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Highlight report 5th Meeting of the industry stakeholder platform on the operation of the centralised procedure for human medicines

3 December 2020

Chair: Radhouane Cherif

Role	Name
Chair:	Radhouane Cherif
Present:	**Industry:** **AESGP:** Klavdija Kmetic. **EFPIA:** Aimad Torqui, Anja Hoeffle-Maas, Emma Du Four, Isha Arora, Pär Tellner, Patrick Middag. **EUCOPE:** Andrea Braun-Scherhag, David KaneJoao Duarte, Julie Kieffer, Kieran Maher, Lars Hyveled-Nielsen, Laura Liebers, Lucia D'Apote, Maren von Fritschen. **EuropaBio:** Budhesh Dhamija, Christiane Abouzeid, Esteban Herrero-Martinez, Laura Liebers, Marcello Milano, Pedro Franco, Stephen Gareth Fawbert. **EuroPharm SMC:** Alain Verrijdt, Graeme Ladd, Jozseph Peter Pallos. **Medicines for Europe:** Ana Belen Grima Morales, Beata Stepniewska, Britt Vermeij, Dora Halmai, Ekkehard Baader, Janina Dzambazoska, Koppen Mirko, Navneet Ubhi, Yeosun Hong. **Vaccines Europe (VE):** Anna Czwarno, Anne de Bock, Emmanuelle Pirat, Michel Stoffel, Monica Pagni, Muriel Paste, Susanne Heiland-Kunath. **EMA:** Radhouane Cherif, Alexis Nolte, Alberto Ganan Jimenez, Alexios Skarlatos, Anthony Humphreys, Caroline Blanc, Caroline Pothet, Christelle Bouygues, Florence Daleska, Joaquin Berenger Jornet, Marie-Helene Pinheiro, Thomas Castelnovo, Thomas Girard, Victoria Palmi Reig. **EMA scientific committees and working parties:** Martina Schüssler-Lenz and Sabine Strauss.

This was the fifth event in a series of meetings (the last one was held in 2017 before the business continuity plan developed by the Agency between regulators and representatives of industry stakeholder organisations aiming to foster a constructive exchange with these stakeholders on general updates and more focused discussions on specific processes and issues to support continuous improvement. The purpose of the platform is to provide an opportunity for both general updates and more focused discussions on specific processes or issues to support continuous improvement, and generally to foster a constructive dialogue with industry stakeholders.

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Launch of Marketing Status IRIS

As part the EMA's strategy to digitalise its operations, the Agency is developing a new electronic reporting tool of Marketing Status data electronically by Industry for centrally authorized human medicinal products; the reporting from MAHs being a legal requirement. The tool is another expansion of the IRIS platform and will enabled data to be reported in a structured way, provide overview of such reported data and, facilitate a better data management overall.

The information to be reported is in line with data currently reported to the Agency (i.e. data at presentation level (EU number) of CAPs for each EU/EEA MS on the date of placing on the market, the date of cessation to market, the type of cessation (permanent/ temporary), the reasons for cessation and where applicable, the expected date of reintroduction in the market).

The new reporting system is intended to be launched in 1Q2021. For CAPs not yet launched in any EU/EEA MS, the MAH should report initial placing on the market and any subsequent updates via IRIS from the launch of the system. CAPs already marketed in at least one EU/EEA MS require a baseline submission of the current marketing status in all EU/EEA MS for all presentations before starting to report any changes of marketing status in IRIS. EMA presented a proposal where all updates of the marketing status of marketed CAPs should only be reported via IRIS after 2 months of the launch of the tool and that all baseline data on marketing status in EU/EEA MS for all CAPs should be provided within 6 months of launch of the tool by the Agency. Industry expressed some concerns about the timelines especially considering that some MAHs may have a significant number of CAPs. The Agency agreed to take them into due consideration and to inform Industry stakeholders on the final timelines as post meeting communication.

The Agency is working on technical developments to facilitate the submission of baseline data and also developing /updating technical and regulatory guidance to support a smooth transition to the new way of reporting including an IRIS user guide detailing what and how reporting of the Marketing status should be performed.

The following topics were identified for follow-up:

- Follow-up on feasibility of the request for multiple reporting at product level.
- EMA to inform Industry stakeholders of timelines for reporting products marketing status in IRIS and on the feasibility for multiple reporting.

  Post-meeting note: For marketed CAPs, any update of marketing status can be reported to EMA via email or via IRIS during the first 4 months after launch of IRIS-Marketing status. After this period, reporting should only be performed via IRIS. A submission of baseline data is required before the first reporting of marketing status update in IRIS. All MAHs will be required to report the baseline data on marketing status in EU/EEA MS for all CAPs **within 6 months of launch of the tool by the Agency**.

KPIs CP: IMAA and use of checklist

A validation checklist for initial marketing authorisation application (MAA) was published on February 2019 as a follow-up of the tripartite survey on the centralised initial marketing authorisation application (MAA) procedure.

EMA presented the analysis of Applicant's MAA validation issues between 2018 and 2020 and the impact of the publication of the validation checklist (see presentation here).

During this period, it was highlighted that the number of validation issues was still high (validation issues occur in 99.5% of initial MAAs (iMAAs)) however this number is reduced when the checklist was used. Industry conducted a specific survey among EU trade associations and presented the findings during this meeting and exchanged on improvement suggestions for the validation checklist (direct link to template, version number etc.), communication with Validation Officer and PIP compliance. EMA indicated that the checklist is regularly updated to include information on latest information requirements e.g. "Brexit", Nitrosamines validation requirements etc.

Further to the discussion, it was agreed that Industry stakeholders should use and submit the latest version of the validation checklist together with their applications.

The following topics were identified for follow-up:

- EMA validation checklist will be updated to add a version number (with a tab listing changes vs. the previous one) and to clarify that the risk assessment for nitrosamines should be included in Module 3.2.
- EMA will explore updating the checklist to include links to all template documents available and add relevant updates further to comments made/sent by Industry stakeholders
- EMA informed industry of the upcoming in-depth analysis of GMP validation issues encountered in the past 2 years. Relevant guidance will be included in future updates as appropriate.
- Industry PIP compliance check comments will be discussed as part of the planned Paediatric R&D focus group follow-up discussions.

EMA experience on eCPPs

Following the introduction of the new electronic format for Certificates for Medicinal products (eCPP) in March 2020 further to the global COVID-19 pandemic and EMA COVID-19 BCP phase 1 declarations, the Agency presented at the meeting with Industry stakeholders the experience gained so far with this new format, and detailed the measures taken by the Agency towards a worldwide implementation. These include measures to ensure authenticity and integrity of these eCPPs (see presentation here) to further support their acceptability by non-EU countries and experience sharing with other issuing authorities.

During COVID-19 pandemic, it was important to pursue the issuance of CPPs electronically to avoid any potential disruption of regulatory activities and timely access for medicines in importing countries outside EU, where such Certificates are key documentation use by MAHs as proof of regulatory compliance and facilitate medicines approval processes.

EMA has issued more than 7700 eCPPs since March 2020, with more than 99% of them were issued within published timelines or beyond upon public health need.

With regards to measures to assure authenticity and integrity of eCPPs, EMA provides a signed letter of authorisation with each eCPP request. In addition, an email address to verify that the eCPPs is established

for non-EU countries or interested parties and a guidance document explaining the safety features of eCPPs was published in April 2020.

The Agency is exploring the use of an additional webtool intended where MAHs, third countries and any other interested party could confirm online the details of an eCPP issued any the Agency.

With regards to measures to support acceptability of eCPPs, the Agency has strengthened further the collaboration with WHO and shared experience to interested issuing non-EU Regulatory authorities to increase and foster the change of process and increase eCPPs uptake. The Agency has sent directly letters to receiving authorities and provided letters in English and Spanish to MAHs confirming that EMA does not issue printed CPPs and urging third countries to adapt their regulatory systems.

EMA considers eCPPs as the permanent solution for issuing CPPs and continue supporting a worldwide implementation of electronic CPPs and requested Industry to continue providing feedback (at company level) on their experience to better improve this process.

The following topic was identified for follow-up:

- Industry to inform EMA on any specific non-EU MSs eCPPs acceptance (certificate@ema.europa.eu).

Analysis on Accelerated Assessment

- EMA presented an analysis of the experience gained since 2016, following the introduction of the new Accelerated Assessment (AA) procedure including subset analysis of PRIME products and ATMPs amongst other. The analysis was conducted to understand trends or bottlenecks, and to identify the need for any specific and/or additional changes or updates (see presentation here).
- In that analysis, it was highlighted that unsurprisingly most PRIME medicinal products have been confirmed AA prior to filing initial MAA, when requested.
- For initial MAA requests for AA, the main reasons for rejection are namely, the inadequate or insufficient substantiation of the unmet medical need claim in the proposed targeted patient population whilst only 22% appear to lack enough strength of evidence.
- EMA noted Industry's need for additional guidance on the expectations from the different sections and requirements to support a claim of unmet medical need. To that effect, a revised AA request template was developed and will be published in due course. This was welcomed by Industry, as will be the specific AA timetable for ATMPs.
- Industry concurred with the need for a better dialogue prior to submission of a request for AA and highlighted that multi-stakeholder (e.g. HTAs) early dialogue for both accelerated assessment and conditional marketing application (CMA) could foster post-MA needs whilst allowing early patient access.
- Most applications had a positive opinion, however not all applications were finalised under accelerated timeline. The main reason to switch to standard timetable were major objections not compatible with AA timelines.
- For all applications, the identification of the indication for which the risk-benefit balance is positive (vs. the studied population) seems to be the biggest bottleneck in the assessment and applicants are requested to increase their efforts in building up the evidence required for the applied indication.

- For ATMPs, quality and manufacturing were considered the most critical parts of the assessment with lack of demonstrated comparability, lack of experience with commercial manufacturing process, and potency testing issues commonly raised during the evaluation.
- Non-clinical or safety major objections were rarely raised.
- The accelerated review for ATMPs seems particularly challenging and the pre-submission dialogue should be reinforced to build up a more comprehensive dossier and increase success rates.
- Even when reverting to standard timetable, the total assessment time is, on average, faster than never having started it. But timelines are very challenging for applicants and for regulators, so a robust data package is key to maintain AA.

The following topics were identified for follow-up:

- EMA will publish a revised AA request template and AA timetables specific to ATMPs (both for the request and the initial MAAs).
- EMA will run a deeper analysis of the experience with ATMPs and reflect on potential enhancement opportunities during pre-submission interactions to help applicants in increasing dossier maturity.
- *EMA will review the experience with CMAs and ask Industry to collect feedback on potential hurdles with CMAs - for discussion at a future CP stakeholder platform meeting.*

Working Parties new Operational Model

EMA presented information on the proposal for the Working Parties operational model (objectives, high level principles, architecture, and next steps). Industry welcomed the information shared and is looking forward to collaborating and providing any feedback on the future project development at the next centralised platform meeting in 2021.

The following topic was identified for follow-up:

- *EMA will provide further updates on the project at the next centralised platform including industry interactions and guideline development process.*

The audience was informed that EMA will continue to hold industry stakeholders platform meeting, likely to be 3th and 4th Quarter 2021, pending the evolution of COVID-19 pandemic and EMA BCP status. Further information will follow.