EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Outcome of the European Medicines Agency (EMA) survey on centralised initial marketing authorisation procedure 2016/2017

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1. Executive summary

In 2013-14 the Agency reviewed and re-designed all the established processes for the evaluation of human medicinal products. Its aim was to simplify the existing ways of working and provide better support to its Scientific Committees and the Network.

In April 2015, the EMA therefore carried out a survey of its own staff and of industry stakeholders to assess their experience of the re-designed **post-authorisation** procedures. The outcome of the survey can be found in here.

In September 2016, a further EMA-Industry-Rapporteurs Survey was launched to collect feedback from EMA staff, CHMP rapporteurs and industry applicants on the performance of the centralised **initial** marketing authorisation (MAA) procedure, and on the level of satisfaction of all stakeholders concerned across the three phases of the evaluation procedures.

Across the three phases of the evaluation procedures, the survey results showed a high level of overall satisfaction from all three categories of respondents in term of quality and timeliness of the interaction.

During the evaluation, applicants considered the assessment reports, questions and major objections to be of high quality in term of clarity, consistency and substantiation; as were the comments made on the product information and mock-ups.

Satisfaction levels with the content of the submitted dossiers and responses to questions, as rated by rapporteurs, were moderate to very good. Submissions had followed scientific advice (where given) in the majority of cases. However, about 25% of the dossiers were considered not fully mature (in a sense that not all pivotal data were included in the initial submission) or it was difficult to locate information.

About two-thirds (62%) of applications involved a clarification meeting, and 22% involved a request for accelerated assessment. Applicants had a very good level of awareness of the guidance for clarification meetings and accelerated assessment, where applicable. Clarification meetings were valued for their usefulness, and overall were considered to facilitate the progress of the procedure. However, it is important that applicants understand the main purpose of the meeting is to make sure that the issues with the application are well understood and to facilitate the preparation of responses, but not to pre-assess or endorse the responses. The need for such a meeting should therefore be considered on a case-by-case basis and a clear outline of the response strategy should be presented upfront to make the most of the meeting.

Interactions between applicants, EMA and rapporteurs were rated positively at all stages of the evaluation procedure. Generally there was a high level of interaction during pre-submission phase, essentially through pre-submission meetings, which were positively rated by the respondents.

Quality and timeliness of EMA feedback were rated very positively. There was a high level of satisfaction with the EMA's support in facilitating finalisation of documents for the opinion. The quality of information provided by applicants and timeliness of the interaction, especially progressing towards the opinion phase, were very well rated.

Overall, it can be concluded that the centralised procedure for initial marketing authorisation applications runs well at all stages (from pre-submission to validation, via the 1st and 2nd phases of the evaluation to adoption of the opinion). However, the survey also identified areas that would benefit from optimisation.

EMA should investigate opportunities to increase applicants' understanding of the validation process (i.e. publish most common issues encountered and how to address them) since a high number of administrative issues with MAA validations were observed in the survey. Increased consistency between application form, PI and the dossier submitted by applicants would also reduce administrative validation comments.

The circulation timelines and communication about any delay for assessment reports and final opinion were identified as areas for improvement. The timing of requests for Annex II conditions to the marketing authorisation was also identified as requiring optimisation, as they often occur in the last stages of the evaluation. Further clarification regarding who to contact (EPL or PM) was suggested.

The impact on resource workload distribution in the network from delays in applicants' submissions was highlighted. Applicants should communicate any delays in MAA submission as early and promptly as possible.

The presentation of the application in general (ease of locating information, use of hyperlinks) was highlighted. Increased awareness of the pre-authorisation guidance, enhanced adherence to the PI guidelines (SmPC & QRD) and better substantiation of the proposed PI in the clinical overview and subsequently in the responses during the evaluation were identified by the survey as areas that would also benefit from improvement. The need for mature dossiers and responses during the evaluation was stressed, as late submission of large datasets renders the finalisation of the procedure challenging.

Section 7 of this report outline actions currently ongoing or planned to address the areas identified for improvement.

2. Background, objectives and scope of the survey

The objective of this EMA-Industry-Rapporteurs Survey was to obtain detailed feedback from CHMP (Co)-Rapporteurs, EMA staff and industry stakeholders on the initial marketing authorisation application procedure (centrally authorised medicinal products only).

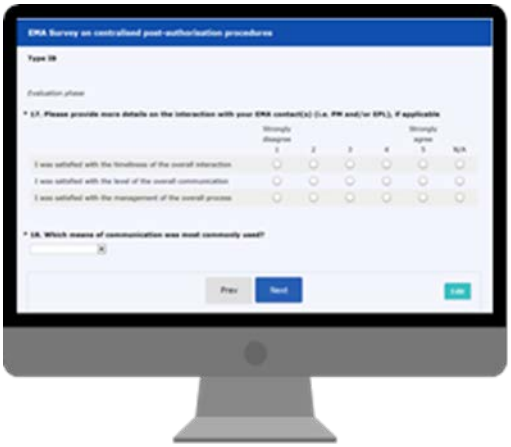
The survey aimed at setting a baseline for this procedure and understanding how well it works from the three different stakeholders' perspectives. It was intended to improve mutual understanding of the issues that may arise and to provide further increased transparency on the interactions between the three stakeholder groups. Ultimately, this supports continuous improvement of the process and related guidance.

The survey covered the three phases of each initial MAA, namely:

- pre-submission to validation;
- the 1st phase of the evaluation until Day 121;
- the last phase of the evaluation up to opinion.

For each of the three phases, questions covered both procedural and content related topics. For all phases there were also questions on the general satisfaction from the three stakeholders' perspective on the quality of the interactions as well as its timeliness.

3. Methodology

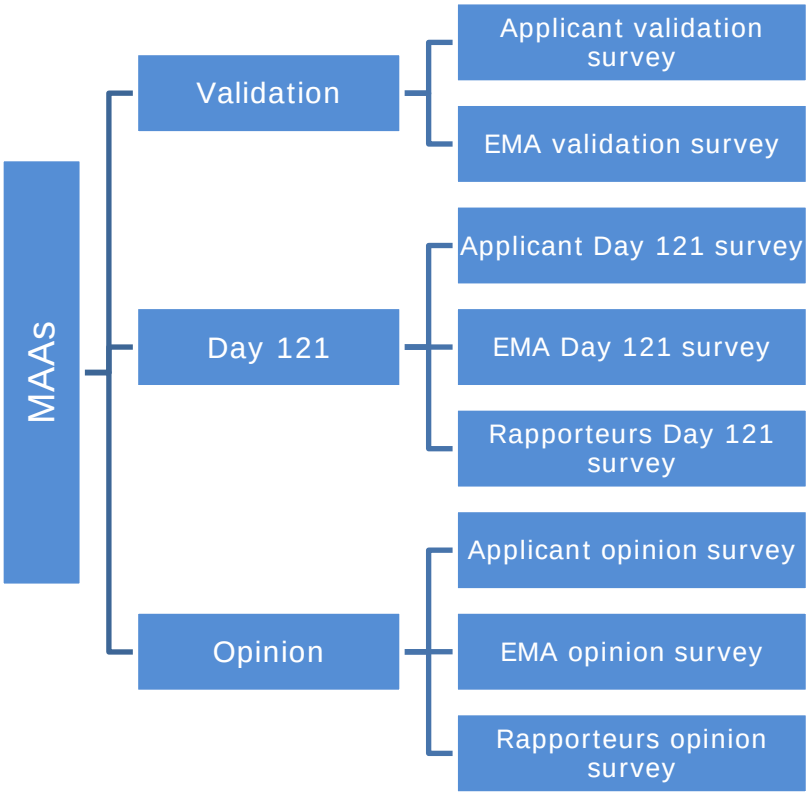


The survey was coordinated online by the EMA and anonymised. The dedicated questionnaires to all three stakeholders were prepared and jointly agreed between EMA, the CHMP and Industry Organisations prior to launch. The "EU Survey" management tool hosted by the European Commission was used for this survey.

The survey covered the different phases of the MAA evaluation procedure: pre-submission to validation, Day 1 to 121 (primary assessment phase) and Day 121 to opinion (secondary assessment phase).

During the survey period each MAA reaching one of these stages was captured in the survey.

The consultation took place over a 6-month period from 5th September 2016 to end of February 2017. During this survey period, eight sets of questions were dispatched each month to the relevant participants as indicated below.



The survey combined the following response formats, depending on the nature of the question:

- Dichotomous Scale (Yes/No answers)
- 5-point Rating Scale (1 Strongly disagree; 2 disagree; 3 Neither agree nor disagree, 4 Agree; 5 Strongly agree; Not Applicable)
- Multiple choice and multiple response
- Free text

For the analysis presented in this document, responses rated 1 and 2 were considered as "disagreed" and responses rated 4 and 5 were considered as "agreed".

The outcome of this survey was co-presented by EMA and representatives from industry associations in the Industry Stakeholder Platform Meeting / Operation of the centralised procedure on 3rd July 2017 (link).

4. Sample captured and completion rate

The set objective was to capture 50% of the total annual volume of centralised Marketing Authorisation Applications (i.e. 40 to 50 MAAs) reaching Validation, Day 121 or Opinion stage. Sixty-five MAAs were captured at validation phase, 45 at Day 121, 49 for the Rapporteur surveys and 48 at opinion stage. The survey completion rates from each stakeholder were distributed as follows:

Table 1 Survey completion rate *per* stakeholder and per assessment phase

Stakeholders / Survey (N=MAA surveyed)	EMA	Industry	Rapporteurs	Co-Rapporteurs
Validation (N=65)	100%	97%	NA	NA
Day 121 (N=45)	100%	87%		
(Co-) Rapporteurs (N=49)			76%	79%
Opinion (N=48)	100%	92%	88%	90%

The objective of capturing 40 to 50 MAAs for all the 3 stages was achieved for all EMA surveys. The objective was reached for the Industry survey for the validation and opinion stage and missed by one application for the Day 121 stage. The objective was reached for the rapporteurs' survey for the opinion stage and missed by 3 applications for the Day 121 stage.

5. Survey results

The following sections summarise the results for the three phases of the survey for the Industry, EMA and Rapporteurs.

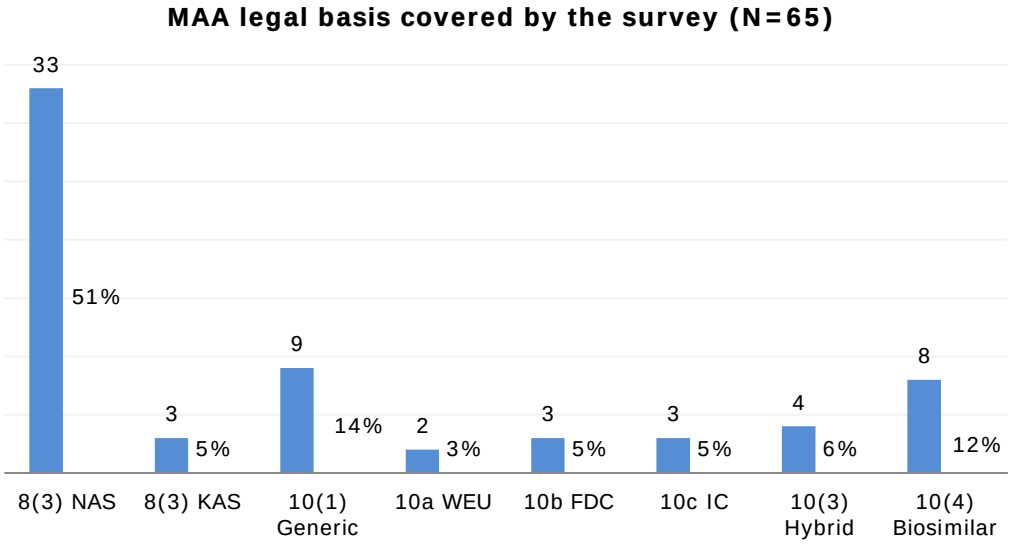
5.1. Pre-submission to validation phase

5.1.1. Survey results from Industry

The survey investigated 6 main topics through 27 questions: 1/application details, 2/pre-authorisation guidance, 3/pre-submission meeting, 4/accelerated assessment, 5/validation: impact on the procedure and 6/ overall feedback on the interaction during the pre-submission phase.

5.1.1.1. Applications details

The legal basis for the 65 applications covered in the survey, as retrieved from the EMA internal database, is presented below.



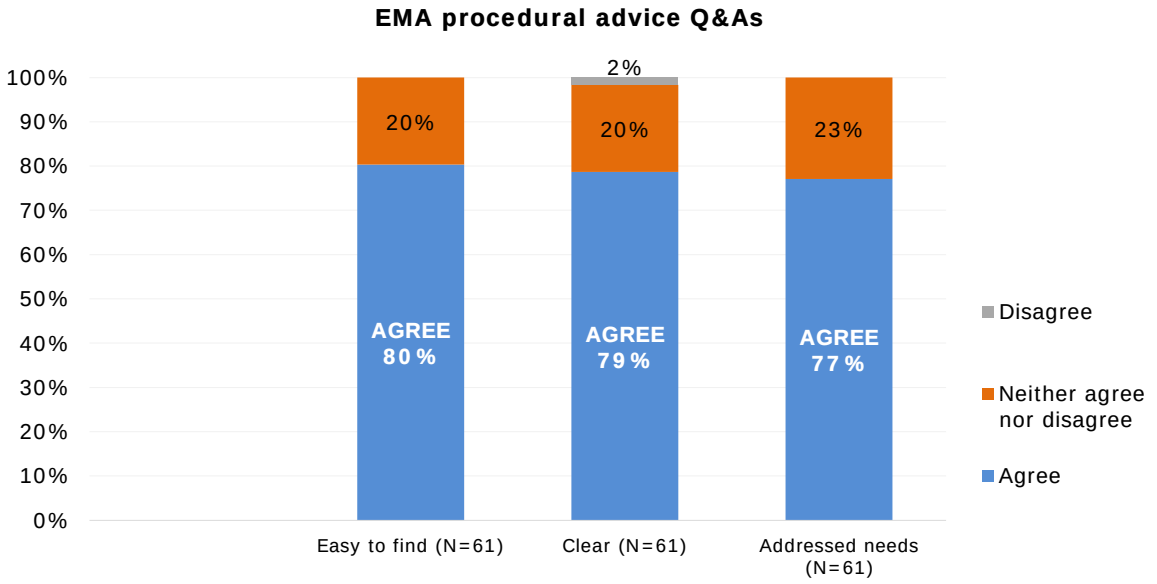
New Active substance: NAS; Known Active substance: KAS; Well-Established Use: WEU; Fixed Dose Combination: FDC; Informed Consent: IC.

Of the 65 applications captured, applicants answered the survey for 63 of them; EMA answered the survey for all 65 applications captured (see section 4). Overall there was a majority of new active substances (51%), followed by Generics (14%) and Biosimilars (12%), which is in line with the current trend of applications to the EMA through the centralised procedure. The sample surveyed captured a significant number of orphan medicinal products (30%) and 26% of applicants had SME status, in line with EMA records of previous years.

In conclusion, the sample of applications captured in the survey was considered representative and in line with EMA records of applications for previous years.

5.1.1.2. Pre-authorisation Guidance

Almost all applicants, 97% (61/63) stated that they consulted the EMA procedural advice Q&As. Approximately 80% (49/61) agreed that the information was easy to find. None disagreed. Approximately 79% (48/61) of the applicants agreed that the information was clear. Only 1 disagreed. Approximately 77% (47/61) of the applicants agreed that the information addressed their needs. None disagreed.

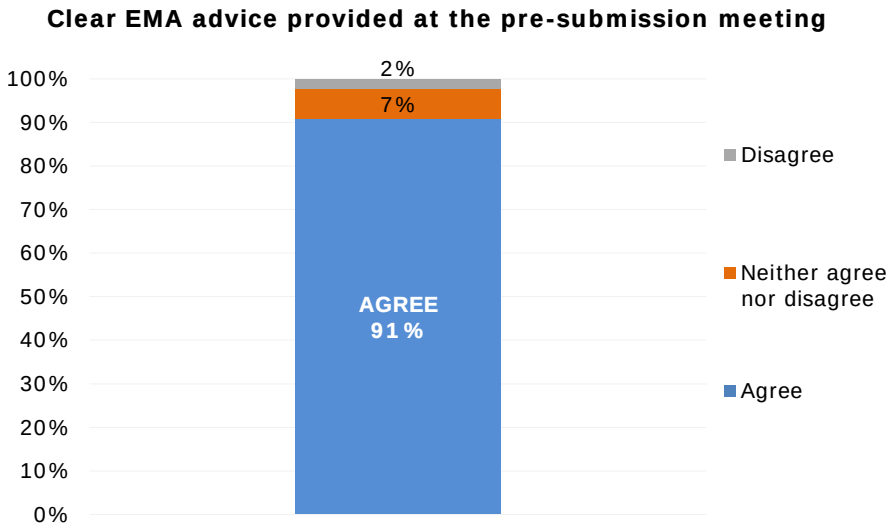


Overall, EMA Q&A guidance was considered as a valuable aid to submission preparation. Written free comments contrasted with the above good results and indicated that improvement of the guidance is possible in term of clarity, accessibility to the right information and level of details provided.

5.1.1.3. Pre-submission meeting

Almost 70% (44/63) of the applicants had an EMA pre-submission meeting. In almost half of the cases (48%, 21/44) the meeting happened 2 to 5 months prior to the submission. In 41% (18/44) the meeting happened 6 months prior to submission. In 11% (5/44) of the cases the meeting happened 2 months prior to submission.

Approximately 91% (40/44) of applicants agreed that they had an opportunity to get advice on their questions. None disagreed. Approximately 91% (40/44) of applicants agreed that EMA advice provided at the meeting was clear. Only 1 disagreed. Approximately 89% (39/44) of applicants agreed that the meeting was useful. Only 1 disagreed.



Approximately 68% (30/44) of applicants agreed that the meeting helped them understand potential issues regarding validation. Approximately 25% neither agreed nor disagreed. Three disagreed. Approximately 55% (24/44) of applicants agreed or strongly agreed that the meeting helped them understand potential issues regarding the assessment phase. Four disagreed.

In approximately 68% (43/63) of the cases the applicants had a separate pre-submission meeting with the (Co)-Rapporteurs at national level. When a meeting happened, in all cases this involved the Rapporteurs, in 86% of the cases also the Co-Rapporteurs and in 23% of the cases the PRAC rapporteurs.

In almost 67% of cases (42/63) the applicants did not request further advice from EMA on preparing their submission beyond the pre-submission meeting. For those who did request further advice, approximately 81% (17/21) of the applicants agreed that the advice helped them understand potential issues regarding validation. None disagreed. Approximately 76% (16/21) of the applicants agreed that the advice helped them understand potential issues regarding the assessment phase. Three disagreed. All of the applicants agreed that the advice was useful. None disagreed.

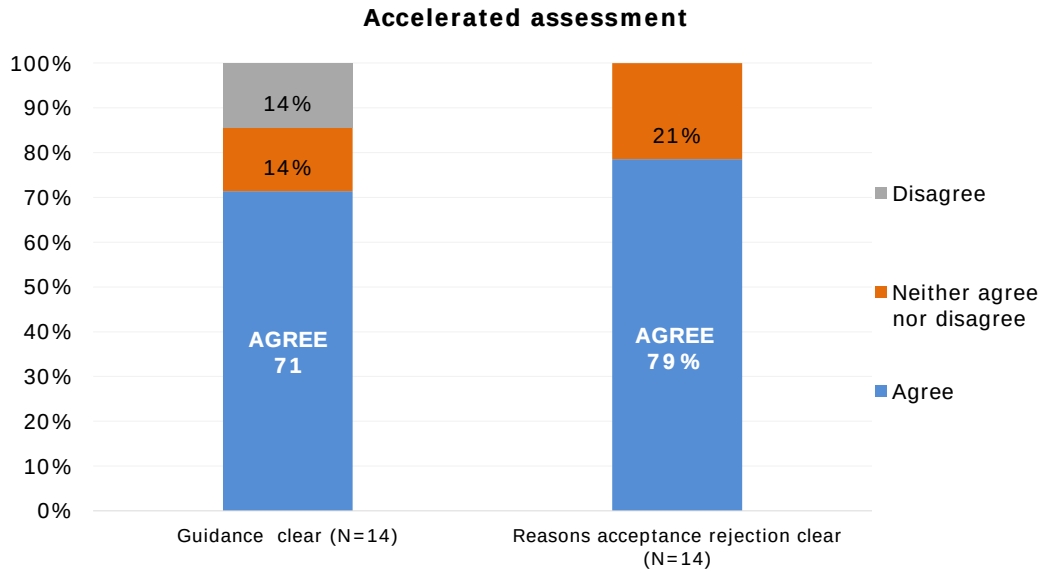
Overall EMA pre-submission advice is highly appreciated and considered useful. The opportunity to meet with EMA, (co-)rapporteur or other members of the assessment team is frequently used and highly valued. Additional aspects to be covered at the meeting could be the sharing of recent EMA experience on common validation issues and discussion of the eAF submitted by the applicant.

The most valuable aspects of pre-submission meetings with the Rapporteurs assessment team include: the possibility to introduce the product, development strategy and dossier, points of focus during dossier review and potential issues, addressing specific questions on the clinical package, addressing potential gaps in the submission, discussing the applicants' intent to provide updated information at day 121, and gaining better understanding of regulatory expectations overall.

5.1.1.4. Accelerated assessment

Accelerated assessment request was submitted in approximately 22% (14/63) of the applications surveyed. Approximately 71% (10/14) of the applicants agreed that the guidance for preparing the

accelerated assessment request is clear. Two disagreed. Approximately 79% (11/14) agreed that the reasons for the acceptance/rejection of the accelerated assessment were clear. None disagreed.



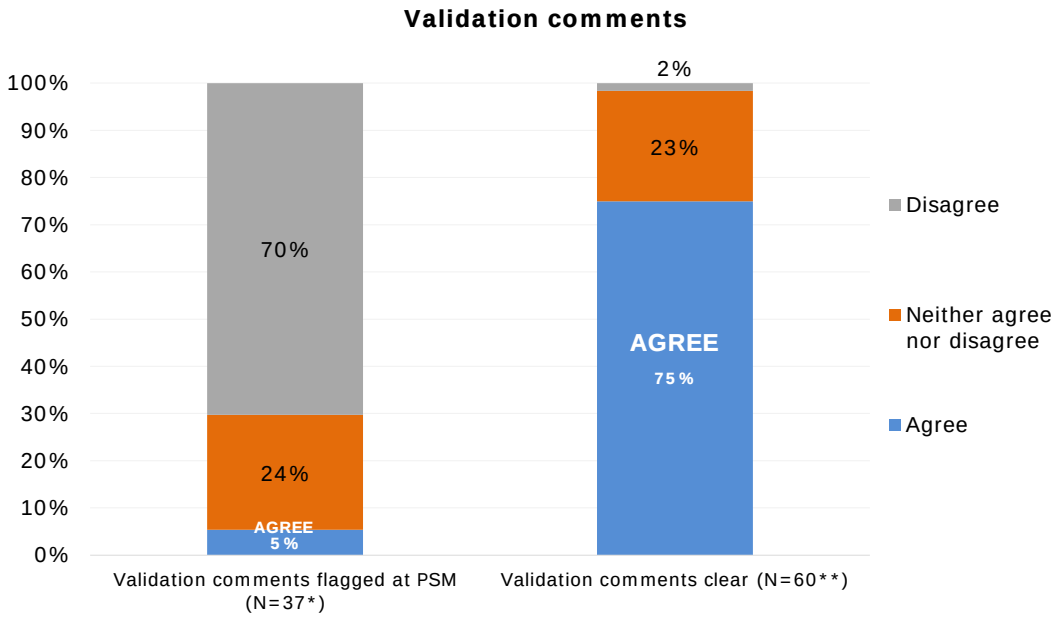
5.1.1.5. Validation: impact on procedure

Some 59% (37/63) of the applications were submitted on the date indicated in the letter of intent. In approximately 41% of cases (26/63) the applicants did not submit on the declared date. In those cases, 65% (17/26) informed the Rapporteurs and the EMA and 35% (9/26) did not.

Applicants indicated in 83% (52/63) of the cases that they did not encounter any difficulties with the gateway that delayed their submission. In 17% (11/63) issues were encountered that delayed their submission.

Applicants stated that the EMA comments received during validation related to amendment of documents in 89% (56/63) of the cases and missing documents in 48% (30/63) of the cases. Approximately 70% (26/37) of the applicants disagreed that the deficiency which led to EMA validation comments had been flagged at pre-submission meeting. Only 2 agreed that this was flagged. In 41% of responses (26/63), applicants informed that the question was not applicable. EMA validation comments however did not delay the start of the procedure in 95% (58/61) of the cases. In 3% (2/63) applicants informed that the question was not applicable.

Approximately 75% (45/60) of the applicants agreed that the EMA validation comments were clear. Only 1 disagreed. In 5% (3/63) applicants considered that the question was not applicable. Approximately 96% (51/53) of the applicants agreed that the questions regarding the validation were dealt with satisfactorily.



* minus 26 participants considering question as not applicable
** minus 3 participants considering question as not applicable

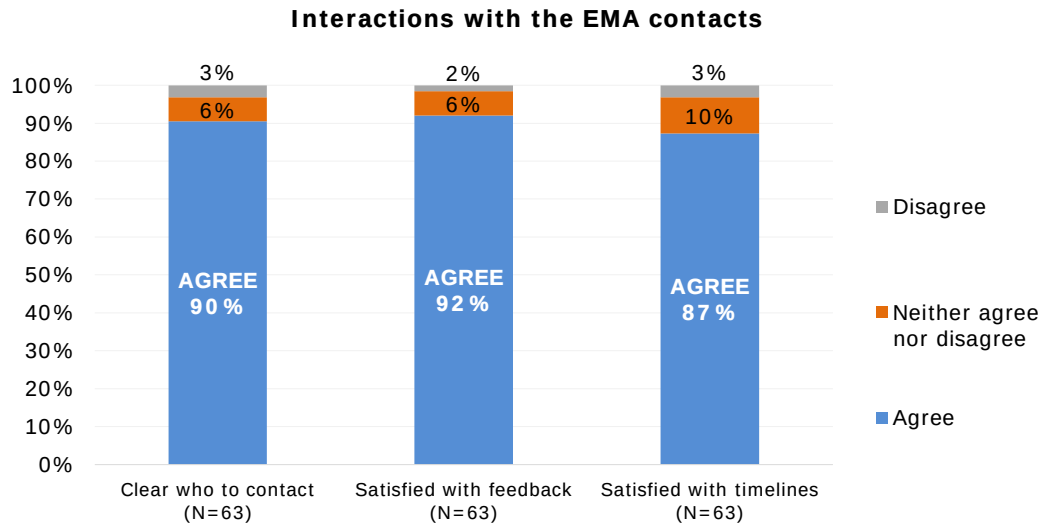
Overall, although the pre-submission meeting (PSM) generally is highly rated, it does not appear to pick up all validation issues, which included missing documents in almost half of submissions. However, it was noted that these validation issues did not delay the start of the procedure in 95% of the applications submitted.

Validation issues were considered to occur too frequently, creating an administrative burden for both Industry and EMA. Possible solutions were suggested such as: attendance by EMA validation team at the PSM, introducing a discussion of the application form as a mandatory item at the PSM, increase awareness of the most common issues at validation by publishing them in the pre-authorisation Q&A.

A substantial number (41%) of applicants did not submit their application as indicated in their letter of intent; 35% of them did not inform the EMA and the Rapporteurs about that delay. Accuracy of MAA submission date as well as communications of delays from the applicants to EMA and Rapporteurs were highlighted as areas for further improvements.

5.1.1.6. Overall feedback on interaction during pre-submission phase

Approximately 90% (57/63) of the applicants agreed that the guidance on who to contact at the EMA was clear. Two disagreed. Approximately 92% (58/63) of the applicants agreed that they were satisfied with the quality of EMA feedback on procedural/regulatory aspects. One disagreed. Approximately 87% (55/63) of the applicants agreed that they were satisfied with the timeliness of the interaction. Two disagreed.



5.1.2. Survey results from EMA staff

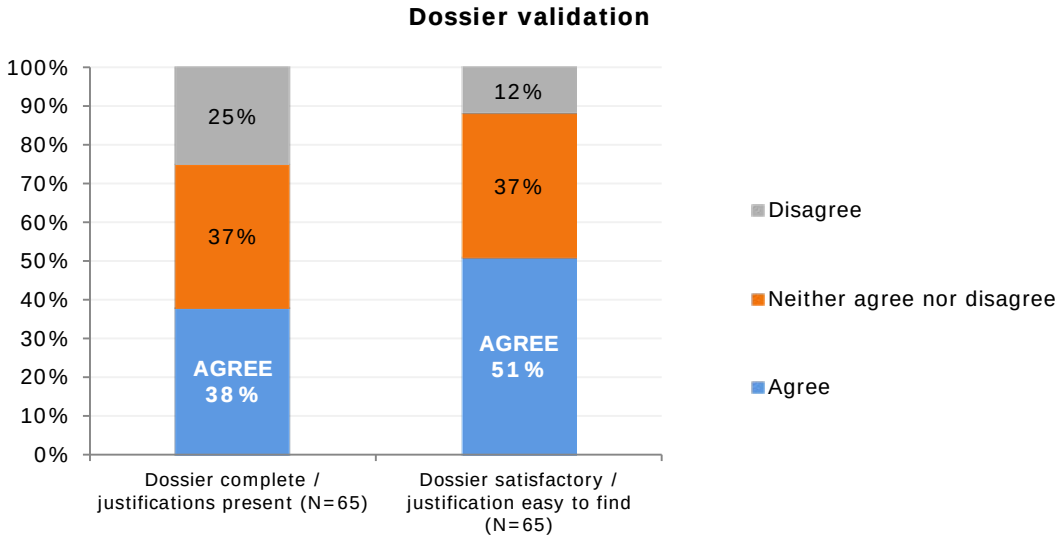
The survey investigated 6 main topics through 24 questions: application details, validation: impact on the procedure, pre-authorisation guidance, pre-submission meeting, accelerated assessment and overall feedback on the interaction during the pre-submission phase.

5.1.2.1. Applications details

See sections 5.1.1.1 above.

5.1.2.2. Validation impact on the procedure

A slightly greater number of the EMA respondents agreed that the dossier was complete (38% [25/65]) and presented in a satisfactory way (51% [33/65]). There were non-negligible proportions of "neither agree nor disagree" ratings for both queries as shown below.



Validation questions were raised in almost all MAA submitted i.e. 97% (63/65). Almost all applicants responded to the validation questions according to the agreed timelines (94% [59/63]); however in

approximately half of cases (56% [35/63]) the responses provided required further follow-up with applicants in order to complete the validation.

The most frequent validation issues were purely administrative and would not block the start of the procedure. The areas most often cited were:

- Quality and GMP aspects (92% [58/63]): most frequent issues related to inconsistencies of the Application Form (90% [52/58]) and the qualitative and quantitative composition of the medicinal product (62% [36/58]);
- Clinical/nonclinical and GCP/GLP aspects (83% [52/63]): more than half of the issues related to GLP/GCP information;
- Product information (30% [19/63]): 95% of issues in this area relate to inconsistencies with the application form (ATC, strength, pharmaceutical form, route of administration, container, pack size, product name)

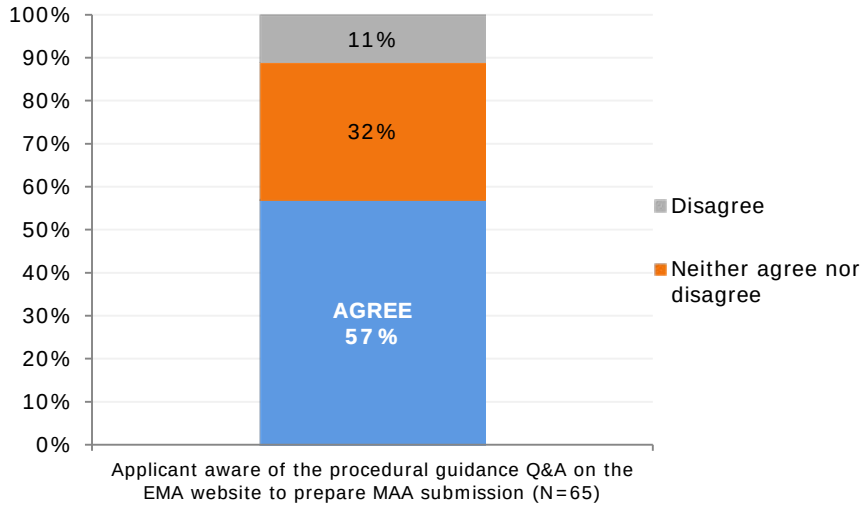
The application form was commented on in almost all applications. Most queries related to quality and GMP matter (81%); the Applicant's contact person & details & (75%) and the Nonclinical/clinical and GCP/GLP aspects (65%).

Results indicated that EMA should look for ways to increase awareness about the validation process and the most common issues encountered at validation (published on EMA website), as well as the procedural pre-submission guidance available to applicants. For the latter, which details the regulatory elements required to start the evaluation, EMA should identify any possible gaps in the guidance and how the information can be better presented. Applicants also need to work to increase their awareness of EMA requirements; particular focus could be on reducing discrepancies in the application form and the dossier submitted. Applicants are encouraged to request clarifications prior to submission.

5.1.2.3. Pre-submission guidance

The majority of the respondents (57%) agreed that applicants were aware of the procedural guidance (Q&A on EMA website). There was a non-negligible proportion of "neither agree nor disagree" ratings. An analysis by legal basis and SME vs non SME status did not show a clear pattern.

Pre-submission guidance awareness

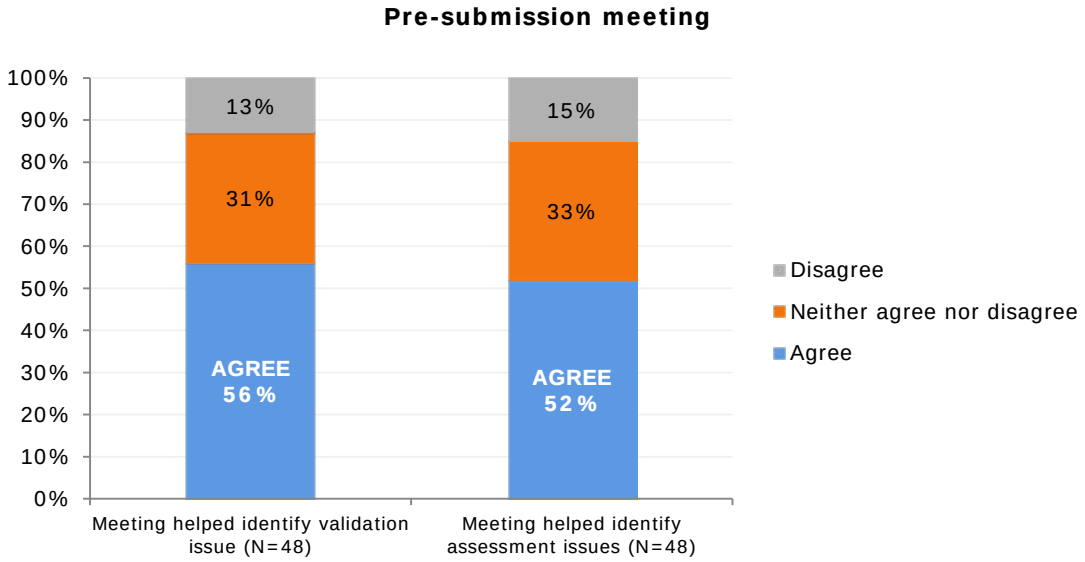


Combined with the almost 100% validation questions rate, these results reinforced the previous conclusion on the need for EMA to increase general awareness and ease access to the procedural pre-submission guidance

5.1.2.4. Pre-submission meeting

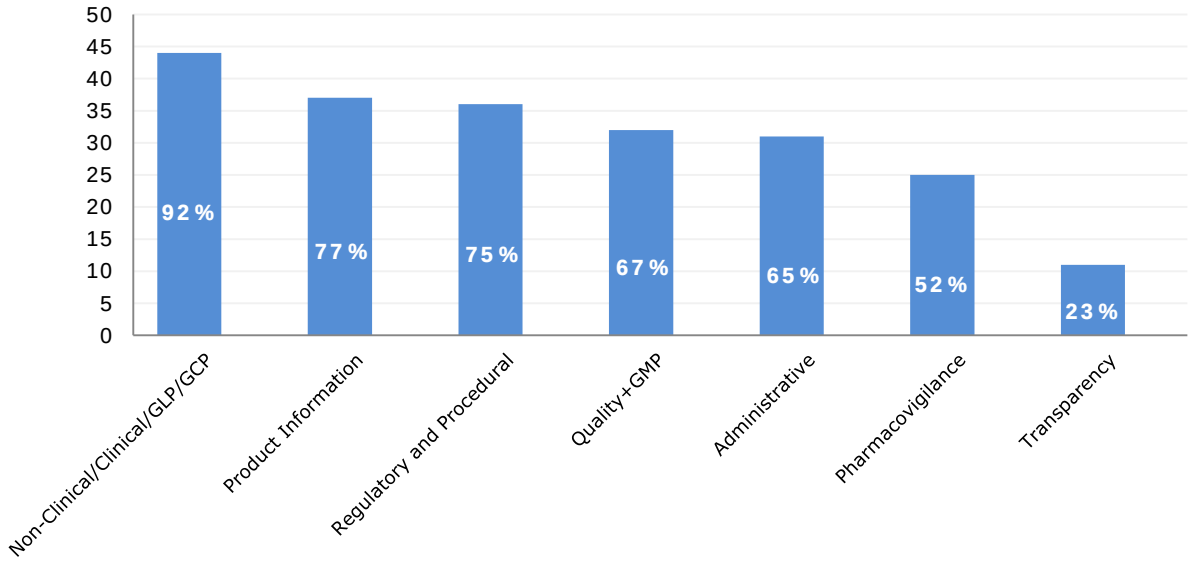
Overall a pre-submission dialogue between EMA and applicants took place in 83% (54/65) of the applications submitted. A pre-submission meeting occurred in almost three quarters (74%, 48/65) of the applications submitted. Around 10% (6/65) of applicants requested written/verbal advice from the EMA instead of a pre-submission meeting. No interaction with the EMA took place prior to submission for 11 applications (approximately 15%). The majority of applications for which no pre-submission meeting was requested concerned either generic products or informed consent applications. In approximately 25% (13/48) of the meetings there was a follow-up to the advice provided during the pre-submission meeting. Most of the applications from SMEs (14/17) and orphan medicinal product applications (17/19) involved a pre-submission meeting.

In just above half (56%, 27/48) of the meetings EMA respondents considered that the meeting helped to identify potential validation issues. Similarly just above half (52%, 25/48) of the meetings were considered to help identify issues regarding the assessment phase.



The high level scopes, numbers and overall proportion of the most frequent areas (more than 20% of cases) raised by applicants during pre-submission meetings are displayed below.

Scope, numbers and overall proportion of pre-submission questions raised by applicants



Analysis of the above most prevalent scopes:

- Non-clinical/clinical/GLP/GCP matters: In the 44 meetings where these scopes were discussed, the most common topics were clinical development (80% - 35/44); paediatric development (48% - 21/44); non-clinical development (39% - 17/44); the orphan designation (34% - 15/44); the environmental risk assessment or ERA (30% - 13/44).

- Product information: was discussed in 37 meetings and the most common topics related to the SmPC guideline and QRD templates (70% - 26/37); consultation with target patient group (62% - 23/37); mock-up and specimen (41% - 15/37); ATC and INN or invented names (both 27% - 10/37).

- Regulatory and procedural aspects were discussed in 36 meetings: the most common topics related were the legal basis (39% - 14/36); the accelerated review (36% - 13/36); SME status (22% - 8/36); eligibility, legal status and multiple applications were each discussed 17% (6/36). Conditional MA/MA under exceptional circumstances and data exclusivity/market protection were discussed in less than 14% of the meetings.

- Quality and GMP matters: the most common topics related to quality development (72% - 23/32) and GMP inspections (56% - 18/32).

- Administrative: the most common topics related to the dossier submission requirements (65% - 20/31); the dossier format (61% - 19/31); and the applications fees (55% - 17/31). The timetable of assessment was discussed in 29% of the meetings (9/31).

- Pharmacovigilance was discussed in 25 meetings: the most common topics related to the RMP. This was discussed in all 25 meetings. Pharmacovigilance system (3/25) or inspections (1/25) were rarely discussed.

Overall, there is a very high level of interaction with EMA prior to submission, mostly via pre-submission meetings. Pre-submission meetings helped prevent validation questions that could block the application in 95% of the applications. However, almost 100% of applications have non-blocking administrative validation issues. EMA should investigate opportunities to make better use of pre-submission meetings to further anticipate and prevent the non-blocking validation issues.

5.1.2.5. Accelerated assessment

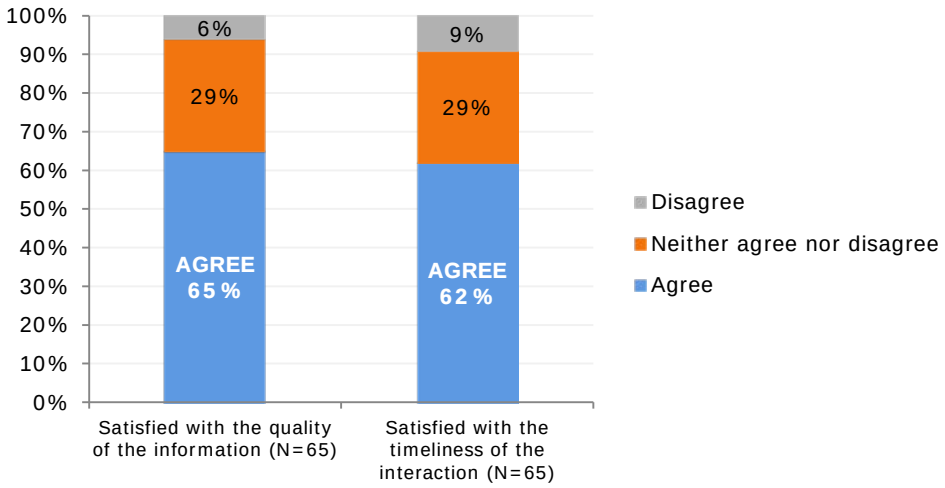
Accelerated assessment was requested in 22% (14/65) of all validated MAAs. All except one of these requests were discussed at the pre-submission meeting and all except one were received 2-3 months before the actual submission in accordance with the guideline on accelerated assessment. In all cases the justifications for requesting accelerated assessment were in line with the available EMA template.

Almost a quarter 22% (14/65) of the MAAs requested accelerated assessment. The confirmation that almost all cases were discussed at the pre-submission meeting and that the requests for accelerated assessment were made according to the most up-to-date EMA guidance confirm the very good level of awareness from applicants aiming to follow that evaluation path.

5.1.2.6. Feedback on interaction during pre-submission activities

In approximately 65% (42/65) of cases, EMA agreed that they were satisfied with the quality of the information provided by applicants. In approximately 6% (4/65) of the cases EMA disagreed. In approximately 62% (40/65) of cases, EMA agreed that they were satisfied with the timeliness of the interactions with applicants. In 10% (6/65) EMA disagreed. In approximately 29% (19/65) of the cases EMA neither agreed nor disagreed for both queries.

Interaction with applicants during pre-submission activities



Overall, EMA was satisfied with the quality of the information & timeliness of interactions with applicants during the pre-submission phase.

5.2. Day 1 to 121: primary assessment phase

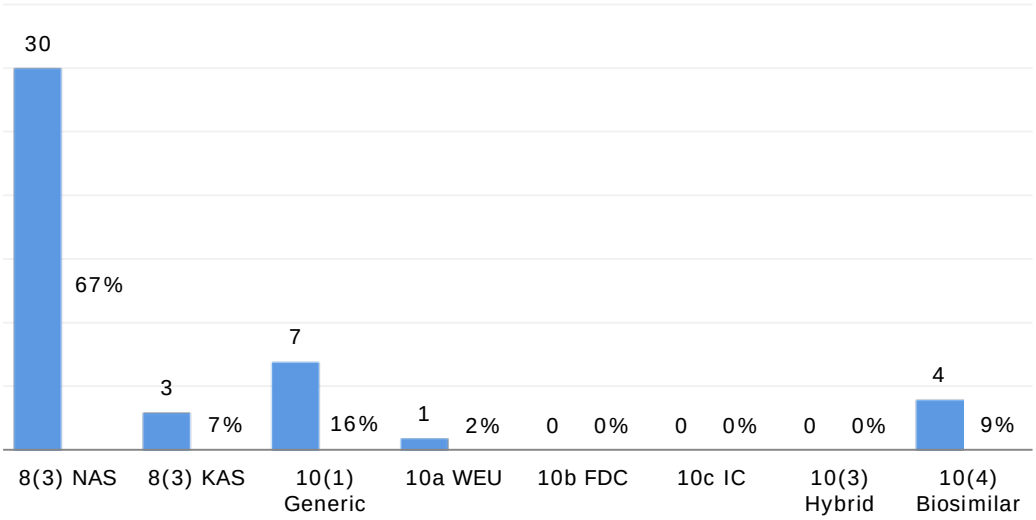
5.2.1. Survey results from Industry

The survey investigated 4 main topics through 16 questions: application details, assessment report in primary assessment phase, labeling review in primary assessment phase, clarification meeting and overall feedback on the interaction during the primary assessment phase.

5.2.1.1. Application details

The legal basis of the 45 applications captured in the survey, as retrieved from the EMA internal database, is presented below. Applicants answered the survey for 39 of the 45 applications; EMA answered the survey for all 45 (see section 5.2.2.). Overall there was a majority of new active substances (67%), followed by generics (16%) and Biosimilars (9%) in line with the previous phase of the survey. The sample surveyed captured significant numbers of orphan medicinal products (24%) as well as applicants with SME status (27%).

MAA legal basis covered (N=45)



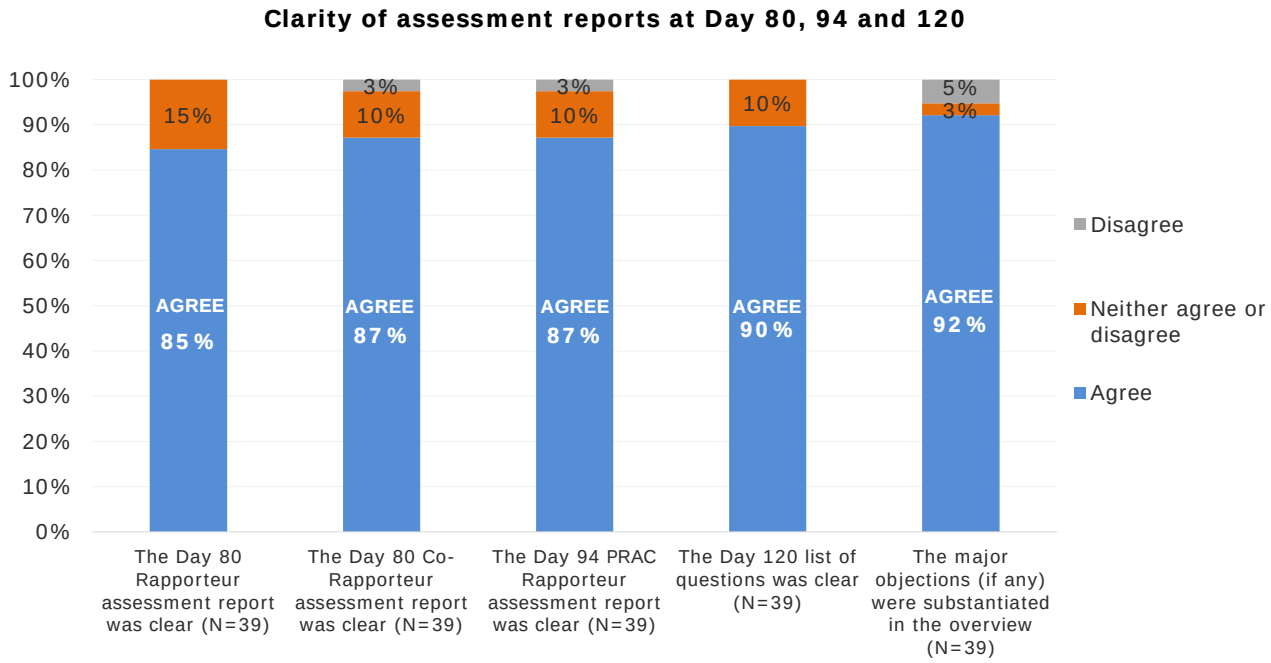
New Active substance: NAS, Known Active substance: KAS, Well-Established Used: WEU, Fixed Dose Combination: FDC, Informed Consent: IC

5.2.1.2. Assessment reports in primary assessment phase

The Day 80 Rapporteur Assessment Report (AR) and Day 80 Co-Rapporteur AR were received within 2 working days of the due date in 54% (21/39) and 67% (26/39) of the cases respectively. Day 94 PRAC Rapporteur AR was received within 2 working days in 79% (31/39) of the cases. Applicants were generally (i.e. in 70% [14/20] of cases) not informed proactively when delay was greater than 2 working days.

Approximately 85% (33/39) and 87% (34/39) of the applicants agreed that Day 80 Rapporteur AR and Day 80 Co-Rapporteur AR were clear. Only one applicant disagreed for a Co-Rapporteur AR. Approximately 87% (34/39) of the applicants agreed that Day 94 PRAC Rapporteur AR was clear. One applicant disagreed.

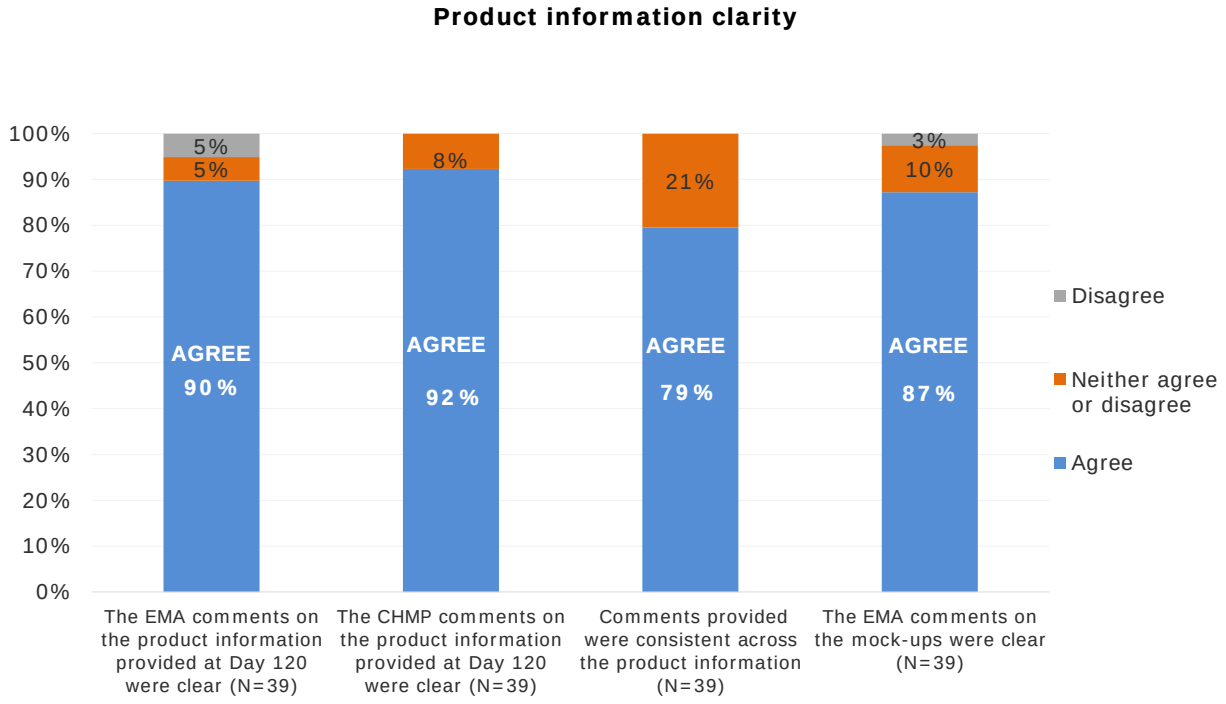
Approximately 90% (35/39) of the applicants agreed that the Day 210 LoQ was clear. None disagreed. Approximately 92% (35/38) of the applicants agreed that the major objections were substantiated in the overview. Two applicants disagreed.



Overall, assessment reports, questions and major objections are of high quality (clarity and consistency). Although assessment reports are usually provided in accordance with the timetable, delays are not uncommon and are not always proactively communicated to the Applicant. Circulation timelines and communication of delays for assessment reports were therefore highlighted as areas for improvement.

5.2.1.3. Labeling review in primary assessment phase

In almost all cases 95% (37/39) applicants received at Day 120 a single file of product information (PI) including comments from both CHMP and EMA as per the EMA process. Approximately 90% (35/39) of the applicants agreed that the comments on the PI provided at Day 120 were clear. Two applicants disagreed. Approximately 79% (31/39) of the applicants agreed that the comments provided were consistent across the PI. None disagreed. Approximately 87% (34/39) of the applicants agreed that the EMA comments on the mock-ups were clear. Only one applicant disagreed.

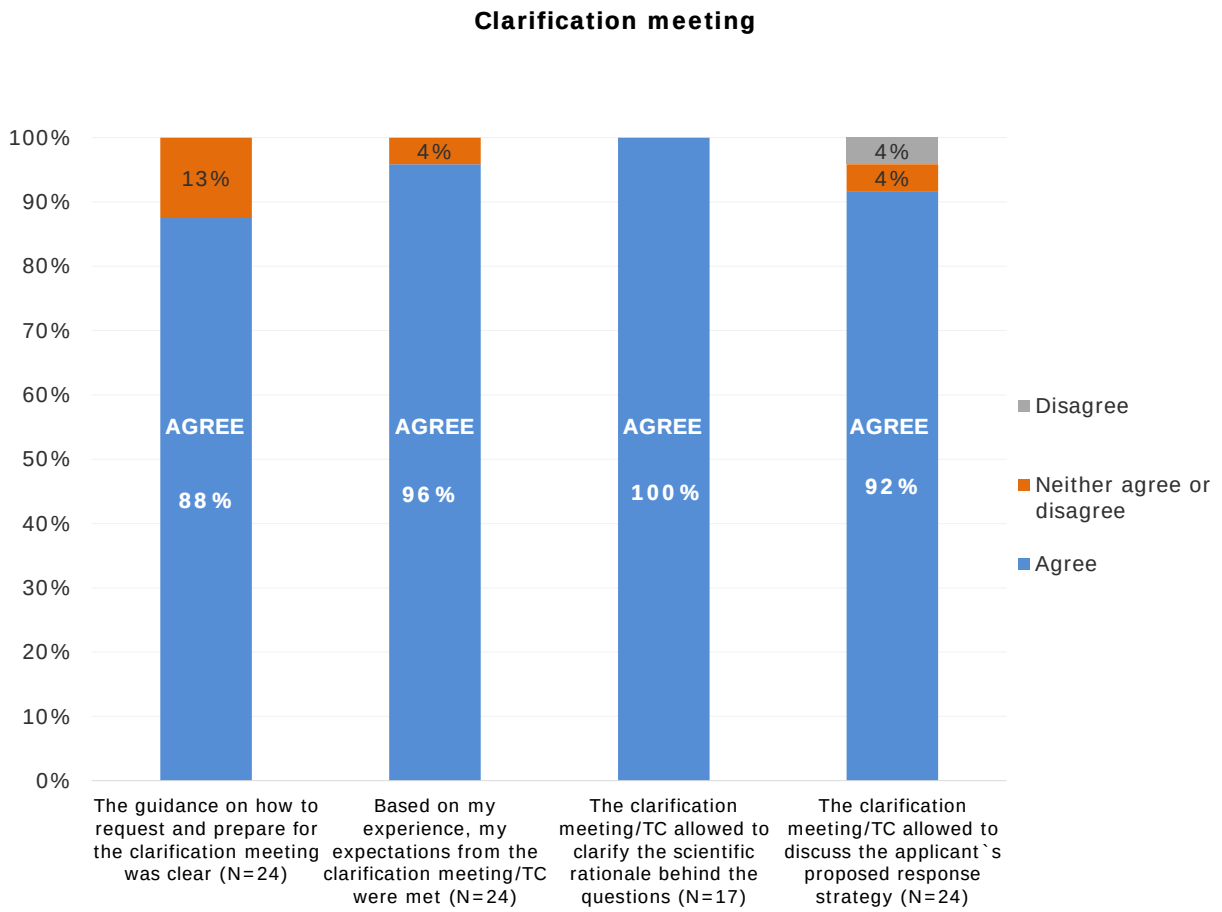


Overall, the majority of respondents received a single file encompassing comments from both the CHMP and EMA as per the EMA process. The comments on the product information and mock ups are of high quality.

5.2.1.4. Clarification meeting

Of the 39 surveyed applications reaching Day 120, a clarification meeting or teleconference (TC) was held in 24 cases (62%). In all cases the goal was to discuss the applicants' proposed response strategy. In 58% (14/24) of the cases the goal was also clarification on questions or the scientific rationale behind the questions.

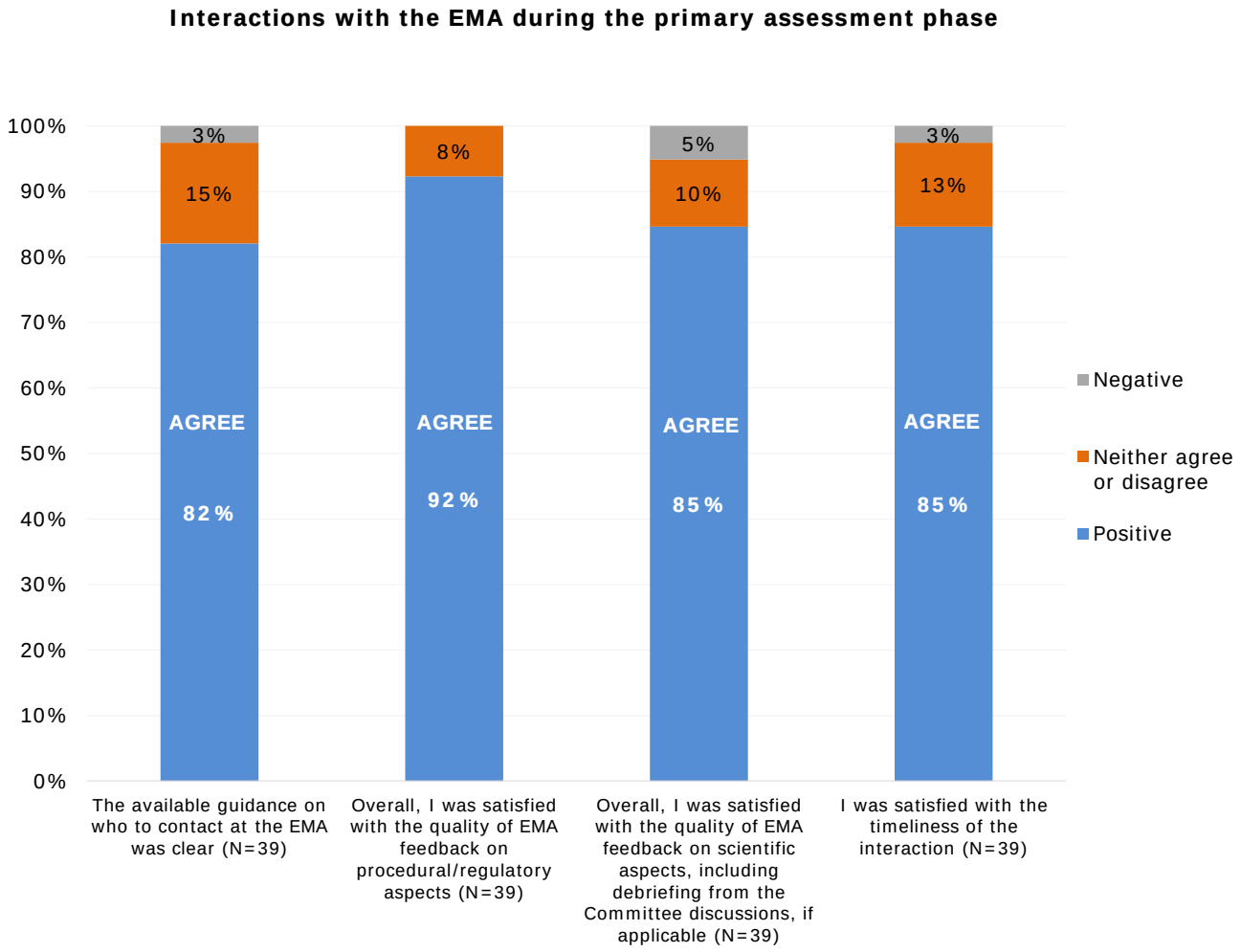
Approximately 88% (21/24) of the applicants agreed that the guidance on how to request and prepare for the clarification meeting was clear, and almost all (96% [23/24]) agreed that their expectations from the clarification meeting/TC were met. None disagreed on either point. All of the applicants (17/17) agreed that the meeting/TC had clarified the scientific rationale behind the questions. Almost all applicants (92% [22/24] agreed that the clarification meeting/TC allowed discussion of their proposed response strategy. One disagreed.



Overall, clarification meetings are valued for their usefulness, especially for discussing the applicants' responses strategy.

5.2.1.5. Overall feedback on interaction during primary assessment phase

Approximately 82% (32/39) of the applicants agreed that the available guidance on who to contact at the EMA was clear. Only one applicant disagreed. Almost all applicants, 92% (36/39), agreed that they were satisfied with the quality of EMA feedback on procedural/regulatory aspects. None disagreed. Approximately 85% (33/39) of the applicants agreed that they were satisfied with the quality of EMA feedback on scientific aspects, including debriefing from the Committee discussions. Two disagreed. Approximately 85% (33/39) of the applicants agreed that they were satisfied with the timeliness of the interaction. Only one applicant disagreed.



Overall, interactions with the EMA during the primary assessment phase were very positive. Although 82% of responders thought the guidance clear on who to contact at the EMA, the free comments referred to some uncertainty regarding contacting the PM or the EPL, hence requiring clarifications.

Taking into consideration all response for this phase of the survey results indicate that Day 0 to 120 of the centralised procedure is well run.

5.2.2. Survey results from EMA

The survey investigated 4 main topics through 13 questions: application details, labeling review in the primary phase, clarification meeting and overall feedback on the interaction with applicants during the primary assessment phase.

5.2.2.1. Application details

See section 5.2.1.1 application details.

5.2.2.2. Labeling review in primary assessment phase

EMA staff mainly neither agreed nor disagreed on whether the submitted PI by the applicant was presented in a satisfactory way and followed the relevant guidance such as QRD and/or SmPC guidance. This represented almost half of the cases (49% [22/45]). In approximately 38% of cases

(17/45) EMA agreed that the PI was satisfactory. In 13% (6/45) of the cases EMA disagreed that the PI was satisfactory.

Written comment supporting the above rating were: “Info displayed mostly useless for the prescriber”; “SmPC not in line with SmPC guideline principles (especially section 4.5, 4.8 and 4.9)”; “Principles of the SmPC guideline were not always correctly implemented, especially for section 4.1 (inclusion of endpoints) and section 4.8 (where too much information on clinical trials were included)”; “Poor compliance with the QRD template and with the SmPC guideline”; “Various remarks, regarding clarity of statements, especially pertaining sections 4.2, 4.3, 4.4 and 4.8 SmPC”; “QRD template version 10 [needs] to be followed.”

Overall it was concluded that EMA should investigate opportunities to increase applicants’ awareness of existing guidelines as applicants needed to improve their awareness of and adherence to SmPC and QRD guidelines and template.

5.2.2.3. Clarification meeting

There was a clarification meeting in approximately 62% (28/45) of the applications reaching a Day 121. In almost all cases (26/28) EMA considered that applicants clearly specified the scope and the topics to be discussed for the meeting. In a good majority 79% (22/28), the briefing document was provided at least a week prior to the meeting as requested by the EMA guidance. Approximately 71% (20/28) of the EMA staff agreed that the meeting facilitated the progress of the procedure. Three EMA respondents disagreed.

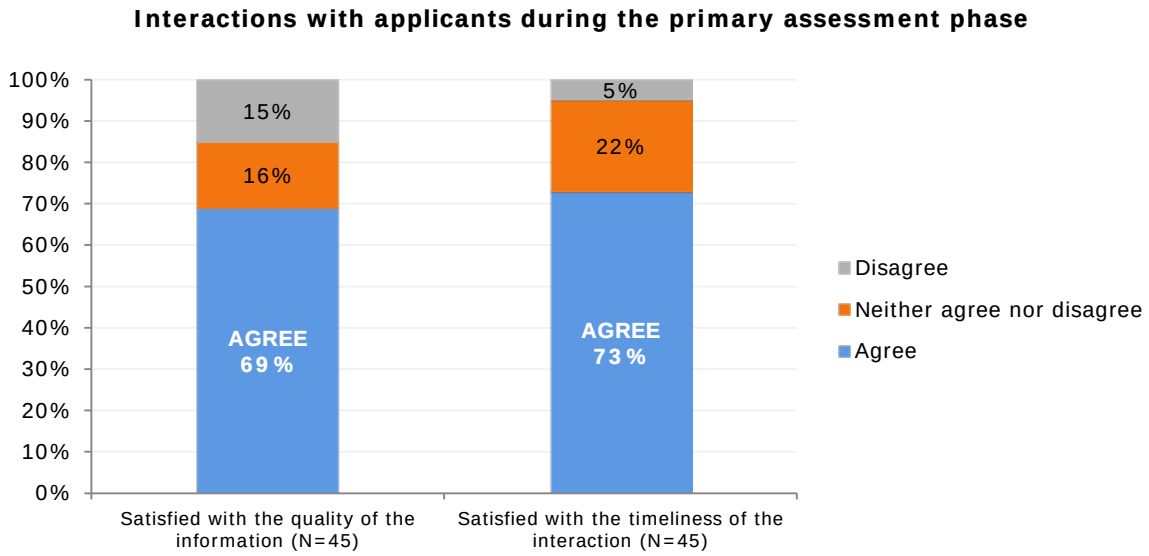
Clarifications meetings most often happened when the applications concerned a new active substance (85%, 24/28) and/or an orphan medicinal product (82%, 9/11) and/or when the applicants had an SME status (83%, 10/12).

Overall the majority of applicants displayed very good awareness and adherence to the clarification meeting guidance requirements (clarity of scope and topics and briefing documents provided in a timely fashion). Positive free-text comments were noted supporting the usefulness of the clarification meeting.

5.2.2.4. Overall feedback on interaction during the primary assessment phase

In approximately 69% (31/45) of the cases EMA agreed that they were satisfied with the quality of the information provided by applicants during the interactions. In approximately 16% (7/45) of the cases though, EMA disagreed. The results indicate room for improvement in the quality of the information provided by applicants. However, no suggestions on how to do this were included in the free text comments.

In approximately 73% (33/45) of the case EMA agreed that they were satisfied with the timeliness of the interactions with applicants. In less than 5% (2/45) EMA disagreed.



Overall EMA concluded that interactions with the applicants during the primary assessment phase were positive; both in terms of quality of the information provided and timeliness of the interaction. Positive free text comments were noted supporting this conclusion.

5.2.3. Survey results from Rapporteurs

The survey to rapporteurs investigated 5 topics through 11 questions: application/responder identifiers, the submitted dossier, adherence to scientific advice, labeling review in primary assessment phase, clarification meeting, and overall feedback on interaction during the primary assessment phase.

Overall, the survey was completed by 37 Rapporteurs and 31 Co-Rapporteurs, i.e. a total of 68 responses were received. The responses of both teams followed the same trend. Where "(Co-) Rapporteurs" results are mentioned, this refers to the responses of Rapporteurs and Co-Rapporteurs combined.

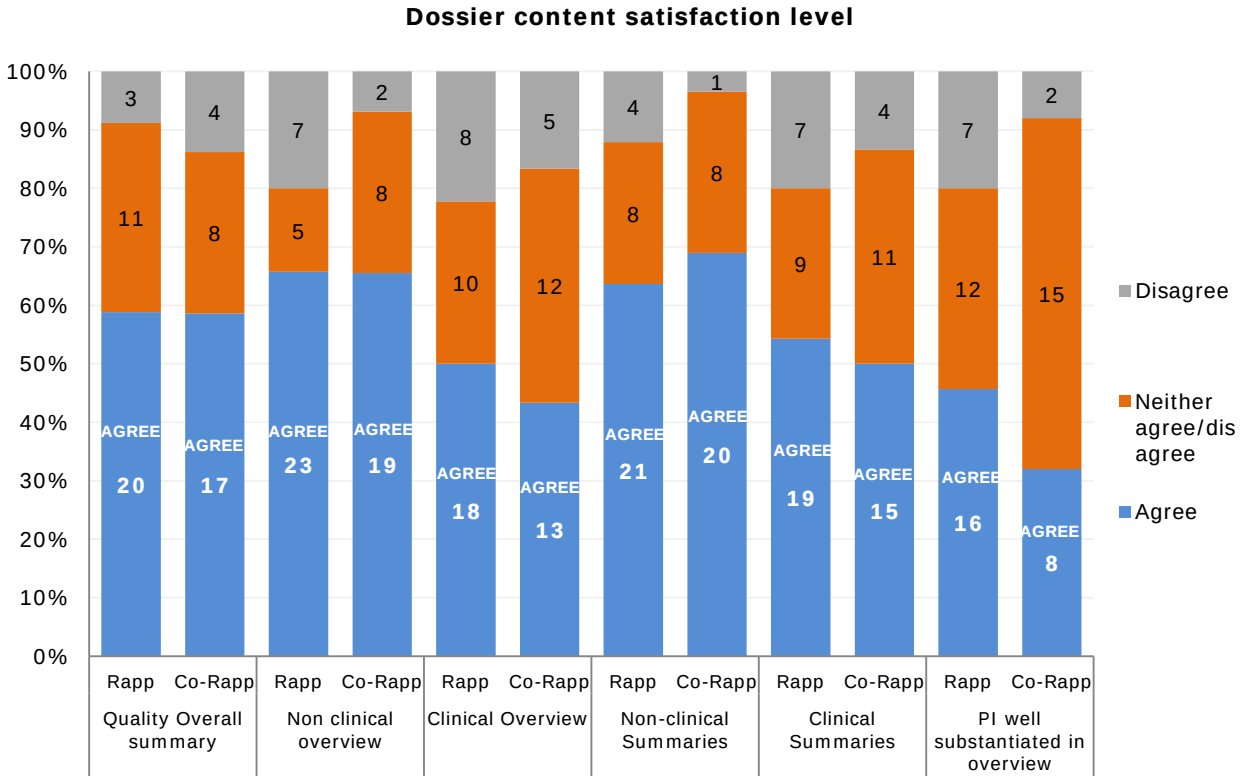
5.2.3.1. The submitted dossier

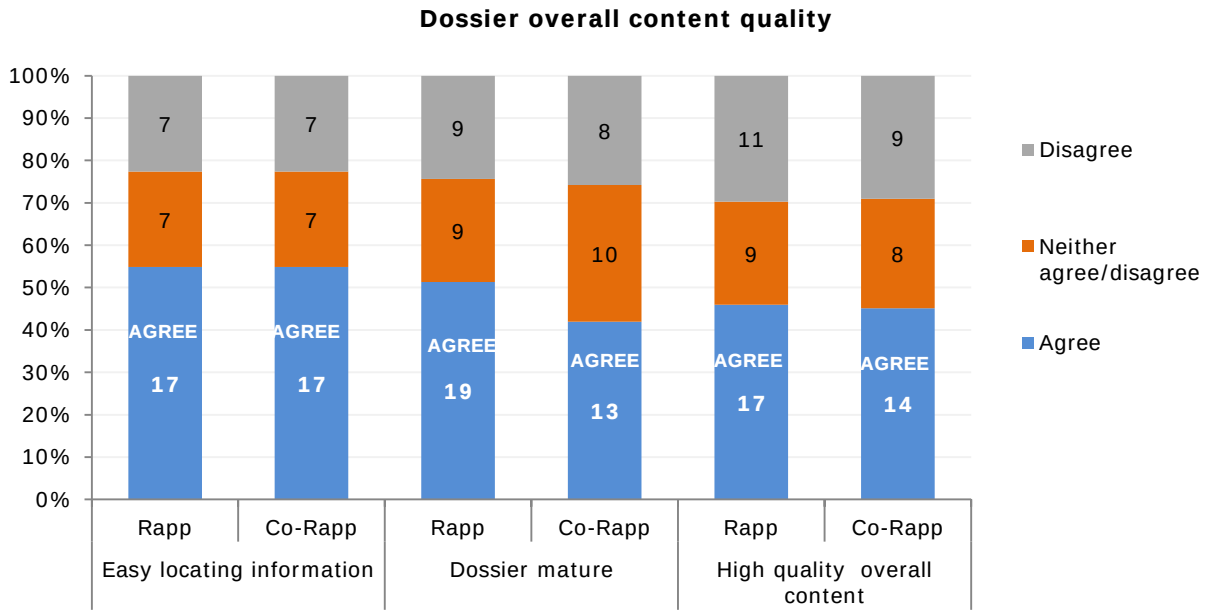
Ratings by the (Co-) Rapporteurs for the adequacy of the applicants' dossier content are shown in the 2 charts below. The charts exclude the answer 'not applicable'. There was generally good agreement between summary ratings of Rapporteurs` and Co-Rapporteurs` teams.

In summary:

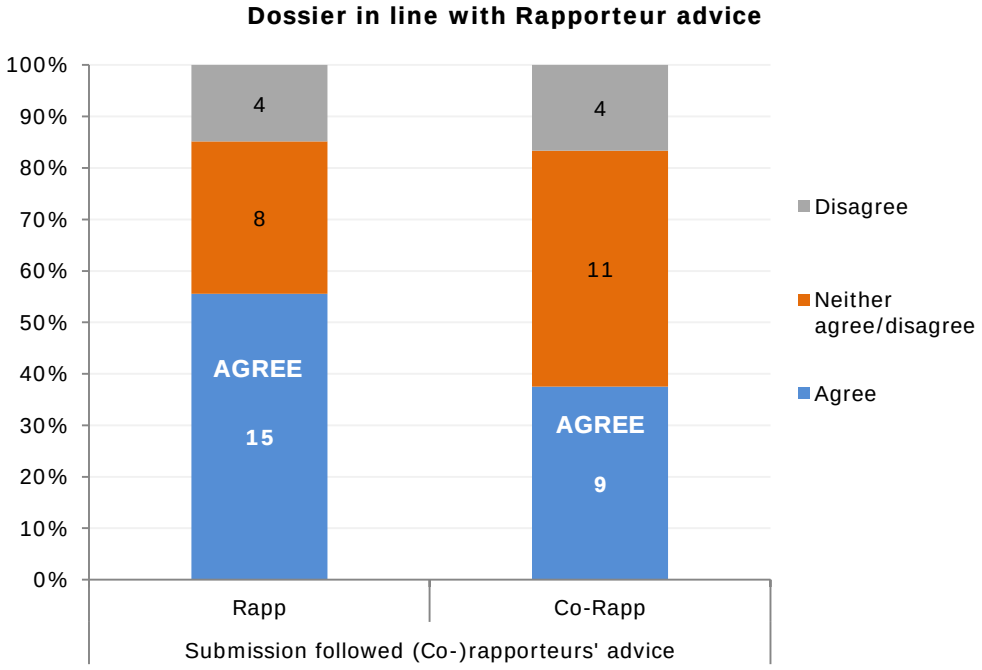
- 59% (37/63) of the (Co-) Rapporteurs considered the Quality Overall Summary adequate (rating 4-5).
- 66% 42/64) of the (Co-) Rapporteurs considered the non-clinical overview adequate.
- 47% (31/66) of the (Co-) Rapporteurs considered the clinical overview adequate.
- 66% (41/62) of the (Co-) Rapporteurs considered the non-clinical summaries adequate.

- 52% (34/65) of the (Co-) Rapporteurs considered the clinical summaries adequate.
- 54% (37/68) of the (Co-) Rapporteurs rated positively how easy it was to locate the relevant information in the dossier.
- 47% (32/68) of the (Co-) Rapporteurs rated the overall maturity level of the dossier positively.
- 46% (31/68) of the (Co-) Rapporteurs rated the quality of the content of the dossier overall positively.





The following chart summarises the ratings of the (Co-) Rapporteurs on how well the submission took into account the advice provided by the (Co-) Rapporteurs in the pre-submission dialogue.



Overall, 47% (24/51) of the (Co-) Rapporteurs` responses agreed positively that the submission took their advice into account (rating 4 or 5); for a further 37% of the response rating was neutral.

Overall, positive ratings (scores 4 -5) concerning specific sections of the dossier varied from 40% to 66% (combined ratings). There was a non-negligible proportion of “neither agree nor disagree”

ratings. The lowest ratings concerned the substantiation of the proposed PI in the applicant's overview and adequacy of the Clinical Overview (e.g. critical appraisal). Overall, 47% of the (Co-) Rapporteurs` responses agreed that the submission followed their advice.

In almost half of the responses the overall maturity (47%) and overall quality of content (46%), of the applicants' dossier was rated positively (scores 4-5). Respectively 28% and 25% of responses were neutral (rating 3) and 25 % and 29% of responses received negative ratings (ratings 1 – 2).

This indicates overall a moderate level of satisfaction of the (Co-) Rapporteurs with the quality of the initially submitted dossier.

Some explanations for the lower scores are (based on the free text comments, as summarized):

Poorly structured submissions, incomplete module 3 leading to substantial data to be submitted in D121 responses, incomplete clinical overview, absent non-clinical overview, missing documents (validation of analytical procedures), inconsistencies between different sections, and lack of adequate analysis and presentation (e.g. no safety summary tabulations, no summaries of lab data, no pooling of safety data across trials, lack of integrated immunogenicity summary for Biosimilars).

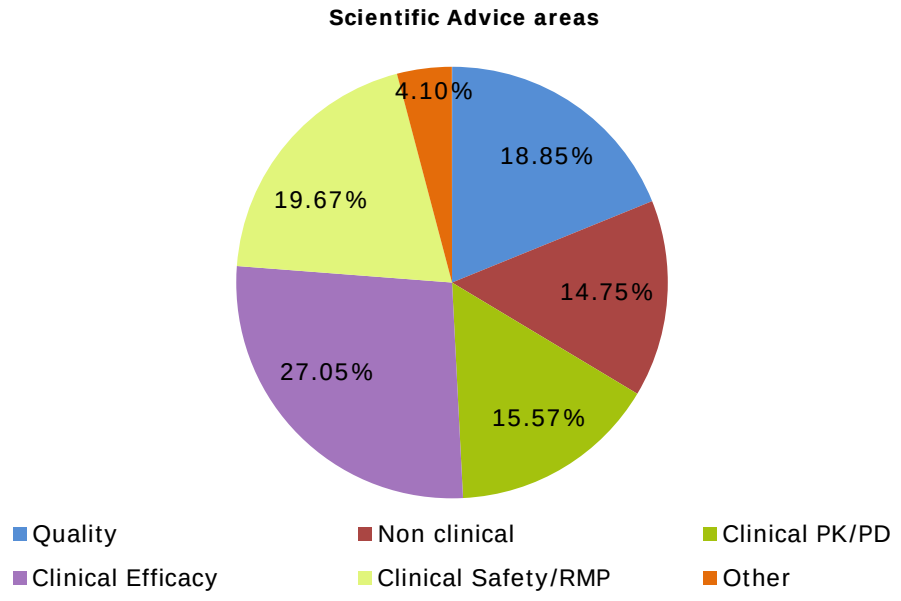
These issues make the work of the (Co-) Rapporteurs and the assessment teams more difficult.

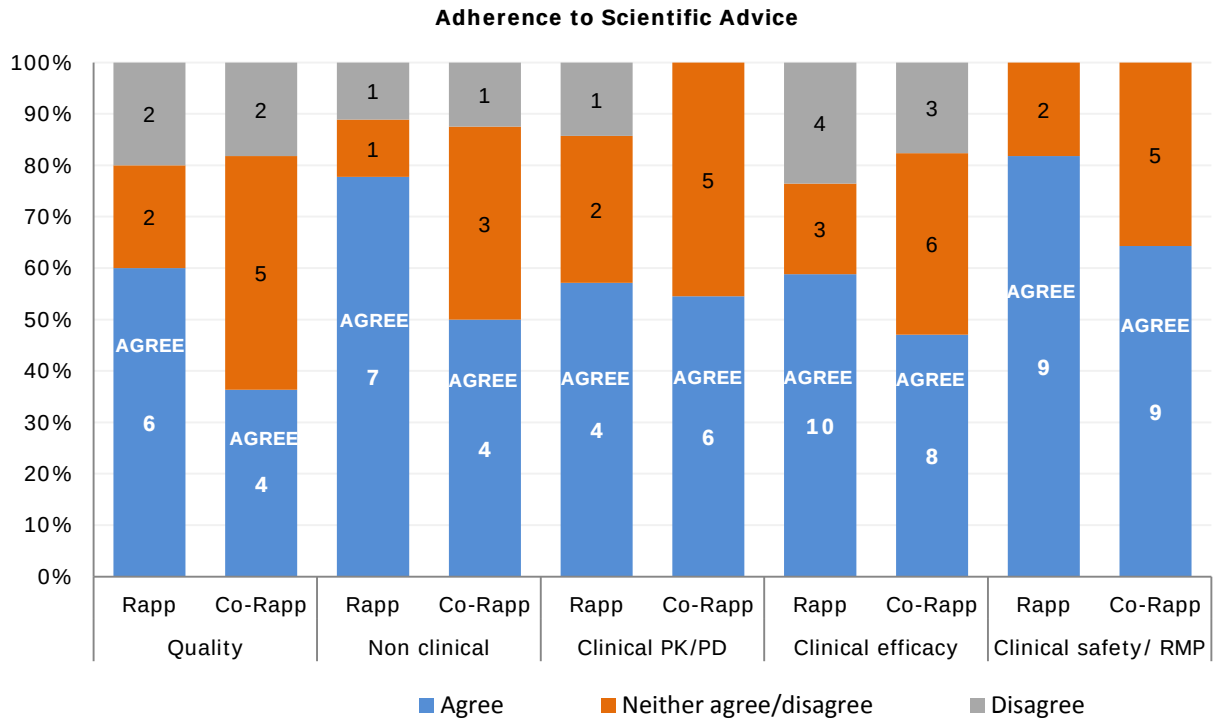
5.2.3.2. Adherence to Scientific Advice

Survey responses received from (Co-) Rapporteurs in relation to Scientific Advice (SA) or Protocol Assistance (PA) showed that in 40 out of 68 responses the applicant had sought SA or PA, below jointly referred to as "SA".

SA was most frequently sought for aspects related to clinical development. Only 3 out of the 40 requests for scientific advice referred to above did not involve any clinical aspects.

The below charts summarise the frequency of areas covered by Scientific Advice in the MAA covered by the Survey and how the (Co-) Rapporteurs` rated the level of adherence of the submitted dossier with the Scientific Advice.





Adherence to scientific advice in the various areas was rated positively or neutrally in the majority of responses (rating of 3-5 in > 80% of responses).

The areas with the highest proportion of negative ratings (1-2) were:

- Quality: 4/21 responses (19%)

- Clinical efficacy: 7/34 responses (21%)

Applicants should be reminded that where a submission is deviating from the Scientific Advice received, it is recommended to proactively present justification(s) in the relevant overview section.

5.2.3.3. Labeling review in primary assessment phase

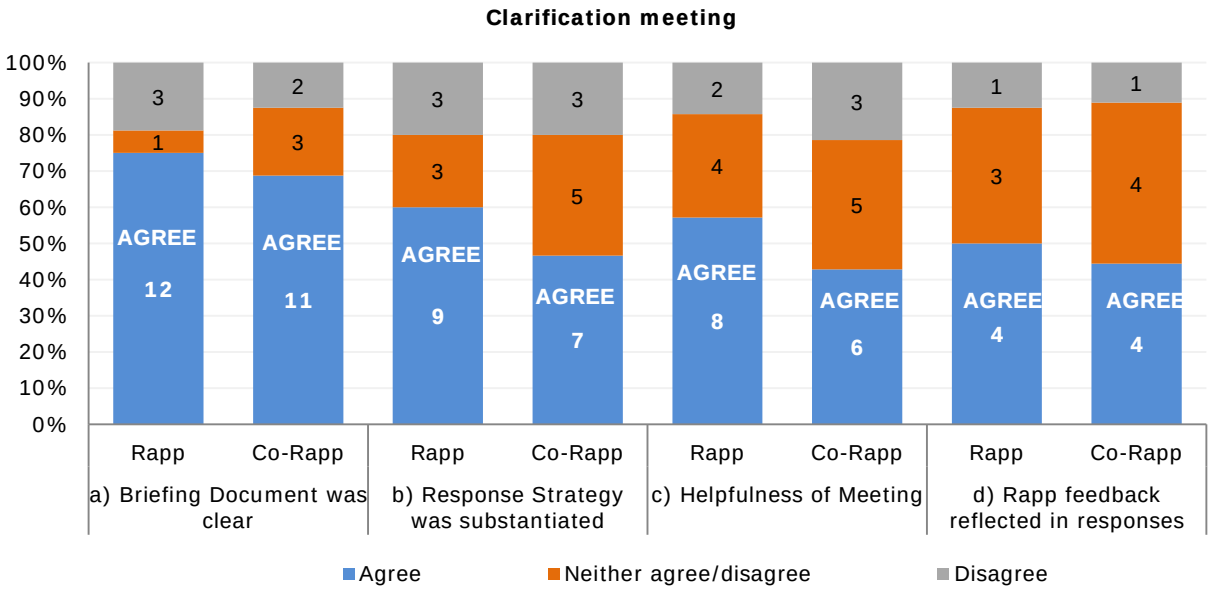
Overall, in 24 out of 60 (40%) responses (Co-) Rapporteurs responded positively (rating 4-5) to the question of how well the PI was substantiated in the Overview. A further 27 out of 60 (45%) got a rating “neither agree nor disagree”.

The (Co-) Rapporteurs ratings of the statement “The proposed PI was well substantiated in the Applicant`s Overview” have been included in the graph presented in section 5.2.3.1

Survey results show that (Co-) Rapporteurs` satisfaction levels with how well the proposed PI was substantiated in the Applicant`s Overview were modest. This may be an area for applicants to consider when preparing MAA submissions.

5.2.3.4. Clarification meeting

A total of 35/68 (51.47%) of the (Co-) Rapporteurs confirmed that a clarification meeting was held during the primary phase of the assessment.



The briefing document was considered clear on the issues requiring clarification by 23/30 (71.88%) of the (Co-) Rapporteurs. However, only 16/30 (Co-) Rapporteurs (53.33%) were of the view that the proposed response strategy was well substantiated. The actual clarification meeting was considered helpful by half of the (Co-) Rapporteurs (14/28, 50%) and 8/15 (47.05%) confirmed that the applicant took into account the (Co-) Rapporteurs' suggestions in their responses. However, for 18 of the 35 meetings the question of whether the applicant took into account the Rapporteurs' suggestions in the response documents was not applicable, as Survey responses had been submitted before receipt of those response documents.

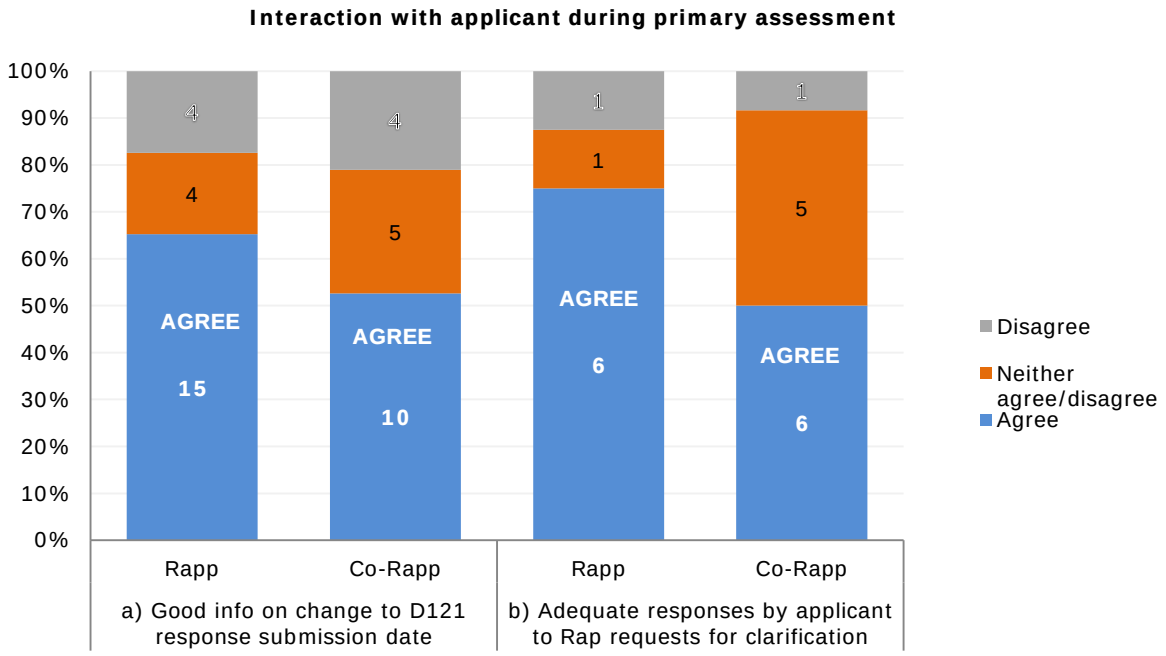
There was overall good agreement between the Rapporteurs' and Co-Rapporteurs' feedback (see chart).

Overall, the clarification meeting was rated as helpful in half of the survey responses (with 32% neither agreeing nor disagreeing). While the briefing documents were mostly rated as being clear on the topics that the applicants wished to discuss (72%), the proposed response strategy was only considered to have been well substantiated in the briefing documents in 53% of cases.

As a general rule, if applicants wish to have a clarification TC/meeting, a clear outline of the response strategy should be presented to make the most of the meeting. Applicants should furthermore be reminded that the primary purpose of the meeting is to ensure that the main issues identified by the CHMP are well understood and to facilitate the preparation of responses, but not to pre-empt the assessment of responses.

5.2.3.5. Overall feedback on interaction during the primary assessment phase

The ratings of the (Co-) Rapporteurs on the interactions with the applicant during the primary assessment phase are summarised in the chart below. The chart excludes responses where the answer 'not applicable' was given.



Overall, 25 out of 42 (60%) (Co-) Rapporteurs confirmed they had been kept well informed on any changes in submission timelines of the Day 121 response (score 4-5); 9 out of 42 (21%) of the ratings neither agreed nor disagreed (score 3) on this point.

A particular example was mentioned, where after an extension of clock stop had been agreed, the applicant submitted the Responses 2 months early without advance warning to (Co-) Rapporteurs.

Overall, 60% (12/20) of the (Co-) Rapporteurs stated that the applicant had adequately responded to clarification requests raised by rapporteurs during the primary assessment phase.

There was generally a moderate degree of satisfaction with interaction aspects during the primary assessment phase.

Only small numbers of (Co-) Rapporteurs were dissatisfied (i.e. ratings of 1-2) with the information on changes to timelines (n=8) or the responsiveness by the applicants to clarification requests (n=2).

5.3. Day 121 to Opinion: final assessment phase

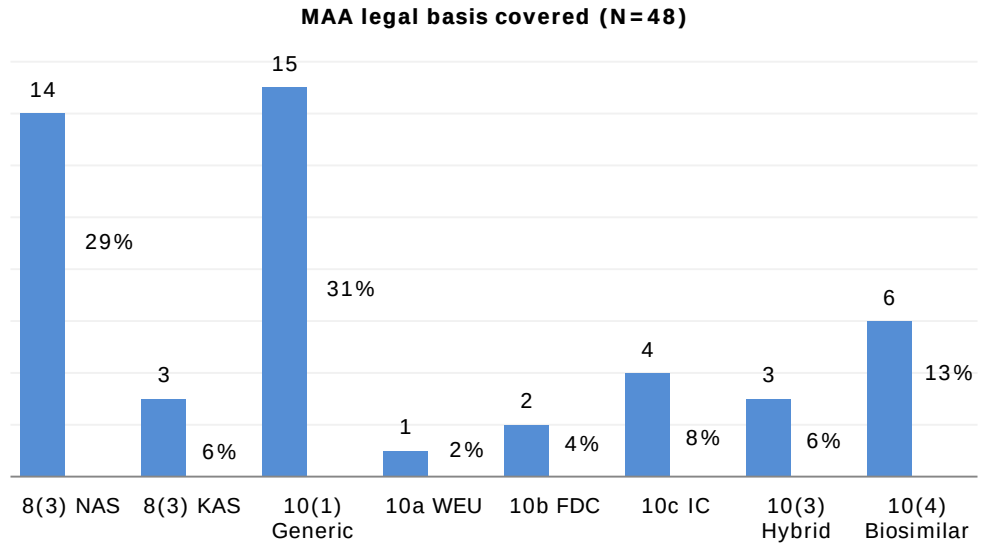
5.3.1. Survey results from Industry

The final phase survey investigated 7 main topics through 25 questions: application details, clarification meeting, scientific advisory groups, oral explanation at committee plenaries, finalisation of commitments and opinion document and overall feedback on the interaction during the final assessment phase.

5.3.1.1. Application details

The legal basis of the 48 applications captured in the survey is presented below. Applicants answered the survey for 44 of them; EMA answered the survey for all 48 applications captured (see section 4). Overall there was a majority of generics (31%) followed by new active substance legal bases (29%),

and Biosimilars (13%). The sample surveyed captured numbers of orphan medicinal products (10%) as well as applicants with SME status (17%) in line with EMA records of previous years.



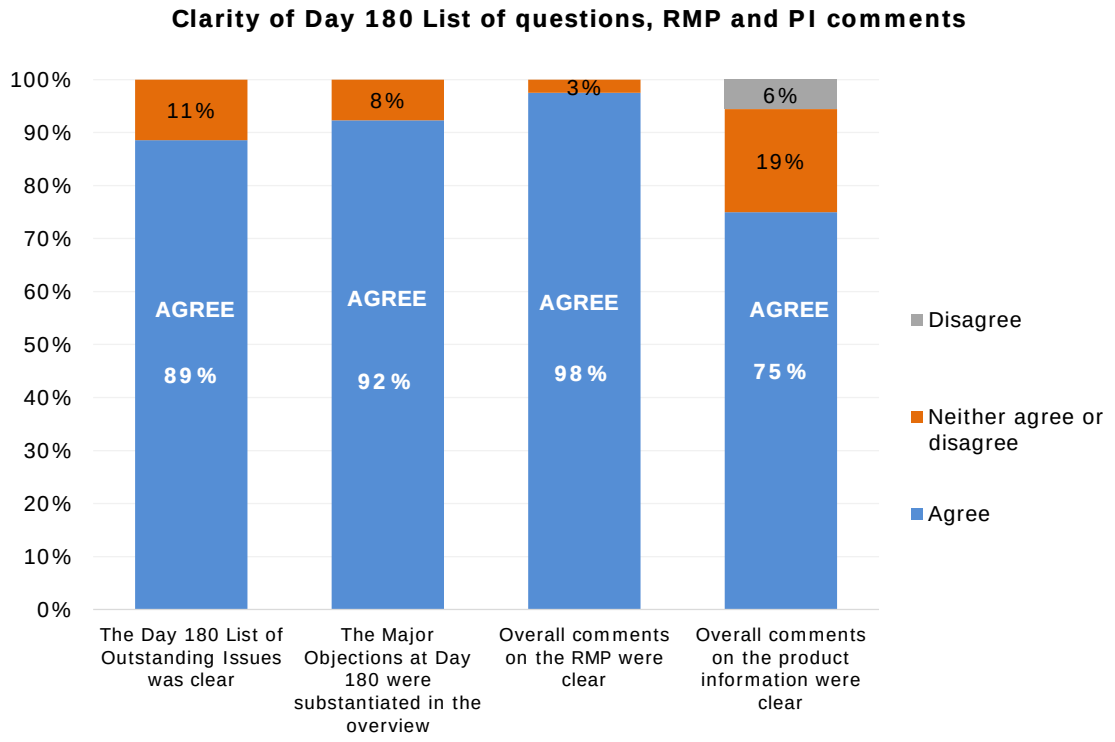
New Active substance: NAS; Known Active substance: KAS; Well-Established Used: WEU; Fixed Dose Combination: FDC; Informed Consent: IC

The proportion of generic and informed consent applications represented almost 40% of the opinions captured in this phase of the survey. This represents a shift compared to the previous phases of the survey that may explain certain results of this survey phase i.e. lower number of clarification meetings, SAGs/Ad-hoc expert groups and oral explanations.

5.3.1.2. Assessment reports in final assessment phase (Day 121 to opinion)

The day 150 joint and 194 joint assessment reports were received within 2 working days of the due date in 50% and 68% of the cases respectively. Applicants were generally not informed proactively when delay was greater than 2 working days (70%).

Approximately 86%, 92% and 98% of the applicants agreed that respectively the Day 180 list of outstanding issues was clear, major objections at Day 180 were substantiated in the overview and comments on the RMP were clear. No applicant disagreed on these 3 points. Approximately 75%, of the applicants agreed that comments on the product information provided at Day 180 were clear, 2 applicants disagreed. Applicants duly received a single file of the commented product information at day 180, encompassing comments from CHMP and EMA review, in approximately 95% of the cases (34/36), as per the EMA process.

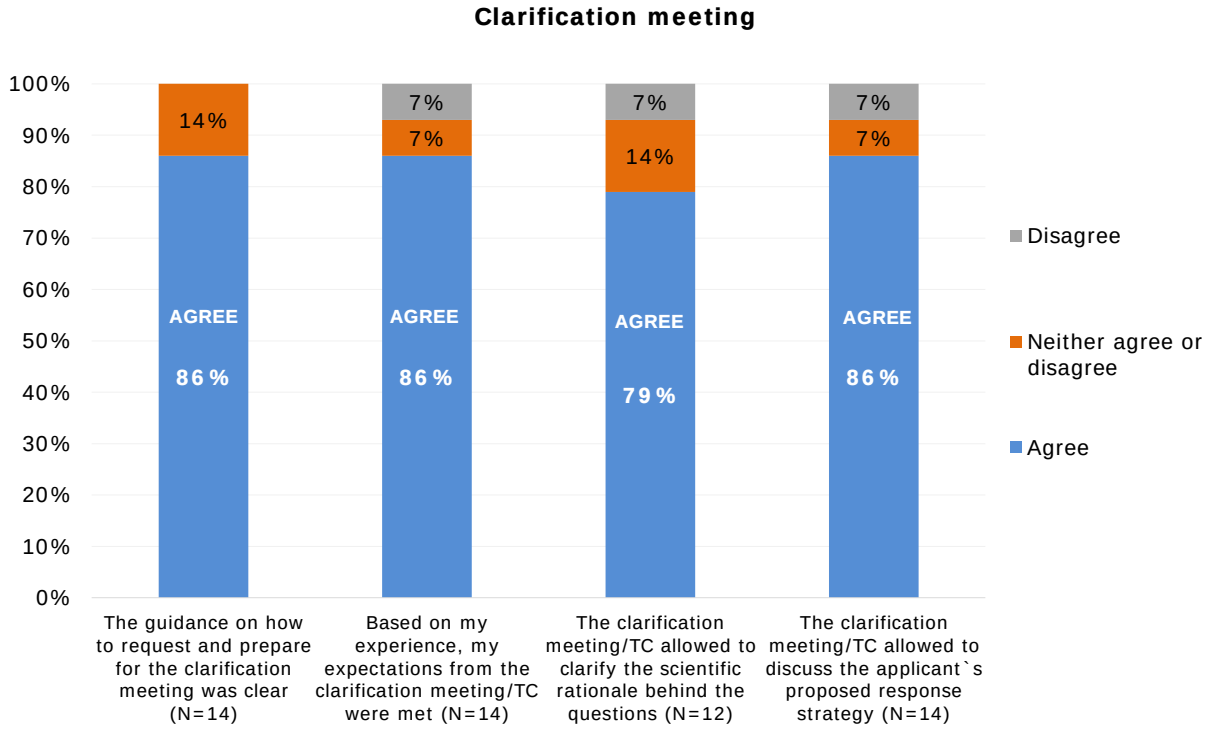


Lists of questions and comments were considered clear and well substantiated in the assessment reports. In line with the assessment reports from the previous phase of evaluation, questions and major objections are considered of high quality (clarity and consistency). Although the majority of assessment reports are usually provided within 2 days of the due date, delays are not uncommon and are not always proactively communicated to the applicant. As for the previous assessement phase, circulation timelines and communication of delays for assessment reports were therefore highlighted as areas for improvement.

5.3.1.3. Clarification meeting

There was a clarification meeting in 32% (14/44) of the applications reaching Day 180 for which a survey response was submitted. In all cases (14/14) the goal was to discuss the applicants' proposed response strategy. In 71% (10/14) of the cases the purpose was also clarification on questions or the scientific rationale behind the questions.

Approximately 86% (12/14) of the applicants agreed that the guidance on how to request and prepare for the clarification meeting was clear. None disagreed. Almost all of the applicants (86% [12/14]) agreed that their expectations from the clarification meeting/TC were met. One applicant disagreed. Approximately 79% (11/14) of the applicants agreed that the clarification meeting/TC clarified the scientific rationale behind the questions. One applicant disagreed. Almost all of the applicants (86% [12/14]) agreed that the clarification meeting/TC allowed discussion of the applicant`s proposed response strategy. Only one applicant disagreed.



Overall, in line with the previous assessment phase clarification meetings are valued for their usefulness, especially for discussing the applicants' response strategy.

5.3.1.4. Scientific Advisory Groups

Only 2 scientific advisory groups or ad-hoc expert groups were reported in the survey for this stage. In both cases applicants agreed that they were given the opportunity to present and defend their position. In one case the applicant was satisfied with the EMA support and in the other was strongly dissatisfied with the support. Difficulties in convening the SAG and consequential delay in the procedure were the reasons for the dissatisfaction.

5.3.1.5. Oral explanation

The number of oral explanations before the CHMP for MAAs having reached an opinion during the survey was also low, with only 3 reported. All applicants were satisfied with EMA's support in preparing for the oral explanation. Two applicants considered they were given an opportunity to present and defend their position. One neither agreed nor disagreed with the statement.

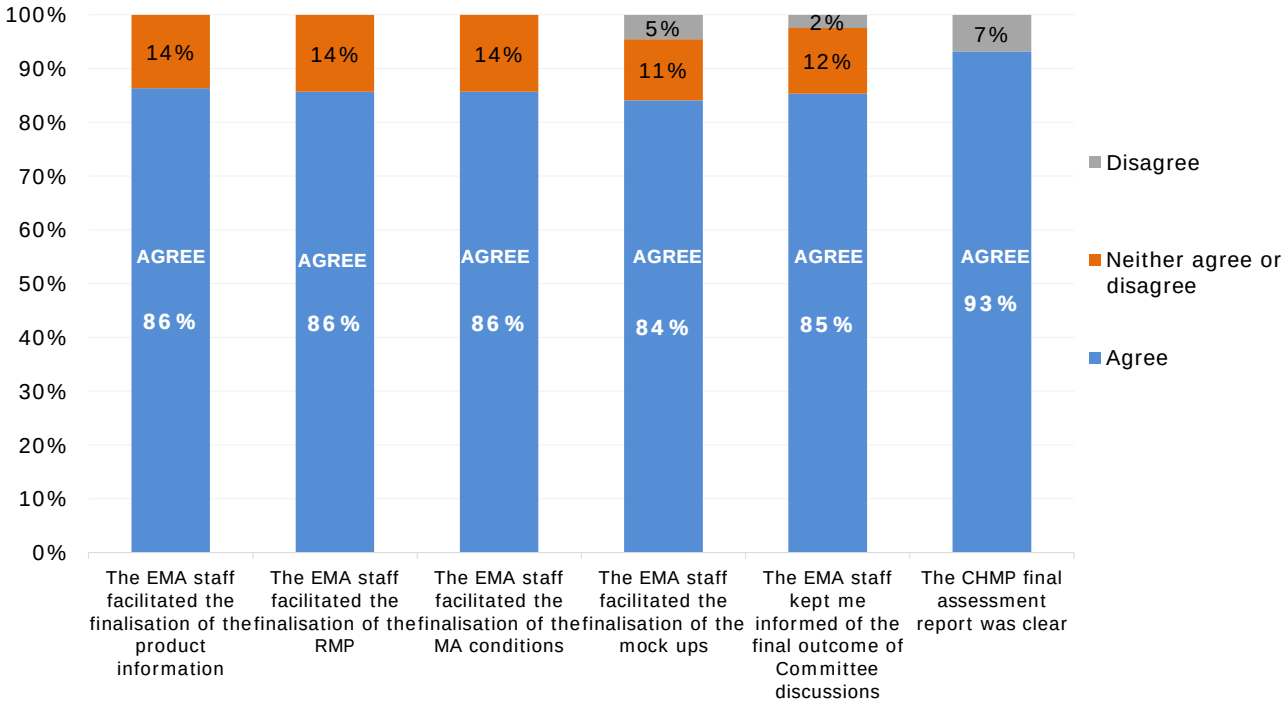
5.3.1.6. Finalisation of commitments and opinion documents

Approximately 86%, 86%, 86% and 84% of the applicants agreed respectively that the EMA staff facilitated the finalisation of the product information, the RMP, the conditions (ANX/SOB/MEA) and/or recommendations when applicable, and the finalisation of the mock-ups. No applicant disagreed, except for the mock-ups finalisation where 2 applicants disagreed.

Approximately 85% of the applicants agreed that EMA kept them informed of the final outcome of the Committee discussions. One applicant disagreed. Approximately 94% of the applicants agreed that the CHMP final assessment report was clear. Three applicants disagreed.

Approximately 61% (27/44) of the applicants received the adopted opinion on the adoption day (Thursday) or the next day (Friday). Approximately 20% received it on the Monday after CHMP. For 18% the opinion was received more than four days after adoption.

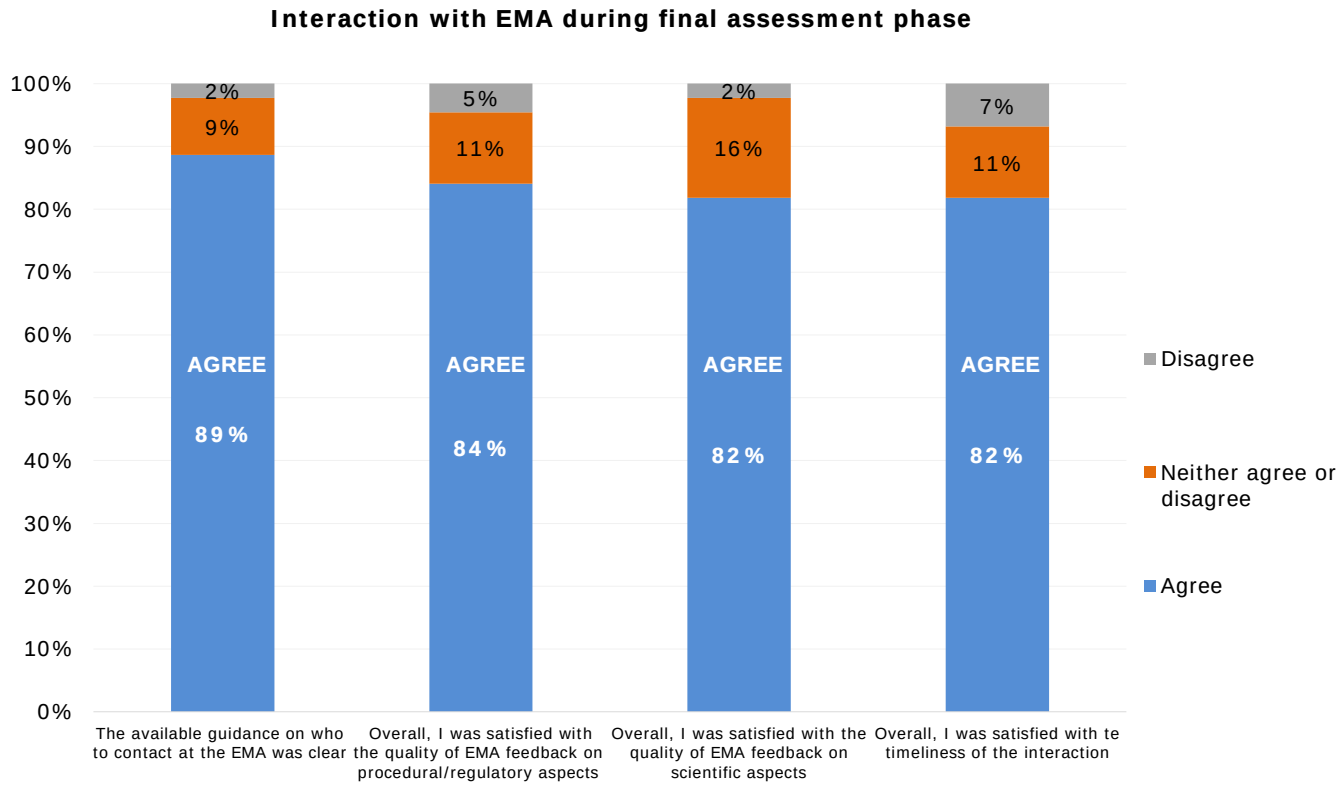
Finalisation of opinion documents



Overall it is concluded that applicants have high levels of satisfaction with EMA interaction during the finalisation stages up to CHMP opinion. EMA's interaction and support in finalising documents for the opinion stage are viewed very positively. The CHMP opinion is usually provided within 2 days of the due date, but delays are not uncommon and concerns regarding timelines for providing translated annexes were stressed. Circulation timelines for the CHMP opinion were therefore highlighted as areas for improvement. Lack of awareness regarding timing/content of the CHMP meeting press release was also reported.

5.3.1.7. Overall feedback on interaction during final assessment phase

Approximately 89% (39/44) of the applicants agreed that the available guidance on who to contact at the EMA was clear. One applicant disagreed. Approximately 84% (37/44) of the applicants agreed that they were satisfied with the quality of EMA feedback on procedural/regulatory aspects. Only two applicants disagreed. Approximately 82% (36/44) of the applicants agreed that they were satisfied with the quality of EMA feedback on scientific aspects, including debriefing from the Committee discussions. Only 1 applicant disagreed. Approximately 82% (36/44) of the applicants agreed that they were satisfied with the timeliness of the interaction. Three applicants disagreed.



Overall, contact with the EMA was regarded by applicants as positive and fulfilling its procedural/regulatory role during this phase.

5.3.2. Survey results from EMA

The survey investigated 6 main topics through 25 questions: application details, clarification meeting, SAGs/Ad-hoc expert group meetings, oral explanation at committee plenaries, finalisation of commitments and opinion documents and overall feedback on the interaction with applicants during the final assessment phase.

5.3.2.1. Clarification meeting

Less than half (42% [20/48]) of the applicants required a clarification meeting in the second phase of the assessment. In all cases (20/20) EMA considered that applicants clearly specified the scope and the topics to be discussed for the meeting. In the vast majority 80% (16/20), the briefing document was provided at least a week prior to the meeting as requested by the EMA guidance. In approximately 85% (17/20) of the meetings EMA agreed that the meeting facilitated the progress of the procedure. Only 2 EMA staff disagreed.

As in the primary assessment phase most of the clarification meetings involved applications with a new active substance (40%, 8/20) and/or an orphan medicinal product (7/8) and/or when the applicants have an SME status (3/5).

Overall the majority of applicants displayed very good awareness and adherence to the guidance requirements for clarification meetings (clarity of scope & topics and briefing documents provided in a timely fashion). Positive free text comments were noted supporting the usefulness of the meeting. It

was noted that the high number of applications related to generic products may explain the low number of meetings.

5.3.2.2. SAGs or Ad Hoc Expert group meeting

The number of scientific advisory groups or ad hoc expert groups for the MAAs covered by the final phase survey was low, with only 2 reported. The briefing documents and presentation held by the applicant were considered informative and clear for one meeting. In both cases a debriefing meeting occurred with the applicant as per EMA process. In both cases, the EMA agreed that the discussion at the meetings contributed to reaching the final outcome of the procedure.

Although no trend can be identified or formal conclusion drawn from these 2 cases, results indicated that all parties (applicants, Rapporteurs and EMA) showed high process compliance.

5.3.2.3. Oral Explanation (OE) at Committee plenaries (CHMP/CAT/PRAC)

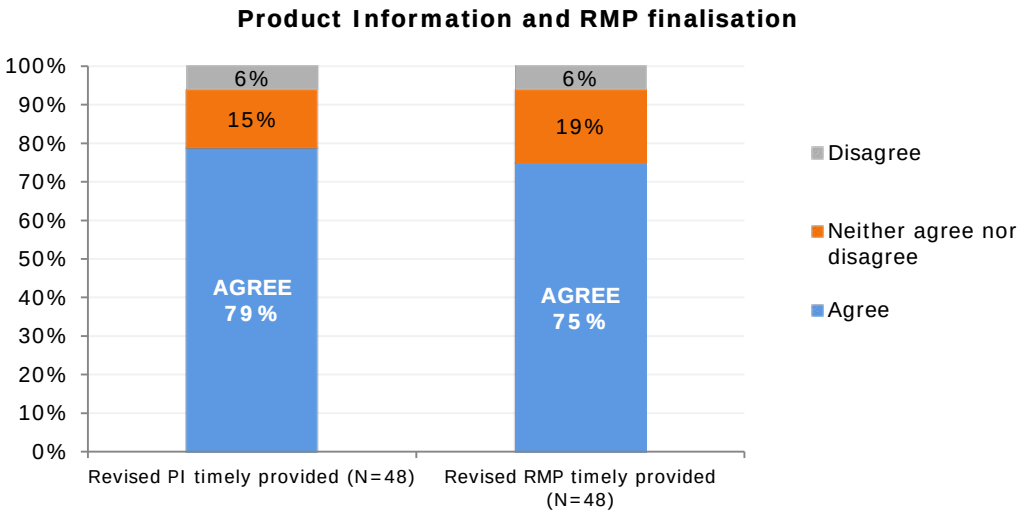
There were only 3 OEs among the applications covered by the final phase survey, all at CHMP plenary. One OE had a primary focus on efficacy, a second one on safety and a third related to a biowaiver/bio-equivalence matter. In 2 cases the basis for the OE was raised rather late, at Day 180, while the topic of the last OE was raised in the Day 120 list of questions.

EMA staff reported that applicants submitted the documents for the OE in a timely fashion in all cases. A debriefing meeting after the OE occurred systematically as per EMA process; this was systematically attended by the Rapporteurs, EPL and PM. Other specialists (Regulatory, Quality, RMS) attended on an ad-hoc basis.

Although no trend can be identified or formal conclusion drawn from these 3 cases, results indicated that all parties (applicants, Rapporteurs and EMA) showed high process compliance.

5.3.2.4. Finalisation of commitments and opinion documents

During the finalisation of the opinions document, the EMA agreed in approximately 84% (38/48) and 75% (36/48) of cases respectively, that the requested revisions for the PI and the RMP finalisations were provided in a timely fashion. EMA disagreed in approximately 6% in both cases for the PI and for the RMP finalisation.

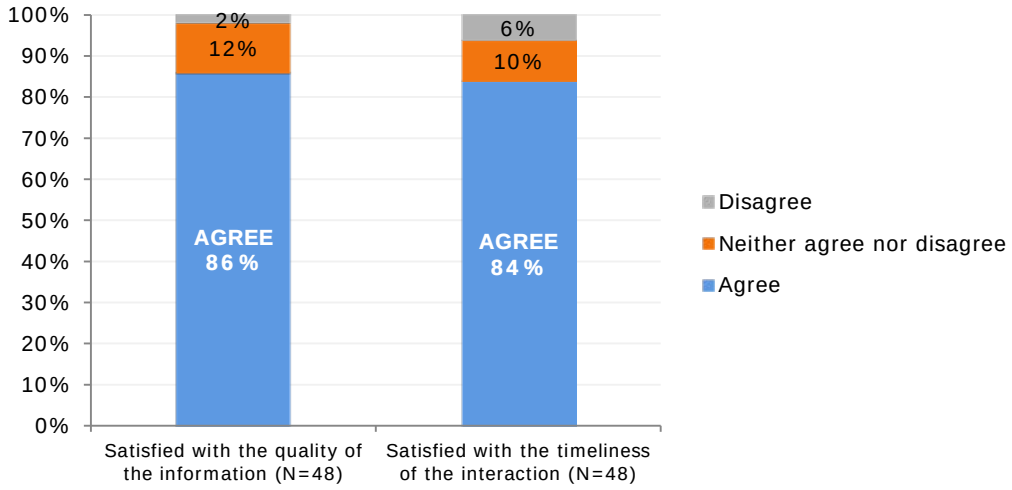


When an Annex II condition has been imposed this happened from Day 120 of the procedure in 41% (7/17) of the cases or at Day 180 in 18% (3/17) and after Day 180 in 41% (7/17). Therefore in almost 60% of the cases the trigger for the condition happened at Day 180 or later.

Overall, a substantial majority of applicants provided the requested PI and RMP revisions for finalisation in a timely manner. The majority of the annex II conditions were requested at the very last stages of the evaluation. EMA and its Committees could investigate opportunities to trigger any necessary conditions to the MA earlier, in order to optimise the finalisation of applications.

5.3.2.5. Overall feedback during the final assessment phase

Iin approximately 85% (40/48 and 41/48) of the cases EMA staff agreed that they were satisfied with the quality of the information provided and the timeliness of the interaction. EMA was not satisfied in one case about the quality of the information and three times about the timeliness of the interaction.



Overall EMA concluded that interactions with the applicants during the final assessment phase were very positive in terms of the quality of the information provided and the timeliness of the interaction. Multiple positive written comments were noted supporting this conclusion.

5.3.3. Survey results from Rapporteurs

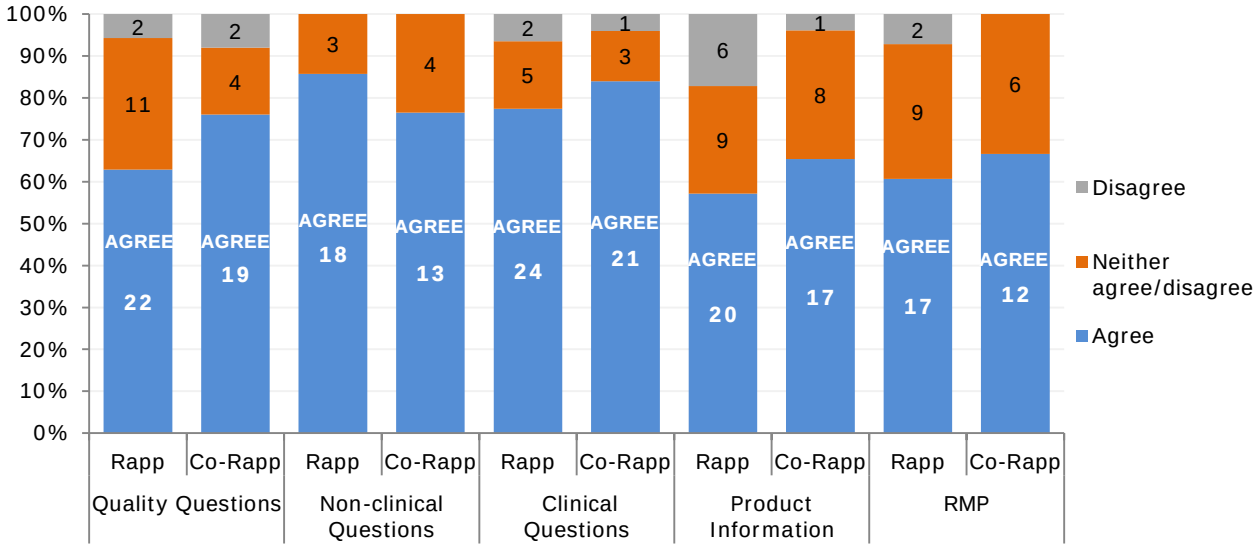
The final phase survey investigated 6 main topics through 10 questions: information on the product, submitted responses and labelling, clarification meeting, SAGs/Ad-hoc expert group meetings, oral explanation at committee plenaries, and overall feedback on the interaction with applicants during the final assessment phase.

5.3.3.1. Submitted responses and labeling in final assessment phase

Ratings by the Rapporteurs and Co-Rapporteurs for the comprehensiveness of the applicants' responses to questions/outstanding issues in the final assessment phase are summarised below:

- 68% (41/60) of the (Co-) Rapporteurs were satisfied (ratings of 4-5) with the *responses to quality questions*. There was good agreement between Rapporteurs and Co-Rapporteurs: 22/35 (63%) Rapporteurs and 19/25 (76%) Co-Rapporteurs considered the responses comprehensive. Ten (14.3%), (Co-) Rapporteurs selected 'not applicable' for this question.
- Overall, 82% (31/38) of the (Co-) Rapporteurs were satisfied (ratings of 4-5) with the *responses to non-clinical questions*. There was good agreement between Rapporteurs and Co-Rapporteurs: 18/21 (86%) Rapporteurs and 13/17 (76%) Co-Rapporteurs considered the responses comprehensive. Thirty-two (45.7%) (Co-) Rapporteurs selected 'not applicable' for this question.
- Overall, 80% (45/56) of the (Co-) Rapporteurs were satisfied (ratings of 4-5) with the *responses to clinical questions*. There was good agreement between Rapporteurs and Co-Rapporteurs: 24/31 (77%) Rapporteurs and 21/25 (84%) Co-Rapporteurs considered the responses comprehensive. Fourteen (20.0%) (Co-) Rapporteurs selected 'not applicable' for this question.
- Overall, 61% (37/61) of the (Co-) Rapporteurs were satisfied (ratings of 4-5) with the *revised product information* provided with the Day 121 responses. There was good agreement between Rapporteurs and Co-Rapporteurs: 20/35 (57%) Rapporteurs and 17/26 (65%) Co-Rapporteurs considered the revised product information to have addressed all comments raised. Nine (12.9%) (Co-) Rapporteurs selected 'not applicable' for this question.
- Overall, 63% (29/46) of the (Co-) Rapporteurs were satisfied (ratings of 4-5) with the *revised RMP* provided with the Day 121 responses. There was good agreement between Rapporteurs and Co-Rapporteurs: 17/28 (61%) Rapporteurs and 12/18 (67%) Co-Rapporteurs considered the revised RMP to have addressed all comments raised. Twenty-four (34.3%) (Co-) Rapporteurs selected 'not applicable' for this question.

Satisfaction with Applicants' response to List of List of Questions/List of Outstanding Issues

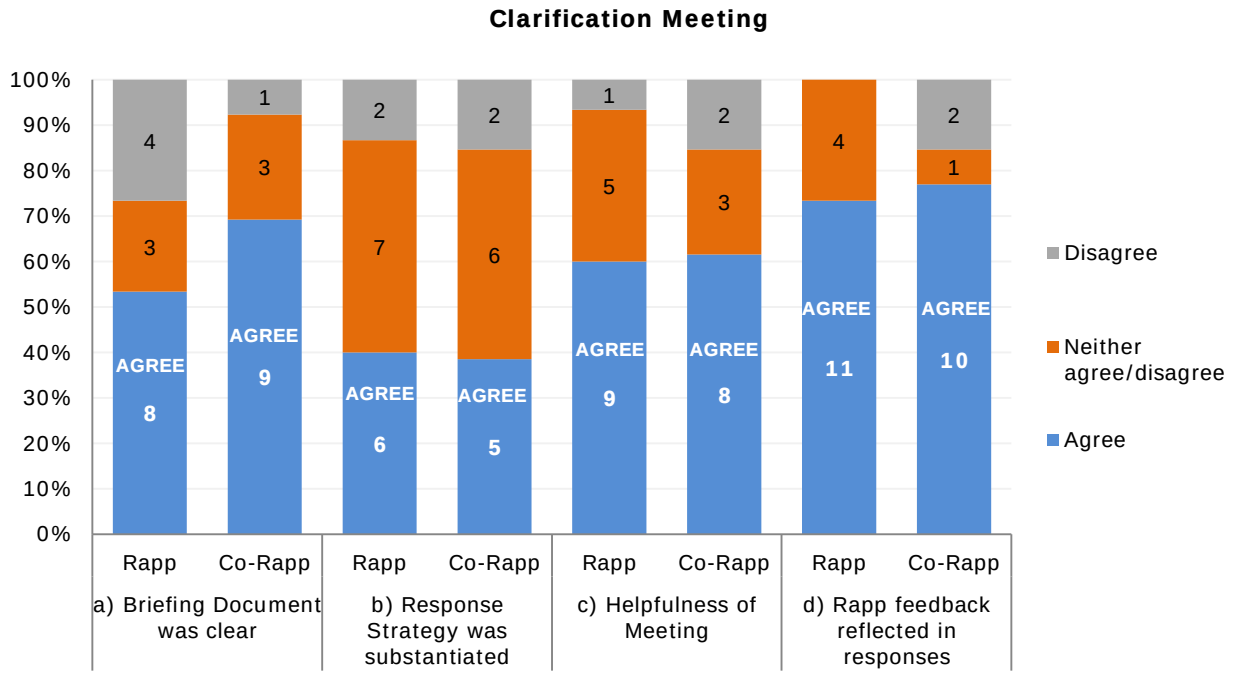


Free text comments identified the need for mature dossiers and responses as an aspect that could be improved in the final phase in order to facilitate the assessment. Late submission of large datasets is clearly a problem for the assessment teams and should be avoided.

In the vast majority of cases (approximately 60-80%), the applicants' responses were considered comprehensive by both Rapporteurs and Co-Rapporteurs (ratings of 4 [agree] or 5 [strongly agree]). Very few negative ratings were received, i.e. 1 [strongly disagree] or 2 [disagree], indicating a generally high level of satisfaction of the (Co-) Rapporteurs with the quality of the applicants' responses at Day 121 and thereafter. The satisfaction with the updates to the product information and RMP was slightly lower compared to the other areas in the survey (quality, non-clinical and clinical questions). As a general rule, all CHMP comments on the product information and RMP should be carefully considered in the applicants' responses. When deviating from CHMP requests, applicants should explain the reasons for doing so.

5.3.3.2. Clarification Meeting

A total of 28/70 (Co-) Rapporteurs confirmed that a clarification meeting had been held during the second phase of the assessment (see chart below for an overview of the responses).



The briefing document was considered clear on the issues requiring clarification by 17/28 (61%) of the (Co-) Rapporteurs. However, only 11/28 (Co-) Rapporteurs (39%) were of the view that the proposed response strategy was well substantiated. Most (Co-) Rapporteurs neither agreed nor disagreed on this point. The actual clarification meeting was considered helpful by the majority (17/28, 61%) of the (Co-) Rapporteurs and 21/28 (75%) confirmed that the applicant took into account the (Co-) Rapporteurs' suggestions in their responses.

There was overall good agreement between the Rapporteurs' and Co-Rapporteurs' feedback (see above for a comparison of the survey results for Rapporteurs and Co-Rapporteurs).

The majority of the (Co-) Rapporteurs considered the clarification meeting to be helpful and the briefing documents to be clear on the topics that the applicants wished to discuss. However, a relatively large number of ratings of 3 (neither agree/disagree) were received in relation to the quality of the response strategy, which may possibly represent the view that part of the response strategy was well supported whereas other parts were not. The general principles for clarification TCs/meetings as outlined in section 5.2.3.4. apply.

5.3.3.3. SAG / Ad hoc Expert Group

Five responses were received from (Co-) Rapporteurs (3 Rapporteurs and 2 Co-Rapporteurs) in relation to 2 SAGs or ad-hoc expert group meetings and 1 consultation of a Working Party. Four out of the 5 (Co-) Rapporteurs agreed (1 rating of 5, 3 ratings of 4) that the briefing documents and the presentation held by the applicant were informative. The remaining Rapporteur neither agreed nor disagreed. Three of the (Co-) Rapporteurs were of the view that the discussion at the SAG/ad-hoc expert group meetings had contributed to reaching the final outcome of the procedure (2 ratings of 5, 1 rating of 4). Two Rapporteurs neither agreed nor disagreed on this point.

The number of SAGs/ad-hoc expert group meetings for MAAs having reached an opinion during the survey was small. The responses were overall positive, but no firm conclusion can be drawn from these few cases.

5.3.3.4. Oral Explanation at Committee plenaries

An oral explanation was only held for 3 applications that reached an opinion during the period covered by the survey. [There were 8 oral explanations on initial MAA during the 6 months covered by the survey but only 3 reached an opinion step].

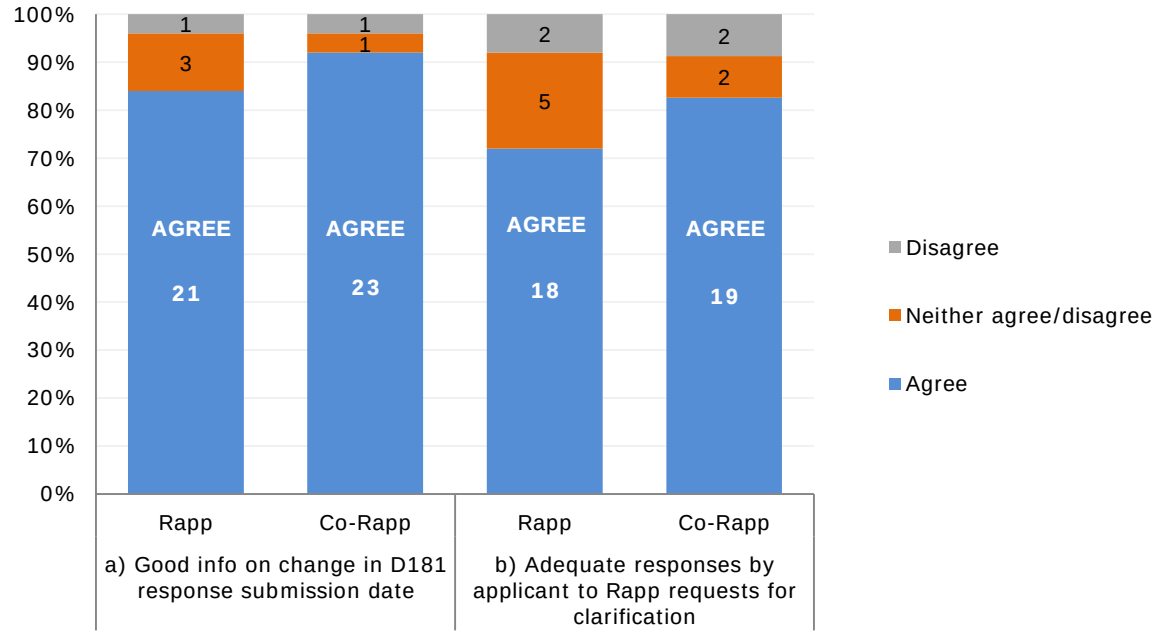
Three responses from (Co-) Rapporteurs were received (2 from Co-Rapporteurs, 1 from a Rapporteur), each in relation to a different product. Of these, 2 (both Co-Rapporteurs) agreed (rating: 4) that the applicants' presentation had been concise. The Rapporteur neither agreed nor disagreed (rating: 3). Regarding the questions (i) if the applicant's presentation addressed the critical issues, and, (ii) if the Oral Explanation contributed to reaching the final outcome of the procedure, one Co-Rapporteur disagreed (rating: 2), the Rapporteur neither agreed nor disagreed (rating: 3), and the other Co-Rapporteur agreed (rating: 4).

The number of Oral Explanations for MAAs covered by the final phase survey was low. No firm conclusion can be drawn based on these few cases.

5.3.3.5. Overall feedback on interaction with applicant during Opinion finalisation phase

The ratings of the (Co-) Rapporteurs on the interactions with the applicant during the final Opinion phase are summarised in the chart below. The chart excludes the answer 'not applicable' which was given by 17/42 Rapporteurs and 3/28 Co-Rapporteurs for a) *Change in submission date of Day 181 responses*, and by 17/42 Rapporteurs and 5/28 Co-Rapporteurs for b) *Responses to Rapporteur clarification requests*.

Interaction with applicant during final assessment phase



Overall, 88% (44/50) of the (Co-) Rapporteurs confirmed to have been well informed on any change in the submission date of the Day 181 responses. There was good agreement between Rapporteurs and Co-Rapporteurs: 21/25 (84%) Rapporteurs and 23/25 (92%) Co-Rapporteurs either agreed or strongly agreed on this point.

Overall, 74% (37/50) of the (Co-) Rapporteurs stated that the applicant had adequately responded to clarification requests. There was good agreement between Rapporteurs and Co-Rapporteurs: 18/25 (72%) Rapporteur and 19/25 (76%) Co-Rapporteurs either agreed or strongly agreed on this point.

There was generally a high degree of satisfaction with the interaction with the applicants at the final Opinion phase. Only very few (Co-) Rapporteurs were dissatisfied (ratings ≤4) with the information provided on changes to timelines or the responsiveness of the applicants to clarification requests.

6. Conclusions from the survey

Results from this survey clearly indicated that there was a high level of overall satisfaction across the 3 phases of the evaluation; satisfaction levels were higher at the last stage of evaluation up to the CHMP opinion. Generally there was a high level of interaction during pre-submission phase, essentially through pre-submission meetings, which were positively rated by the respondents. During the evaluation, the assessment reports, questions and major objections were considered of high quality in term of clarity, consistency and substantiation, as were the comments made on the product information and mock-ups.

Applicants had a very good awareness of the guidance for clarification meetings and accelerated assessment. Clarification meetings were valued for their usefulness, and overall were considered to help the progress of the procedure. However, the need for a clarification meeting should only be considered on a case-by-case basis, when there is a need to make sure that the issues with the application are well understood and to facilitate the preparation of responses, and cannot pre-assess or endorse the responses. If applicants wish to have a clarification meeting, a clear outline of the response strategy should be presented upfront to make the most of the meeting.

Interactions between applicants, EMA and rapporteurs were rated positively at all stages of the evaluation procedure. Quality and timeliness of EMA feedback were rated very positively. There was a high level of satisfaction with the EMA's support in facilitating finalisation of documents for the opinion. The quality of information provided by applicants and timeliness of the interaction, especially progressing toward the opinion phase were very well rated.

Satisfaction levels with the content of the submitted dossiers and responses to questions, as rated by rapporteurs, were moderate to very good; a non-negligible proportion of the dossiers were considered not mature enough or it was difficult to locate information. Submissions were adherent to scientific advice in the majority of cases.

Overall, responses and results from surveys across the 3 stakeholder groups involved (i.e. Industry, Rapporteurs and EMA) allow to conclude that the centralised procedure for initial marketing authorisation applications runs well at all stages from pre-submission to validation and in the 1st and 2nd phases of the evaluation until adoption of the opinion.

The survey also helped identify areas that would benefit from optimisation.

EMA should investigate opportunities to increase awareness of applicants about the validation process (i.e. publish most common issues encountered and how to address them) to optimise MAA validations.

The circulation timelines and communication of delay for assessment reports and final opinion were also identified as areas for improvement. In addition, the timing for the request of Annex II conditions to the marketing authorisation was also identified as requiring optimisation since it was not uncommon for it to occur in the late stages of the evaluation.

Further clarification regarding who to contact (EPL or PM) was suggested.

The impact of delays of applicants' submissions on network and resource workload distribution was highlighted. Delays should be communicated by applicants as early and promptly as possible.

The presentation of the application in general (ease of locating information, use of hyperlinks) and the need for consistency between application form, PI and the dossier submitted were highlighted; the latter could reduce the number of administrative validation issues. Increased awareness of the pre-authorisation guidance, enhanced adherence to the PI guidelines (SmPC and QRD) and better substantiation of the proposed PI in the clinical overview and subsequently in the responses during the evaluation were identified by the survey as areas that would also benefit from improvement. The need for mature dossiers and responses during the evaluation was stressed, as late submission of large datasets renders the finalisation of the procedure challenging.

7. Survey follow-up actions

Based on the feedback of the survey, actions are currently ongoing or planned to address the areas identified for improvement:

- **Increase awareness of applicants about the validation process:** EMA plan to publish the validation checklist and an update of the most common validation issues by Q2-2018 (target date).
- **Improve circulation timelines for assessment reports and final opinion, and the communication of potential delay to applicants:** optimise the EMA review before assessment reports circulation by Q3 2017, earlier provision of the final PI at opinion to allow applicants starting translations on time by Q1 2018, use of existing IT tool to better track reports and communicate delays by Q4 2018.
- **Optimise timing for the request of the Annex II condition to the marketing authorisation:** EMA should develop an earlier prompt to the committee during the MAA process on the potential need to request for conditions to the marketing authorisation by Q2-2018.
- **Clarification regarding who to contact (EPL or PM):** initiatives are ongoing to strengthen EMA support to stakeholders by operating the Procedure Management Department according to therapeutic areas and introducing an end-to-end responsibility for the product lifecycle for assigned portfolios. This also aims at ensuring business continuity in the context of the upcoming EMA relocation.

8. Additional remarks

This exercise has been undertaken as part of European Medicines Agency (EMA) stakeholder relations management framework and the Framework for interaction between the European Medicines Agency and industry stakeholders to interact and gather the Agency's feedback from its stakeholders.

This survey was the second to be undertaken by EMA with Industry stakeholders since the reorganisation of EMA in 2014 and the work to redesign and optimise its procedures. It set up a baseline for future surveys of similar kind.

In the spirit of continuous improvement and stakeholder engagement, the Agency will continue to review the performance its evaluation procedures in the pre- and post-authorisation phases. The scope and frequency of each survey will be defined based on the findings of previous surveys, feedback received from Industry, changes introduced and EMA overall planning priorities and strategy.