EUnetHTA 21

Project Plan

D5.1 JCA/CA SUBMISSION DOSSIER TEMPLATE

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DOCUMENT HISTORY AND CONTRIBUTORS

Version	Date	Description
V1.0	**03/12/2021**	Final Project Plan

Disclaimer

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CEB	

The work in EUnetHTA 21 is a collaborative effort. While the agencies in the Hands-on Group will be actively writing the deliverable, the entire EUnetHTA 21 consortium is involved in its production throughout various stages. This means that the Committee for Scientific Consistency and Quality (CSCQ) will review and discuss several drafts of the deliverable prior to validation. Afterwards the Consortium Executive Board (CEB) will endorse the final deliverable prior to publication. For further information on stakeholder involvement in this deliverable, please see section 3.2.

Copyright

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LIST OF ABBREVIATIONS

CEB	Consortium Executive Board
CSCQ	Committee for Scientific Consistency and Quality
COI	Conflict of Interest
CUR	Health problem and current use of the technology (domain of the HTA Core Model)
EFPIA	European Federation of Pharmaceutical Industries and Associations
EUnetHTA	European Network of Health Technology Assessment
HOG	Hands-on Group
HTA	Health Technology Assessment
HTD	Health Technology Developer
JA	Joint Action
JCA	Joint Clinical Assessment
JSC	Joint Scientific Consultation
MAH	Marketing Authorisation Holder
MD	Medical Device
OT	Other Technologies (non-Pharmaceutical Technologies, including medical devices, diagnostics and procedures)
PICO	Patient-Intervention-Comparison-Outcome (question)
pMAH	Prospective Marketing Authorisation Holder
PT	Pharmaceutical Technologies
REA	Rapid Relative Effectiveness Assessment
SOP	Standard Operating Procedures
TC	Teleconference
TEC	Description and technical characteristics of technology (domain of the HTA Core Model)

1 INTRODUCTION

In the technical offer, submitted on 04/05/2021, deliverables for the production of Joint Clinical Assessments (JCA) templates have been defined.

This Project Plan describes the objectives, approach and timelines for the deliverable D5.1. on Submission Dossier Template.

2 BACKGROUND

According to the tender specifications, a template for the submission dossier by health technology developers (HTD) shall be developed.

JCAs or Rapid Relative Effectiveness Assessments (REAs) of Pharmaceutical Technologies (PT) are based on submissions from the HTD of the new drug under assessment. The required data, as specified in the "submission requirements", are submitted in the form of a submission dossier. For rapid REAs (JCAs) of Other Technologies (OT) in JA3, EUnetHTA only requested a submission dossier for the assessment of high-risk medical devices (class IIb and III) and certain in vitro diagnostic medical devices; authors could select questions from the dossier template relevant for their assessment (mainly for the domains TEC and CUR); however, literature search and appraisal was always done by the authors. The HTD had to provide a submission dossier which must include all the information required to perform a robust and complete assessment according to the needs of Member States which plan to use the assessment for their national decision making. As such, the submission dossier must consider the research question(s) and scope of the assessment as defined in the Project Plan of the assessment.

In EUnetHTA JA3, working groups were established in order to revise the templates in the pharmaceutical branch, based on experiences from assessment teams. These activities included, amongst others, revisions of the submission dossier and assessment report template and aimed to increase consistency and transparency of the assessments, but also to better match the assessment team's expectations. Several of the revised templates were tested by the assessment teams of different pharmaceutical assessments and areas for improvement were identified. Early discussions in the subgroup working hands-on on the submission dossier template for pharmaceutical assessments led to an approach according to which the submission dossier template developed in JA2 was used in all JA3 assessments. The subgroup aimed to develop general recommendations for a future submission dossier template, which were compiled in the document "Recommendations for a Submission Dossier Template for Pharmaceutical Rapid REA" (2021) [3]. To gather feedback from the EUnetHTA partners on the draft recommendations, an online survey was conducted in summer 2020 that asked for feedback on the relevance and required comprehensiveness of each topic and content item as well as for missing items or topics in the draft recommendations. After endorsement of the paper by the EUnetHTA Executive Board, the document was shared with EFPIA (European Federation of Pharmaceutical Industries and Associations) for their feedback, which was attached as an appendix to the document for information.

Besides the work on the templates, Standard Operating Procedures (SOPs) for all process steps of a rapid REA (JCA) were developed in JA3. Three of these SOPs are related to the submission dossier and describe in detail:

1. The processes to be taken to request a submission dossier from the HTD;

2. How to perform a formal check of completeness of the submission dossier (medicinal products only);

3. The procedures to be initiated if the wording of the licensed indication changes compared to the expected wording during the regulatory process and the submission dossier has to be amended (medicinal products only).

4. The process for internal review of the completeness of the data set provided in the Submission Dossier.

Feedback on the SOPs and all other parts of the EUnetHTA Quality Management System has been collected continuously from the assessment teams after publication of each assessment report. The

feedback implies that the timeframe for the check of completeness of the submission dossiers was too short and that the SOPs might benefit from a more concrete guidance on the process steps to be taken by the authoring team when requesting data from HTD.

Table 2.1. Existing EUnetHTA documents

Title	Scope
EUnetHTA. Pharmaceutical Joint Assessments: Submission Requirements. 2019. [1]	(PT) This document describes the structure and principle content of the Submission Dossier, when the Submission Dossier is required and EUnetHTA's policy on publishing the Submission Dossier. The requirements also specify which pharmaceutical products are eligible for the EUnetHTA Relative Effectiveness Assessment (REA) process. *This document will be revised if needed.*
EUnetHTA. Relative effectiveness assessment of pharmaceutical technologies: pharmaceutical evidence submission dossier (template). 2020. [2]	(PT) This template is used by the HTD to provide a submission dossier which must include all the information required to perform a robust and complete assessment according to the needs of Member States which plan to use the assessment for their national decision making. *This template will be revised.*
EUnetHTA. Recommendations for a Submission Dossier Template for Pharmaceutical Rapid REA. 2021. [3]	(PT) This document presents recommendations for a submission dossier template based on the work of a hands-on submission dossier group during JA3 with feedback from the whole EUnetHTA network. Attached is feedback from EFPIA, which did not lead to any revisions of the content. *This document will be used as basis for the work. It contains feedback from the whole EUnetHTA network as well as from the industry.*
EUnetHTA. PT-02-SubDos Submission Dossier: Standard Operating Procedure for Rapid REA Pharma. 2019.[4]	(PT) This SOP refers to the formal check of completeness of the Submission Dossier. *This SOP will be revised if needed.*
EUnetHTA. PT-02-IntRevSD Internal Review of Submission Dossier: Standard Operating Procedure for Rapid REA Pharma. 2019. [5]	(PT) This SOP describes how the study pool provided by the pMAH in the submission dossier should be assessed for completeness and for relevance to the research question(s) formulated in the project plan for the assessment. The assessment steps described in this SOP take place after the formal check of the completeness (formal check of the completeness is described in the SOP PT-02-SubDos) of the submission dossier and are part of the assessment phase. The purpose of these assessment steps is to define the pool of relevant studies that serve as the evidence base for the REA. *This SOP will be revised if needed.*
EUnetHTA. PT-03-InfRetr Information Retrieval: Standard Operating Procedures for Rapid REA Pharma. 2018. [6]	(PT) This SOP covers the assessment of information retrieval documented in the submission file provided by the MAH. *This SOP will be revised if needed.*
EUnetHTA. Submission Requirements: Other Technologies. 2019. [7]	(OT) This submission requirements document describes which other technologies are eligible for the EUnetHTA REA process. The requirements specify the principal content of the submission dossier, when the submission dossier is required and EUnetHTA's policy on publishing the submission dossier information. *Relevant recommendations for the revision of this document will be identified*
Submission Dossier Template: Other Technologies (Short Form / Long form - template). 2015. [8]	(OT) This template is used by the HTD to provide a submission dossier which must include all the information required to perform a robust and complete assessment according to the needs of Member States which plan to use the assessment for their national decision making.

	Relevant recommendations for the revision of this template will be identified
EUnetHTA. OT-02-ScoDevDPPSubDos. Scoping, Developing 1st Draft of the Project Plan and Submission Dossier: Standard Operating Procedure for Rapid REA Other Technologies. Updated 2021. [9]	(OT) This SOP describes the process steps and responsibilities related to developing the scope, direction of the project and writing the 1st draft of the project plan. Other steps include request of patient input and the manufacturer submission file if it was decided to involve patients and manufacturers. *This SOP will be revised if needed.*

The replies to the survey conducted by the hands-on submission dossier group and the discussions within the assessment teams in JA3 reveal the following divergent views of partner organisations:

1. Relevance of topics and content items: Generally, the vast majority of topics and items suggested by the pharma submission dossier subgroup were strongly supported by the respondents of the survey. Nevertheless, the ranges of the answers covered the full range of the scale (1-4) showing that individual respondents considered some of the items less relevant;

2. Required comprehensiveness of topics and items: The levels of agreement on the required comprehensiveness of the presentation of topics and content items was slightly below those of relevance. At the same time for most items, responses covered the full range of the scale from 1 to 4 points, i.e. at least one of the respondents required an extended presentation of information on the specific item;

3. Requirement of complementary analysis: In most assessments, the need for complementary analyses (e.g. subgroup analyses and sensitivity analyses) was discussed within the assessment team. There is a need for a consensus on which complementary analyses should be requested by EUnetHTA and how these requirements should be reflected in the submission dossier templates;

4. Procedure when submissions do not follow the EUnetHTA PICO: Experiences in JA3 reveal that there is a lack of guidance on how to handle submission dossiers from HTD, which do not meet the requirements of the PICO question(s) defined by EUnetHTA;

5. Alignment of submission dossier templates and submission requirements for Pharmaceutical Technologies and Other Technologies: In EUnetHTA JA3, only recommendations for a future submission dossier template and related guidance for rapid REAs of Pharmaceutical Technologies have been developed. Moreover, the submission requirements (i.e. the evidence requested from HTD) developed in JA3 vary between branches (i.e. assessments of pharmaceutical technologies and other technologies). There are diverging views among partners on whether the submission requirements and submission dossier templates for the assessment of Other Technologies should be aligned with those for the assessment of Pharmaceutical Technologies or whether different approaches are justified.

The submission dossier templates, submission requirements and related guidance documents for the assessment of Pharmaceutical Technologies will be further developed taking the following recommendations based on the subgroup work into account:

Recommended general requirements

1. The evidence submitted for assessment is complete and not selective with regard to the available studies and data that could inform the assessment;

2. The data must have been analysed using appropriate methods to answer the research question(s) of the assessment;

3. The data presentation must be well-structured and transparent to allow an appropriate assessment within the limited timeframes available and to support the understanding of the submission and the assessment by third parties;

4. The submission dossier must include underlying documentation of the information presented to allow the assessors to check the content of the submission.

3 OBJECTIVE AND METHODS

The objective of this deliverable is to:

1. Update the JCA/CA Submission Dossier Template, submission requirements and related guidance documents;

2. Ensure the templates follow the outputs as developed in EUnetHTA 21, e.g. methodological updates.

3.1 Methods to achieve the objectives

For all of the objectives below the future EU HTA regulation will serve as the basis and the past JA3 experiences will be taken into account.

3.1.1 Objective 1: Update the JCA/CA Submission Dossier Template, submission requirements and related guidance documents based on the recommendations of JA3.

Based on the recommendations described above, submission dossier templates, submission requirements and related guidance documents for the assessment of *Pharmaceutical Technologies* will be developed. For the development of submission dossier templates, submission requirements and related guidance documents for the assessment of medical devices and *in vitro* diagnostic medical devices (henceforth "*Medical Devices", MDs)* relevant recommendations will be identified. The templates and guidance documents based on national requirements will be developed with the objective of providing input to a potential new EU legal framework on HTA based on mandatory submission of evidence by industry. Potential use by regional cooperation on HTA and/or national HTA organisations will be taken into account when developing the templates and guidance documents listed above.

Two different teams with different focus (PT and MDs) will work in the development of the deliverables. Documents derived from JA3 will be the starting point for the work; in addition, the specifications introduced by the new EU legal framework on HTA need to be considered. Further issue-based structured discussions are needed on the level of detail and methodological requirements to be included in the dossier template and company justification on methods. Moreover, the teams need to discuss how the request for data from complementary analyses should be reflected in the submission dossier template. The teams working on the documents for the assessment of Pharmaceutical Technologies and Medical Devices will discuss to what degree an alignment of outputs is possible, i.e. what are the common requirements and which specificities need to be considered. The work on the update of the submission dossier templates, submission requirements and related guidance will take the future HTA regulation into consideration.

The submission dossier template should be accompanied by sufficient guidance to dossier authors to support efficient development of a complete submission dossier that meets the requirements. This guidance can be provided in the submission dossier template itself or in additional guidelines for authors. This guidance would need to consider possibly different requirements by different partners, e.g. concerning level of detail and company justification on methods.

For the development of submission dossier templates, submission requirements and related guidance documents for the assessment of Medical Devices, the applicability of existing EUnetHTA documents (7,8) needs to be discussed taking into account the European HTA Regulation as well as the needs of Member States.

3.1.2 Objective 2: Ensure the templates follow the outputs as developed in EUnetHTA 21, e.g. methodological updates.

Coherence and consistency between the submission dossier template and the assessment report template as required will be discussed considering the overlap between the respective hands-on groups.

To ensure the JCA/CA submission dossier template will follow the developed outputs of EUnetHTA 21, hands-on groups working on methodological guidelines will be involved to provide input in order to define if further update of the deliverables is needed and to execute this accordingly.

There will be an exchange with the JCA teams (5.4 Production) on the experiences of working with the revised/new submission dossier templates, submission requirements and related guidance documents. Recommendations for future revisions based on these experiences will be produced, if deemed necessary.

3.2 Stakeholder inclusion

EUnetHTA 21 Stakeholder Pool is composed of HTA bodies (HTAb) outside of EUnetHTA 21 consortium, as well as stakeholder groups on patients, health technology developers (HTD), healthcare professionals (HCP), payers, and regulatory agencies from the EU/EEA countries.

Non-consortium HTAb (i.e. those not part of the EUnetHTA 21 consortium) who will be involved in the future subgroups of the HTA Regulation, should participate in the development of this project in order to ensure the deliverables are applicable to all European HTAb. They should be consulted at the beginning of the project. Additionally, they will be invited to review, at the same time as the Committee for Scientific Consistency and Quality (CSCQ), the 1st draft of the deliverable and the pre-final draft that will be submitted for public consultation.

In addition, the Hands-on Group (HOG) will consult specifically Health Technology Developer (HTD) to collect their point of view during development of the deliverable.

Other members of the EUnetHTA 21 Stakeholder pool will also be involved in this project. Their involvement will include, at minimum, participation in an informational kick-off meeting and regular stakeholder fora. They will also be invited to contribute to the work through public consultation.

4 ORGANISATION OF THE WORK

4.1 Mode of collaboration and frequency of meetings

The work will be distributed evenly between the agencies of the hands-on group (HOG). All HOG members will review each other's work prior to review by the CSCQ. The HOG will appoint one agency to interact with the three CSCQ configurations and the CEB.

The HOG will have meetings/email updates when needed, but at least monthly meetings, to update each other on the progress. In addition, when needed, the HOG will also have regular meetings with the other relevant HOGs.

4.2 Timelines

Table 4.1. Timetable

Milestones	Start date	End date
Project duration	07/02/2022	29/07/2022
1st Draft deliverable	07/02/2022	23/02/2022
Public consultation	02/05/2022	31/05/2022
Validate final version deliverable (CSCQ)	12/07/2022	
Endorsement final version deliverable (CEB)	27/07/2022	
Estimated finalisation date of the deliverable *	29/07/2022	

*publication date may fluctuate depending on the outcome of the Consortium Executive Board endorsement

5 REFERENCES

1. EUnetHTA. Pharmaceutical Joint Assessments: Submission Requirements. 2019.
2. EUnetHTA. Relative effectiveness assessment of pharmaceutical technologies: pharmaceutical evidence submission dossier (template). 2020.
3. EUnetHTA. Recommendations for a Submission Dossier Template for Pharmaceutical Rapid REA. 2021.
4. EUnetHTA. PT-02-SubDos Submission Dossier: Standard Operating Procedure for Rapid REA Pharma. 2019
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