplinary Guidelines



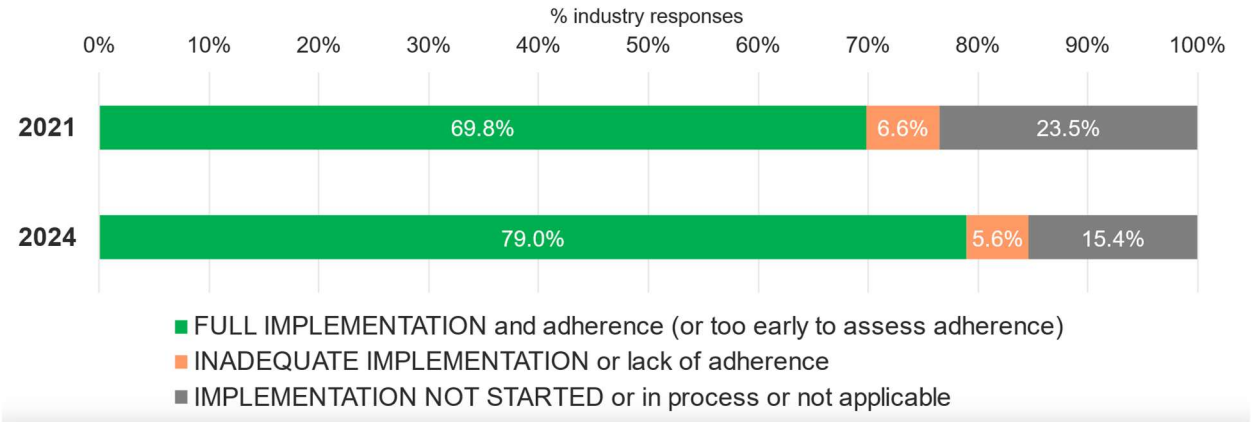
Number in the bar shows how many responses were obtained from across the organisations

Comparison to Previous Survey Results

Results from this study, based on the industry perception, were compared to the 2021[10] results for Tier 3 Guidelines using a consistent cohort of authorities (ICH Non-Founding, Non-Standing Regulatory Members) and companies which were included in both studies.[11]

Key Messages

- Based on industry perception, implementation and adherence increased from 70% in 2021 to 79% in 2024 for ICH Non-Founding, Non-Standing Regulatory Members
- This was driven by an increase in implementation by three authorities
- The shift occurred primarily from 'implementation not started (or in the process or not applicable)' to 'full implementation (or adherence or too early to assess adherence)'; 'inadequate implementation' remained low at 7% in 2021 and 6% in 2024



[10] https://www.ich.org/page/ich-guideline-implementation

[11] Guidelines: 49 Guidelines; Companies: data from 18 companies
Authorities: ANVISA, Brazil; NMPA, China; HSA, Singapore; MFDS, Republic of Korea; TFDA, Chinese Taipei; TITCK, Türkiye

RESULTS PART 2: ICH FOUNDING AND STANDING REGULATORY MEMBERS (SELECTED TIER 3 GUIDELINES)

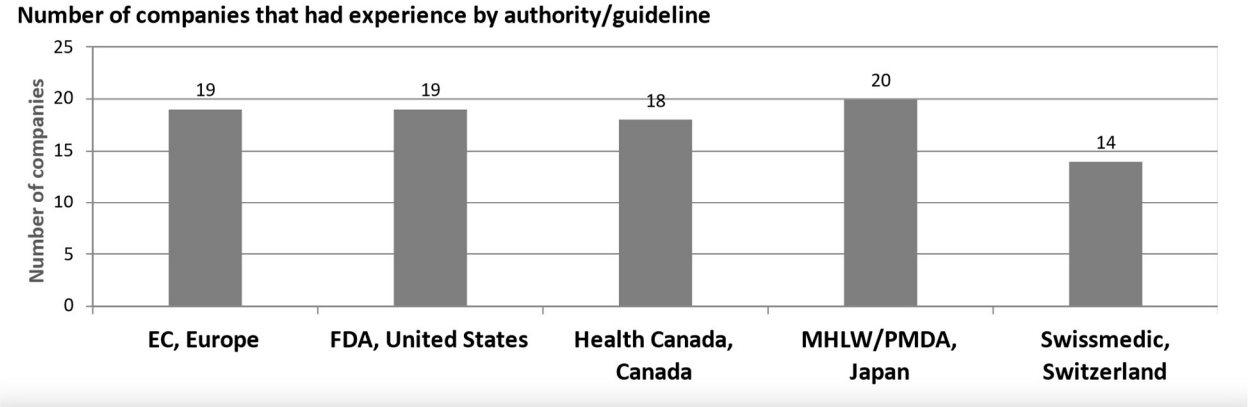
Characteristics of participating companies

Key Messages

- 23 companies participated out of 37 invited companies (62% response rate)
- There was a good level of experience among the participating pharmaceutical companies regarding implementation of selected new Tier 3 ICH Guidelines by ICH Founding and Standing Regulatory Members

Method: Question 1i (see Appendix 2)

Number of companies that had experience by authority/guideline

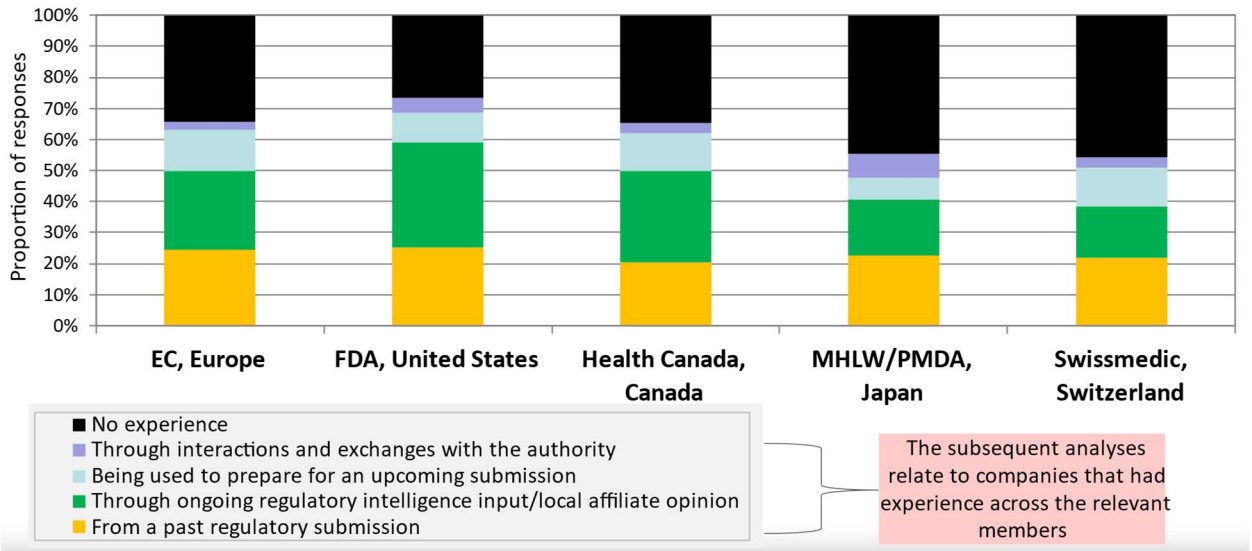


Companies' Experiences with ICH Non-Founding, Non-Standing Regulatory Members: Participating companies were asked for their most recent/relevant experience regarding a Guideline for a selected authority.

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, 85% of them were submitted in 2022 or later

Method: Question 1a (see Appendix 2)

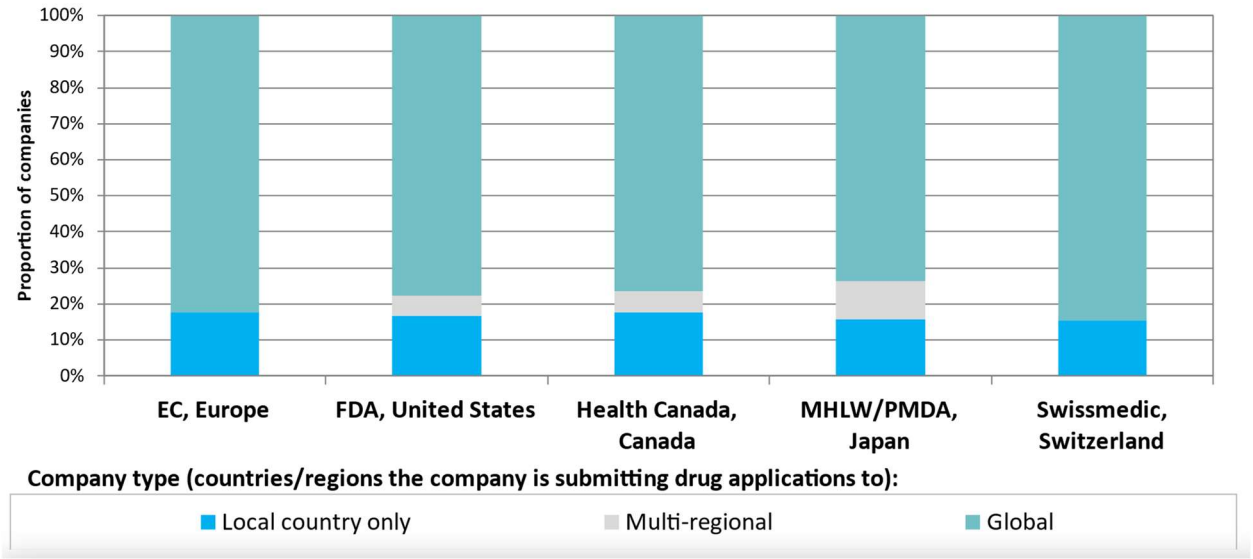


Company type: Companies were asked to specify their company type based on the countries/regions where they submitted drug applications.

Key Messages

- The majority companies were global

Method: Question 1i (see Appendix 2)

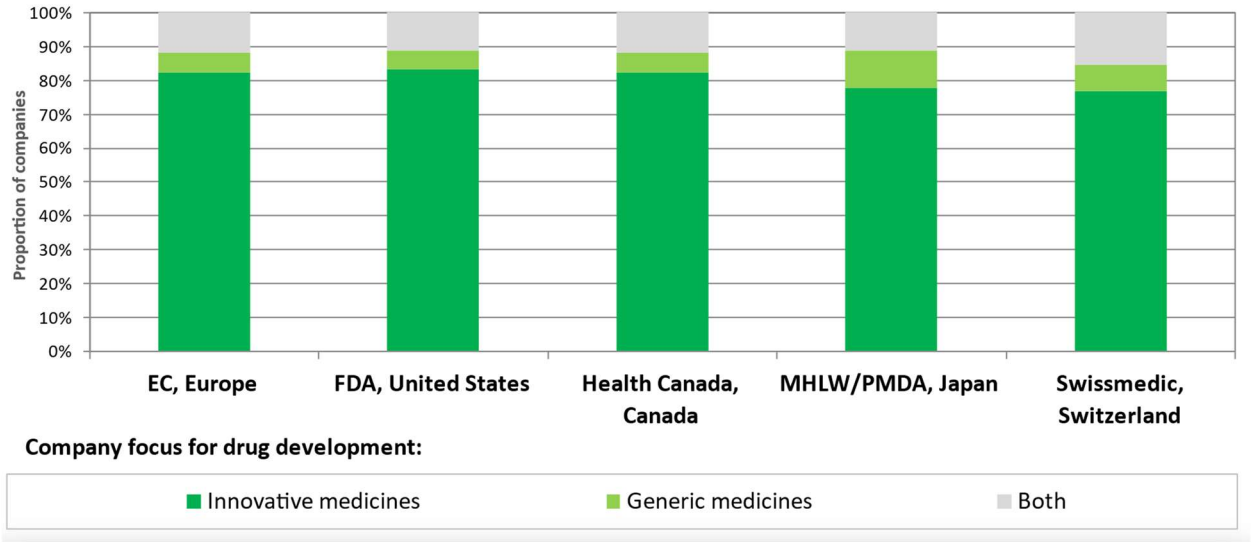


Company Focus: Companies were also asked to specify their focus for drug development, i.e. innovative and/or generic medicines.

Key Messages

- The majority of surveyed companies were innovative companies

Method: Question 1ii (see Appendix 2)



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 ICH Founding and Standing Regulatory Members), and the second bar shows the number of responses across the companies.

Key Messages

- Most of the Guidelines were seen as implemented
- Company perception of implementation status was generally aligned with agency self-declaration
- M10 and Q13 had the highest proportion of 'in the process of implementation' responses

Method: Question 1 (See Appendix 2)

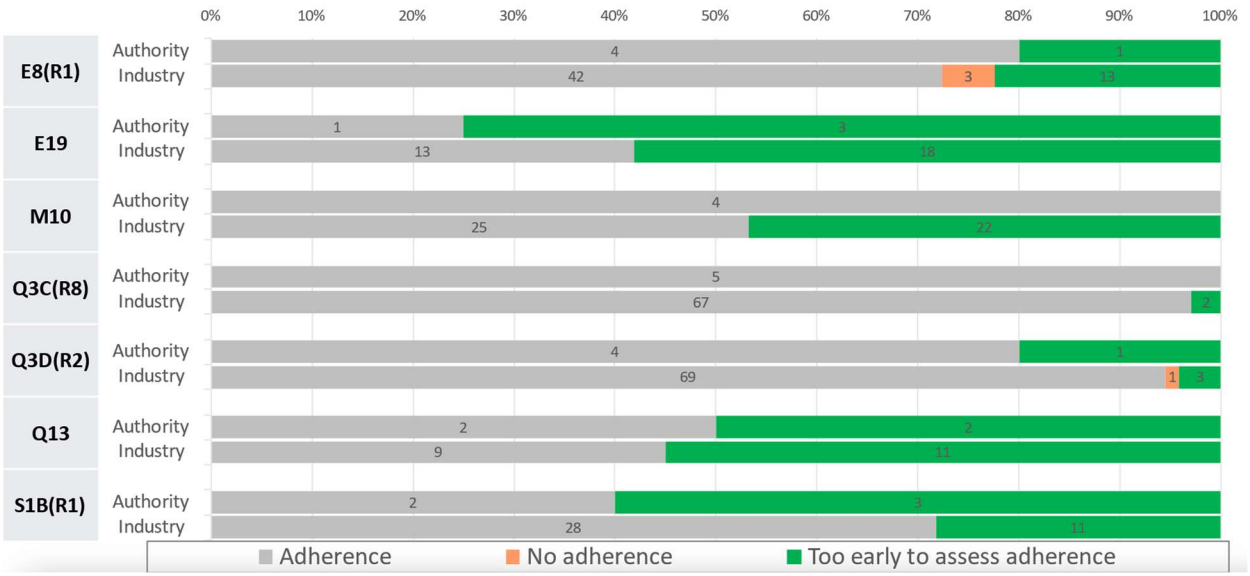
Number in the bar shows how many responses were obtained from across the organisations

Adherence status: Organisations that confirmed that a Tier 3 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.

Key Messages

- Where implementation was confirmed, the perceived level of adherence to the Guidelines was high or too early to assess, particularly for E19, Q13 and S1B(R1)

Method: Question 1.3 (See Appendix 2)



Number in the bar shows how many responses were obtained from across the organisations

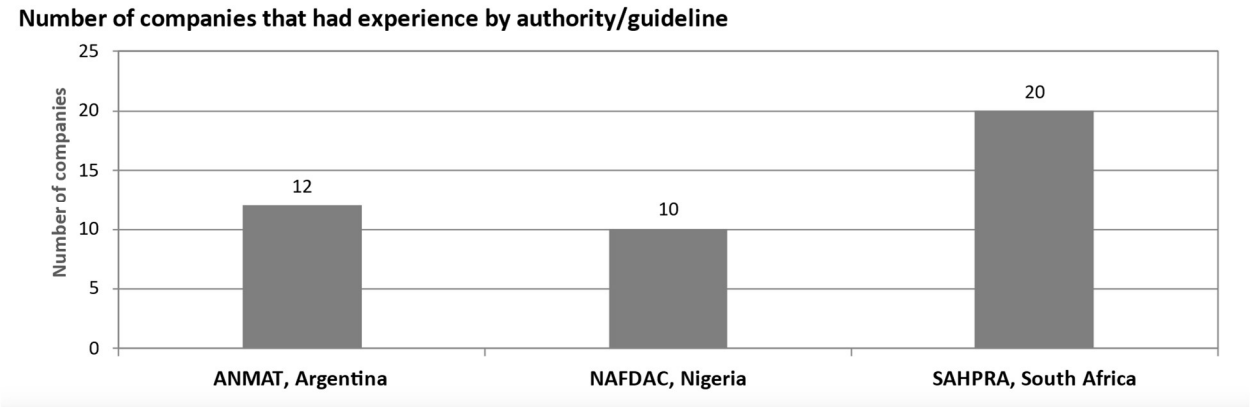
RESULTS PART 3: ICH REGULATORY OBSERVERS (TIER 1 GUIDELINES)

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)

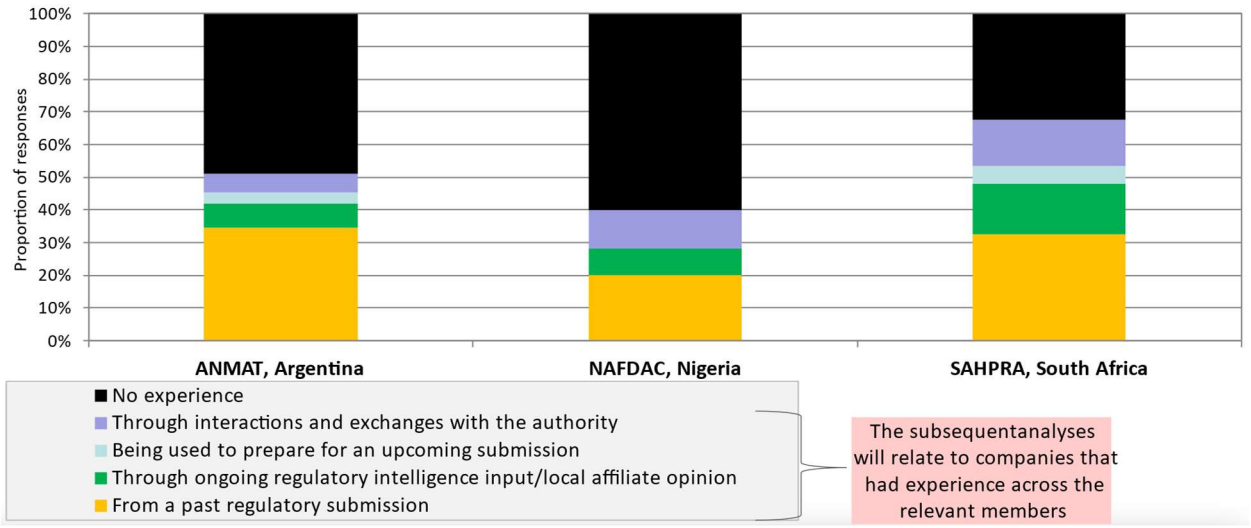


Companies' Experiences with ICH Observers: Participating companies were asked for their most recent/relevant experience regarding a Guideline for a selected authority.

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, 76% of them were submitted in 2022 or later

Method: Question 1a (see Appendix 2)

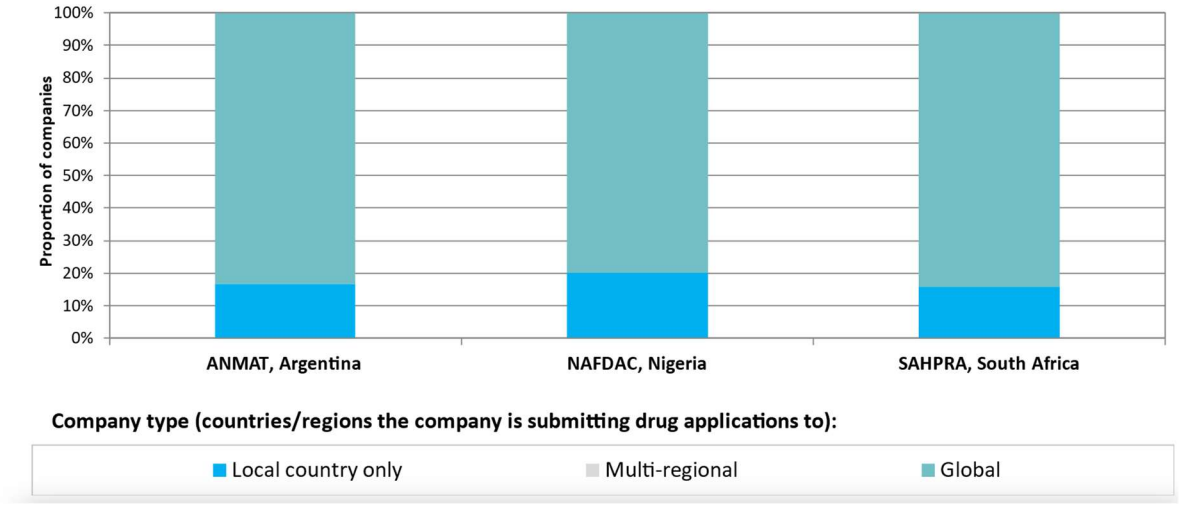


Company type: Companies were asked to specify their company type based on the countries/regions where they submitted drug applications.

Key Messages

- The majority of companies were global

Method: Question 1i (see Appendix 2)

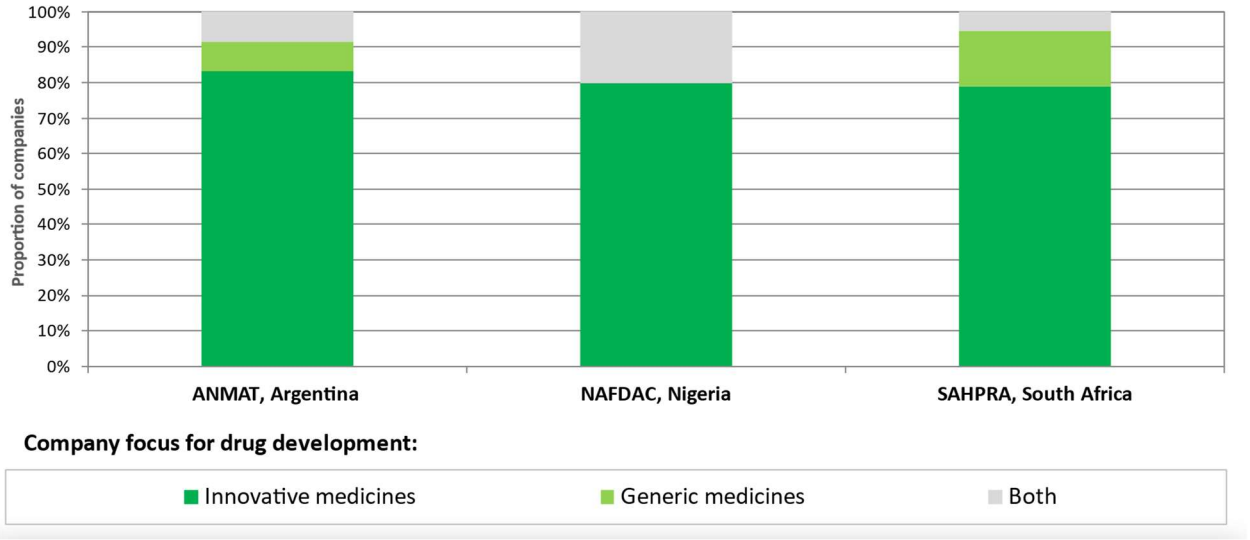


Company Focus: Companies were also asked to specify their focus for drug development, i.e. innovative and/or generic medicines.

Key Messages

- The majority of companies were focused on innovative medicines

Method: Question 1ii (see Appendix 2)

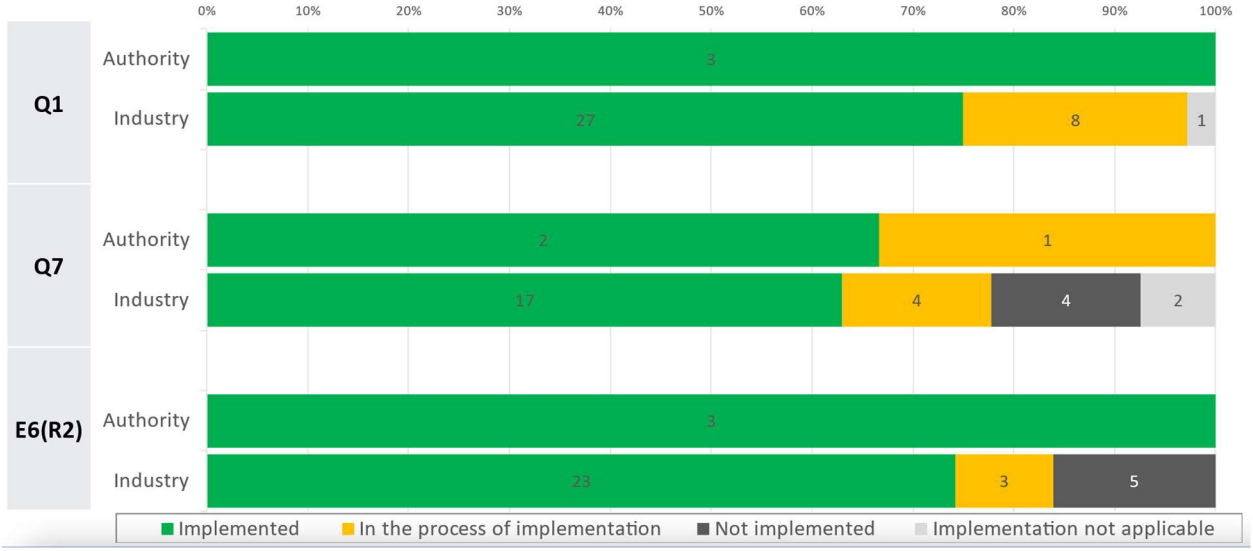


Implementation status: Authorities and companies were asked about their views on the Tier 1 Guidelines' implementation status. The first bar in the graph below corresponds to the self-declaration by the authorities (aggregated results across the ICH Observers), and the second bar shows the number of responses across the companies.

Key Messages

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

Method: Question 1 (See Appendix 2)



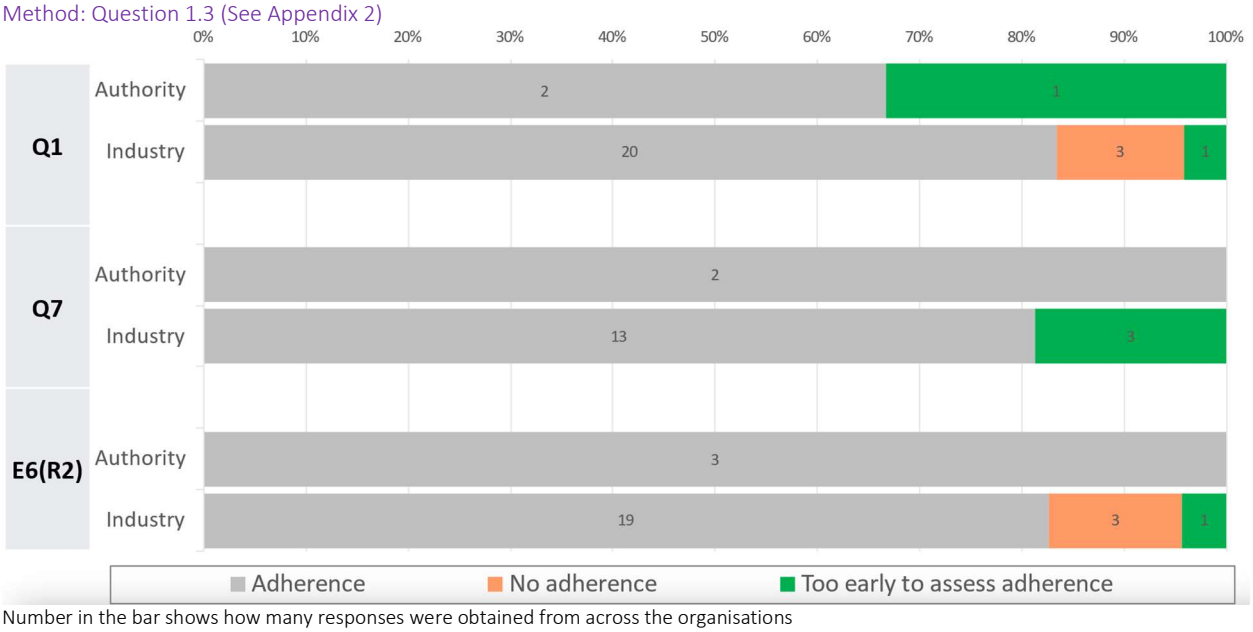
Number in the bar shows how many responses were obtained from across the organisations

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.

Key Messages

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

Method: Question 1.3 (See Appendix 2)



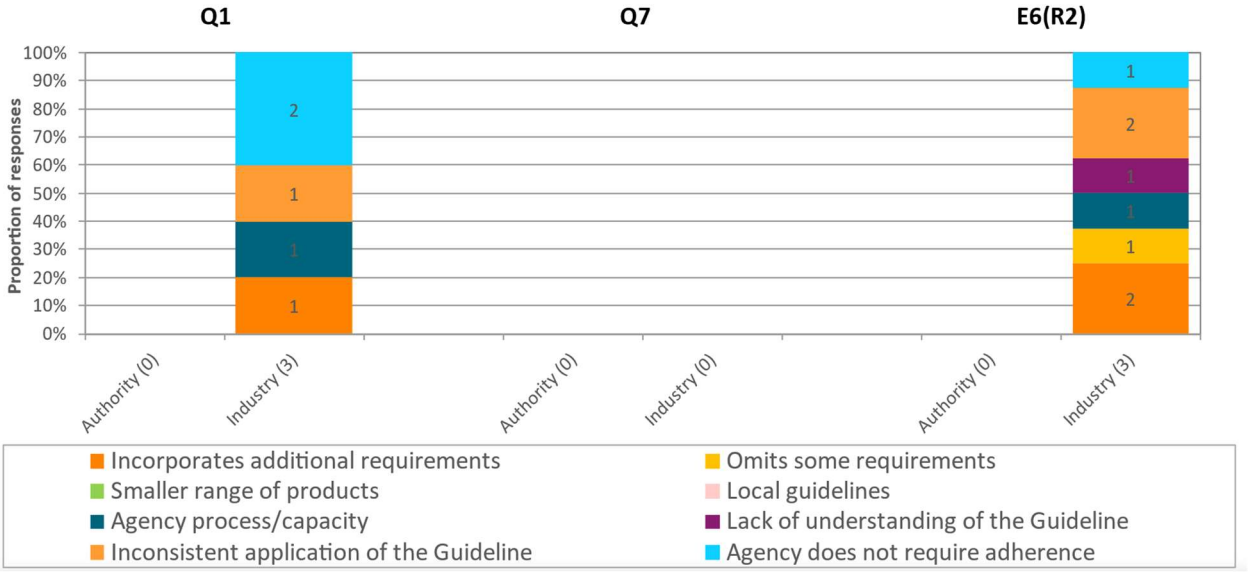
Number in the bar shows how many responses were obtained from across the organisations

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 E6(R2) only)
- The rationale for lack of adherence was mixed

Method: Question 2 (See Appendix 2)



(n) = number of companies or authorities

Number in the bar shows how many responses were obtained from across the organisations

Blank = EITHER if number of companies <3, no data were shown OR not applicable based on how the previous question was answered

RESULTS PART 4: SUMMARY TABLES - ICH REGULATORY MEMBERS AND OBSERVERS

RESULTS PART 4.1: 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 Non-Founding, Non-Standing Regulatory Members

Key Messages

- Seven out of the ten authorities implemented all of the Tier 2 Guidelines
- All of the authorities implemented the E2A, E2D and M1 Guidelines

Guideline	E2A	E2B	E2D	M1	M4
% of authorities where the Guideline was implemented (no. of authorities out of 10)	100% (10)	70% (7)	100% (10)	100% (10)	90% (9)

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

B. Implementation of Tier 3 Guidelines by ICH Non-Founding, Non-Standing Regulatory Members

Key Messages for all Guidelines

- Seven out of the ten authorities implemented at least 40 of the 56 Tier 3 Guidelines (71%; 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

Key Messages for Quality Guidelines

- Five out of the ten authorities implemented at least 16 of the 19 Tier 3 Quality Guidelines (84%; data not shown but were shared with participants)
- All of the authorities implemented Q2(R1) and Q5C

Guideline	Q2(R1)	Q3A(R2)	Q3B(R2)	Q3C(R8)	Q3D(R2)	Q4B	Q5A(R1)	Q5B	Q5C	Q5D	Q5E	Q6A	Q6B	Q8(R2)	Q9	Q10	Q11	Q12	Q13
% of authorities where the Guideline was implemented (no. of authorities out of 10)	100% (10)	80% (8)	80% (8)	80% (8)	70% (7)	50% (5)	90% (9)	70% (7)	100% (10)	80% (8)	90% (9)	90% (9)	80% (8)	80% (8)	70% (7)	90% (9)	70% (7)	10% (1)	10% (1)

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

b) Safety Guidelines

Key Messages for Safety Guidelines

- Four out of the ten authorities implemented all of the Tier 3 Safety Guidelines (data not shown but were shared with participants)

Guideline	S1A	S1B(R1)	S1C(R2)	S2(R1)	S3A	S3B	S4	S5(R3)	S6(R1)	S7A	S7B	S8	S9	S10	S11
% of authorities where the Guideline was implemented (no. of authorities out of 10)	80% (8)	50% (5)	70% (7)	70% (7)	70% (7)	70% (7)	80% (8)	70% (7)	80% (8)	80% (8)	70% (7)	70% (7)	80% (8)	60% (6)	60% (6)

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

c) Efficacy Guidelines

Key Messages for Efficacy Guidelines

- Four out of the ten authorities implemented at least 16 of the 18 Tier 3 Efficacy Guidelines (89%; data not shown but were shared with participants)
- All of the authorities implemented E2C(R2) and E2E

Guideline	E1	E2C(R2)	E2E	E2F	E3	E4	E5(R1)	E7	E8(R1)	E9(R1)	E10	E11(R1)	E14	E15	E16	E17	E18	E19
% of authorities where the Guideline was implemented (no. of authorities out of 10)	70% (7)	100% (10)	100% (10)	70% (7)	90% (9)	70% (7)	80% (8)	70% (7)	50% (5)	60% (6)	80% (8)	90% (9)	60% (6)	40% (4)	60% (6)	80% (8)	60% (6)	30% (3)

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

d) Multidisciplinary Guidelines

Key Messages for Multidisciplinary Guidelines

- Six out of the ten authorities implemented at least three of the four Tier 3 Multidisciplinary Guidelines (75%; data not shown but were shared with participants)

Guideline	M3(R2)	M7(R1)	M9	M10
% of authorities where the Guideline was implemented (no. of authorities out 10)	60% (6)	70% (7)	70% (7)	40% (4)

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

C. Implementation of selected new Tier 3 Guidelines by ICH Founding and Standing Regulatory Members

Key Messages

- All five authorities implemented at least six of the seven selected Tier 3 Guidelines (86%; data not shown but were shared with participants)
- All of the authorities implemented E8(R1), Q3C (R8), Q3D(R2) and S1B (R1)

Guideline	E8 (R1)	E19	M10	Q3C (R8)	Q3D (R2)	Q13	S1B (R1)
% of authorities where the Guideline was implemented (no. of authorities out of 5)	100% (5)	80% (4)	80% (4)	100% (5)	100% (5)	80% (4)	100% (5)

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

D. Implementation of Tier 1 Guidelines by ICH Observers

Key Messages

- One authority implemented all Tier 1 Guidelines
- All three authorities implemented Q1 and E6(R2) Guidelines

Guideline	Q1	Q7	E6(R2)
% of authorities where the Guideline was implemented (no. of authorities out of 3)	100% (3)	33% (1)	100% (3)

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

RESULTS PART 4.2: SUMMARY TABLES - 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 Non-Founding, Non-Standing Regulatory Members

Key Messages

- Six out of the ten authorities adhered to all of the Tier 2 Guidelines
- E2A and M1 were considered as adhered to by all of the authorities

Guideline	Adherence category	E2A	E2B	E2D	M1	M4
% of authorities (no. of authorities out of 10)	Adherence	100% (10)	60% (6)	90% (9)	100% (10)	90% (9)
	No adherence	0	0	0	0	0
	Too early to assess adherence	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)

B. Adherence to Tier 3 Guidelines by ICH Non-Founding, Non-Standing Regulatory Members

Key Messages for all Guidelines

- Across all ten authorities, adherence to the Tier 3 Guidelines ranged from 5%-95%; where adherence was low, this was due to the Guideline being not implemented and/or too early to assess adherence
- Five out of the ten authorities adhered to at least 42 of the 56 Tier 3 Guidelines (75%; data not shown but were shared with participants)
- The results for the Tier 3 Guidelines were organised below according to the topic

a) Quality Guidelines

Key Messages for Quality Guidelines

- Most of the Quality Guidelines were considered as adhered to by seven or more authorities

Guideline	Adherence category	Q2(R1)	Q3A(R2)	Q3B(R2)	Q3C(R8)	Q3D(R2)	Q4B	Q5A(R1)	Q5B	Q5C	Q5D	Q5E	Q6A	Q6B	Q8(R2)	Q9	Q10	Q11	Q12	Q13
% of authorities (no. of authorities out of 10)	Adherence	80% (8)	80% (8)	80% (8)	80% (8)	50% (5)	40% (4)	70% (7)	70% (7)	100% (10)	80% (8)	80% (8)	60% (6)	70% (7)	60% (6)	50% (5)	50% (5)	50% (5)	0	0
	No adherence	0	0	0	0	10% (1)	0	0	0	0	0	0	0	0	10% (1)	0	10% (1)	0	0	0
	Too early to assess adherence	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	10% (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)

b) Safety Guidelines

Key Messages for Safety Guidelines

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

Guideline	Adherence category	S1A	S1B(R1)	S1C(R2)	S2(R1)	S3A	S3B	S4	S5(R3)	S6(R1)	S7A	S7B	S8	S9	S10	S11
% of authorities (no. of authorities out of 10)	Adherence	70% (7)	30% (3)	70% (7)	70% (7)	70% (7)	70% (7)	80% (8)	60% (6)	80% (8)	70% (7)	60% (6)	70% (7)	80% (8)	60% (6)	60% (6)
	No Adherence	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Too early to assess adherence	10% (1)	10% (1)						10% (1)			10% (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)

c) Efficacy Guidelines

Key Messages for Efficacy Guidelines

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

Guideline	Adherence category	E1	E2C(R2)	E2E	E2F	E3	E4	E5(R1)	E7	E8(R1)	E9(R1)	E10	E11(R1)	E14	E15	E16	E17	E18	E19
% of authorities (no. of authorities out of 10)	Adherence	60% (6)	90% (9)	90% (9)	60% (6)	90% (9)	60% (6)	60% (6)	70% (7)	40% (4)	30% (3)	70% (7)	70% (7)	50% (5)	40% (4)	50% (5)	50% (5)	60% (6)	20% (2)
	No Adherence	0	10% (1)	0	0	0	0	0	0	0	0	0	0	0	0	0	10% (1)	0	0
	Too early to assess adherence	0	0	0	0	0	10% (1)	10% (1)	0	0	0	10% (1)	0	0	0	10% (1)	10% (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)

d) Multidisciplinary Guidelines

Key Messages for Multidisciplinary Guidelines

- M3(R2) and M7(R1) Guidelines were considered as adhered to by six of the authorities

Guideline	Adherence category	M3(R2)	M7(R1)	M9	M10
% of authorities (no. of authorities out of 10)	Adherence	60% (6)	60% (6)	40% (4)	20% (2)
	No Adherence	0	0	0	0
	Too early to assess adherence	0	0	10% (1)	20% (2)

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)

C. Adherence to selected new Tier 3 Guidelines for ICH Founding and Standing Regulatory Members

Key Messages

- E8(R1), Q3C(R8) and Q3D(R2) were considered as adhered to by four or more of the authorities

Guideline	Adherence category	E8 (R1)	E19	M10	Q3C (R8)	Q3D (R2)	Q13	S1B (R1)
% of authorities where the Guideline was implemented (no. of authorities out of 5)	Adherence	80% (4)	0	20% (1)	100% (5)	80% (4)	20% (1)	40% (2)
	No Adherence	0	0	0	0	0	0	0
	Too early to assess adherence	20% (1)	40% (2)	0	0	20% (1)	40% (2)	40% (2)

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 (See Appendix 2 and Appendix 3)

D. Adherence of Tier 1 Guidelines by ICH Observers

Key Messages

- Two Observers adhere to the Q1 and E6(R2) Guidelines

Guideline	Adherence category	Q1	Q7	E6(R2)
% of authorities (no. of authorities out of 3)	Adherence	67% (2)	33% (1)	67% (2)
	No Adherence	0	0	33% (1)
	Too early to assess adherence	33% (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)

CONCLUSION

The results demonstrate a strong level of implementation and adherence to the ICH Guidelines with a good alignment between the perception of the pharmaceutical companies and the self-declaration from the assessed authorities.

ICH Non-Founding, Non-Standing Regulatory Members: Tier 2 Guidelines were implemented and adhered to by most of the ICH Non-Founding, Non-Standing Regulatory Members. For Tier 3 Guidelines, there is evidence that most of the Guidelines in this Tier were implemented and adhered to by the authorities, or that they are in the process of implementation or too early to assess adherence. By comparing industry results from previous studies, in general, the studies demonstrated, that the implementation of Tier 2 and Tier 3 Guidelines increased in the recent years.

ICH Founding and Standing Regulatory Members: Results showed that the ICH Founding and Standing Regulatory Members implemented and adhered to most of the assessed Tier 3 Guidelines, particularly E8(R1), Q3C(R8) and Q3D(R2).

ICH Observers: Results showed that the ICH Observers implemented and adhered to most of the 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. The regulator makes publicly available 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 does not provide any objective	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 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,

Term	Definition	Comments
	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.	in exceptional cases, may be accepted if objectively justified.
Adherence[12]	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).

[12] 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 ICH GUIDELINES

ICH Tier 1 Guidelines

Q1
Q7
E6(R2)

ICH Tier 2 Guidelines

E2A
E2B(R3)
E2D
M1
M4

ICH Tier 3 Guidelines

E1
E2C(R2)
E2E
E2F
E3
E4
E5(R1)
E7
E8(R1)*
E9(R1)
E10
E11(R1)
E14
E15
E16
E17
E18
E19*

M3(R2)
M7(R1)

M9
M10*

Q2(R1)
Q3A(R2)
Q3B(R2)
Q3C(R8)*
Q3D(R2)*
Q4B
Q5A(R1)
Q5B
Q5C
Q5D
Q5E
Q6A
Q6B
Q8(R2)
Q9
Q10
Q11
Q12

Q13*

S1A
S1B(R1)*
S1C(R2)
S2(R1)
S3A
S3B
S4
S5(R3)
S6(R1)
S7A
S7B
S8
S9
S10
S11

***New addition comparing to previous 2020-2021 survey, assessed for Founding and Standing Regulatory Members.**

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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