Worksharing in the Evaluation of Active Substances

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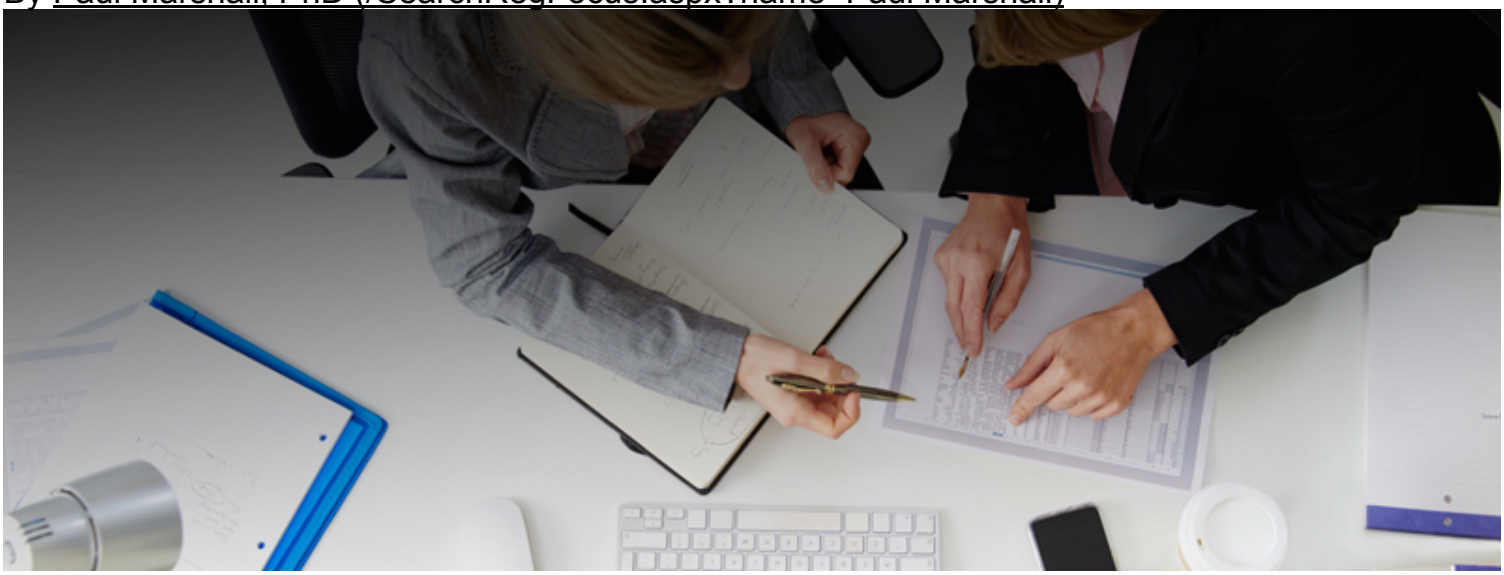

This article describes ongoing procedures and initiatives for 'worksharing' in the evaluation of active substance dossiers by regulatory authorities around the world.

Introduction

An Active Substance or Drug Master File (ASMF/DMF) can be used to describe the chemistry, manufacture and controls for an active substance. It is typically divided into an applicant's or open part and a restricted or closed part. The applicant's part is provided to the Marketing Authorization Holder (MAH) or applicant and allows them to take full responsibility for the quality and quality control of the active substance. The restricted part contains the confidential, detailed manufacturing process and controls information of the active substance manufacturer, which is provided to the regulatory authorities along with the applicant's part. An ASMF allows the valuable confidential intellectual property or 'know how' of the active substance manufacturer to be protected while allowing regulatory authorities access to all the information necessary to evaluate the active substance.[1]

The scope of an ASMF procedure can vary from region to region. In Europe, an ASMF can only be used to submit information on chemical and herbal active substances. Biological active substances are excluded from the procedure because extensive knowledge of the production process and controls are required for the characterization and determination of the quality of the active substance. The MAH/applicant does not have access to confidential manufacturing knowledge and is unable to take responsibility for the quality and quality control of the active substance in the medicinal product.[2]

By contrast, Japan's Pharmaceuticals and Medicinal Devices Agency (PMDA) allows a master file to be submitted for active substances, intermediates, pharmaceutical product materials (materials of pharmaceutical products with special dosage form, except for over-the-counter products unless a new active substance is used), excipients, pre-mix excipients, materials for medical devices and container/packaging materials.[3]

Health Canada allows a master file to be used for a drug substance or intermediate in the manufacture of a

drug substance, such as an active substance, vaccine antigens, excipients of biological origin (with the exception of gelatin); adjuvants (except for alum) or albumin) (Type I); container closure systems or components (Type II); excipients, colorants, flavour's and other additives, including alum and growth media (Type III); dosage forms and drug product intermediates (e.g., blend of drug substance and excipients) (Type IV).[4]

In the US, the Food and Drug Administration (FDA) permits the following Drug Master Files (DMF):

- Type I - manufacturing site, facilities, operating procedures and personnel
- Type II - drug substance, drug substance intermediate and materials used in their preparation or drug product
- Type III - packaging material
- Type IV - excipient, colorant, flavour, essence or material used in their preparation
- Type V - FDA accepted reference information

The FDA recommends updating DMFs annually.[5]

Europe's Worksharing Model for ASMF Evaluation

The manufacture and supply of active substances is a global business. Often, the same ASMF is submitted in support of more than one Marketing Authorization Application (MAA) or Variation (MAV) in more than one country or region. Consequently, this may lead to the same ASMF being evaluated repeatedly by different regulatory authorities, each potentially resulting in inconsistent decision making, numerous updating of the ASMF and a lack of regulatory oversight of the ASMF (by the ASMF holder, MAH/applicant and regulatory authorities). In response to this potential situation, European regulatory authorities initiated a Joint CMD*h*/CMD*v*/CHMP/CVMP Working Group in 2010[6] to develop a worksharing procedure for evaluating ASMFs. This initiative involved:

- A centralized European numbering system (EU/ASMF/XXXXX/YYYY) to identify conclusively when the same ASMF is submitted in regulatory procedures and European member states
- Common criteria for issuing EU/ASMF numbers (also adopted for non-worksharing ASMFs)
- A centralized repository for worksharing ASMF assessment reports, accessible by all European regulatory authorities to facilitate easy sharing of ASMF evaluations
- Common assessment report templates, standardizing the layout and content of information concerning an ASMF evaluation
- Revised ASMF submission details form (Annex 3)[7]to standardize the administrative information or "meta-data" for an ASMF
- Revised letter of access and withdrawal of access templates (Annex 2 and 4)[8] to allow sharing of evaluation reports and withdraw access to an ASMF when it is no longer used in a marketing authorization (e.g., replaced by a Certificate of Suitability (CEP))
- Procedural guidance on ASMF worksharing[9]and completing Annexes 2, 3 and 4 of the CHMP guidance on ASMFs.[10] The latter includes guidance on version control of the ASMF, supplementary to that covered as

part of Good Manufacturing Practice (GMP)[11]
- Questions and answers on the ASMF procedure and ASMF worksharing procedure[12]
- Comprehensive training on ASMF worksharing procedure and associated systems for industry and regulatory authorities

ASMF worksharing procedures were designed to work within the existing legislation and regulatory procedures, strengthening existing *ad hoc* sharing of evaluation reports among the European regulatory authorities. The timetables of the associated Marketing Authorization (MA) procedures are used to determine the parent reference member state, which is responsible for the drafting and circulation of the evaluation report. If the ASMF is used by more than one MA procedure, there is the possibility that the parent RMS may change after any clock-stop period, for example, if there is a delay in re-starting the initial lead procedure. Consequently, the worksharing model was termed the "floating rapporteur" model.

More information can be found on web page of the Joint CMD*h*/CMD*v*/CHMP/CVMP Working Group on ASMF procedures (http://www.hma.eu/306.html (http://www.hma.eu/306.html)).

- CMD*h* is the Coordination Group for Mutual Recognition and Decentralized Procedures – Human
- CMD*v* is the Coordination Group for Mutual Recognition and Decentralized Procedures – Veterinary
- CHMP is the Committee for Medicinal Products for Human Use
- CVMP is the Committee for Medicinal Products for Veterinary Use

ASMF Worksharing Pilot

On 1 December 2013, the Joint Working CMD*h*/CMD*v*/CHMP/CVMP Working Group launched a pilot project to test the feasibility of ASMF worksharing. Initially, the pilot was to run for one year, but the timeline was later extended to two years in order to develop more experience with the worksharing procedure. The scope of the pilot covered new ASMFs submitted in either decentralized or centralized procedures with updates to "worksharing ASMFs" being submitted by any regulatory route. A new ASMF was defined as 'not being previously approved' in a decentralized, centralized or mutual recognition procedure; ASMFs submitted in national procedures could still be used in the pilot, but might undergo re-evaluation. Also, active substances undergoing evaluation for a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability (CEP) were eligible. It should be noted the European regulatory authorities and EDQM have mutual access to each other's evaluation reports database).

At the end of the pilot project (30 November 2015), evaluation data revealed:

- 19 EU/ASMF were awaiting the start of evaluation
- 28 EU/ASMFs were undergoing evaluation
- 4 EU/ASMFs had been accepted for use in a marketing authorization
- 1 EU/ASMF had been withdrawn (at the request of the ASMF holder)

A survey of those companies taking part in the pilot found:

- 75 percent of EU/ASMF numbers were issued within nine days of the initial request
- Majority had a good/neutral experience of the assessment
  - Although 15-20 percent had experienced difficulties

- 90 percent of companies would use the procedure again
- 70percent of companies would recommend the procedure to colleagues

The uptake of the pilot and the results from the survey positively endorsed the European ASMF worksharing procedure. However, survey results also indicated room for improvement, although difficulties experienced by participating companies occurred during the early days of the pilot when the procedure was new for companies and for regulatory agencies.

Europe's Next Steps for ASMF Worksharing

Following the success of the pilot, the ASMF worksharing procedure is being adopted as a formal procedure. The Joint Working Group is currently evaluating ways in which a list of those worksharing ASMFs subsequently accepted for use in a medicinal product can be made publically available. Widening the scope to include existing authorized ASMFs has broad support among the pharmaceutical industry and would likely lead to a significant increase in the use of the procedure. A change in the worksharing model from a floating rapporteur to a fixed rapporteur/co-rapporteur worksharing model may be a possible future evaluation of the procedure and may potentially lead to the evaluation or review of the ASMF becoming independent of the MA application or variation (i.e., similar to the EDQM CEP procedure or the US FDA Drug Master Files).

International Generic Drug Regulator's Program

Worksharing initiatives are not limited to Europe. The International Generic Drug Regulators Program (IGDRP), created in 2014 following a successful pilot from 2011-2014, aims to promote collaboration and convergence in generic drug regulatory programs in order to address the challenges posed by increasing workloads, globalization and complexity of scientific issues.[13]

The following agencies and organizations participate in IGDRP:[14]

- Brazil Agencia Nacional de Vigilancia Sanitaria (ANVISA)
- China Food and Drug Administration (CFDA)
- European Directorate for the Quality of Medicines and Healthcare (EDQM) (Observer)
- European Union: (European Commission - DG SANTE (EC); Coordination Group for Mutual Recognition and Decentralized Procedures - Human(*CMD*); European Medicine Agency (EMA))
- Mexico Federal Commission for the Protection against Sanitary Risk (COFEPRIS)
- Russia Federal Service for Surveillance in Healthcare and Social Development
- Health Canada
- Singapore Health Sciences Authority (HSA)
- Japan Ministry of Food and Drug Safety (MFDS)

- Japan Ministry of Health, Labour and Welfare (MHLW)
- South Africa Medicines Control Council (MCC)
- New Zealand Medsafe
- Swissmedic
- Taiwan Food and Drug Administration (TFDA)
- Australian Therapeutic Goods Administration (TGA)
- US Food and Drug Administration (US FDA)
- World Health Organization (WHO) (Observer)

In 2013, the IGDRP formed an ASMF/DMF working group to foster international collaboration through information sharing and potential mutual reliance/worksharing of ASMF/DMF evaluations. The working group took into account established international initiatives, e.g., European worksharing procedure, EDQM certification scheme and the WHO prequalification program for active substances.

The working group has conducted a gap analysis of the ASMF procedures used in the members' jurisdictions to identify areas of convergence and divergence. (The analysis will be published soon. Common templates for an ASMF/DMF application form and the ASMF assessment report have been developed. The group is currently developing guidance on compiling the assessment report as well as looking at ways to share information on ASMF/DMF evaluations.[15]

EDQM Certification of Suitability (CEP) Procedure

Although not an ASMF, the Certification of Suitability to the Monographs of the European Pharmacopoeia (CEP) procedure is an established worksharing model for evaluating information on active substances. The procedure was piloted in 1992 and fully adopted in 1994 for chemical purity of pharmaceutical substances. Its scope was extended in 1999 to include products with a risk of Transmissible Spongiform Encephalopathy (TSE), e.g., gelatin, then further revised to include herbal and herbal drug preparations. An inspection program for manufacturing sites covered by a CEP application was initiated in 1999.[16]

The procedure allows manufacturers or suppliers - regardless of geographical location - of active substances, excipients and TSE products or herbal products, as described in monographs of the European Pharmacopoeia, to apply to the EDQM for a CEP. The application is evaluated by the EDQM Certification of Substances Division, assessors from European Regulatory Authorities, Health Canada and the Australian Therapeutics Good Administration (TGA).[17]

The CEP confirms that by applying the relevant monographs of the European Pharmacopoeia, with a supplementary annex to the certificate if necessary, it is possible to check whether or not the quality of the active substance is suitable for use in a medicinal product.[18] The certificate is not a GMP certificate, nor does it certify batch compliance for the active substance. A chemical CEP may be used in lieu of a full Module 3.2.S or an ASMF in initial MA authorization applications or variations[19] and certain Investigational Medicinal Product (IMP) dossiers.[20] TSE CEPs can be used to avoid the need to evaluate the product's TSE risks as part of a MAA/MAV. The use of herbal CEPs are more limited in both development and use at the current time.

CEPs are recognized by the 38 European Pharmacopoeia members, which include:

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Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Montenegro, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, "the former Yugoslav Republic of Macedonia," Turkey, Ukraine, United Kingdom and the European Union.[21]

CEPs also are recognized by some European Pharmacopoeia observer countries, e.g., Albania, Algeria, Australia, Azerbaijan, Canada, Georgia, Israel, Malaysia, Moldova, Morocco, Saudi Arabia, Singapore, South Africa, South Korea and Tunisia. CEPs also are accepted by the Taiwan Food and Drug Administration, New Zealand, Kyrgyzstan and Uzbekistan.[22]

Benefits of Worksharing for Active Substance Evaluations

Worksharing procedures for active substance evaluations offer several benefits to active substance manufacturers and MAH/applicants. For example, repeated assessment of the active substance dossier by different regulatory authorities is largely avoided, resulting in improved consistency of decision making, fewer requests for further information and increasing the speed to market for the medicinal products using the ASMF which, in turn, will increase the availability of medicines to healthcare professionals and patients. This results in the need for the information on the active substance to be updated less frequently by regulatory authorities which, in turn, reduces regulatory burden on the active substance manufacturer and MAH/applicant. Finally, the regulatory oversight and control on the active substance dossier by all parties is improved.

Of course, there are challenges to worksharing of ASMF evaluations. The quality requirements and standards for active substances are not harmonized in the different regulatory jurisdictions. For example, the selection and justification of regulatory starting materials remains a contentious issue[23] and is currently the focus of the International Conference on Harmonisation (ICH) Q11 Implementation Working Group.[24] Stability data requirements also vary around the world.[25]

Where the active substance is used in different products types (e.g., solid oral dosage forms, oral solutions or parenterals) or has been manufactured by different synthetic routes or is available in different grades (e.g., sterile or non-sterile), this may result in different quality requirements and standards that can prove challenging for a worksharing approach. However, the European worksharing model had foreseen this issue early, and taken steps to resolve this when developing the common criteria for issuing EU/ASMF numbers. Separate ASMFs are required if the critical quality characteristics of the active substance are different. In this case, of course, much of the ASMFs will be common, and thus the evaluation from one can be shared with the other.

Additionally, the regulatory procedures for submission of active substance information are not harmonized. Brazil's ANVISA, for example, only accepts ASMFs for certain active substances while South Africa's MCC currently does not require submission of the restricted part of the ASMF. However, on the whole, worksharing and information sharing on ASMF evaluations is a positive development, facilitating the supply of medicinal products to healthcare professionals and patients.

Conclusion

The manufacture and supply of active substances for medicinal products is a global business and often the same information on the chemistry, manufacture and control are submitted to regulatory authorities for evaluation. Several initiatives are examining information sharing with regard to these evaluations, leading to true worksharing of the evaluations by regulatory authorities. These initiatives will benefit the pharmaceutical industry in that they will reduce the number of times an active substance dossier is evaluated, leading to improved decision making, fewer requests for further information and updates to the master file and improved regulatory oversight of the quality and quality control of the active substance. These initiatives also will facilitate regulatory approval of the associated marketing authorization applications and variations, increase speed to market for medicinal products and improve supply of products to healthcare professionals and patients.

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SANDRA MOSQUERA

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