

2019 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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CIRS - The Centre for Innovation in Regulatory Science Limited - is a neutral, independently managed UK based subsidiary company, forming part of Clarivate Analytics (UK) Limited. CIRS' mission is to maintain a leadership role in identifying and applying scientific principles for the purpose of advancing regulatory and HTA policies and processes. 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 medical products through these activities. This is CIRS' purpose. CIRS is operated solely for the promotion of its purpose. 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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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. Since its inception in 1990, ICH has gradually evolved, to respond to the increasingly global face of drug development. 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 the introduction of organisational changes in October 2015, ICH, as an independent, international, non-profit organisation, has grown and now includes sixteen Members and thirty-two Observers.

Acknowledgments

With special thanks to the ICH Implementation Subcommittee, chaired by Petra Doerr and Jerry Stewart, as well as to the participating pharmaceutical companies, ICH Regulatory Authority Members and Observers.

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Version 1.4

EXECUTIVE SUMMARY

Background: According to the ICH Articles of Association, the regulatory members of ICH are expected to implement ICH Guidelines. 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 in this regard providing current state of play of the implementation and adherence to the ICH Guidelines.

Objectives: The goal of this survey was to undertake a gap analysis by obtaining authorities' and companies' viewpoint on the implementation and adherence to the ICH Guidelines. The long-term objectives would be to establish a sustainable ICH-driven mechanism to assess Guidelines over time to inform ICH stakeholders on multiple areas as specified in the goals.

Method: An online questionnaire and definitions were developed by Centre for Innovation in Regulatory Science (CIRS) in collaboration with ICH and the ICH Implementation Subcommittee. The questionnaire was completed by companies (assessing all the participating authorities) and by authorities (assessing themselves only) in order to undertake a gap analysis.



Assessment of implementation/adherence across 11 ICH Guidelines



15 ICH Regulatory Authority Members/ Observers undertook a self-assessment



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

The following authorities participated: All ICH Regulatory Members (Founding Regulatory, Standing Regulatory, Regulatory) and the following Observers (voluntary basis): GHC (GCC central drug registration program); NPRA, Malaysia; SAHPRA, South Africa; TITCK, Turkey and Roszdravnadzor, Russia. *The following Guidelines were assessed:* Tier 1: Q1, Q7, E6(R2); Tier 2: E2A, E2B, E2D, M1, M4 and Tier 3: M3(R2), M8, E17 Guidelines.

Results: In general, there was strong evidence of adequate implementation and adherence to the Guidelines.

- *ICH Guideline implementation status:* implementation of Guidelines based on self-declaration from the authorities was highest across Founding/Standing Regulatory Members, followed by Regulatory Members and Observers. Company perception of implementation status was generally aligned with agency perception, but some differences were noted – e.g. E2B and M8.
- *Adequacy of ICH Guideline implementation (based on modifications):* In general, authorities declared that Guidelines were mostly implemented without modifications (=adequate implementation), though some Guidelines had more amendments e.g. Q1, Q7, E2D. Where there were modifications, all the authorities felt that these were objectively justified (=adequate implementation) and in general, company perception and authority self-declaration were aligned.
- *Adherence to ICH Guidelines:* Where implementation was confirmed, all the authorities felt that they were adhering to the Guidelines i.e. adequately applying them in day-to-day practice. In general, company perception and authority self-declaration were aligned or too early to assess based on limited experience e.g. E17.

Conclusion: Phase 2a of the study demonstrated that a comprehensive perception survey could be undertaken, where the response rate was excellent indicating strong interest in this initiative. Responses, supported by evidence-based rationale, identified general agreement between agencies and companies, but with some divergences. These differences were largely supported by justifications and specific examples, whereas gaps and divergences could be used to support training and capacity building efforts across agencies and companies.

It should be noted that there are some limitations to the data and that there is a possibility that companies may have misrepresented the status of implementation of a guideline in a region based on either a misunderstanding of the survey question or limited experience with the Agency. For example, some companies indicated that a guideline was not adhered to in instances where modifications were anticipated and well justified e.g. translation requirements. Therefore, while it may be possible to use the results to support decisions related to ICH membership applications, the transparent communication of Guideline implementation status as well as future revisions of ICH Guidelines, careful consideration should be given as to the appropriate use of the survey results and also whether the results can be verified.

BACKGROUND

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 in this regard providing current state of play of the implementation and adherence to the ICH Guidelines. ICH Regulators are expected to implement all ICH Guidelines in the future and are encouraged to do so through direct reference to the ICH Guidelines. In order to achieve harmonisation, adding regulatory requirements to or omitting important regulatory requirements from the ICH Guidelines should be avoided in the implementation process unless these deviations are justified on objective grounds. It is also recognised by ICH that not all Guidelines are of equal importance and therefore, the ICH Guidelines have been prioritised as Tier 1, 2 and 3.

For the Regulatory Members, which have not been Members of ICH prior to the establishment of the ICH Association, it is recognised that implementing all the Guidelines will take some time and that adherence can only be assessed 2-3 years following the end of the process of implementation. The focus of this assessment is therefore on the adequacy of implementation and adherence to already implemented Guidelines.

On behalf of ICH it was agreed by the ICH Founding Industry Members that a pilot study, Phase 1, would be conducted in 2017 to obtain feedback from companies on their perspective and perception of the implementation to the ICH Guidelines. An independent third party (CIRS) developed and conducted 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.

The aim of this phase of the project described in this report, namely Phase 2a, was to build on the outcomes and lessons learned from Phase 1. ICH again selected CIRS to conduct the Phase 2a study to monitor the adequacy of implementation and adherence to ICH Guidelines by regulatory authorities. CIRS subsequently developed the study questionnaire and the online data collection tool (DCT) in collaboration with ICH. The questionnaire was completed by companies and the authorities (assessing themselves only) in order to undertake a gap analysis.

Goals and Objectives

The goal of this study was to obtain authorities' and companies' viewpoint on the regulatory implementation and adherence to the ICH Guidelines in order to undertake a gap analysis. The overall study objectives were to:

- Inform the ICH decision making related to Regulator membership applications
- Provide ICH Members and Observers with additional data for internal considerations
- Identify regulatory training and capacity building needs
- Inform related industry and agency initiatives

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. It should be noted that the responses presented in this report were analysed by CIRS and shared with the participating authorities and were also presented at the 2019 ICH Assembly and Management Committee Meetings held in Amsterdam.

METHOD

CIRS developed a study questionnaire and an online data collection tool (DCT) in collaboration with ICH. The ICH Implementation Subcommittee also developed jointly with CIRS definitions for ‘implementation’ and ‘adherence’ to Guidelines (see Appendix 1). The questionnaire was completed during February-April 2019 by companies (assessing all the participating authorities) and by authorities (assessing themselves only) in order to undertake a gap analysis. Four short questions were used to assess the implementation/ adherence to each of the Guidelines within each authority (see Appendix 2 for full questionnaire):

1. Implementation status of the Guideline (based on authority declaration): Not implemented; In the process of implementation; Implemented, Not applicable
2. Modifications to the ICH Guideline and whether these are objectively justified by the authority (i.e. provide clarity and facilitate implementation by industry, but not increase burden)
3. Adherence status to the Guideline (based on authority practice): Adhered to; Not adhered to; Too early to assess due to limited experience
4. Rationale for selection if ‘not implemented’ or ‘not adhered to’ were selected, including specific evidence and examples

The following ICH Guidelines were assessed:

- **Tier 1:**
 - Q1 – Stability (*all subparts considered*)
 - Q7 – Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients
 - E6(R2) – Good Clinical Practice (GCP)
- **Tier 2**
 - 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 3¹**
 - M3(R2) - Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals
 - M8 - Electronic Common Technical Document (eCTD)
 - E17 - General principles for planning and design of Multi-Regional Clinical Trials

The following organisations participated in order to undertake a gap analysis:

- **15 Regulatory Authorities** (assessing themselves only) from across:

ICH Founding/Standing Regulatory Members

- EC, Europe (*centralised procedure with EC, EMA*)
- FDA, United States
- MHLW/PMDA, Japan
- Health Canada, Canada
- Swissmedic, Switzerland

ICH Regulatory Members

- ANVISA, Brazil
- NMPA, China
- HSA, Singapore
- MFDS, Republic of Korea
- TFDA, Chinese Taipei

ICH Observers (voluntary basis)

- GHC, *GCC central drug registration program*
- NPRA, Malaysia
- Roszdravnadzor, Russia
- SAHPRA, South Africa
- TITCK, Turkey

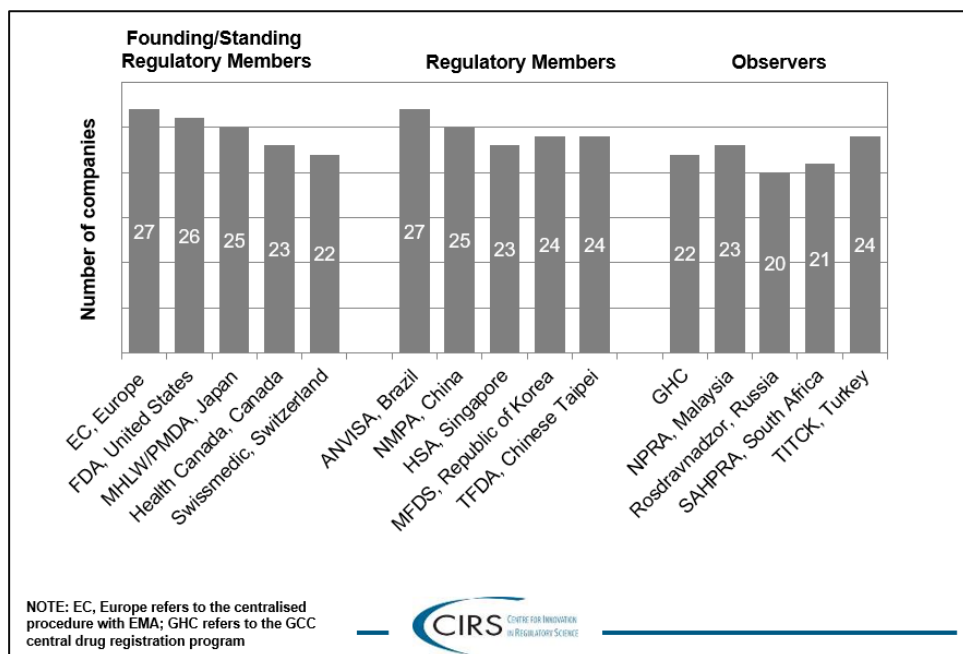
- **52 Major Pharmaceutical Companies** (assessing all the participating authorities) were invited to participate from across PhRMA, EFPIA, JPMA, BIO and IGBA companies.

¹ The listed Tier 3 Guidelines do not constitute the entire Tier 3 Guidelines, but only a small subset identified for inclusion in the first implementation survey.

RESULTS PART 1: CHARACTERISTICS OF PARTICIPATING COMPANIES

All in all, out of the 52 invited companies, 32 provided responses across the 15 authorities.

Method: Question 1i (see Appendix 2)

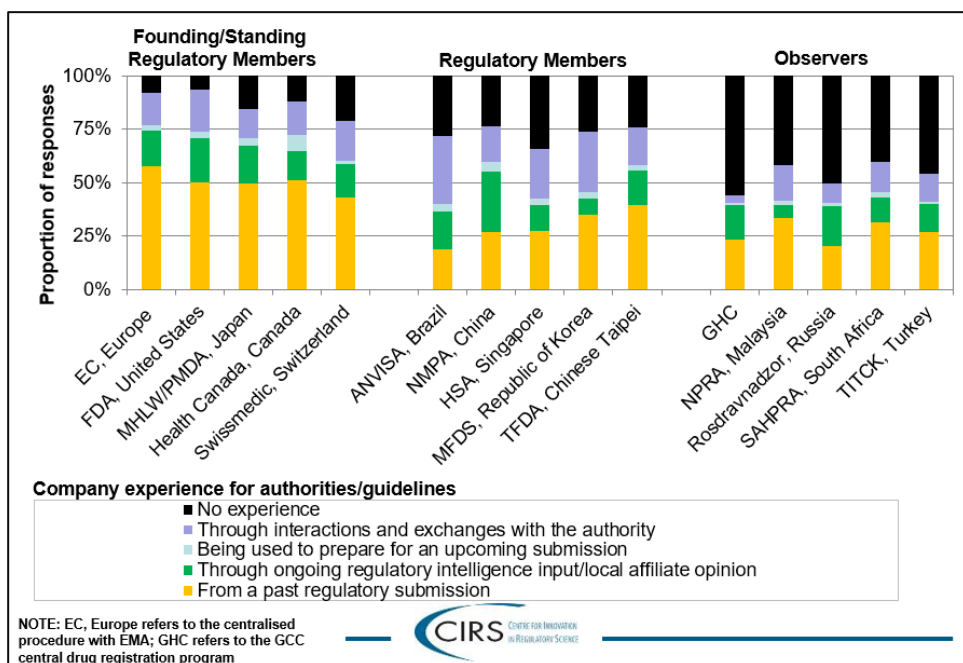


Experience: Companies were asked for their most recent/relevant experience regarding a Guideline for a selected authority.

Key Messages

The majority of the companies had experience across all the authorities, where industry experience was highest across Founding/Standing Regulatory Members, followed by Regulatory Members and Observers.

Method: Question 1a (see Appendix 2)



Only companies that had experience in a specific authority (through interactions with the agency or a regulatory submission) were invited to respond to the rest of the questionnaire, noting that responses in the subsequent questions were intended to relate to a company's general experience, and not only to the single submission/experience selected.

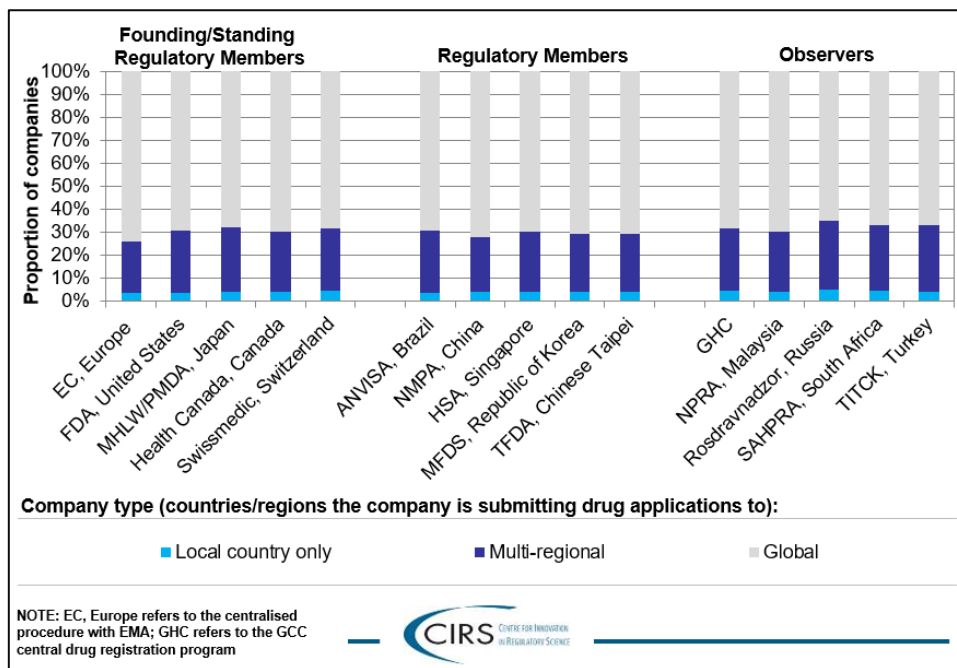
RESULTS PART 1: CHARACTERISTICS OF PARTICIPATING COMPANIES (CONT.)

Company Type: Participating companies were categorised according to the countries/regions the company is submitting drug applications to i.e. local, regional, global.

Key Messages

Approximately 70% companies were global, and this was consistent across the different authorities.

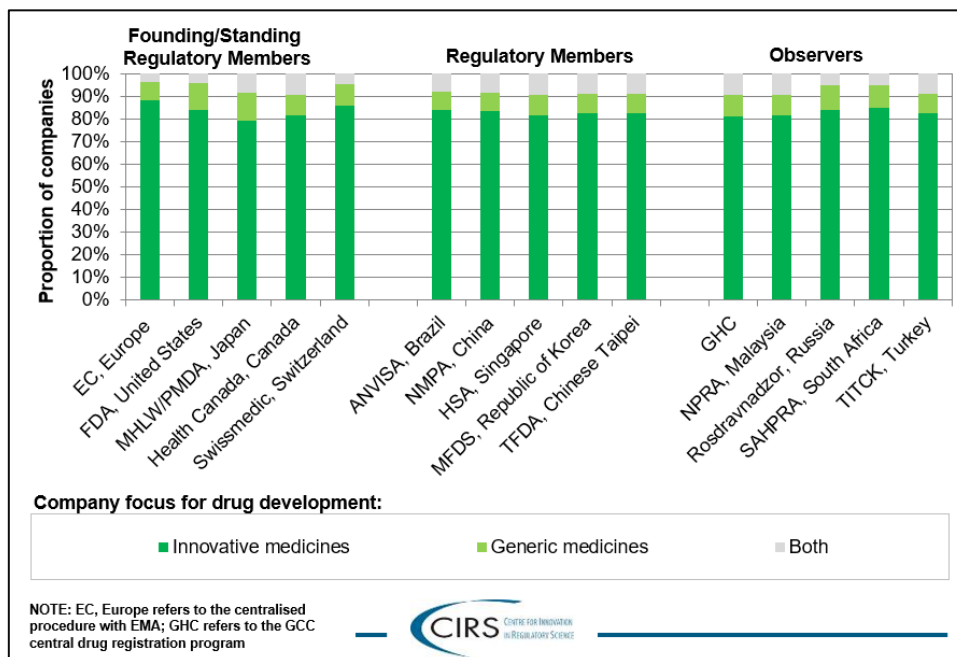
Method: Question 1i (see Appendix 2)



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

Key Messages Approximately 80% companies focused on innovative companies.

Method: Question 1ii (see Appendix 2)

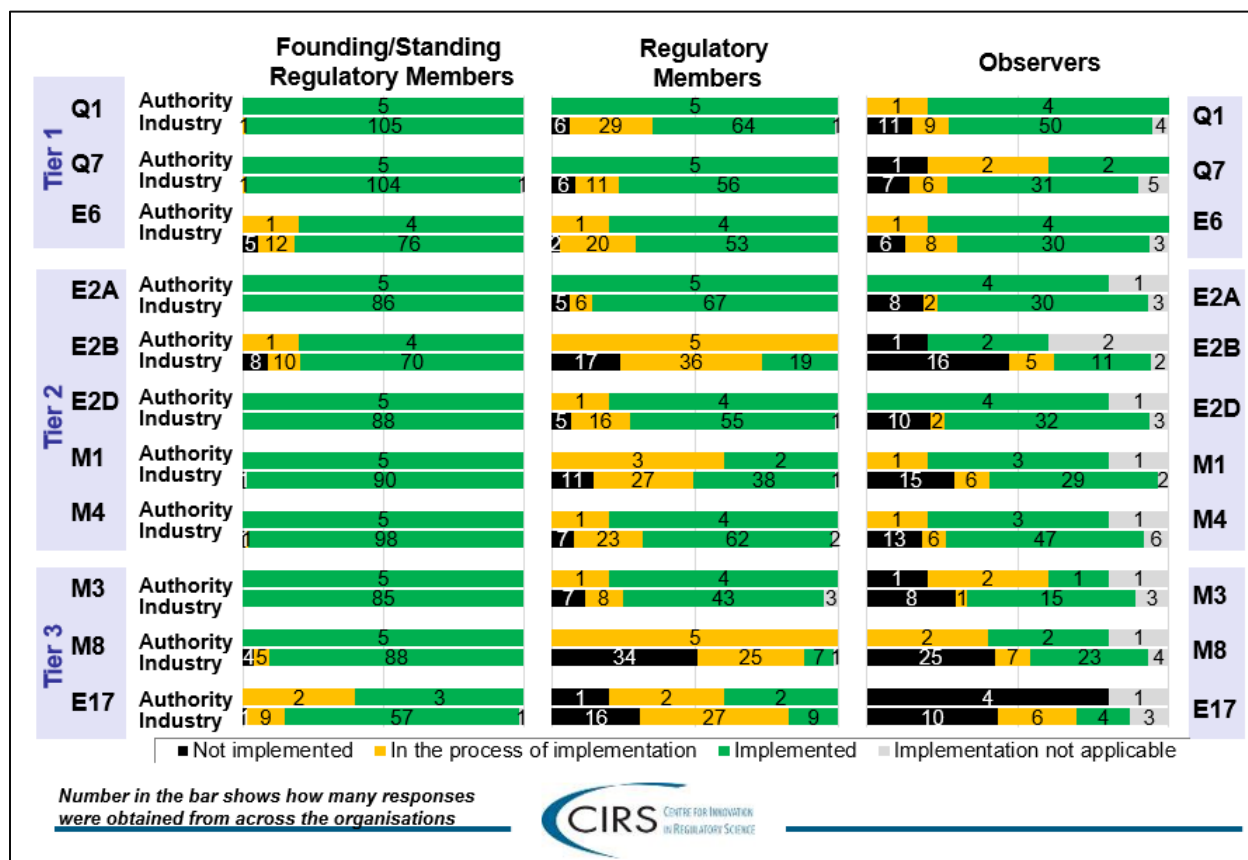


RESULTS PART 2: GUIDELINE IMPLEMENTATION

Implementation status: Authorities and companies were asked on their views on the implementation status for selected Guidelines. The first bar in the graph below corresponds to the self-declaration by the authority and the second bar shows the number of responses across the companies. Authorities were combined according to their ICH membership status, and Guidelines were organised according to Tier 1, 2 and 3. The combined responses across all the 15 participating authorities have also been summarised in Appendix 3.

Key Messages

- Implementation of Guidelines based on self-declaration from the authorities was highest across Founding/Standing Regulatory Members, where the Guidelines were generally perceived as implemented, followed by Regulatory Members and Observers, where the implementation was either in process (reached a specific milestone), has not yet started (i.e. not implemented) or that the Guideline is not applicable based on a justification.
- Implementation was highest across Tier 1 Guidelines, followed by Tier 2 and Tier 3.
- Company perception of implementation status was generally aligned with agency perception, but some differences were noted – e.g. E2B and M8, which should be explored further.
- Such divergences could be due to differences of interpretation regarding what constitutes implementation. Other rationales could be due to a time lag, or incomplete knowledge within organisations, which could suggest need for education and/or better communication of authority status regarding Guideline implementation.



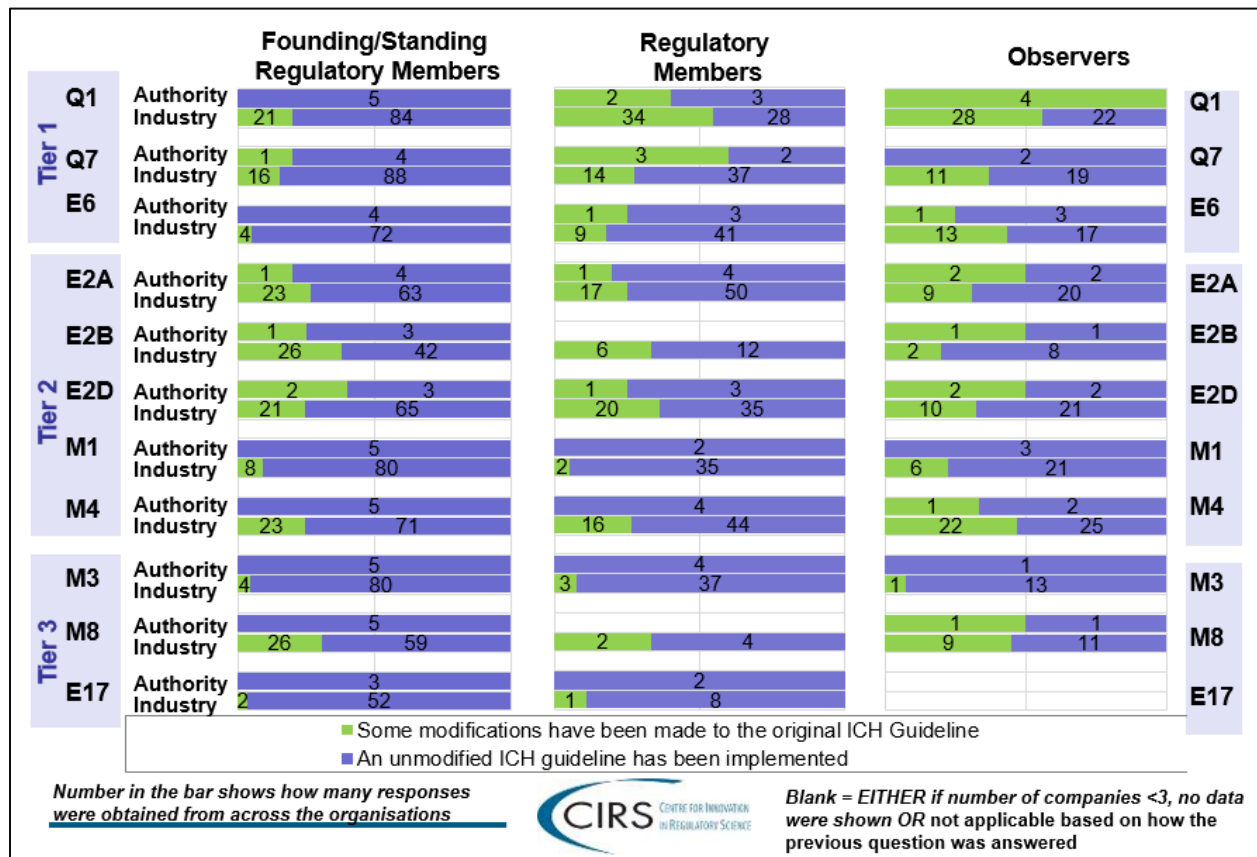
Method: Question 1 (See Appendix 2)

RESULTS PART 2: GUIDELINE IMPLEMENTATION (CONT.)

Modifications to the implemented Guidelines: Organisations which responded that a Guideline was ‘implemented’ were then asked whether an unmodified ICH Guideline was implemented (which corresponds to adequate implementation) or whether modifications have been made to the original ICH Guideline either by adding or altering certain elements, concepts or principles. It should be noted that modifications to ICH Guidelines may be acceptable and can still result in adequate implementation as long as the modifications are objectively justified - this was queried in the next question. Nevertheless, the purpose of this question was to determine whether any modifications, justified or unjustified have been made.

Key Messages

- In general, authorities declared that Guidelines were mostly implemented without modifications (=adequate implementation).
- The proportion of modifications was highest for Observers, followed by Regulatory Members and finally Founding/Standing Regulatory Members. In addition, some Guidelines had more modifications e.g. Q1, Q7, E2D.
- Overall, company perception and authority self-declaration was aligned.
- Some differences were noted, which could suggest differences in interpretation of the Guidelines. These seem to be primarily authority-specific issues, but certain Guidelines had more divergence e.g. M4.



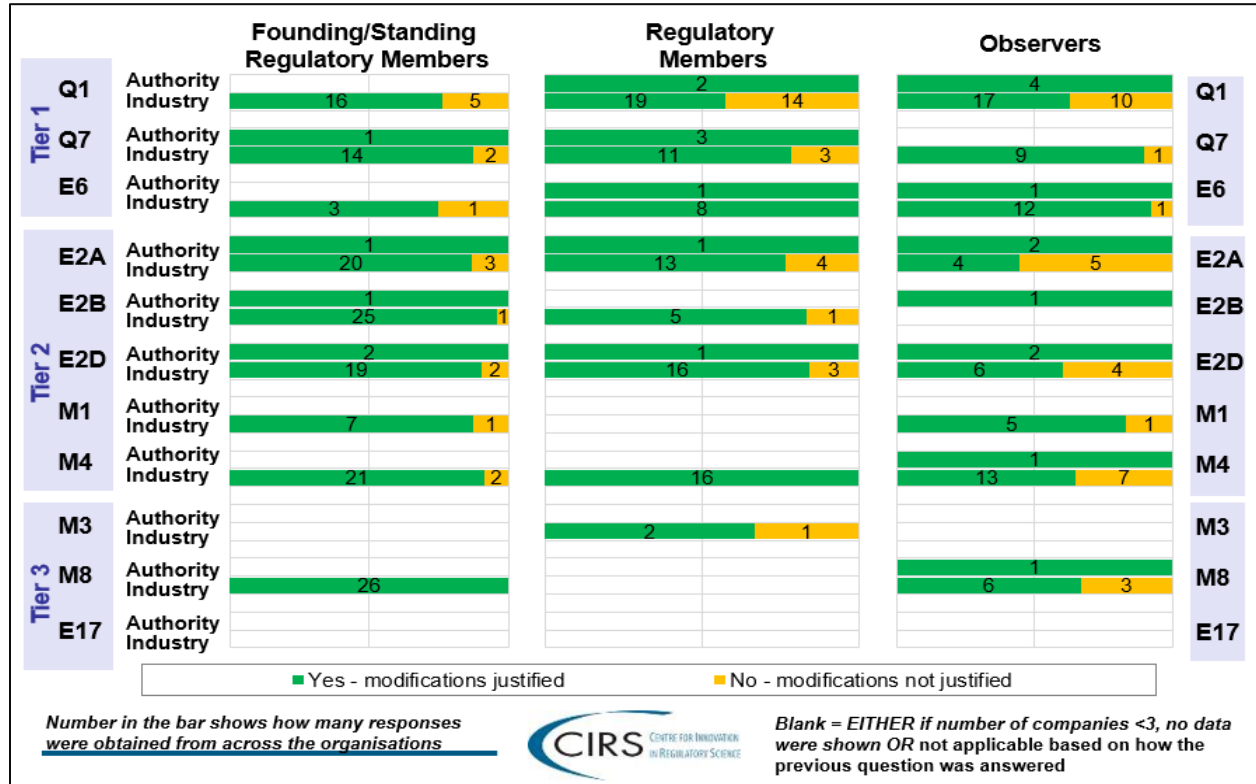
Method: Question 1.2 (See Appendix 2)

RESULTS PART 2: GUIDELINE IMPLEMENTATION (CONT.)

Justifications to the modified Guidelines: Organisations which responded that ‘a modified ICH Guideline has been implemented’, were asked whether the modifications were objectively justified by the authority, which also corresponds to adequate implementation. This may include implementation of the Guideline to 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. Modifications which are not objectively justified by adding regulatory requirements result in inadequate implementation. Omitting important regulatory requirements may also lead to inadequate implementation.

Key Messages

- Where there were modifications, all the authorities felt that these were justified i.e. to provide clarity and facilitate implementation by industry, but do not increase regulatory requirements.
- In general, company perception and agency self-declaration was aligned. The company perception suggested furthermore that the introduction of alleged unjustified modifications to Guidelines was low, noted mainly across Observers, followed by Regulatory Members.
- Overall, minor divergences were noted between authority/company responses and could have multiple reasons: 1) In cases where the number of divergent companies was low, this could suggest a company specific experience and potential need for internal training/education for the company; 2) Where the number of divergent companies was more considerable, it could suggest a need for internal considerations by agencies relating to Guideline understanding and/or interpretation.
- Certain Guidelines had in general more modifications that were perceived unjustified - suggests need for clarification relating to the Guideline itself e.g. Q1.



Method: Question 1.2.1 (See Appendix 2)

RESULTS PART 2: GUIDELINE IMPLEMENTATION (CONT.)

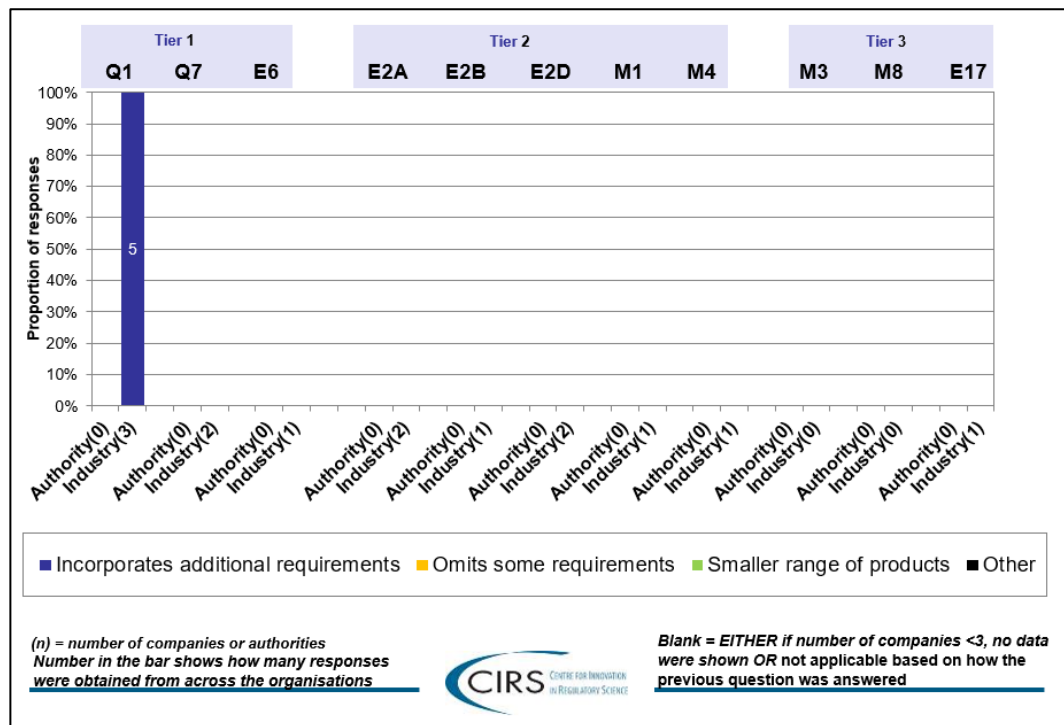
Rationale for inadequate implementation: The three graphs below outline, for Founding/Standing Regulatory Members, followed by Regulatory Members and Observers respectively, the rationale for selecting that the modifications to the Guidelines were not considered justified, thereby resulting in inadequate implementation.

Key Messages

- Overall, looking across all the authorities, the Guideline with the highest response rate for lack of adequate implementation was Q1. More specifically, across the Founding/Standing Regulatory Members, rationale was provided by companies for Q1, for Regulatory Members it was Q1 and E2A, and finally Q1, E2A, E2D and M4 for Observers (number of companies > 3).
- The main rationale for inadequate implementation was due to ‘Incorporating additional requirements beyond those defined in the ICH Guideline without objective justification in cases where clear guidance is provided’. The second most common rationale was the fact the Guideline ‘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’.
- Analysis of free text comments for Q1 identified high level reasons given for the rational selected across all the authorities:
 - Site specific stability requirements that go beyond ICH requirements (n=4)
 - Timing and length of testing (n=4)
 - Local or regional requirements (n=4)
 - Extra analytical analysis (n=4).

Founding / Standing Regulatory Members

Only Q1 had n > 3 companies that provided rationale for inadequate implementation, which was due to additional requirements.



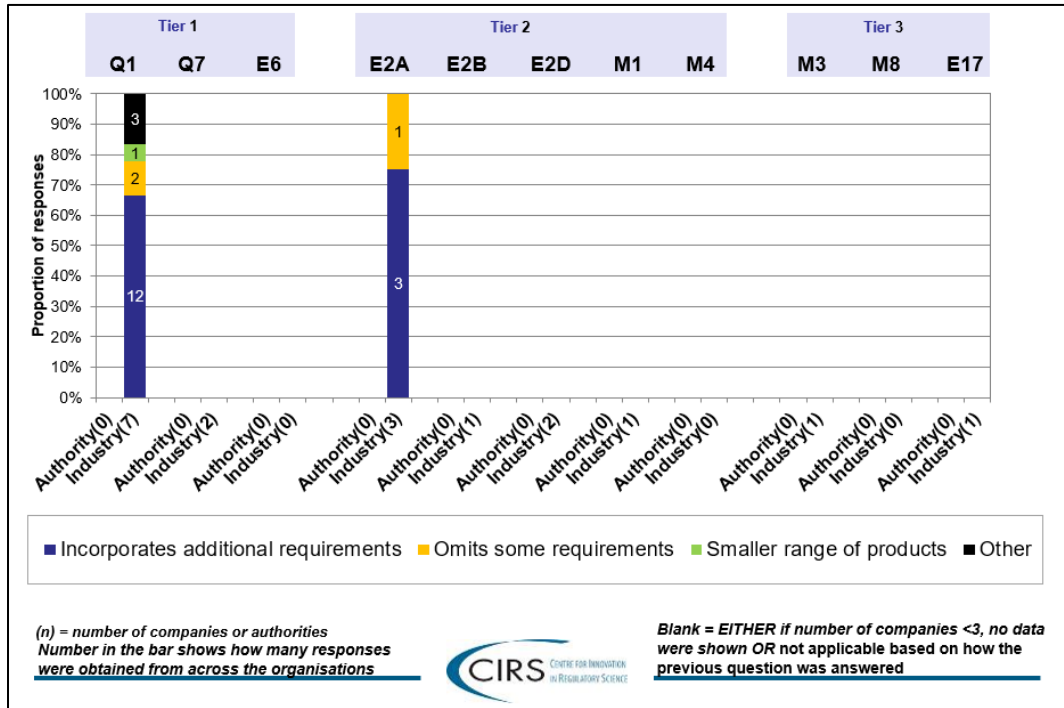
Method: Question 2 (See Appendix 2)

RESULTS PART 2: GUIDELINE IMPLEMENTATION (CONT.)

Rationale for inadequate implementation (cont.)

Regulatory Members

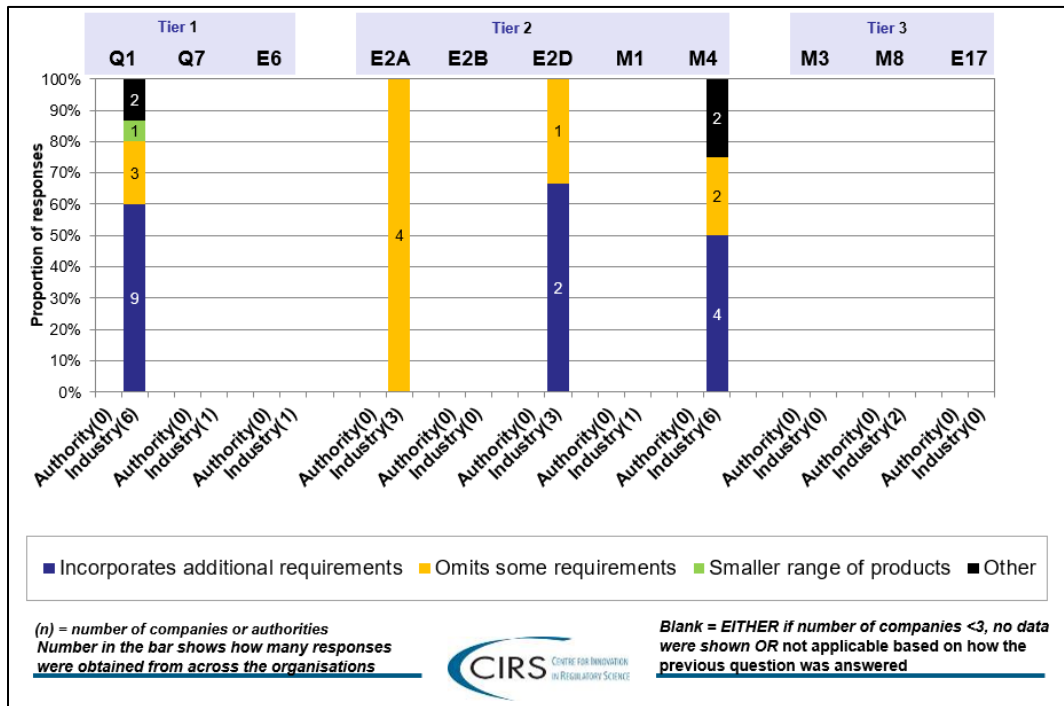
Both Q1 as well as E2A had n>3 companies providing responses, mostly around additional requirements, though other reasons such as omitting requirements were also suggested.



Method: Question 2 (See Appendix 2)

Observers

Q1, E2A, E2D as well as M4 had n>3 companies providing responses, mostly around additional requirements, followed by omitting requirements (particularly E2A) were also suggested.



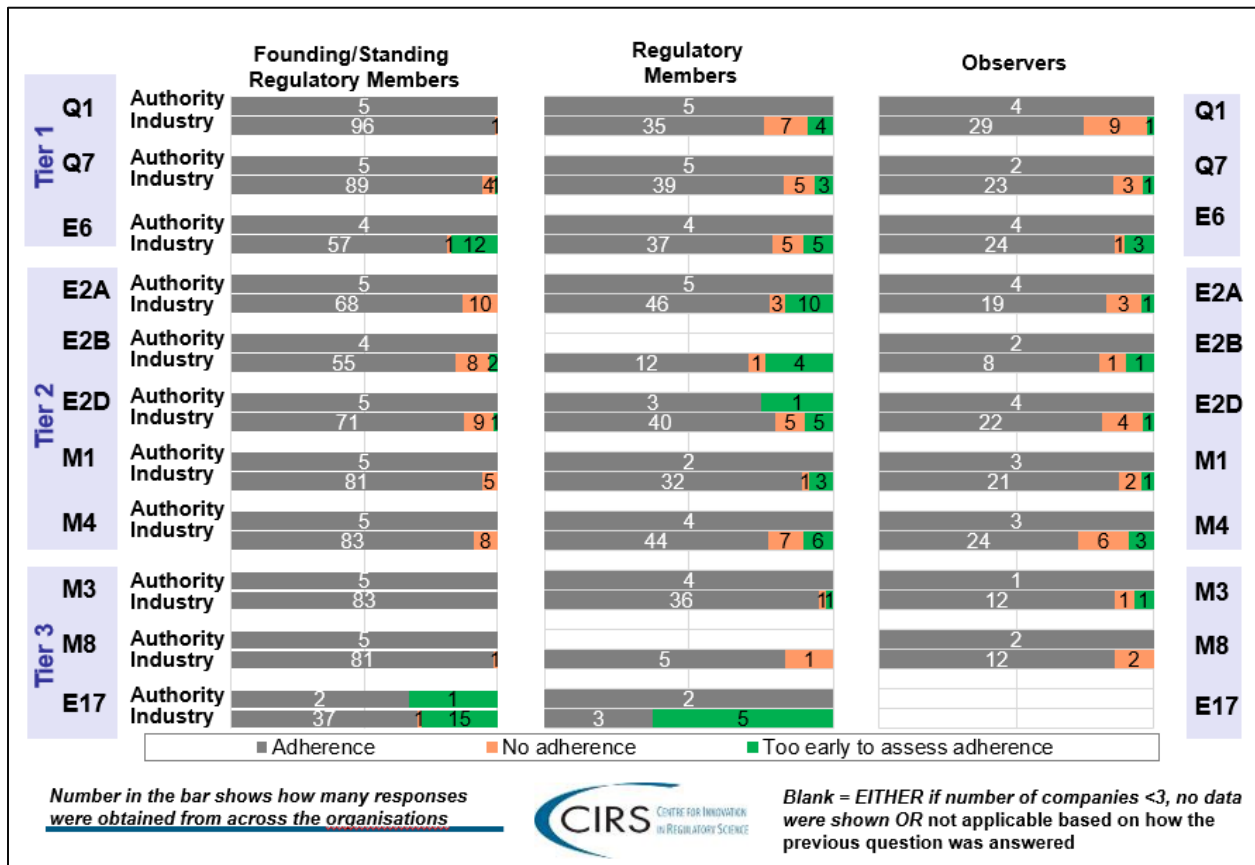
Method: Question 2 (See Appendix 2)

RESULTS PART 3: GUIDELINE ADHERENCE

Adherence status: Organisations which confirmed that a Guideline has 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. Authorities were combined according to their ICH membership status, and Guidelines were organised according to Tier 1, Tier 2 and Tier 3.

Key Messages

- Where implementation was confirmed, all the authorities felt that they were adequately adhering to the Guidelines. In general, company perception and agency self-declaration was aligned or too early to assess, based on limited experience with the Guideline e.g. E17. Company’s perception on adherence to Guidelines was highest across Founding/Standing Regulatory Members, followed by Regulatory Members and Observers.
- Minor divergences were noted between authority/company and could have multiple reasons.
 - 1) As with implementation, if the number of divergent company responses was low, it could suggest a company specific experience and potential need for internal training/education for the company.
 - 2) If the number of divergent companies was more considerable, this suggests need for internal considerations by the authorities relating to Guideline interpretation and/or training to ensure consistency.
- Certain Guidelines had in general more divergences - suggests need for clarification relating to the Guidelines themselves e.g. M4, E2A, Q1.



Method: Question 1.3 (See Appendix 2)

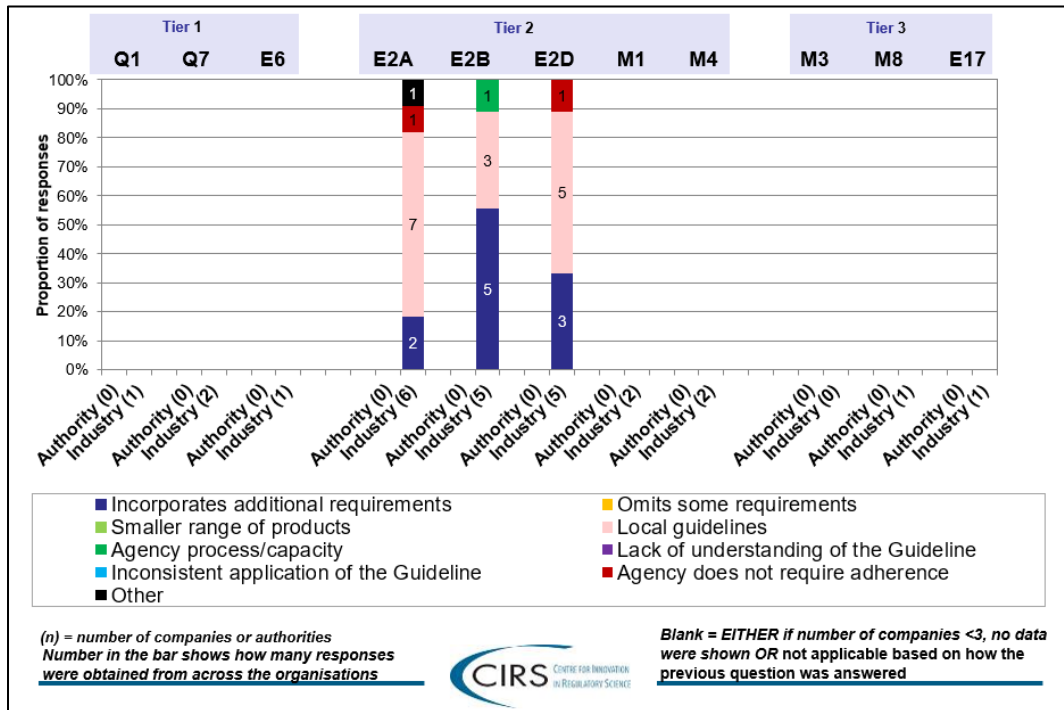
RESULTS PART 3: GUIDELINE ADHERENCE (CONT.)

Rationale for lack of adherence: The three graphs below outline, for Founding/Standing Regulatory Members, followed by Regulatory Members and Observers respectively, the rationale for selecting that there is lack of adherence for the selected Guideline. The same rationale options were provided to respondents as regarding to inadequate implementation, as well as five additional options relating specifically to authority practice and experience (see Appendix 2).

Key Messages

- Similar to the findings regarding the rationale for inadequate implementation, looking across all the authorities, the Guideline with the highest response rate for lack of adherence was Q1. More specifically, across the Founding/Standing Regulatory Members, rationale was provided for E2A, E2B and E2D, for Regulatory Members it was Q1, Q7, E6, E2A, E2D, M4 and finally Q1, Q7, E2A, E2D, M1 and M4 for Observers (number of companies > 3).
- Rationale for lack of adherence was mixed, but primarily due to incorporation of additional elements (similarly to rationale for inadequate implementation) as well as the fact that ‘other local guidelines conflict with the ICH Guideline and prevent full adherence to the Guideline. For Regulatory Members and Observers, the other major rationale was the ‘Inconsistent application of the Guideline; e.g. adherence and interpretation varies by submission/review division/reviewer’

Founding / Standing Regulatory Members
 E2A, E2B and E2D had n>3 companies providing responses, mostly around conflicting local guidelines, followed by incorporation of additional requirements.



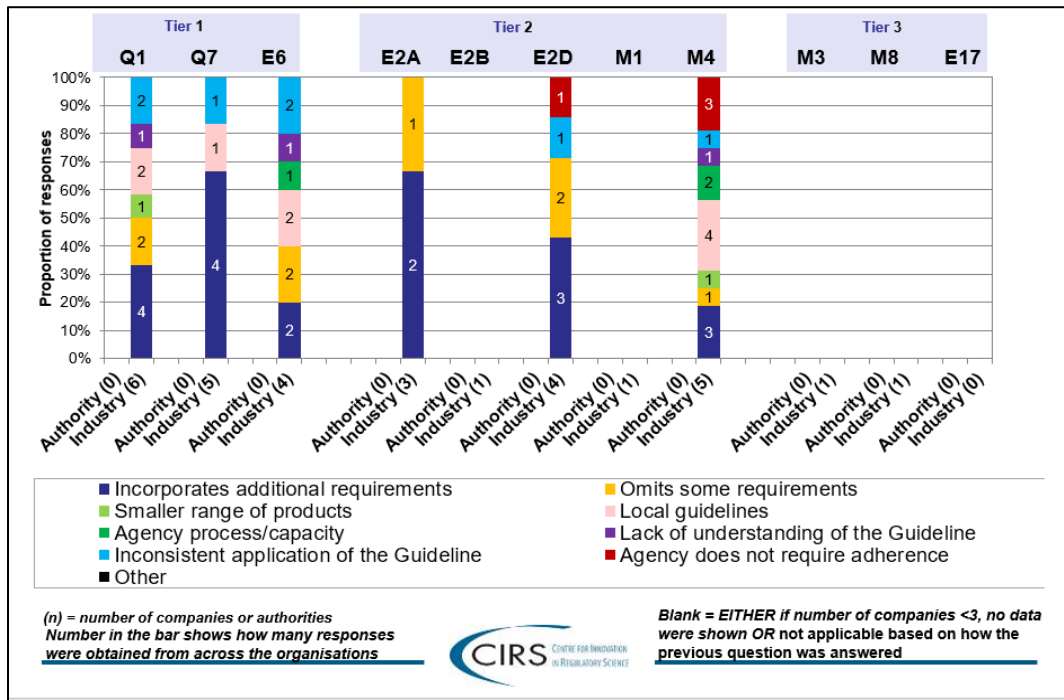
Method: Question 2 (See Appendix 2)

RESULTS PART 3: GUIDELINE ADHERENCE (CONT.)

Rationale for lack of adherence (cont.)

Regulatory Members

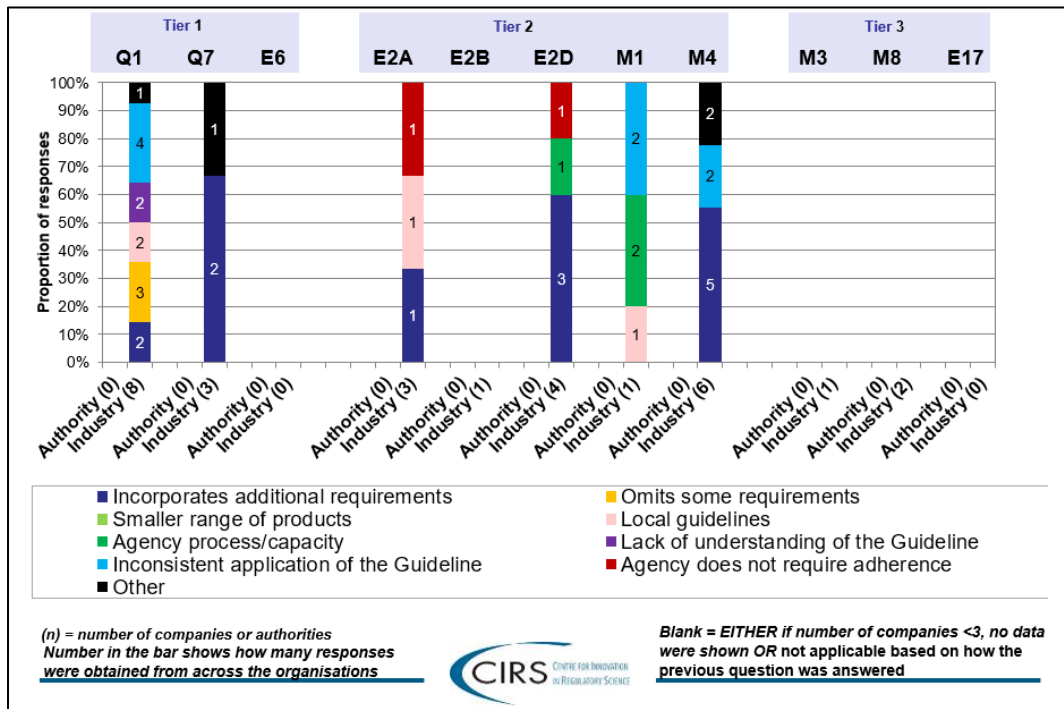
Q1, Q7, E6, E2A, E2D and M4 had n>3 companies providing responses, where the responses were mixed but mostly around incorporation of additional requirements.



Method: Question 2 (See Appendix 2)

Observers

Q1, Q7, E6, E2A, E2D, M1 and M4 received responses from n>3 companies, where the rationale was mixed but mostly regarding incorporation of additional requirements as well as inconsistent application of the Guideline.

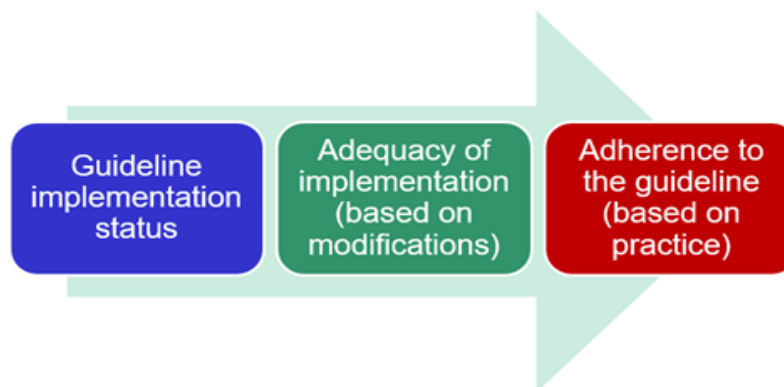


Method: Question 2 (See Appendix 2)

CONCLUSION

Phase 2a of the study demonstrated that a comprehensive perception survey could be undertaken, where the response rate was excellent indicating strong interest. Results, supported by evidence-based rationale, could be summarised as follows:

- **There was a generally strong evidence of Guideline implementation and adherence across the authorities and the self-declaration of the authority was in line with company perception for the majority of Guidelines and authorities.**
- **ICH Guideline implementation status:** implementation of Guidelines based on self-declaration from the authorities was highest across Founding/Standing Regulatory Members, followed by Regulatory Members and Observers. Company perception of implementation status was generally aligned with the agency perception of the authority.
- **Adequacy of ICH Guideline implementation (based on modifications):** In general, authorities declared that Guidelines were mostly implemented without modifications and where there were modifications, all the authorities felt that these were objectively justified. In general, company perception and self-declaration of the authority was aligned.
- **Adherence to ICH Guidelines:** Where implementation was confirmed, all the authorities felt that they were adhering to the Guidelines i.e. adequately applying them in day-to-day practice. In general, company perception and self-declaration of the authority was aligned or too early to assess based on limited experience.



All in all, the gap analysis revealed a strong agreement between the self-declaration of the authority and company perception, but with some divergences. These differences were largely supported by objective justifications and specific examples, whereas gaps and divergences could be used to support training and capacity building efforts across authorities and companies.

Furthermore, the results 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. Finally, the next steps could be to further refine the method based on the feedback from this study, in order to repeat the study as a way of monitoring any change as well as to apply it to additional Guidelines and regulators, particularly in the view of growing interest to expand ICH membership.

APPENDIX 1 – DEFINITIONS

DEFINITIONS OF TERMS IN THE CONTEXT OF THE IMPLEMENTATION OF ICH GUIDELINES

<i>Term</i>	<i>Definition</i>	<i>Comments</i>
<i>Not (yet) implemented</i>	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.
<i>In the process of implementation</i>	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.
<i>Implemented</i>	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.
<i>Adequately implemented</i>	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.
<i>Not adequately implemented</i>	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	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.

<i>Term</i>	<i>Definition</i>	<i>Comments</i>
	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.
<i>Adherence²</i>	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.
<i>Lack of adherence</i>	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.
<i>Confirmed implementation/adherence</i>	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).
<i>Not applicable</i>	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 recognized Pharmacopoeias. Hence, the ICH Q4B Guideline is not applicable (and does not need to be implemented).

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² 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). For more information regarding the DCT design, please see an additional document 'DCT design notes'.

Companies will have to answer the following general questions:

Question 1i (Companies only): Please specify your company type:

- Local company (operates in one country)
- Regional company (operates in one region)
- Multinational company (operates in multiple countries and regions)

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

- Innovative medicines
- Generic medicines
- Both

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).

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).

- 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 4. 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

APPENDIX 2 – STUDY TOOL (CONT.)

references internationally recognized 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. 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 1.2.1, respondent redirected to Question 2.

If ‘Yes’ to Question 1.2.1, 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.

APPENDIX 2 – STUDY TOOL (CONT.)

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), including details regarding any unjustified modifications made to the Guideline (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, including any objectively justified modifications made to the Guideline by the authority and well as future plans regarding the status of the guideline in the authority with key milestones and timelines if available.

(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)

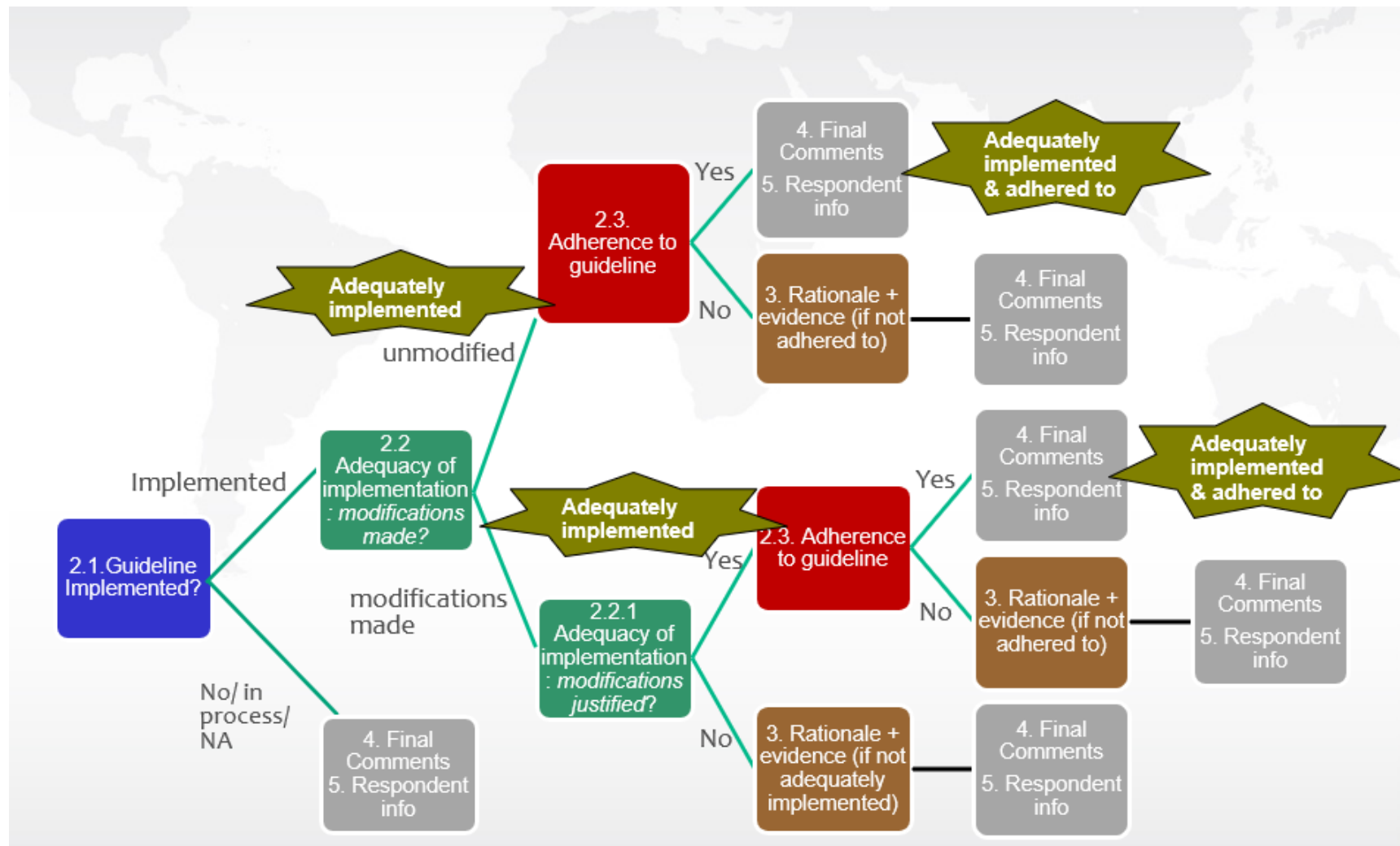
4.3. (Company only question) Location of respondent. Select one.

- Head office
- Local/regional office

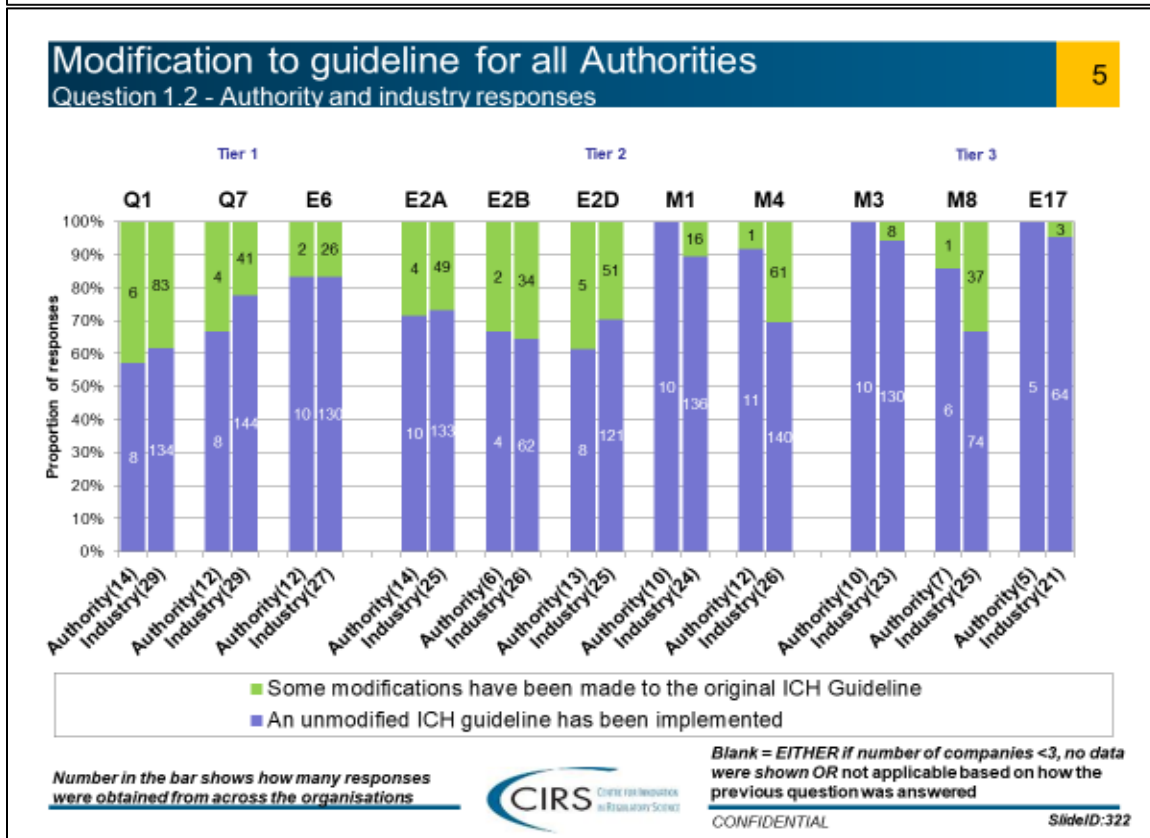
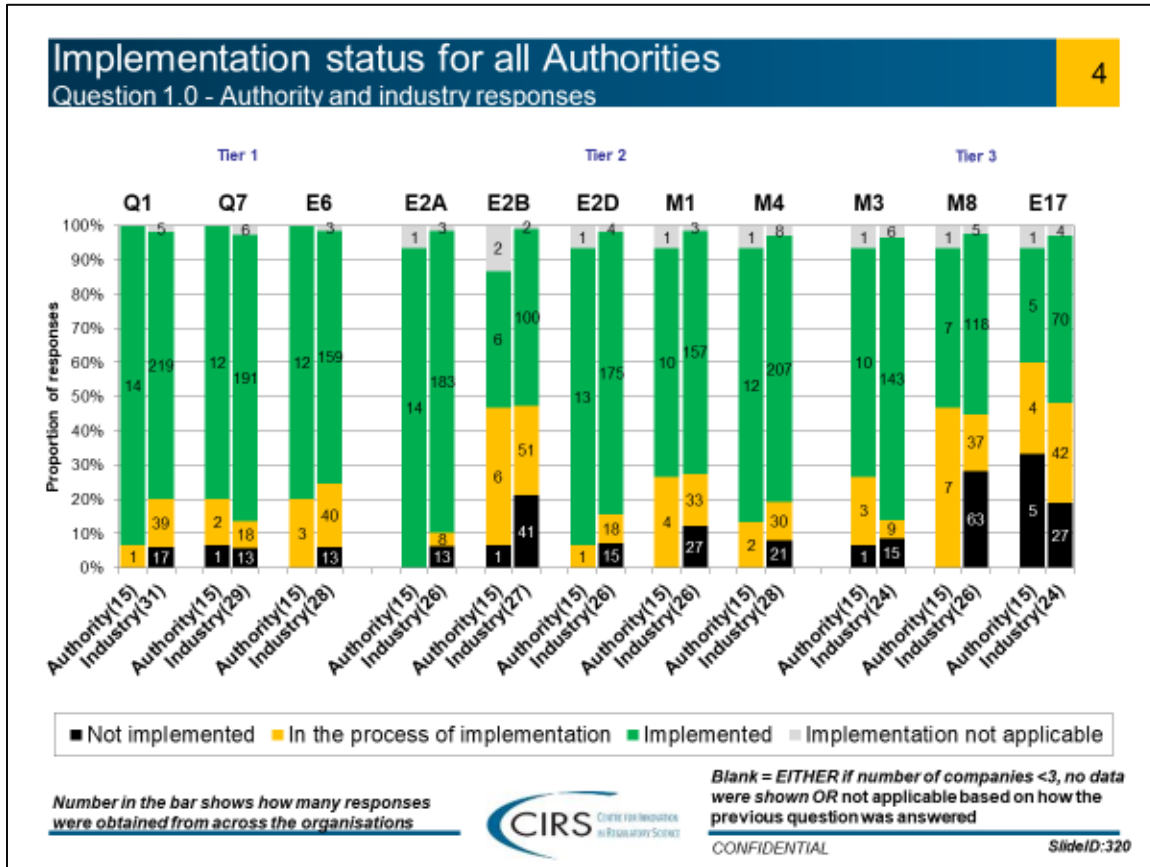
Completion tickbox: Respondent tick 'complete' if section completed. This will enable tracking of response rate in a summary table for each organisation.

APPENDIX 2 – STUDY TOOL (CONT.)

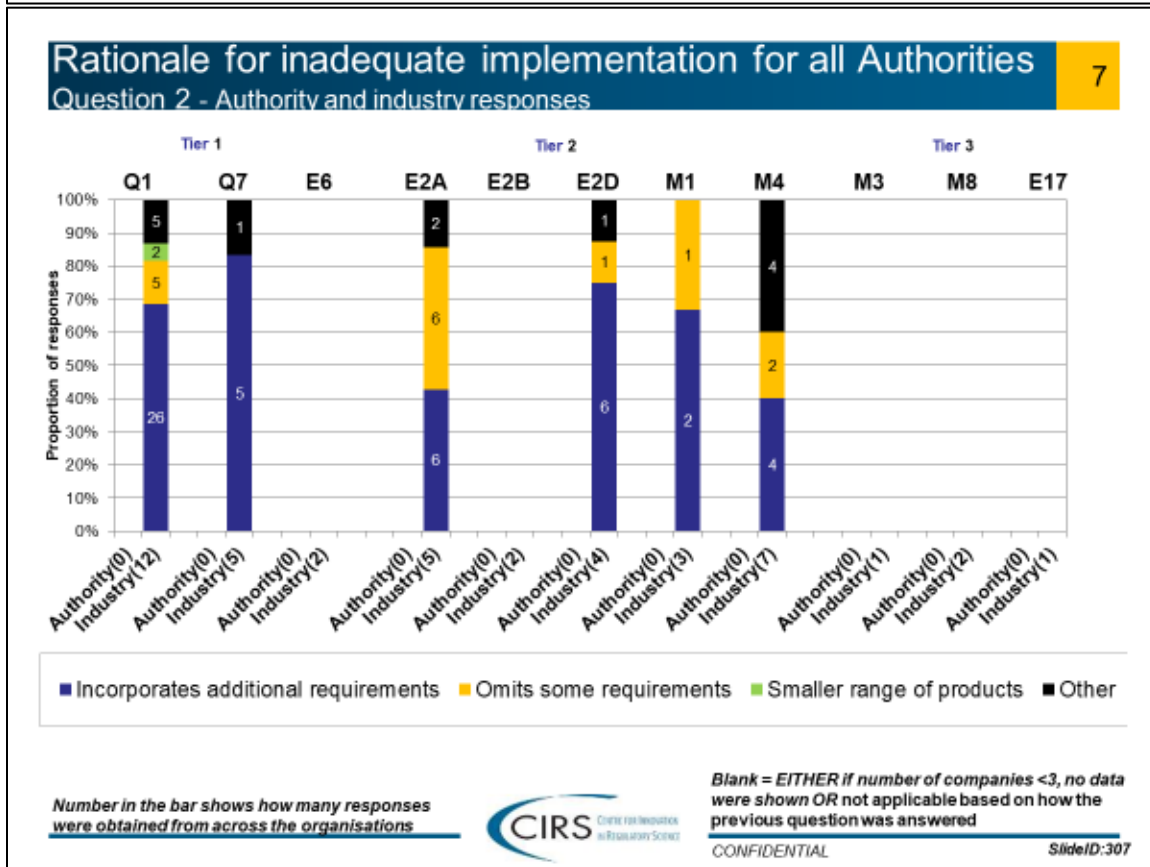
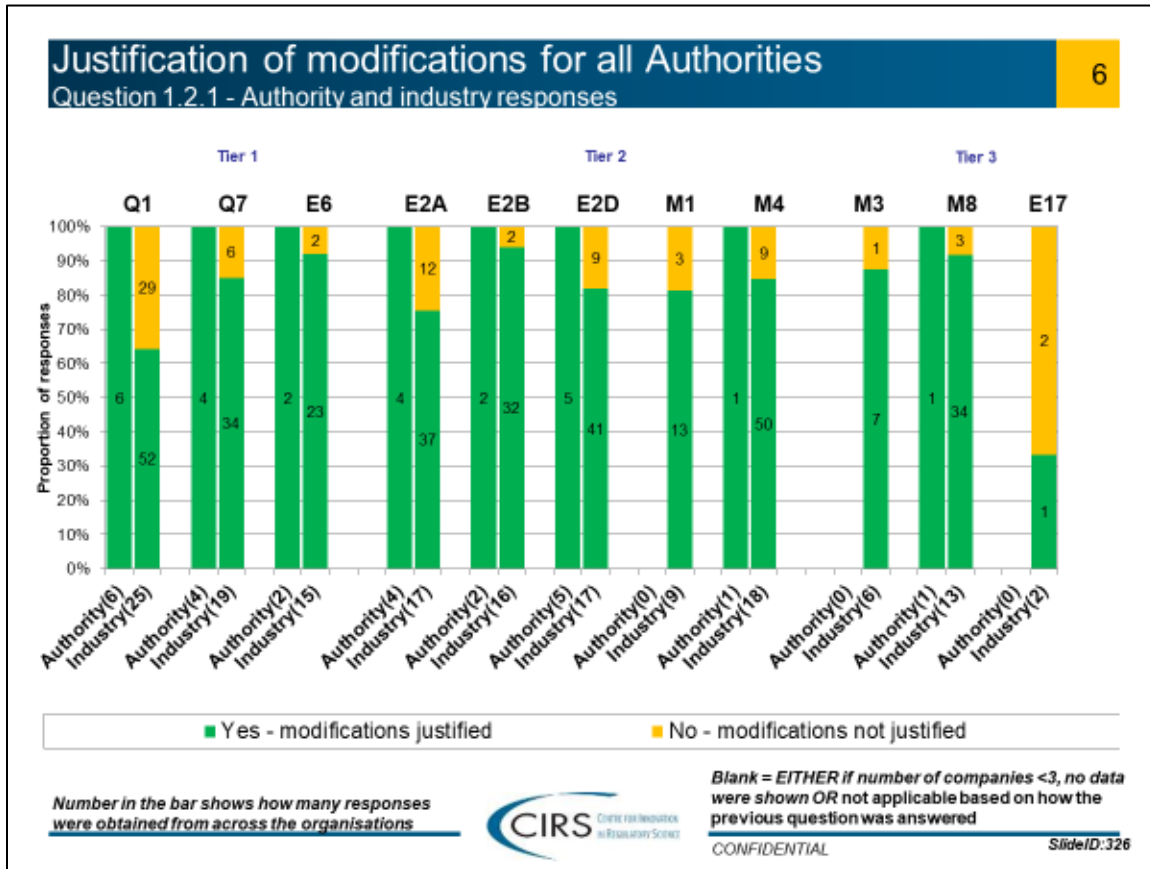
Questionnaire logic



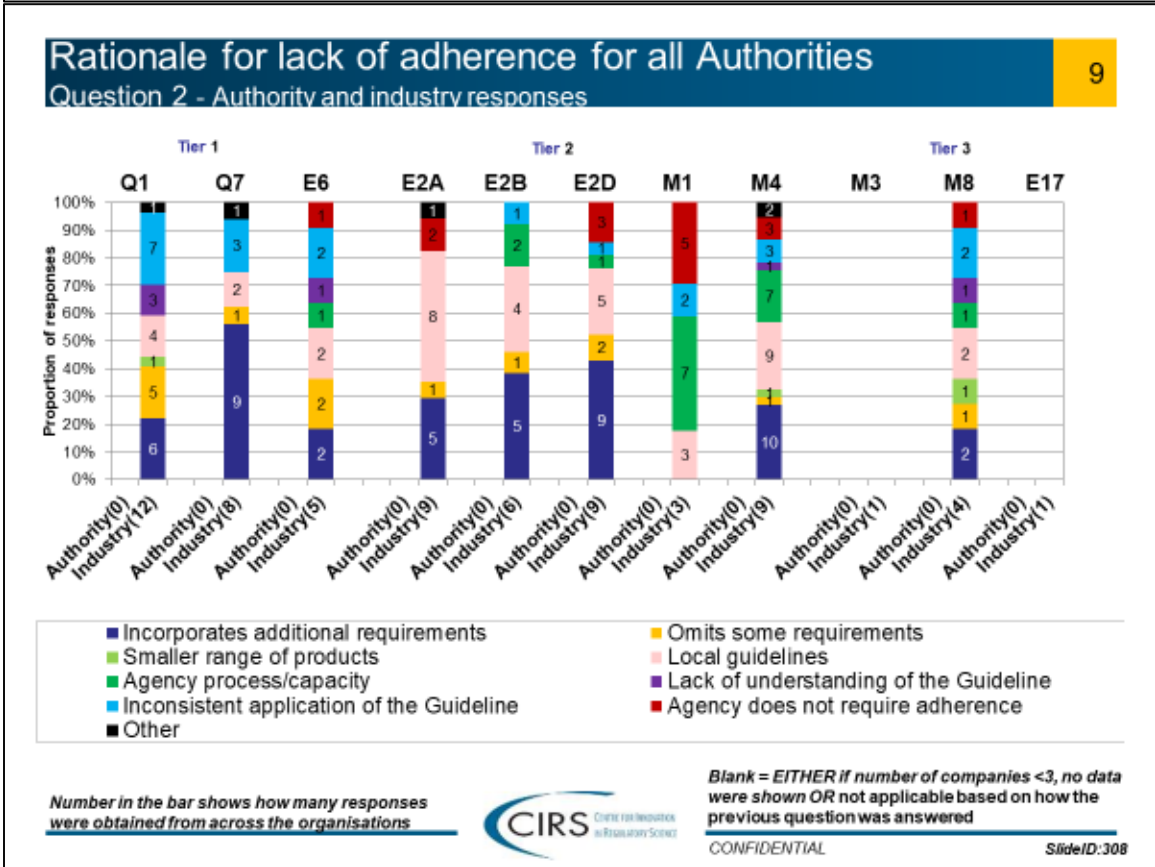
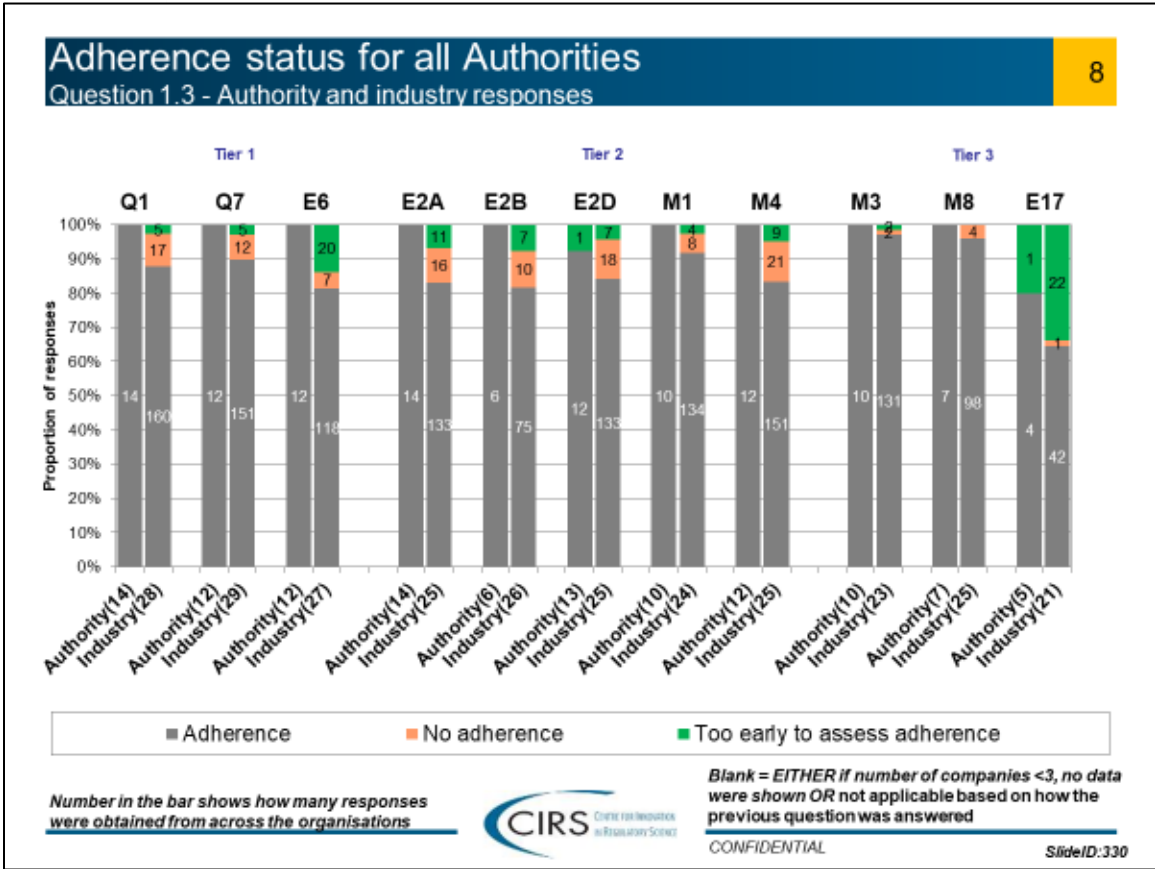
APPENDIX 3 – COMBINED RESPONSES ACROSS ALL THE AUTHORITIES (CONT.)



APPENDIX 3 – COMBINED RESPONSES ACROSS ALL THE AUTHORITIES (CONT.)



APPENDIX 3 – COMBINED RESPONSES ACROSS ALL THE AUTHORITIES (CONT.)



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

Report date: 1 November 2019

Version 1.4

