# Acceptance of stakeholder comments during EMA scientific guidelines public consultations: legitimacy of the quadruple helix model of innovation

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**Abstract**

Aim: Guidelines establish a framework for how therapeutics and vaccines are developed, assessed and approved. They influence which innovations are likely to be approved in the EU, and by that, they have an impact on the pipeline decisions taken by the research-based industry. This study analyses the level of acceptance for changes suggested by stakeholders within the authoring groups at the EMA. Methods: We looked at 87 guidelines from EMA Working Parties (WPs) launched for consultation between 2013-2017. Acceptance of stakeholder proposals and the time between the end of consultation and guideline adoption were studied as well as the openness of different Working Parties to accept changes. Results: Adoption of a guideline after the close of public consultation took at least 4 months, with average 12-16 months. The number of accepted and rejected comments were nearly equal across the stakeholders, with government having slightly higher chance for acceptance. Academia and NGOs had generally higher chances to have their comments accepted for general and indication-level guidelines. Government and individual companies had highest acceptance for molecule-level guidelines and trade associations for indication-level guidelines. The EMA WPs working with emerging technologies were more open to accept proposed changes. Conclusion: This pattern of progress in regulatory science at EMA demonstrates the essential and interrelated role of academia, industry, government and civil society – described as the quadruple helix model - to promote establishment of a strong innovation ecosystem in Europe. Further integration and utilisation of competences of each stakeholder is necessary for guideline development.

## Introduction

Scientific guidelines for medicines and vaccines are a part of the complex governance framework for pharmaceutical innovation in Europe. Scientific and technological advances are crucial to improve patients' health, and support a more efficient, and cost effective, way of discovering and using medicines [1]. Allowing patients in the European Union (EU) to benefit from state-of-the art healthcare. As recognized in the European Medicines Agency (EMA) Regulatory Science Strategy to 2025, the EU network is responsible for providing a regulatory environment that supports innovation and the development of new and better medicines to meet human and animal health needs [2].

Regulatory guidelines aim to optimize and increase the predictability of innovative developments by providing the standards of evidence that must be met to determine the benefit/risk profile or quality to be achieved. These guidelines should reflect and build on the most up-to-date scientific knowledge [3] in providing a harmonized approach how pharmaceutical industry develops and subsequently how regulatory bodies perform their assessment of new marketing authorisation applications or updates to marketing authorisations.

The EMA follows the principles and standards set by the European Commission guideline on better regulation [4]. The four principles set forth by the Commission are participation, openness and accountability,

effectiveness and coherence. The aim is to ensure as representative and inclusive consultation process as possible but also to give stakeholders a real opportunity to influence before the document under development is finalised. The Commission guideline also highlights the importance of prioritization of stakeholders on the basis of impact, responsibility for implementation and interest in the topic [4]. When assessing stakeholders with an interest, it is also critical to identify which competence and knowledge these different stakeholders can bring to the creation process. Academia, government, industry and civil society, are often referred to as "quadruple helix model". Quadrable helix model is a construct in which the four stakeholders are recognized as contributors to the innovation system. Their engagement is supported through partnerships, networks and relationships with the aim to have the whole society involved in the co-creation process of innovations and technological advancements [5]. The quadruple helix model can enhance knowledge translation process which is necessary and valuable for evidence-based policymaking [6].

A well-designed evidence collection and interpretation processes can reduce the inherent risks of unintended consequences and negative externalities associated with regulatory guidelines [7]. The World Health Organization (WHO) Good Regulatory Practice Guidance calls for conducting a regulatory impact assessment to consider all the different perspectives and to allow for various stakeholders to provide timely input [8]. This proposed consultation will provide an indication to which extent there is an impact assessment process which ensures a harmonized approach amongst all stakeholders based on the the most up-to-date scientific knowledge and/or real-life experiences. Additionally, the likelihood of compliance with regulations is increased when affected parties understand the underlying policy considerations and feel that their input has been seriously considered.

**Guideline development process**

Scientific guidelines issued by the European Medicines Agency are normally developed in accordance with the following steps [3] (see table 1 for relevant timelines)*:*

1. Selection of topic and inclusion in the relevant work programme(s)
2. Appointment of rapporteur (and,if necessary, co-rapporteur)
3. Development of concept paper
4. Adoption and release for consultation of concept paper
5. Preparation of initial draft guideline
6. Release for consultation of draft guideline
7. Collection and assessment of comments
8. Preparation of final version of guideline
9. Adoption of final guideline for publication
10. Implementation

*Concept paper*

The initial stage is the concept paper phase, which is intended to convey the need for discussing specific issues, innovations or controversial key-points at any stage of the development of medicinal products with a view to laying down the foundation for future guidelines[3]. Comments collected on the concept paper will give stakeholders to provide directional input on the direction of the future guideline. Comments provided will be considered in the development of the future guideline[3].

*Draft guideline*

Subsequently, the assigned rapporteur(s) prepares the draft text taking into account the comments received during the consultation period on the concept paper (if any). The (co)-rapporteur may consult appropriate experts to provide input. The guideline is further developed to a point where the views of the members of the responsible working party (WP) are clearly presented, the draft guideline is submitted for adoption at the main scientific committee - Committee for Medicinal Products for Human Use (CHMP) of the draft document (guideline, Q&A, reflection paper etc) for release for consultation[3].

Providing comments is not exclusively for the medicine and vaccine developers and manufacturers, but as important is to involve a wide range of other stakeholders. In general comments could be received from:

- Governmental organisations in Member States of the EEA/EFTA countries, such as national regulators or HTA bodies;
- Other regulatory authorities (e.g. FDA, European Directorate for the Quality of Medicines (EDQM) , other (V)ICH partners);
- European industry associations;
- European scientific/academic societies and patient/consumer groups/health care professionals;
- Other interested parties.

The WHO **Good Regulatory Practice Guidance** emphasizes the importance of transparency [8]. If consultations have been conducted throughout the development of the proposal, a summary should be prepared of the comments received and how they were taken into consideration. This feedback provides transparency and credibility to the consultation process and increases the efficiency and effectiveness of regulation likelihood of regulatory success, supports shared learning and alignment. Therefore, all comments are carefully considered and discussed by the rapporteur and/or drafting group responsible for the guideline. Comments provided by stakeholders are systematically published on the EMA website, unless they contain commercially confidential information and/or the author has specifically objected to their publication. The publication of the received comments will include an overview explaining the rationale behind the acceptance or non-acceptance[3].

Table 1. Public consultation timelines

| **Consultation step / document type** | **Timelines** |
|---|---|
| Concept paper | 2-3 months consultation |
| Draft guideline | 3-6 months consultation |
| Implementation / effective | 6 months after adoption guideline |
| Publication stakeholders comments (incl. acceptance/rejection) | 1 month after adoption guideline |

## Research question

The research question for this study is to analyse the level of acceptance for changes suggested by stakeholders within the authoring WPs at the EMA and how the guidelines contribute to the quadrable-helix model.

## Methods

*Selection and extraction*

We selected 'scientific guidelines' and 'related documents' (defined as: reflection papers, public statements and questions and answers documents) via the EMA scientific guideline search functionality [3], which were adopted and published in the period 2013-2017. Excluded from the extraction were product specific bioequivalence guidance, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidance and concept papers (as for the latter comments are not published).

*Data collection*

1. Type of document: scientific guideline or related document
2. Scientific discipline / therapeutic area
3. Dates:
4. End date public consultation
5. Adoption date CHMP
6. Stakeholders comments:
7. Published (y/n)

8. Number of stakeholders
9. Type of stakeholder:
10. *Government (Regulatory authorities or HTA bodies)*
11. *Academic/NGOs*
12. *Academics: Learned societies, universities, hospitals, specialists)*
13. *Civil society: patient associations, NGOs*
14. *Industry associations and commercial entities*
15. *Trade associations*
16. *Individual companies (including consultancies)*

*Analysis of the procedural elements*

Only guidelines with published comments were included in the study (n=87). The key dates of the guidelines were listed as end date of the consultation and adoption date of the guideline. The time elapsed between the two dates was measured as days.

Question and answer documents were not assigned an author and they are missing from the subgroup analysis comparing the WPs. Only the WPs that authored at least three guidelines were included in the subgroup analysis.

*Guideline classification, scoring method and statistical analysis*

The guidelines were classified based on their type. The categories were as follows:

- Overarching guidelines with procedural elements (eg. stability testing), (quasi-)universal scope (eg. first-in-human trials, pharmacogenomics in pharmacovigilance) or intended for a specific category of medicines (eg. Biosimilar medicines; common routes of administration)
- Guidelines intended for a therapeutic area or an indication (eg. products for urinary incontinence)
- Guidelines intended for a molecule (API or excipients), (eg. products containing interferon beta), or administration (eg. IV liposomal products)

The EMA has a template for collecting comments, which involves a first section on overall comments to the draft (Section 1) and a second section for the collection of detailed comments and proposed changes (Section 2). The comments in Section 1 were excluded from the analysis because they are more general in nature and do not refer to a line item in the guideline and lacks a clear indication provided whether they were accepted or rejected. Comments provided in Section 2 that relate to contents of the draft guideline were considered. To allow quantitative analysis of the accepted and rejected comments from different parties, a scoring system was developed. Each fully accepted comment was scored as 2 points, partially accepted as one point and rejected comments as no points. Acknowledgements, duplicates (same comment included in multiple submissions) or comments that were regarded as not applicable did not score points but were counted towards the total comments. In the case of duplicates, only the comment indicated by the EMA as the first comment with the same content was counted towards scoring. This decision was taken because they would not have direct impact on the final content of the guideline. There were only a few guidelines with many duplicate comments and this approach is unlikely to shift the overall trend. Table 2 indicates the scoring system based on the wordings used by the EMA in the document outlining all comments.

Table 2. Scoring system aligned with EMA wording

| Scoring | 2 | 1 | 0 |
|---|---|---|---|
| EMA wording | accepted; supported; endorsed | Partly/partially accepted; wording amended, softened or clarified | Not accepted; not endorsed; not supported; not applicable/NA; duplicate comment/addressed earlier; acknowledged; noted (no clear indication of acceptance) |
| Categorised as | Accepted | Partially accepted | Rejected Other (NA/acknowledged/noted/duplicate) |

Descriptive statistical analysis was applied to the final scores and total comments to calculate mean scores for each stakeholder group. The mean scores (per stakeholder group and per guideline) were then utilised for aggregate analysis in different steps: relative shares of accepted, partially accepted and rejected comments; average scores per guideline category (general/indication-level/molecule-level) in each year (2013-2017); and average scores for guidelines authored by different committees (aggregate result for all years). In the subgroup analysis, the mean scores were calculated for each guideline category and guidelines from a given WP. A separate subgroup analysis was conducted for trade associations and companies.

**Results**

The cohort had altogether 87 guidelines for analysis. Table 3 indicates how the guidelines were distributed across the years and their classification, and the volume of submitted comments. The distribution was relatively even across the years, with a range of 14 guidelines per year as the lowest total and 20 at the highest.

The total volume of comments increased steadily. For the period as a whole (2013-2017), industry provided 36% of all comments, just slightly below the share submitted by trade bodies (38%). As a share of all comments, 2014 was exceptional, with individual companies providing nearly two-thirds of all comments. In that year (2014), the majority of guidelines under review were more general in nature and impacted both pharmaceutical and device manufacturers, which may have increased the volume of industry comments (*see Table 3* ).

The second most active group included academics and NGOs (civil society). In the analysis, they were grouped together because across the years, patient associations and NGOs submitted altogether 10 submissions, which as a separate stakeholder would not have given a meaningful statistical result. The governmental stakeholders, including regulators from the EU, outside of the EU as well as HTA bodies, submitted approximately 8% of the comments. Although a relatively smaller share amongst commenting organizations, the number of governmental stakeholders submitting comments is growing, almost tripling over the years from 5 to 14.

Table 3. Overview of the included guidelines and comments from stakeholders

| | 2013 | 2014 | 2015 | 2016 | 2017 | Total |
|---|---|---|---|---|---|---|
| No of guidelines | 13 | 15 | 20 | 20 | 19 | 87 |
| General | 6 | 7 | 4 | 6 | 4 | 27 |
| Indication level | 3 | 5 | 6 | 11 | 3 | 28 |
| Molecule-level | 5 | 3 | 10 | 3 | 12 | 33 |
| Total number of comments | 738 | 1980 | 1297 | 1468 | 2056 | 7539 |

| | 2013 | 2014 | 2015 | 2016 | 2017 | Total |
|---|---|---|---|---|---|---|
| Governmental | 87 | 68 | 125 | 173 | 145 | 598 |
| Academia, NGOs, societies | 100 | 262 | 331 | 257 | 453 | 1393 |
| Trade associations | 281 | 443 | 443 | 754 | 911 | 2842 |
| Companies | 270 | 1207 | 398 | 284 | 547 | 2706 |
| Submissions total | | | | | | |
| Governmental | 5 | 13 | 18 | 22 | 15 | 74 |
| Academia, NGOs, societies | 12 | 31 | 33 | 44 | 39 | 161 |
| Trade associations | 19 | 41 | 29 | 33 | 47 | 173 |
| Companies | 39 | 75 | 48 | 36 | 77 | 277 |
| Submitters total | | | | | | |
| Governmental | 5 | 6 | 7 | 14 | 13 | |
| Academia, NGOs, societies | 12 | 28 | 29 | 39 | 31 | |
| Trade associations | 11 | 20 | 16 | 14 | 27 | |
| Companies | 35 | 58 | 45 | 27 | 48 | |

The time between the end of consultation and adoption of the final guideline is not specified in the law. Generally, the final guideline development phase took a minimum of four months after the end of the consultation with the median as 12-16 months, but there were six cases that the guideline was adopted after more than two years (Figure 1).

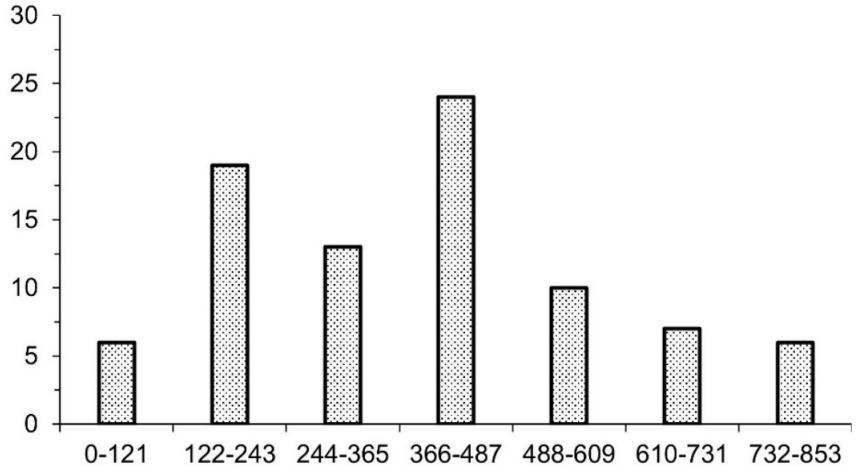


Figure 1. Days between the end of the public consultation and adoption of the guideline

Figure 2 indicates the trends for acceptance and rejection across stakeholder groups. For government and trade associations, the average share of accepted comments is higher than for rejected comments, while for academia/NGOs and individual companies the average share for accepted and rejected comments is approximately the same. Average share of rejected comments is lower for government than other stakeholders.

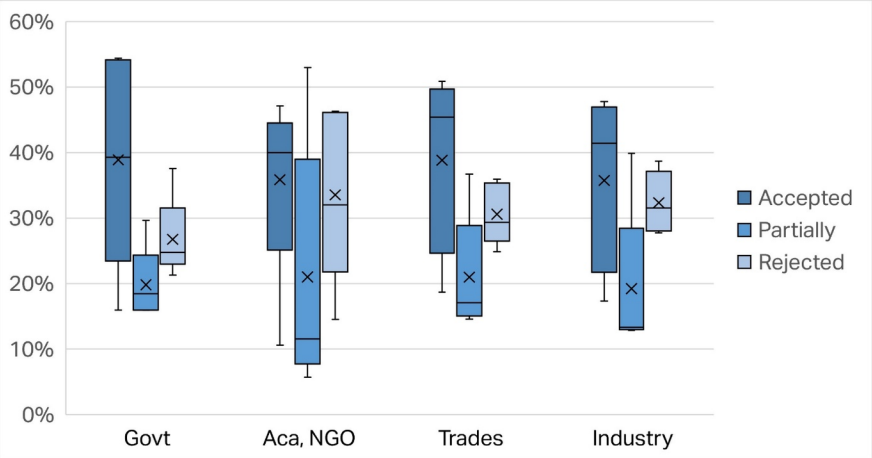


Figure 2. Comparison of level of acceptance and rejection of stakeholder comments

Figure 3 compares stakeholder scores on different types of guidelines over the years as a heatmap, to avoid aggregating the data too much and showing trends against different parameter (year, stakeholder type, guideline class). The closer to 2, the higher the acceptance level and the darker the green colour. A mean score close to 0, indicated by a darker red colour, indicates a higher rejection level. Overall, academic stakeholders have highest likelihood for acceptance in both indication-level and general guidelines. Surprisingly, governmental stakeholders had highest chances for acceptance for guidelines on molecule-level. Yet, the trend shows that government comments had good acceptance for general guidelines and the exceptionally low score in 2014 (a result of multiple guidelines with no accepted comments, i.e. mean score 0) impacts the overall average score disproportionally. Trade association and individual company comments are most likely to be accepted for indication-level guidelines (mean score 1.01 and 1.12). Comments from individual companies also were more likely to be accepted for molecule-level guidelines than those from trade associations (mean scores 1.01 vs 0.80), while comments from trade associations were more likely to be accepted for general guidelines (mean scores 0.92 vs 0.80).

| | **2013** | **2014** | **2015** | **2016** | **2017** | **Overall** | |
|---|---|---|---|---|---|---|---|
| **Govt** | 1.17 | 0.15 | 1.62 | 1.09 | 0.72 | 0.95 | *Generic* |
| | | 0.44 | 1.35 | | | 0.89 | *Indication* |
| | 1.33 | | 0.95 | | 0.74 | 1.01 | *Molecule* |
| **Academia, NGOs** | 1.36 | 0.91 | 1.23 | 0.83 | 0.81 | 1.03 | *Generic* |
| | | 1.23 | 1.08 | 0.93 | 1.56 | 1.20 | *Indication* |
| | 0.99 | | 0.81 | 0.50 | 0.90 | 0.80 | *Molecule* |
| **Trades** | 1.11 | 0.79 | 0.96 | 1.01 | 0.72 | 0.92 | *Generic* |
| | 0.65 | 1.19 | 1.44 | 1.03 | 0.75 | 1.01 | *Indication* |
| | 0.94 | 0.78 | 0.95 | 0.98 | 0.62 | 0.85 | *Molecule* |
| **Companies** | 0.96 | 0.59 | 0.76 | 1.11 | 0.59 | 0.80 | *Generic* |
| | 1.44 | 1.16 | 0.85 | 1.05 | 1.08 | 1.12 | *Indication* |
| | 0.93 | 0.78 | 0.66 | 1.85 | 0.82 | 1.01 | *Molecule* |

Figure 3. A heatmap of mean scores per type of guideline across stakeholder groups (green indicates higher acceptance, red lower)

A subgroup analysis (Figure 4) revealed that the Blood Products and Quality Working Parties have a lower acceptance level for comments overall. The results were similar to guidelines that are authored by multiple

working parties. The Biosimilar Medicines and Pharmacokinetic Working Parties have been receptive towards comments from governmental authorities, but less so for others. The Biologics, Cardiovascular, Safety and Rheumatology/Immunology Working Parties do not reflect any trends with scores above or close to 1 for other stakeholders than government.

| | No of guidelines | Govt | Academia, NGOs | Trades | Companies | Overall |
|---|---|---|---|---|---|---|
| Biologics | 10 | 0.81 | 1.13 | 1.12 | 0.91 | 0.99 |
| Cardiovascular | 9 | 0.64 | 1.09 | 0.91 | 1.07 | 0.93 |
| Blood Products | 9 | | 0.75 | 0.73 | 0.82 | 0.77 |
| Cross-WP authorship | 9 | 0.64 | 0.93 | 0.89 | 0.96 | 0.85 |
| Quality | 7 | 0.58 | 0.97 | 0.76 | 0.65 | 0.74 |
| Safety | 5 | 0.93 | 1.12 | 1.10 | 0.98 | 1.03 |
| Biosimilar Medicines | 4 | 1.38 | 0.53 | 0.67 | 0.34 | 0.73 |
| Rheumatology / Immunology | 3 | 1.153333 | 1.31 | 1.38 | 0.85 | 1.17 |

Figure 4. Heatmap of acceptance of comments by different committees (n > 2 guidelines published; green indicates higher acceptance, red lower)

**Discussion**

The regulatory environment is an aggregate of law, regulations and practices. A good regulatory environment is critical to support innovation systems and enable technological advancement [9]. Guidelines are an integral element of the regulatory environment. In the present study, we aimed to analyse the level of acceptance for changes suggested by stakeholders for draft EMA scientific guidelines during public consultations. Stakeholder input is a part of the process of understanding the potential impact of the guideline, intended and unintended. It facilitates predicting and anticipating causal connections between the adopted guideline and observed changes in the regulated environment. A thorough Regulatory Impact Assessment to understand costs (externalities) and benefits which are inherently associated with any regulation is an important part of building a regulatory framework [10].

The process of developing guidance is overall long, up to three years. Our results highlight that the time from the end of the consultation to adoption is generally at least half a year but can be longer, even over two years. There is a clear pacing problem with the accelerating speed of science and increasing innovativeness in the research approaches, which aim to adapt to the nature of scientific discoveries. To avoid lengthy and rather laborious guideline development processes, the EMA has also used other mechanisms, such as the publication of commentary or opinion articles in peer-reviewed journals, information days or workshops, as tools to increase clarity into how certain legislative elements are evaluated or to support emerging practices and their acceptability in medicines development [11]. These have proven as helpful measures to increase clarity particularly on the more qualitative elements in regulatory decision making. A stronger focus on regulatory science has been proposed as necessary to address the translation issue between science and future treatments. In Europe, the EMA lists many new guidelines that will be developed in their Regulatory Science Strategy to 2025 [2]. Also the Japanese regulators have suggested to include guideline development under the umbrella of regulatory science processes [12].

The OECD outlines that a successful regulatory strategy requires stakeholder support, which can be achieved through constant dialogue, publicity of the impact and consultation [10]. The results on mean scores of the stakeholder comments indicate that the current process appears to treat the stakeholders equally, with the average acceptance level being close to same for accepted and rejected comments with a mean score around 1 on a scale of 0 to 2. The differences often arise from the nature of the guideline, whether generic or procedural or focusing on an indication. Particularly the working parties are facing rapidly emerging new technological approaches (safety) or novel science (biologics) were more open for stakeholder input, which might be due to the speed of technological development being faster than development of associated regulatory frameworks

with a higher appreciation of (scarce) domain expertise outside of the regulatory network. The observed differences between the EMA WPs can also be driven by elements feeding into regulatory systems, such as behavioral aspects, decision making or knowledge transfer mechanisms [13].

The gradual shift in the role of medicines regulation from gatekeeping against harmful molecules to promoting public health by offering regulatory incentives, such as additional support or faster approvals, for products that are likely to deliver the highest health gains [14] should not go unnoticed. Regulators have a very wide and useful broad general knowledge given their exposure to various products through regulatory processes but tapping onto expertise outside of their own or immediate network can be useful. We found that that the specialist knowledge is more readily accepted for indication level guideline when it comes from scientists affiliated with academia rather than industry. The opportunity cost of favoring one over the other might be to lose out on valuable contributions [15]; scientists working in medicines development and who can strengthen ability to translate scientific discoveries into therapeutics or vaccines come often from the industry side [16].

To respond to the speed of science and innovation, a better utilization of the quadruple-helix model is required to build a competitive and agile regulatory framework. Fostering a culture with aims at pooling all available expert knowledge, regardless of affiliation, is in the interest of the patient [17]. Since science is often not exact, a document-based consultation process with the focus on individual words or sentences may not capture the wealth of expertise in the ecosystem and result in the best possible outcome. A true exchange across all four stakeholder communities is likely to generate a better end result. The research shows that the stakeholders would often prefer a discussion of the results and implications, which would also be helpful for the implementation process for a guideline [6].

**Areas of further research**

Studies on the development and utilization of scientific guidelines is limited. In light of the speed of innovation and technology further research is needed to identify optimal formats of stakeholder inclusion, to understand the impact on research and development and approval of new therapeutics and vaccines as well as to characterize the role of the regulatory framework on the overall innovation system in the pharmaceutical sector.

**Limitations**

There might be challenges with coding of the comments. In some guidelines, it was not clear whether a comment was accepted or not. Some guidelines had many reviewers with different terminology and approach to assessing the comments. The guidelines were coded by the research team and there might be subjective interpretation of some comments that were not clearly marked as accepted or rejected by the EMA.

The trade associations generally submitted a higher volume of comments than individual companies alone. One aim for consolidating comments through trade association is to avoid duplicative comments, but there were also occasions of similar comments coming from different trade associations. Furthermore, while qualitative analysis of the nature of the comments was not included in the study, the scores may be skewed given that some of the comments were of administrative nature, such as typos, which were fully accepted.

Exclusion of the concept papers preceding the actual guidelines from our study was therefore a limitation because some of the ideas are captured in consultations on them, but the summary of consultation responses for the concept papers are not published.

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**Conflict of Interests** The authors are employees and stockholders of MSD.

The data that support the findings of this study are available on the website of European Medicines Agency at www.ema.europa.eu. The documents can be found through the search function using term “overview of received comments”, using the timeframe of 2013-2017.

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