Expanding Master Files for human medicinal products in the EU/EEA

Executive Summary

Sponsors for Marketing Authorisation Applications of biological medicinal products (e.g. recombinant proteins, advanced therapy medicinal products, vaccines) frequently rely on collaboration with third party manufacturers to source components required to produce new, innovative medicines. These materials often have intellectual property held by the third-party suppliers, however, the current European regulatory framework has little capacity to protect proprietary confidential information between collaborating parties for biologicals, whereas small, synthetic molecule products have tools such as Active Substance Master Files with 'open' and 'closed' parts to protect IP. Other Master File tools currently exist in the EU, for vaccines with the Vaccine Antigen Master File (VAMF), the recent veterinary vaccine Platform Technology Master File (vPTMF), and for plasma-derived products with the Plasma Master File (PMF).

Similarly, the absence of a Master File mechanism for biological medicinal products in the EU/EEA results in the reuse of the same information being structured, submitted and re-reviewed by agencies when common components and manufacturing process steps are being described in the Marketing Authorisation Applications for different products that use platform manufacture, formulations, primary container closure systems etc. This is further exemplified by the resubmission and rereview of information when prior knowledge across different products has been described and previously approved in other applications. Indeed, EFPIA proposed in 2017 at the BWP/QWP Prior knowledge workshop *"to consider the Use of a 'Master File' (DMF-type approach) as a way to gather prior knowledge information, where the relevant information can be reviewed and approved once by a competent authority and then cross-referenced in subsequent submissions. As the information needs to be kept current, use of a DMF would also facilitate lifecycle management through ongoing data maintenance and exchange with regulators."* [1]

This position paper proposes a modular, flexible Master File type approach, similar to the Drug Master File procedure of the FDA, by extending the scope of already implemented EU approaches:

- Expansion of the existing Active Substance Master File approach to apply to biological active substances and ATMPs, and to include raw materials, excipients, adjuvants, drug product and product intermediates etc, as a Pharmaceutical Master File (PhMF);
- Expansion of the veterinary vaccine Platform Technology Master File approach as a general Platform Technology Master File that may be applied to innovative technologies, platform manufacturing capabilities and prior knowledge data across different molecules, as applicable for all types of human medicinal products;
- Allowance for clinical trial applications to make reference to approved, commercial product Master Files, and implementation of investigational master files following the concepts outlined above, however relying on abbreviated procedures and appropriate quality requirements for investigational medicinal products.
- Case studies outlining how a more flexible EU/EEA legal framework extended to modular Master Files could facilitate a more streamlined Marketing Authorisation and Clinical Trial

Application submission and review procedure are provided in Annex 1 in addition to protecting intellectual property.

1. Introduction

The EU directive 2001/83/EC as amended, only provides a legal framework for plasma-derived products and vaccines to use a Master File (MF) approach (Part 3, 1.1 and 1.2, respectively). The EMA guidance for Active Substance Master File (ASMF) EMEA/CVMP/134/02 Rev 1, explicitly rules out applicability of an ASMF procedure for biological medicinal products. However, Applicants frequently source materials and components for the manufacture of a biological medicinal product from third parties who may hold proprietary information on those materials. Since ASMF procedures include 'open' (accessible to the Applicant and agency) and 'closed' restricted (accessible only to the agency) parts, an ASMF is a way to protect a company's Intellectual property (IP) when supplying information concerning that material to the Applicant. Therefore, the current limitation in the legal regulatory framework for biological human medicines, does not support the development of innovative, efficacious, safe medicinal products of high quality through the cooperation between companies. Protection of IP could be afforded by an expanded scope of the ASMF and by a Platform Technology Master File (PTMF), whereby the master file holder can protect its IP, yet give a regulator access to the whole Chemistry, Manufacturing and Controls (CMC) information.

During the registration of a new Marketing Authorisation Application (MAA) or submission of a Clinical Trial Application (CTA) for human medicines and their respective lifecycle submissions, applicants often reproduce the same or similar information in regulatory dossiers which are applicable equally to multiple products, even if this information has already been approved by a competent authority. When this prior-approved information is justified for reuse in a new application, this reassessment of the same information in multiple applications becomes redundant. For human medicinal products, the master files can only be used for small molecules with an active substance master file (ASMF), a Plasma Master File (PMF) and a Vaccine Antigen Master File (VAMF). The ASMF is expected to be resubmitted with each procedure. These limitations also do not support an efficient authoring, submission or review of MAAs or CTAs when materials, components or platform technologies are used that can apply to multiple products.

Of note, in 2022 the European Medicines Agency (EMA) adopted a veterinary Vaccine Platform Technology Master File (vPTMF, see [2]). This approach might also be a valuable option for human medicines if the concept and its scope is extended to human medicinal products of all therapeutic areas and modalities, for platform manufacturing process capabilities and quality attribute prior knowledge, used in the manufacture of the finished drug product.

This position paper focuses on the significant need for an extended master file concept that would be widely applicable across therapeutic modalities (incl. vaccines), materials and components used in the manufacture of finished drug products, such as biological, synthetic, radioactive drug substances and/or its intermediates, excipients, packaging materials, other referenced information, constituent parts of integral drug-device combinations. It would apply across the development and the lifecycle of the materials, and could also support the provision of process and analytical prior knowledge (PrK).

As part of this proposal, we additionally discuss the advantages of an extension of the currently available ASMF approach to a "platform-wise", modular, flexible master file approach (referred to in this position paper as a Pharmaceutical Master File, PhMF), comparable to the one practiced by the US Food and Drug Administration. An expanded master file approach potentially fosters collaboration,

accelerates review and approval processes and ultimately, grant faster access to safe and effective therapies to patients.

2. Pharmaceutical Master File as a needed future state, why it is important, and how to get there.

Regulatory assessments of MAAs and CTAs would be streamlined and accelerated by the use of Pharmaceutical Master Files (PhMFs) as redundant review of the same documentation in multiple applications could be reduced. Furthermore, the PhMF approach would allow for an enhanced intellectual property protection mechanism for confidential information in case of cooperation with different legal entities ("third party").

The PhMF concept could be established as follows:

- On first submission of a PhMF in support of the first MAA/CTA, it would be reviewed and certified to comply with the EU/EEA legislation by the Regulatory Authority (preferably centrally) and a PhMF evaluation report would be provided.
- This initial PhMF certification would be submitted in parallel with any subsequent regulatory submission (initial, lifecycle, or clinical) for which the application of the PhMF can be justified, in full or in part, as described by the Applicant.
- Future agency review of the PhMF would be limited to submissions of data that support an update data of the PhMF, within the context of an approved regulatory submission such as variation to the initial MAA, renewal, or CTA amendment, as applicable.
- Life cycle management of the PhMF should be carried out under the scope of the Variation guideline [14] by the addition of relevant categories and corresponding requirements.

The proposed MF approach allows a reduction of submitted data, while reusing and/or repurposing previously approved documentation, provided there is appropriate justification in the MAA or CTA that making the cross reference to a PhMF is valid. The applicability of the PhMF would need to be suitably justified with a focus on any similarities and differences and their impact on any new product dossier. It is the MAH/sponsor's responsibility to demonstrate that the data provided within the PhMF are applicable to the submission by cross-referencing. The open part of the master file should contain all required information for the MAH/sponsor to justify applicability for the use of the master file in the regulatory submission. Indeed, not all of the MF may be applicable to the new product submission and the Applicant should explain and justify those parts of the PhMF that apply.

While the ASMF procedure is already implemented for new or existing, compendial or non-compendial active substances used in small, synthetic molecules human medicinal products, expanding its scope to cover all therapeutic modalities, biological active substances, materials and components would transform the ASMF to a "Pharmaceutical Master File" (PhMF) with a broader scope that is not limited to small molecule and/or herbal active substances. A second category of PhMF would include Master Files containing data or process operations that can be applied to several different products (most often like-molecules) based on prior internal knowledge regarding product attributes and manufacturing process capabilities as outlined in Table 1, grouped into the concept of Platform Technology Master File (PTMF).

A non-exhaustive list of examples of where a PTMF or PhMF approach would be beneficial is provided in Table 1 .

Table 1: Examples of where a PTMF or PhMF approach would be beneficial

PTMF	
Product Attributes Use of prior knowledge supporting the control strategy (refer to Annex 1, Case study I a)	• A set of stability data used to generate the stability profile, stability models and degradation patterns of 'like-molecules' • Justification of the release and shelf-life specification for quality attributes based on platform data • "Platform" of new analytical technologies or toxicology data • Multi-attributes testing methods, e.g. Mass Spectrometry • Method validation, e.g. Host Cell Protein Enzyme-linked Immunosorbent Assay (HCP ELISA) when the same parent cell line is used (see draft ICH Q14 guideline [3]) for non-product specific procedures) • see also [1] Meeting Report – Workshop on Prior Knowledge
Manufacturing Process Capabilities Use of manufacturing experience supporting process development and/or qualification (refer to Annex 1, Case study I b)	• Platform synthesis and purification of synthetic oligonucleotides, mRNA, synthetic peptides, cationic liposomes, self-assembling dendrimers, therapeutic proteins, or nanoparticles • Standardised (platform) expression systems • Viral inactivation and purification steps, impurities clearance studies • Platform cell line developed for manufacturing multiple products • Continuous manufacturing for chemicals and biologicals • Fusion tag cleavage systems • Conjugation procedure of a linker, payload or a chelator used in the manufacture of antibody-drug conjugates and antibody-chelator conjugates • Facilities • Platform container-closure systems or integral device constituent parts which would not be assessed by a notified body • Emerging technologies, e.g. 3D printing, next generation sequencing
Extended ASMF	
Materials and Components Reference to CMC information and data of materials used in the manufacture of a product (refer to refer to Annex 1, Case study II d and f	• Regulatory Starting Materials and intermediates (e.g. parental cell lines, linkers and chelators, phosphoroamitides, amino acids, etc.) • Drug substance intermediates, including non-radioactive and radioactive precursors used in the manufacture of targeted radiotherapies or targeting moieties and payloads used in the manufacture of antibody drug conjugates • Novel or non-pharmacopeial excipients, including lipid nano particle (LNP), enzymes, pDNA or raw materials • Non-compendial packaging material • Leachables and extractables studies • Media recipes and composition • Adjuvants • WFI for injection supplied as a Drug Product (i.e. in a vial or a pre-filled syringe)

There are existing tools for the management of platform technologies, but to date these have had limited applicability and are limited in their use, see details in Annex 2.

3. Current opportunities and best practices to be explored

When considering how to present information in regulatory documentation for health authority (HA) review, a useful starting point is the US Drug Master File (DMF). The DMF is submitted to the US FDA and cross-referenced to support one or more medicinal product applications. Making reference to an existing DMF in a new submission or its lifecycle provides third party confidentiality of the data and IP protection. In addition, when utilised by the same applicant, it facilitates a smoother review process for reused parts of documentation by reference to the DMF, e.g. the same product intermediate, which can be cross-referenced in multiple submissions.

In the EU/EEA and Switzerland, the concepts of an Active Substance Master File (ASMF, [4]), Vaccine Antigen Master Files (VAMF, [5]) and Plasma Master File (PMF, [6]) have already been adopted for human medicinal products. However, use of these Master Files in EU/EEA is restricted. For example, the current ASMF approach is not applicable to biologicals, and the VAMF or PMF concepts are restricted to specific types of medicinal product. It is proposed to extend the ASMF approach to biologicals, drug substance intermediates, and complex raw materials. The rationale for extending the MF concept is the enhanced product and process understanding and experience for many forms of biological therapeutics gained over the last years/decades, in particular for recombinant protein products. Furthermore, there is a need to preserve data confidentiality (in common to small, synthetic molecules) when cooperating with third parties that can be afforded by a MF mechanism.

In the US [7] and Canada [8], where DMFs are extensively used as part of regulatory submissions, the different DMF types can describe facilities, processes, or materials used in the manufacturing, processing, packaging, and storage of human drug products. DMFs are reviewed by FDA in conjunction with: Investigational New Drug Applications (INDs) and subsequent relevant amendments, New Drug Applications (NDAs) or Biological License Application (BLA), to which the DMF is associated. In the USA, there are several DMF types. The US 'Type V' DMF is close to the proposed concept of the PTMF, as it allows for process-related information (e.g. the sterility control strategy for multiproduct filling lines) to be available for agency review in a single location, avoiding repetition of submission and review in each NDA/BLA.

In Japan [9] as well as in China [10], the Pharmaceuticals and Medical Devices Agency (PMDA) and National Medical Products Administration (NMPA), respectively, have a similar approach for drug substances, excipients and packaging materials, with the difference that DMFs are reviewed as stand-alone applications and go through an approval process at the time of registration by the DMF applicant. Pharmaceutical manufacturers can then refer to those DMFs in their own applications.

Examining the current existing tools and procedures in EU/EEA and Switzerland, including ASMF, VAMF (VAMF/PMF) and the more recent vPTMF, as well as procedures available in other regions including US, Japan and China, an extended ASMF and PTMF approach (all combined under a flexible, modular PhMF system) could essentially rely on similar principles and already implemented procedures and mechanisms to enable a more efficient assessment and to avoid administrative burden, both at the health authorities´ and applicant´s level. However, it is noted that to allow the

introduction of an ASMF approach for biologicals used as human medicinal products, certain limitations laid down in the current legislative framework[1] are required to be removed.

Since the Active Substance Master File concept was introduced in 2004, the manufacture of many biological substances, such as monoclonal antibodies (mAbs), has been standardized and platform processes have been established resulting in a greatly increased experience in the manufacture of biologicals and an enhanced understanding of both manufacturing process and product. While the more recent vPTMF guidance [2] provides a framework for the use of a PTMF for veterinary vaccines, no framework for the variety of platforms used in the manufacture of human medicinal products exists. Of note, since the introduction of the VAMF in 2005, this pathway has been rarely used, probably due to the fact that the VAMF holder cannot differ from the MAH/applicant. The VAMF concept does therefore not foresee the separation of the master file into a confidential or restricted and an open, accessible part. The proposals outlined in this paper may circumvent hurdles observed currently with already existing approaches. The implementation of a master file, in particular with a restricted part, could be accommodated by a risk assessment, addressing and justifying the overall oversight requirements of the manufacturing process on a case-by-case basis.

A summary is provided in Figure 1 that highlights the proposed scope of EU/EEA MFs, while an overview of existing features of globally available master files are provided in Annex 3.

[1] e.g. according to ASMF' CHMP/QWP/227/02 Rev 4/ Corr Annex 5, biological active substances are out of scope [4]

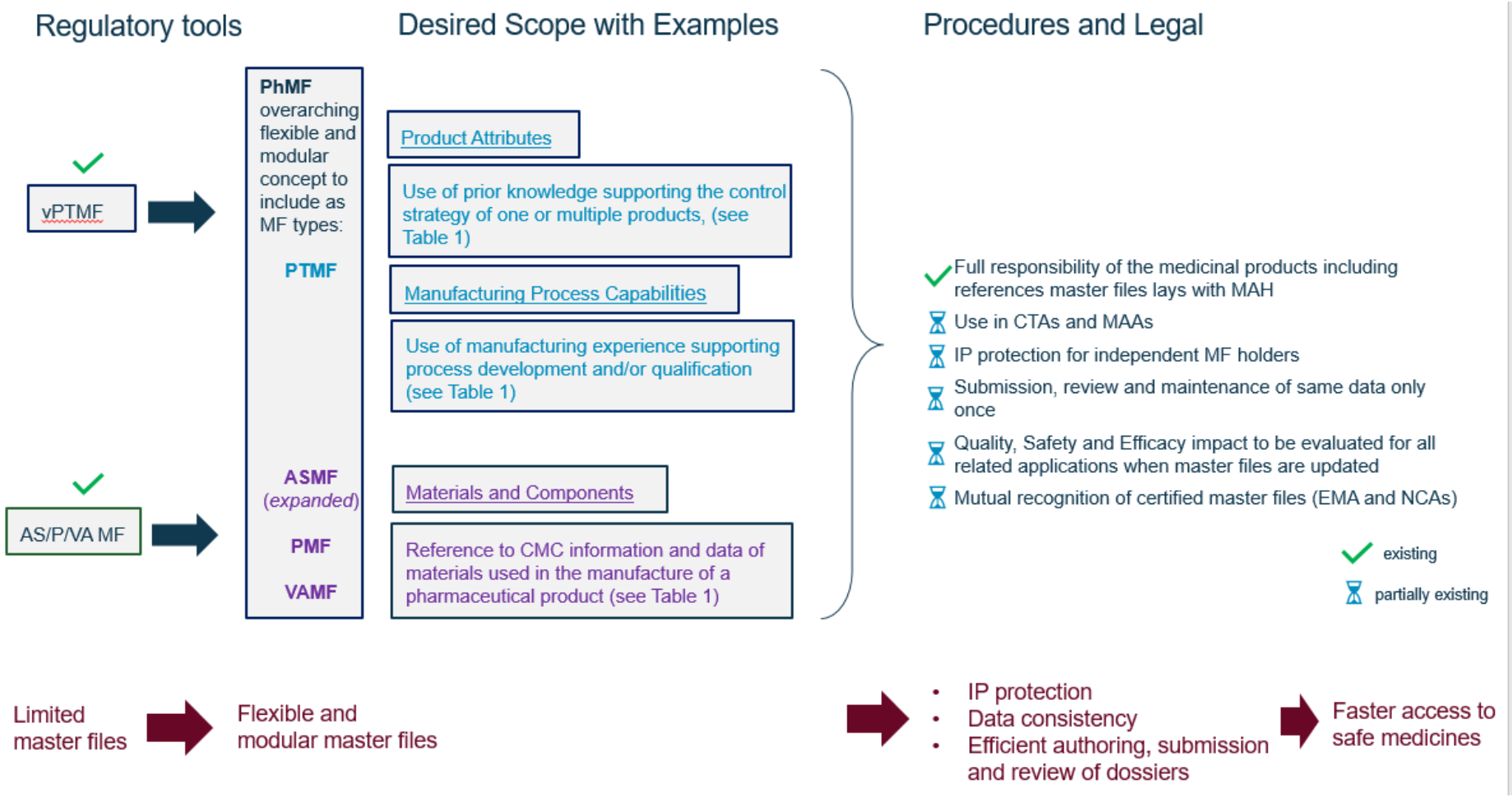

Figure 1: Proposed approach for the extension of existing mater files in the EU/EEA to flexible and module master files to ultimately assuring faster access of novel medicines. For examples, please refer to **Table 1**

4. Specific consideration for the extension of applicability of the PhMF approach to biological products

The concept of an ASMF was first introduced in Annex I of Directive 2001/83/EC, section 3.2.1. Of note, this section applies to both 'medicinal products containing chemicals and/or biological active substances'. This section states that 'for a well-defined active substance' the applicant may arrange the documentation into a separate Active Substance Master File. Therefore, ASMFs are applicable to biological active substances as long as they are 'well-defined'. Unfortunately, no definition of a 'well-defined' active substance was provided. It is noted that the EMA reflection paper [15] on the evaluation of new active substance (NAS) status of biological substances makes a distinction between well-characterised and highly purified active substances vs less well-characterised proteins, complex mixtures of biological active substances, or certain classes of biologicals. Based on this, it might be possible to understand 'well-defined' biological active substance as 'well-characterised and highly pure active substances for which the ASMF approach would be applicable.

However, Annex 5 of the EU/EEA ASMF guidance states the ASMF concept cannot apply to any biologicals as "The characterization and determination of biological active substances' quality requires not only a combination of physico-chemical and biological testing, but also extensive knowledge of the production process and its control. The MAH/Applicant for a biological medicinal product could therefore not comply with the requirement to 'take responsibility for the medicinal product' without having full and transparent access to these quality-related data. The use of an ASMF would prevent such access and should therefore not be allowed for biological active substances. In addition, active substances, which are present in certain medicinal products such as biologicals extracted from natural sources, vaccines or cell therapy medicinal products, do not fit with the concept of a 'well-defined' active substance." [4]

Firstly, we propose to remove this historical restriction from Annex 5 of the EU/EEA ASMF guidance so that an ASMF can equally be used in the context of all modalities. Furthermore, that the ASMF concept is used as a basis to expand to include drug product and drug substance intermediates, materials and components, e.g., starting materials, raw materials, excipients, adjuvants and container closure systems. Both, the original ASMF and the expanded ASMF concept would fall under a Pharmaceutical Master File (PhMF). This proposal is supported by the fact that process and product understanding for biologicals as well as the capabilities of analytical techniques applied to Control Strategies have significantly improved in the last decades. Consequently, the ASMF approach that exists today, having two parts (i.e., an Applicant's Part (AP) and a Restricted Part (RP)) is proposed for all modalities. It is acknowledged that the MAH cannot have access to the RP of the PhMF and that this impacts the degree of responsibility that the MAH is expected to take for their medicinal products. With a view to enabling patients to access faster safe medicines (including innovative ones), we believe that the usual quality agreements between the MAH and the PhMF holder are sufficient. Such quality agreements assign relevant responsibilities to both parties, such that any change having a potential impact on the applicability of the PhMF could be assessed by the Applicant. In case the MAH is equivalent to the PhMF holder, the agreement is not applicable.

Secondly, we propose to extend the scope/application of the vPTMF beyond veterinary vaccines and open this form of MF approach to human biological medicinal products for e.g., quality attribute knowledge and manufacturing process technologies and capabilities; as a Platform Technology Master

File (PTMF). See case studies in Annex 1 for more details to allow the use of a PTMF and the PhMF for human biological medicinal product.

Thirdly, the new master file concepts could also allow investigational medicinal products to refer to master files approved for authorised products, and herewith make early use of existing platforms and data during clinical trial applications.

In addition, we propose that the concepts described in this paper could apply to investigational master files (IMF) for investigational medicinal products. While suggestions of details for an IMF and procedures for clinical trial applications are not in scope of this position paper, EFPIA sees the implementation of the EU Clinical Trial Regulation (CTR) and the Clinical Trials Information System (CTIS) as a unique opportunity to implement the master concept to purely investigational products. The major differences would be the expectation towards Quality requirements that would be in line with the quality requirements for investigational medicinal products [11, 12]. It is acknowledged that the current features of CTIS would first have to be amended before allowing the proposed concepts to become functional.

5. Conclusion

The EFPIA, CEPI and VE see significant value in adopting MF approaches for use in regulatory applications for all human medicinal products in the EU/EEA region. In light of the recently experienced pandemic situation and shortage of medicines, a streamlined supply through faster access of innovative products is key to public health.

Currently there are legislative and EMA guideline restrictions to the use of MFs for biological medicinal products, therefore the opening of the EU human medicines directive 2001/83/EC as amended, provides an opportunity to achieve a legal basis for such MF approaches.

The drivers for legislative change that explicitly allows the use of MFs for all human medicinal products includes the protection of IP for third party suppliers and the applicant, while providing fully visibility to the EMA. the applicant justifies the applicability of the MF to the product and the owner of the MF agrees to inform the applicant of any changes to the MF that may impact the applicability of the MF. A second significant driver for a MF is to streamline the dossier building process, submission and review procedures. The Applicant can refer to and justify the MF instead of creating and submitting repeat documentation, whereas the agency no longer needs to review the same information that has been previously approved.

We acknowledge the extensive work and level of extra effort required to develop and establish/implement a PhMF / PTMF framework in the EU/EEA. However, the Annex to this position paper illustrates how existing approaches could be used to exemplify the benefits and operational mechanisms of the proposed master file approach with the aim that both, applicants and regulators, and ultimately patients can all benefit from an extended Master File approach.

We would welcome the European regulators implementing and promoting the use of novel master file concepts, as described in this publication. This would ultimately contribute to enhanced global harmonization of regulatory dossiers/submissions and procedures, thereby resulting in faster global access to medicines.

6. Glossary of terms

ADC	antibody drug conjugate
ASMF	Active Substance Master File
ATMP	Advanced Therapy Medicinal Products
BLA	Biological License Application
CEP	European Pharmacopoeia and certificates of suitability
CMC	Chemistry, Manufacturing and Controls
CoS	Certificate of Suitability
CT	Clinical Trial
CTA	Clinical Trial Application
CTD	common technical document
CTR	Clinical Trial Regulation
CTIS	Clinical Trials Information System
DMF	Drug Master File
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EU/EEA	European Union/European Economic Area
FDA	US Food and Drug Administration
HCP ELISA	Host Cell Protein Enzyme-linked Immunosorbent Assay
HA	Health Authority
IMF	Investigational Master File
IMPD	investigational medicinal products dossier
IND	Investigational New Drug
IP	Intellectual Property
LoA	Letter of Access
MA	Marketing Authorization

MAA	Marketing Authorisation Application
mAb	monoclonal Antibody
MAH	Marketing Authorization Holder
mRNA	messenger ribonucleic acid
MF	Master File
NMPA	National Medical Products Administration
NCA	National Competent Authority
NDA	New Drug Application
PhMF	Pharmaceutical Master File
PMDA	Pharmaceuticals and Medical Devices Agency
PMF	Plasma Master File
PrK	Prior Knowledge
PTMF	Platform Technology Master File
US(A)	United States (of America)
VAMF	Vaccine Antigen Master File
vPTMF	vaccines Platform Technology Master File

7. References

[1] - Meeting Report: Joint BWP/QWP workshop with stakeholders in relation to prior knowledge and its use in regulatory applications (23 November 2017) - Link to document

[2] - EMA/CVMP/IWP/286631/2021 - Guideline on data requirements for vaccine platform technology master files (vPTMF) - Link to document

[3] - ICH Q14 - Analytical Procedure Development (Draft) - Link to document

[4] - CHMP/QWP/227/02 Rev 4/ Corr - Guideline on Active Substance Master File Procedure - Link to document

[5] - EMEA/CPMP/4548/03/Final/Rev 1 - Guideline on requirements for vaccine antigen master file (VAMF) certification - Link to document

[6] - CPMP/BWP/4663/03 - Guideline on Requirements for Plasma Master File (PMF) certification - Link to document

[7] - FDA Guidance for Industry (draft) - Drug Master Files (rev. 1, October 2019) - Link to document - See also FDA website

[8] - Health Canada Guidance Document: Master Files (MFs) - Procedures and Administrative Requirements (December 1, 2021) - Link to Health Canada website

[9] - PMDA Guidance on Drug Master File System in Japan - Link to document

[10] - Announcement of the National Medical Products Administration on Further Improving the Bundling Review and Approval with Drug Product and its Related Supervision Matters (No. 56, 2019) Issued on Jul 16, 2019 - Summary available in English

[11] - EMA/CHMP/QWP/545525/2017 Rev. 2 - Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials - Link to document

[12] - EMA/CHMP/BWP/534898/2008 Rev. 2 - Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials - Link to document

[13] - EMA/CVMP/184591/2022 - Procedural advice for vaccine platform technology master file (vPTMF) certification - Link to document

[14] - 2013/C 223/01 - Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures - Link to document

[15] - EMA/CHMP/CMDh/CAT/BWP/828612/2022 - Reflection paper on criteria to be considered for the evaluation of new active substance (NAS) status of biological substances - Link to document

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9. Annexes

➢ Annex 1. Case Studies

Presented below are a series of case studies outlining the benefits of an extended European Master File approach, PTMF and PhMF.

The theoretical examples and case studies have been selected to illustrate why industry considers an extension of the currently limited master file framework in the EU/EEA beneficial for the pharmaceutical industry as applicants, regulators as assessors of regulatory submissions and patients who could benefit from earlier access to new medicines. Note, all the examples below could have been subject to the master file procedures currently in place, if the scope of those procedures covered additional therapeutic modalities or materials used in the manufacture of medicinal products such as intermediates, or technologies.

I. Platform Technology Master File (PTMF)

A company has developed a platform manufacturing process for e.g. antibodies, messenger ribonucleic acid (mRNA) vaccines and therapeutics, peptides or nucleotides, or ATMPs, which is used for the manufacture of different drug substances used in different drug products. General information, e.g. regarding development and validation of the manufacturing process and analytical methods, formulation development, as well as stability information applicable for all products manufactured according to the platform process, could be described in a set of PTMFs that focus on specific technologies.

a. PTMF for Product Attributes – use of prior knowledge to support the control strategy

One PTMF could justify the platform-derived products as representative of a family of molecules that behave as a class thereby generating prior knowledge described in the PTMF, applicable to other products of this class. For example, stability data for the family of product types (therapeutic modalities such as monoclonal IgG) could be used to justify shelf life for any new product manufactured using a platform manufacturing process. A set of criteria may be evaluated to assess the impact of differences between the individual prior knowledge products and may include stability data for drug substance, drug product or intermediates from clinical development and marketed products. The criteria would be at the discretion of the MAH and may vary according to the platform and the methodology adopted to evaluate the stability data.

The stability PTMF may evaluate the platform-derived prior knowledge stability data to generate a stability profile model that may be extrapolated to support extension of shelf-life for the new product, beyond the available long-term/real-time stability data for that product, as outlined in the EMA toolbox for products under the PRIME expedited regulatory pathway or for certain products of unmet medical need [15]. The approved PTMF may then be cross-referred to in a new product Marketing Authorisation (MA), or in a new CTA, for the platform stability data and any derived stability profile model that may apply to molecules manufactured using that platform. The applicability of the model would be justified, and risk assessed in the new product MA and verified by ongoing long-term studies post-approval.

The PTMF would be updated as needed and when new stability data are obtained both from new products manufactured using the platform or additional data for the approved products.

b. PTMF for Process Capabilities – use of manufacturing experience supporting process development and/or qualification (e.g. on Bioburden and Sterility Assurance)

Another PTMF may capture data for manufacturing process capability and manufacturing, comparable with the US Type V DMF. A PTMF may be used to provide information and data regarding all data relevant to e.g. the "sterility assurance strategy" for a platform technology used for the manufacture of different sterile products [8, 16].

It includes all sterile validation parameters and results, bioburden data as well as aseptic process simulation, environmental monitoring for drug substance, intermediates and drug product supporting a holistic evaluation of the bioburden and sterility control strategy for aseptically manufactured and sterile products across the manufacturing process.

c. PTMF approach for proprietary analytical methods from a third-party provider

A company may out-source the quality control testing or characterisation of drug substance or drug product for a biological product (e.g., therapeutic proteins, ATMPs, vaccines, but not limited to). The third-party provider has developed a commonly used analytical method for the given modality using proprietary technology and/or experimental conditions.

A confidential part of the PTMF would allow for the retention of such confidential information within the third-party provider company. General information on the nature of the method including interpretation and limitations of results and analytical validation data would reside in a non-confidential part of the PTMF allowing the applicant to retain oversight of the quality attribute state of the drug substance and drug product.

In general, analytical validation from existing compounds of the same platform could be useful to abbreviate method validation of a new compound from the same platform (prior knowledge).

II. Extending the concept of the Active Substance Master File to become a PhMF

The following two case studies describe the benefits of an extension of the current ASMF approach to cover biologicals and not only small molecules, to include raw/starting materials, drug substance intermediates, excipients and other materials besides drug substances transforming the ASMF into a wider-scoped pharmaceutical master file, PhMF.

d. ASMF (PhMF) approach including biological drug substances, as well as raw/starting materials and drug substance intermediates

For example, a company manufactures a monoclonal antibody which is either used as drug substance in a monoclonal antibody therapeutic or as drug substance intermediate further processed into an antibody conjugated to a chemical structure, or as part of a drug-drug combination product that has two active substance components. In all cases, sufficient, and appropriate information and data on the manufacture and quality control strategy needs to be submitted to, and assessed by, health authorities. As of today, the same CMC content would be included in all applications for the antibody being either the active pharmaceutical ingredient (drug substance), or an intermediate for further processing into the final drug product after conjugation with a chemical compound or combining with other drug substance intermediates for a drug-drug combination product. A reference to a master file providing the relevant antibody data would significantly reduce the complexity and size of the individual dossiers, by providing separately a complete Drug Substance section for the biological entity, including Master Cell Bank characterization and virus clearance data. The review and requests

for further information cycles regarding the antibody dossier section would be simplified and streamlined as these activities would be on only one file, instead of three different applications.

In detail, for the above example (a biological entity used either as drug substance or intermediate manufactured by a third party), the applicant(s) would currently submit identical / highly similar quality information for the antibody in three regulatory (e.g. CT or MA) applications, (1) the antibody therapeutic, (2) the antibody-chemical entity conjugate and (3) drug-drug combination product. If a European ASMF procedure for biologicals, as proposed a PhMF, was in place, the applicant(s) could refer to the corresponding (approved) PhMF for the antibody part. Consequently, any antibody-specific quality documentation that has already been assessed and approved by an authority in relation to a CTA or MAA, could be omitted from the application(s) for the final conjugated drug product or drug-drug combination product.

The PhMF for the biological drug substance (or intermediate) being manufactured by a third party, could be structured like an ASMF, with a non-confidential (applicant´s) and confidential (restricted) part. The first to share with the applicant to evaluate the suitability of the drug substance (intermediate) master file and assure quality control of the final drug product. The latter for review/assessment by the authority.

e. ASMF (PhMF) approach including chemical raw/starting materials, drug substance intermediates

A company synthesizes a chemical compound which is used as a raw/starting material/ intermediate/excipient in the manufacture of different medicinal products. The chemical synthesis and quality control of the chemical could be described in an ASMF that has an extended scope to include raw/starting materials and drug substance intermediates (this would also include e.g. linkers used in ADCs, viral vector manufacture for an ATMP). If the proposed PhMF procedure was in place, the applicant(s) could refer to the corresponding PhMF without including specific quality documentation for the chemical compound already approved by an authority, in the individual applications for the final drug products.

For the manufacture of the chemical by a different legal entity (“third party”) the quality information could be divided into non-confidential and confidential information dependent on the recipient. The PhMF could be structured in a similar way as currently an ASMF, with a non-confidential (applicant´s) and confidential (restricted) part. The first shared with the applicant to evaluate the suitability of the chemical and assure quality control of the final drug product, the latter for review/assessment by the authority.

f. ASMF (PhMF) approach for proprietary media from a third-party manufacturing organisation

A company sub-contracts the drug substance manufacture of e.g., a therapeutic protein or an ATMP product to a third-party manufacturing organisation. The third-party organisation has developed a proprietary media composition for the fermentation process to maximize cell viability, cell density and/or specific productivity.

Under the current regulations the third-party provider must disclose the proprietary media composition to the applicant for complete oversight of the manufacturing activities or the advancement in fermentation technology could not be used to produce drug substance for a CTA or MAA. A confidential raw material MF only known to the third-party provider could support the

implementation of novel fermentation ingredients to further enhance current manufacturing capabilities. In case of non-GRAS (generally recognized as safe) components, the third-party manufacturer would also submit information on the removal of raw materials of concern, during the purification of the drug substance within the confidential raw material MF. Oversight of the drug substance quality by the applicant is still ensured by process validation data and control strategy known to the applicant.

➢ Annex 2. Existing MF approaches in EU/EEA

Table 2 provides examples of the existing tools, discusses the issues associated with each and outlines aspects or limitations which could be alleviated by the introduction of a PTMF or an extended ASMF approach

Table 2: The management of platform technology knowledge: known issues and proposed mitigations using a PTMF or extended ASMF.

Issues with and limitations of existing tools for management and registration of platform technology knowledge	Aspects and challenges that could be resolved by implementing a Platform Master File and extended ASMF concept in EU/EEA for human medicinal products
Current EU Master File approaches	
There is currently an exclusive and restricted Master File approach for ASMF, VAMF, PMF, each with its own restrictions and limitations Master Files cannot be referenced in Clinical Trial Applications (CTA)	• Expanding to a modular Master File approach would allow the EU/EEA to take advantage of the system already established in the US via the Drug Master File (DMF) procedure (see Figure 1 for desired features); different types of master files should be allowed for biologicals on a case-by-case basis with a risk-based approach • Modular approach should include more inclusive Master File types that can accommodate novel excipients, biologicals, intermediates, packaging, platform technology and prior knowledge data (e.g. stability data) and process steps like virus inactivation or clearance steps, and certain raw or starting materials. • An extension of the Master File approach for its use in CTAs , as is the case in United States of America (USA) for Investigational New Drug (IND) applications, would increase flexibility early in drug development
Vaccines Antigen Master File (VAMF) and Plasma Master File (PMF)	
The VAMF and PMF procedures require the MAH to have full access to all CMC information of the VAMF/PMF, thus with no 3rd party intellectual property protection No protected third-party information is allowed, nor for the EMA to ask questions to a third party.	• Protection of intellectual property of a third party should be facilitated while enabling access to necessary information for the evaluation of a regulatory application. .

Issues with and limitations of existing tools for management and registration of platform technology knowledge	Aspects and challenges that could be resolved by implementing a Platform Master File and extended ASMF concept in EU/EEA for human medicinal products
Active Substance Master File (ASMF)	
The current ASMF approach cannot be applied in the context of biological medicinal products [4].	• Extension to biological molecules
Re-review of ASMF data every time it is referenced in a regulatory submission, often by multiple national authorities as no central EMA review and certification is possible	• Concept of similar to veterinary vaccines PTMF, whereby the master file is approved and a certificate is issued during its review on first application (initial MAA/CTA), and only reviewed again for update rather than for subsequent relevant regulatory submissions. The certification will lead to reduced data requirements of further dossiers based on the same PTMF, as the data included in the original PTMF will not have to be re-submitted or re-assessed by the Health Authorities. In case of MAA, this is supported by the MA applicant's Quality Expert statement (see more details in section 4). Similar mechanisms for CTAs need to be considered.
Veterinary Vaccines Platform Technology Master File (vPTMF)	
The vaccines Platform Master File (vPTMF) is only applicable to Veterinary vaccines and does not include data and process and specific materials' prior knowledge	• Extension to human medicinal products, including biologicals • Protect the valuable know-how on the used platform, while at the same time allowing the medicinal product applicant to take full responsibility for the overall compound, materials, process, and data from prior knowledge, such as the biologicals, novel excipients, adjuvants, platform data and processes and materials, medicinal product and the quality and quality control thereof. • A way of providing detailed proprietary information to a national competent authority (NCA) and/or European Medicine Agency (EMA) to demonstrate that the quality of the platform adequately supports the marketing authorization application for a respective medicinal product. • To ensure flexibility of review across member states and registration procedure. • Only one review and approval (certification) to other EU/EEA MFs

Issues with and limitations of existing tools for management and registration of platform technology knowledge	Aspects and challenges that could be resolved by implementing a Platform Master File and extended ASMF concept in EU/EEA for human medicinal products
Recently drafted procedural guidance [13] suggests a two-step process consisting of the vPTMF certification in a centralised assessment of the vPTMF application dossier submitted by the applicant/MAH in the first step. As a result, a certificate of compliance to Union legislation will be issued by the EMA. As a second step, the EMA shall take into account the certification, re-certification or variation of the vPTMF for the concerned medicinal product(s).	• There should be the option for different applicants for the vPTMF and the regulatory submission referring to the master file. The guidance does not allow them to be from different legal entities. • Data submitted within the vPTMF certification procedure should not be duplicated in linked regulatory submissions. If data previously included in a regulatory dossier can be removed once a vPTMF certification has been finalized, remains (yet) unclear. • Implementation of vPTMFs being stand-alone submissions independent from other regulatory submissions (similar to the US DMF approach) would ease the regulatory submission planning, especially if third parties are involved.
Certificate of Suitability to European Pharmacopoeia (CoS, also referred to as CEP)	
The European Pharmacopoeia and certificates of suitability (CEP) only apply to materials and standards described in monographs of the European Pharmacopeia	• The proposed EU/EEA modular master file (MF) approach to allow a similar protection of Intellectual Property as the Certificate of Suitability (CoS)/ The European Pharmacopoeia and certificates of suitability (CEP) and with a similar review and approval only once etc.

➢ Annex 3. Desired Features for an Innovative and Efficient Master File System in the EU/EEA

Table 3: Desired features of an innovative EU PTMF and ASMF extension to be used for e.g. platform type, innovative data that could be used independently and repeatedly for multiple marketing authorisations. Expansion of individual master file concepts could lead to an overarching framework of the EU master file concept.

Proposed master file feature	Does the proposed feature exist in other MF approaches?				Rationale for extending EU master file feature
	ASMF (EU)	VAMF/PMF (EU)	vPTMF (EU)	DMF (US)	
Type/Category of master file: MF (similar to US DMF style) to be used for biologicals including vaccines, novel excipients, packaging, medical devices, adjuvants, expression vectors, platform data and processes and materials	No	Partially Yes (For vaccines antigens and plasma materials)	Yes (For platform technologies)	Yes	• Allows the EU/EEA to offer the same advantages that are already available in the US via the DMF system • Reduce redundancy in terms of re-review of approved sections and allow more cross-referencing to avoid repetition of data and information across dossiers • ASMFs, as laid down in Directive 2001/83/EC as amended, cannot be applied in the context of biological medicinal products as discussed in [4]. While this argument might have been true for biologics manufactured by a third party, it is not the case when there is no confidentially issue between the Applicant/MA holder and the ASMF as e.g. in case they are the same. • Since the ASMF introduction in 2004 the manufacture of many biological substances, for example, monoclonal antibodies (mAbs) have been standardized and is operated using platform approaches. It is therefore proposed to extend the use of existing procedures to other modalities, e.g. biologics and their platforms. Applicants could provide a risk assessment for the confidential part.

Applicant and MF holder should be allowed to be from different companies; Reference to MF may be allowed by letter of access (LoA) or inclusion of EMA certification in the applicant´s regulatory submission.	Yes	Partially Yes (MAA needs full access)	No	Yes	• To have a similar approach as ASMF and allow co-developments and protection of intellectual property of 3rd parties involved • Acceptance of the applicant's access only to the applicant's part of MF as sufficient before placing the medicinal product on EU market or clinical studies • Continuous update of PTMFs with current data in line with existing regulatory framework (e.g. variation guideline [14]/investigational medicinal products dossier (IMPD) guidance (13, 14]) to allow for a regular exchange with regulators and facilitate lifecycle management, independent of the regulatory submissions linked (similar to ASMF and CoS/CEP updates mechanisms)
Intellectual Property protection mechanism embedded (e.g. by Applicant's part and Confidential MF parts similar to ASMF)	Yes	No (MF holder and applicant are the same)	No	Yes	
MF information (with Letter of Access in regulatory submission dossier) sufficient for EMA/NCA assessment of regulatory submissions without the need for applicant's access to the Restricted Part	Yes	No	No	n.a.	
MF information flexible framework (common technical document (CTD) format) and its update would contain the appropriate information, as applicable to the type of prior knowledge information	Yes	Yes	Yes	Yes	

MF submitted to EMA/NCA and reviewed once (with appropriate lifecycle), and recognized by National CA as per applicant's needs	No	No	Yes	n.a.	• To review the initial submission only once by EMA/NCA and the PTMF approval certification to be used subsequently • Need to implement also for clinical trials to extend flexibility earlier in drug development • The PTMF certificate issued will be valid for all possible combinations, where those platform type data can be applied to. But, for example in vector vaccines, the possibility to include a second, or more inserts in the same vector platform for a combined vaccine could need a new PTMF certificate and to be evaluated case by case
MF procedure with a clear procedural timetable & certification	No (Only national)	Yes	Yes (Draft)	n.a.	• Need a clear MF procedure, i.e. trigger event for initial MF review
PTMF for human medicinal products, including biologicals (including vaccines)	Partially Yes	Partially Yes	Partially Yes	Yes	• Concept similar to recently adopted vPTMF • Including knowledge base of analytical data (e.g. stability data) of products manufactured with same platform process (i.e. also data of platform process included)

					• The reduced repetitive submission of dossier content, by reference to a certified PTMF, will only be accepted when the certified platform technology submitted in subsequent dossiers is deemed valid and the same platform technology as described in the certification (also considering related changes, by way of variation) is proposed for use. Acceptance criteria for reduced data requirements will be outlined in the new guideline. Although reduced data requirements will primarily relate to quality aspects there will also be a need to consider any safety or efficacy aspects in the new guideline. • The reference to a PTMF or another type of MF would reduce the complexity and size of the dossiers significantly, without lowering the quality standard for the product, by the extent of a complete Drug Substance section for a biological entity; including Master Cell Bank characterization and virus clearance data. • Furthermore, in case of manufacture of the biologic by a third party, the quality information could be divided into non-confidential and confidential information. The extended ASMF approach allows dividing information in an open (applicant´s) and closed (restricted) part. The open part shared with the applicant to evaluate the suitability of the drug substance (intermediate) and assure quality control of the final drug product, the closed part for review/assessment by the authority • The MAA applicant using the certified PTMF, will take full responsibility for the product placed on the market as per the Quality Expert statement included in MA
Open the MF approach and its EMA certification for the usage during the EU	No	No	No	Yes	• This will speed up access to innovative medicines and its clinical development

Clinical Trial Applications, during product development The implementation of the EU Clinical Trial (CT) Regulation 536/2014 is offering the opportunity to submit documents via central EU submission portal (CTIS) which facilitates cross-referring and re-using of certain dossier sections/content across products, companies, applications within the European regulatory network.					• It will protect the IP data, and reduce the complexity of dossiers for CTAs • Extension of the CTIS portal may include the possibility for third parties to centrally submit confidential information for e.g. manufacture of intermediates (e.g. of antibody drug conjugates (ADCs)) directly to the Health Authority in the absence of confidentiality agreements.