EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Ongoing initiatives for the CP

Industry Stakeholder Platform meeting

22 November 2024 - Topic 4

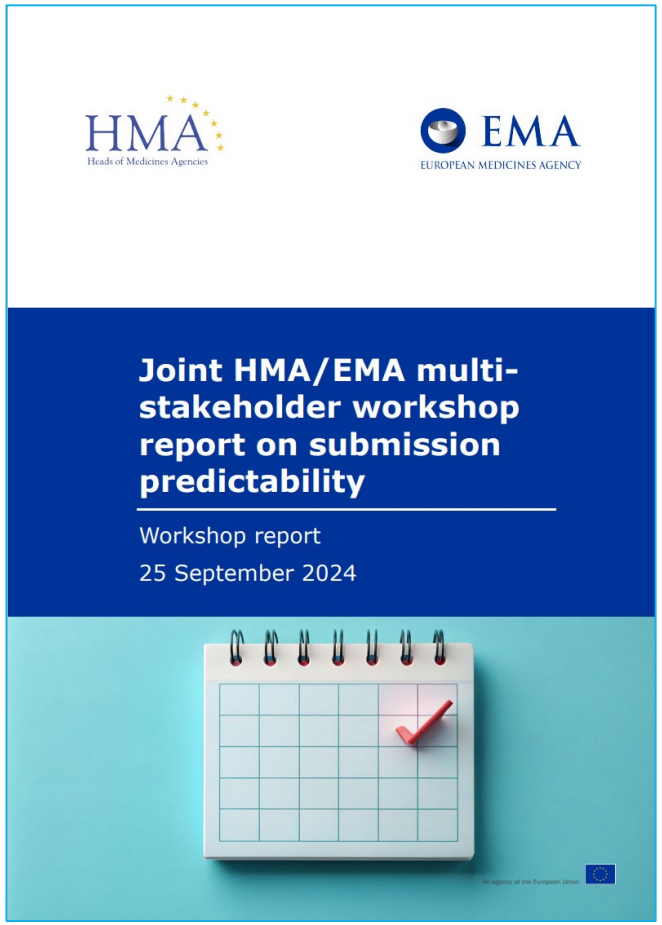
Fran Day

Agenda

Assuring the Network's Sustainability

- Submission predictability workshop
- Revamp pilot
- GIREX II
- Focus group on revamp of pre-submission interactions
- Changes to SmPC published in EPARs

Outcomes



- The workshop was well attended and received a good level of media attention
- Key messages:
  - Enhanced communication
  - Maturity of dossier
  - Submission readiness
- The focus group will continue in 2025

Agenda

- Submission predictability workshop
- Revamp pilot
- GIREX II
- Focus group on revamp of pre-submission interactions
- Changes to SmPC published in EPARs

Reminder – revamp project drivers

Assuring the Network's Sustainability

- Maximise efficiency
- Improve consistency of reports
- No loss of transparency (EPAR)
- Ensure legal and regulatory compliance

Work to date & ongoing

Assuring the Network's Sustainability

Throughout, collaboration with CHMP, CAT, PRAC, industry & internal EMA stakeholders

2022

Step 1 (quick wins)

- WORD versions of key documents in eCTD *Working Documents* folder
- Response template

Oct 2023

Step 2

- New D80 clinical and non-clinical reports used by Assessors

Nov 2023

Step 3

- Pilot with industry
- Applicant completes D80 clinical and non-clinical reports

end 2024

Step 4

- Complete D80 quality report template
- Include D80 quality template in pilot

Jan 2025

Step 5

- Complete CHMP AR/Overview template
- Move to co-authoring on SharePoint between Rapp teams

Parallel stream

- Creation of a dedicated D80 clinical template for Biosimilars

Pilot with industry

Assuring the Network's Sustainability

Background

During the pilot, a small number of companies are being asked to pre-fill the D80 non-clinical and clinical report templates with factual information (clearly designated sections of the templates)

Companies are contacted by EMA at least 3 months ahead of submission

Participation in the pilot is voluntary (for Rapps and companies)

Expectations from companies

- Pre-fill the D80 non-clinical and clinical AR templates with **factual information** (clear instructions provided in the templates)
- Provide the completed AR templates (in Word format via Eudralink – not part of eCTD) by the start date of the procedure (i.e. ~ 1 month after submission)

Close collaboration

- Dedicated meeting with EMA/Rapps prior to submission
- Rapp teams to contact company for any clarifications once ARs received
- Possibility of meetings with Rapp teams during the procedure
- All coordinated via the PL
- Aim to solve any concerns, reduce number and repetition of questions

Pilot with Industry

Assuring the Network's Sustainability

- The factual information provided by the company is in principle the building block for the factual sections of the overview/CHMP AR
- Expected to be time-saving for assessors
- Companies will not be expected to provide updates to the following ARs, just the first, completed version
- Once the assessor receives the pre-filled AR template, it is their choice to change/update, or rewrite, as they see fit
- Feedback from pilot will help develop accurate instructions to the company and will be part of a quality management process with feedback loops

Pilot experience to date

- Good support from Rapporteurs (no one declined participation)
- More than 20 applicants have been contacted
- Over half have declined participation
- Numerous changes of submission dates have been challenging

Actual pilots carried out

Product	Kick-off meeting	Actual submission date	D80	Post-D80 meeting	D210
1	05-Oct-23	23-Nov-23	18-Mar-24	10-Apr-24	exp 12-Dec-24
2	13-Nov-23	21-Dec-23	22-Apr-24	13-May-24	exp 14-Nov-24
3	08-May-24	23-May-24	09-Sep-24	25-Sep-24	exp 22-May-25
4	12-Jun-24	22-Jul-24	04-Nov-24		
5	10-Oct-24	11-Oct-24	exp 03-Feb-25		
6	12-Sep-24	11-Nov-24	exp 03-Mar-25		
7	05-Sep-24	25-Nov-24	exp 31-Mar-25		

- Only 7 pilots have actually started
- So far, we have received the pre-filled templates for 5
- Feedback meetings conducted for 3, post D80

General feedback from applicants

- The pre-fill of the template by the applicant team represented an extensive effort
- Preparation only begins once MAA documents have been finalized – little time (less than 4 weeks)
- It would be very helpful if the document could be harmonized as much as possible with the FDA assessment aid. Also, it is noted that the EMA document contains much more detail.
- Applicants tried to keep the reports short but there is a lot of information requested. It would be good to have more information in the instructions on what to include or not.
- The Instructional text in the templates was clear in general.
- Objective and endpoints: estimand language is not typically used in protocols. Applicants were unsure how to comply with estimand language.

General feedback from applicants

- Consider clarifying in the guidance text that cross-referencing to other sections is acceptable/encouraged when information is repeated.
- Consider clarifying in the guidance text that though referencing to source documents (ie, dossier modules and CSRs) is encouraged, there is no expectation that they will actually be linked since this is a Word document.
- Some confusion whether, when template table is structured to present data in a certain way, it is okay to modify the template table with the data in the way the Sponsor analyzed it, even if it is not exactly the same (eg, age analysis breakdowns, difference in choice of AUC [AUC0-inf vs AUC0-t, etc.]) and there is no expectation to reanalyze the data.
- Applicants keen to see an example of an approved D80 report (ie, "this is a great example and what we are looking for")?

General feedback from Rapporteurs

- In general, it seems that prefilled templates did not make the assessment more efficient.
- Applicants are not able to stick to the factual data; too many interpretations included
- There are a lot of references to the underlying dossier
- In many cases assessors had to delete lots of company text and manually extract the tables and graphs
- In many cases the applicant's choice of what information to include is not the same as what the assessors would choose to include
- In some cases, information is too detailed, in some, not detailed enough
- Harder for assessors to "sort out" what is included, rather than to start from scratch
- In one case, the whole of the safety section had to be deleted as data was based on the wrong analysis set

Reduced number of questions?

- One of the objectives of the pilot was to potentially reduce the overall number of questions at D120 by allowing Rapporteurs to ask simple questions directly to applicants via the PL (e.g. "where is this table?", or "these 2 values don't match, which is correct?", etc.)

	# quality	# non-clin	# clinical
Prod 1	2 MOs; 90 OCs	2 MOs; 14 OCs	6 MOs; 67 OCs
Prod 2	5 MOs; 73 OCs	0 MOs; 12 OCs	1 MO; 68 OCs
Prod 3	0 MOs; 127 OCs	0 MOs; 11 OCs	3 MOs; 43 OCs

Reduced number of questions?

Assuring the Network's Sustainability

Examples of Qs that could have been sorted before D80 (clinical only):

117. The applicant is requested to complete the table below for EMA statistics. Additionally, they should include dose recommendations for elderly patients in the SmPC if necessary.

	Age 65-74 (Older subjects number /total number)	Age 75-84 Older subjects number /total number)	Age 85+ (Older subjects number /total number)
PK Trials			

136. The applicant is requested to clarify the censoring rules for the category "randomisation".

152. For two screened-but-not-enrolled patients, the reason could not be found in the CSR of Study 004, the Applicant is requested to provide the reason for not enrolling these patients in the study.

117. The Applicant is requested to clarify the number of patients enrolled under successive amendments.

157. A total of 1218 records from 57 patients who did not experience any AE were included in the final safety data set with status "No". This is not understood as AE records not deemed treatment emergent were excluded.

113. The specification of criteria or threshold that defines an "emergency" warranting unblinding is requested.

129. The Applicant is requested to provide information on the number of patients who received treatment beyond radiographic progression in Study 005.

114. Information regarding any kind of crossover between treatment arms was allowed or not allowed could not be identified in the dossier. The Applicant is requested to clarify if crossover was allowed or not allowed per protocol.

115. Regarding the population in which ORR is to be tested, the applicant should clarify the discrepancy between SAP (full analysis set, p. 18/56) and CSR (participants with measurable disease at baseline, p. 74/13280).

146. It is not understood why the row AEs (Deaths during study) from Table 9 (SCS, p. 43/102) is completely discrepant from the row on Subjects with 1 or more AEs leading to death in Table 10 (SCS, p. 49/102). This should be explained.

Conclusions

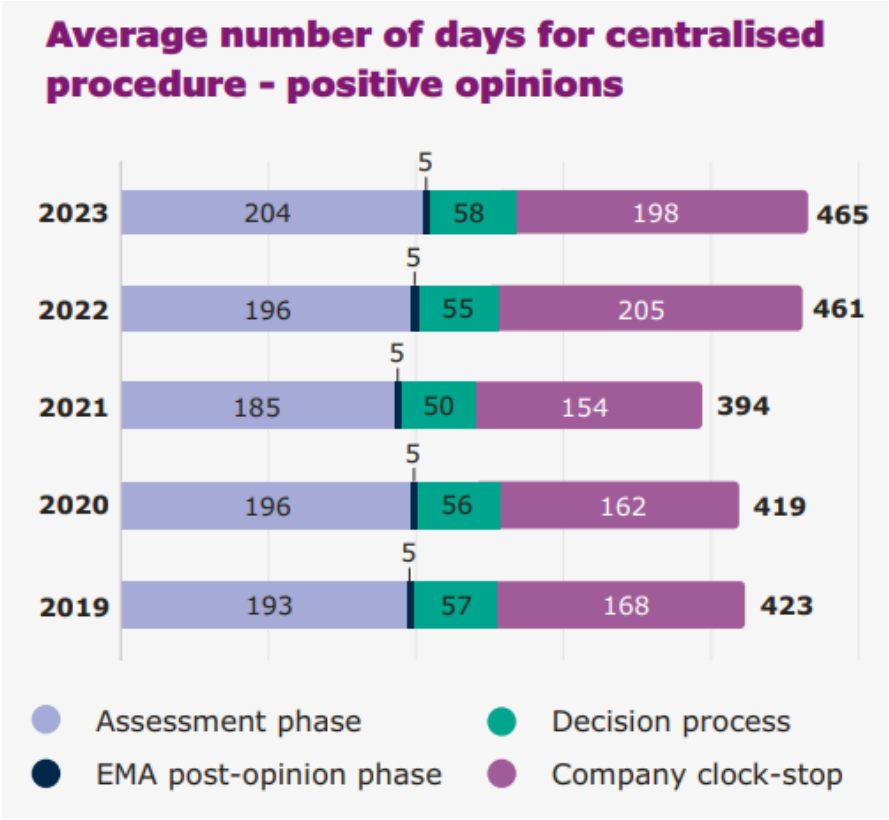
- The pilot continues
- CHMP has agreed to include 3 more dossiers (to a total of 10)
- Companies with submissions in late Q1 2025, will be contacted shortly
- CHMP will perform a comprehensive review once all 10 pilots have completed (likely in late 2025)

Agenda

- Submission predictability workshop
- Revamp pilot
- GIREX II
- Focus group on revamp of pre-submission interactions
- Changes to SmPC published in EPARs

GIREX (Group for Internal Rules for EXtensions of clock-stops)

Assuring the Network's Sustainability



Source: EMA 2023 Annual Report

In October 2023, CHMP reviewed the latest trends on extensions of clock stops and agreed to appoint a dedicated group consisting of members of the key Committees to analyse these and propose measures to minimise them.

GIREX (Group for Internal Rules for EXtensions of clock-stops)

Assuring the Network's Sustainability

(< APPLICANT/MAH NAME/ID/LOGO ON HEADED PAPER >)

Category	**Reason** <delete/duplicate as appropriate>	**Description/Justification(s)**
☐	CHMP requested <GMP/GCP/GLP/PhV> inspection	*<please specify MO(s)/OC(s) and provide detailed justification(s)>*
☐	CHMP requested <Scientific Advisory Group/Ad-hoc Expert Group> meeting	*<please specify MO(s)/OC(s) and provide detailed justification(s)>*
☐	Time needed to address CHMP's Quality <MO(s)/OC(s)>in the <LoQ/LoI/RSI> ☐ Previously identified/discussed at <presubmission/validation/LoQ/LoI/RSI>	*<please specify MO(s)/OC(s) and provide detailed justification(s)>*
☐	Time needed to address CHMP's Non-clinical<MO(s)/OC(s)>in the <LoQ/LoI/RSI> ☐ Previously identified/discussed at <presubmission/validation/LoQ/LoI/RSI>	*<please specify MO(s)/OC(s) and provide detailed justification(s)>*
☐	Time needed to address CHMP's Clinical <MO(s)/OC(s)>in the <LoQ/LoI/RSI> ☐ Previously identified/discussed at <presubmission/validation/LoQ/LoI/RSI>	*<please specify MO(s)/OC(s) and provide detailed justification(s)>*
☐	Time needed to address CHMP's other <over-arching, multidisciplinary, procedural, regulatory> <MO(s)/OC(s)>in the <LoQ/LoI/RSI> ☐ Previously identified/discussed at <presubmission/validation/LoQ/LoI/RSI>	*<please specify MO(s)/OC(s) and provide detailed justification(s)>*
☐	Other	*<please specify MO(s)/OC(s) and provide detailed justification(s)>*

Since 1st April, all applicants are asked to complete a dedicated template for the request of extension of clock stops.

All requests have to be duly justified and declared, if the reasons for extension is new, or previously known.

GIREX (Group for Internal Rules for EXtensions of clock-stops)

Assuring the Network's Sustainability

Starting July 2024, CHMP has agreed to revert to the strict application of the existing 2009 CHMP guideline.

Since July 2024, CHMP has systematically been reviewing in plenary all requests for clock stop extensions.

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

TIME ALLOWED FOR APPLICANTS TO RESPOND TO QUESTIONS AND ISSUES RAISED DURING THE ASSESSMENT OF NEW MARKETING AUTHORISATION APPLICATIONS IN THE CENTRALISED PROCEDURE

The **LoQs at day 120** should be responded to within 3 months. Applicants may request an additional period of up to 3-month for providing their responses by writing to the Chair of the CHMP outlining their reasons. This request will however only be considered by the CHMP if the applicant provides appropriate scientific justification. The CHMP will review the justification for the additional period (up to 3 months) for responding to the LoQs at its next scheduled plenary session following the receipt of the applicant's request and will only grant such requests, in the event that it is considered that this extension will enable the applicant to respond fully to the questions raised. Extensions beyond 6 months from the date of issue of the day 120 LoQs would not normally be accepted.

Following the release of the **LoOIs at day 180**, applicants should respond in writing within 1-month. Only very limited new data derived from new studies would be acceptable at this point of the procedure as assessment time beyond day 180 is extremely limited. In exceptional circumstances, a 1-month extension in submission of the written responses may be granted only upon provision of appropriate scientific justifications to be reviewed and agreed upon by the CHMP. The request for an extension of the timeframe should be submitted as soon as possible and addressed to the CHMP Chairman. In case the LoOIs is to be addressed partly or completely as part of an oral explanation, this will normally be scheduled one month after the submission of the written responses. In preparation for such oral explanation, applicants are advised to consult the "Guidance to applicants on CPMP oral explanations in relation to centralised applications" (CPMP/2390/01 – rev.1):

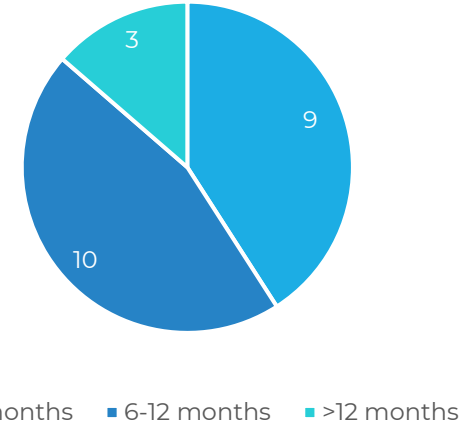
- Additional clock stops would not normally be permitted unless relating to issues of inspection (i.e. need for GCP or GMP inspection instigated by the CHMP) or need for additional expert input (i.e. SAG or ad-hoc expert group).

Clock-stop statistics (1/3)

Assuring the Network's Sustainability

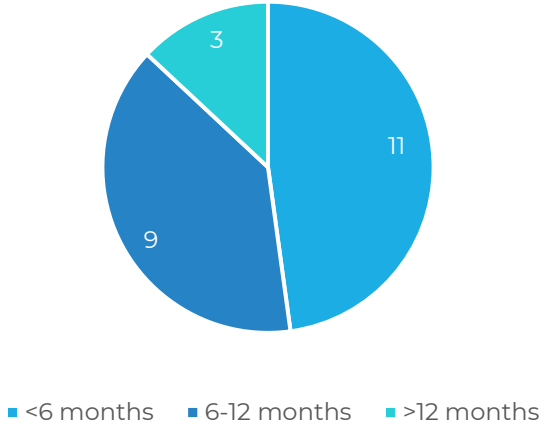
Clock stop extension requests in 2022 and 2023*

2022



Total = 22
@D120 = 9
@D180 = 13

2023



Total = 23
@D120 = 4
@D180 = 19

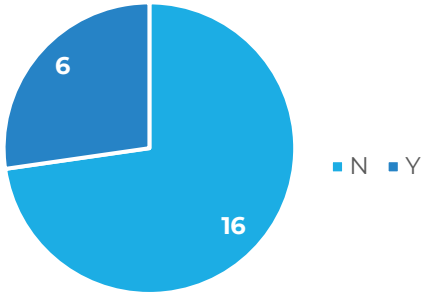
* Note: since there was no consistent monitoring of clock-stop requests in 2022 and 2023, these numbers likely only represent a fraction of requests

Clock-stop statistics (2/3)

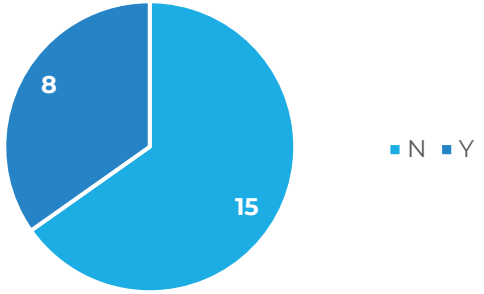
Assuring the Network's Sustainability

Clock stop extension requests by SME status and legal basis

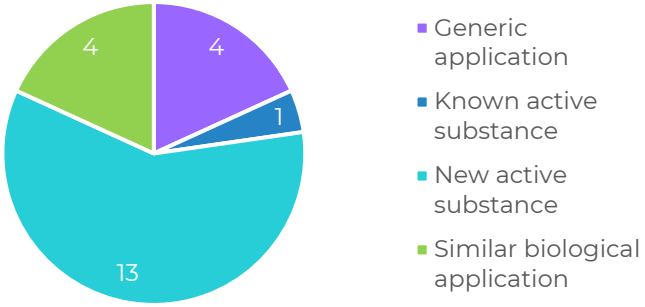
SMEs vs non SMEs - 2022



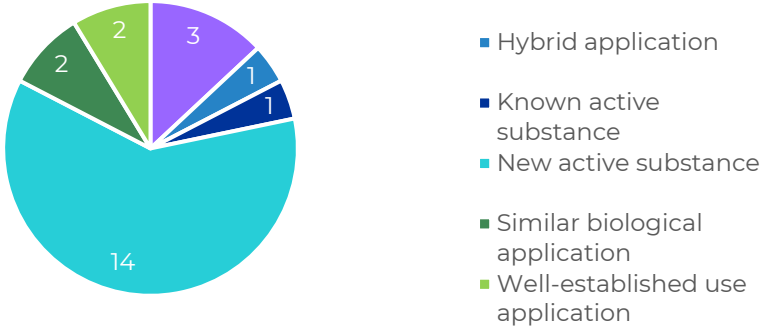
SMEs vs non SMEs - 2023



Per legal basis - 2022



Per legal basis - 2023



Clock-stop statistics (3/3)

Since September 2024, clock stop requests are being monitored much more closely

Month	Request for D120	Request for D180
September 2024	6	3
October 2024	4	7
November 2024*	3	5
Av. length requested (in addition to standard 3 months)	4.07 months	2.0 months

* To 15-Nov-24

GIREX II (Group for Internal Rules for EXtensions of clock-stops)

Assuring the Network's Sustainability

GIREX has now been rebooted

(GIREX II)

Work:

- Proactive review of all clock-stop extension requests, ahead of plenary discussion

Aims:

- Define principles for ensuring consistent decisions on clock-stop extension
- Ensure alignment between CAT and CHMP

As we are now actively monitoring all clock-stop requests, we will be able to provide more reliable data in the future.

Agenda

- Submission predictability workshop
- Revamp pilot
- GIREX II
- Focus group on revamp of pre-submission interactions
- Changes to SmPC published in EPARs

Call for expression of interest

Assuring the Network's Sustainability

- Several EMA activities tackling efficiency of approval process for medicines in the EU
  - Initiative to focus on pre-submission interactions
- Identified lack of visibility on products reaching submission, leading to unnecessary delays at validation & during the assessment
- Need to strengthen the pre-submission interactions & introduce early dialogue to:
  - optimize submission readiness
  - better anticipate assessment issues
  - identify "premature" applications
  - optimise resource capabilities (EMA and its Network)
  - enhance communication
- EMA is setting a working group (EMA Network and Industry): "Pre-submission Revamp"
- Please provide nominees by 06-Jan-2025 - Contact : EMAIndustryLiaison@ema.europa.eu

Call for expression of interest

Assuring the Network's Sustainability

- The focus group will kick-off in Q1 2025
- Aim to share problem statements (EMA, applicants, Rapporteurs)
- Aim to brainstorm possible solutions
- Participation by all applicant representatives (big Pharma, medium Pharma, SMEs) will be critical

Agenda

- Submission predictability workshop
- Revamp pilot
- GIREX II
- Focus group on revamp of pre-submission interactions
- Changes to SmPC published in EPARs

Changes to submission requirements for annexes

- By end of Q1 2025, EMA intends to publish the track-changes word version of the product information (PI) in the EPAR of innovative medicinal products with authorised generic medicinal products.
- This will facilitate the identification the changes approved in the latest procedure affecting Annexes.
- This initiative will facilitate the update of safety data in the PI of generics medicinal products authorised centrally, MRP/DCP or at national level.
- MAHs already provide word track-changed PI documents as part of the final provision of translations or upon submission of minor variations. As part of this initiative, MAHs will be requested to add one (template) sentence on the first page of the document to provide the context of the document.
- Detailed guidance of submission requirements is aimed to be published in Dec 2024.

Any questions?

Further information

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

Follow us on **@EMA_News**