Recommendations to CMDh and EMA on the possibilities for optimization of processes and work-sharing

D7.2

Work package 7: Efficient use of resources

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Supporting the increased capacity and competence building of the EU medicines regulatory network

Contents

1. Introduction

1.1 Background

IncreaseNET is a Joint Action co-funded by the EU4Health Programme and coordinated by the Agency for Medicinal Products and Medical Devices of the Republic of Slovenia (JAZMP), that aims to enhance the capacity, competence and community within the European Medicines Regulatory Network (EMRN). IncreaseNET connects 29 partners from 27 EU/EEA member states and Ukraine.

The EMRN is a formal network of National competent authorities (NCA) and the European Medicines Agency (EMA), which is becoming a more active and inter-dependent community of experts, connecting available competences within the network. There is a need to increase the capacity and competence within the EMRN to meet the demands of Rapporteur appointments for Centralised Procedures (CP) and Reference Member states (RMS) availability for Decentralised Procedures (DCP) and Mutual Recognition Procedures (MRP). Increased capacity is also needed to handle activities to support new scientific development and innovations, seen through Scientific Advice and Clinical trials applications. Increasing the capacity involves increasing the overall number of assessors but also using the assessors in an efficient and sustainable way. The general objectives for work package 7 are to identify capacities and knowledge available in NCAs, facilitate their exchange to support better collaboration between NCAs, and to foster efficient use of resources harmonising the assessment.

1.2 Scope

This report focuses on efficient use of resources by exploring areas and possibilities for this efficient use, such as work-sharing and avoiding duplication of work, and specifically considering expansion of Multinational Assessment Teams (MNATs) to DCPs and Bioequivalence (BE) Work-sharing

This document is a public summary of the specific reports produced in tasks 7.3, 7.4 and 7.5.

This report will be shared with the Coordination Group for Mutual Recognition and Decentralised Procedure-Human (CMDh) and EMA as possibilities for optimization of processes in the EMRN.

2. Efficient use of resources (Task 7.3)

2.1 Introduction

While other tasks in WP7 focus on efficiency gains for specific aspects, task 7.3 explores the potential efficiency gains more broadly. The objective was to create a comprehensive overview of the possibilities for more efficient use of resources and provide an inventory of the existing systems for work-sharing (e.g. Active Substance Master File (ASMF), variations and paediatric work-sharing) with a discussion of their impact and remaining hurdles for further extension.
In addition, new possibilities for work-sharing activities were explored, such as reuse of assessment reports for applications with the same dossier or concurrent purely national procedures in different member states. Furthermore, the introduction of work-sharing in other domains such as ERA or RMP assessment were explored.
The analysis was based on ideas for efficient use of resources proposed by NCAs, CMDh, CHMP, and/or EMA, but also from suggestions received from concerned stakeholders. Challenges for the efficient use of resources are identified and discussed, with explanations of their implications for NCAs. The measures that are already in place or planned within the EMRN and their impact are analysed. Specific recommendations are provided to further improve efficiency, addressed to EMA, HMA, CMDh and/or NCAs. Furthermore, the report illustrates the potential of Information and Communication Technology (ICT) and Artificial Intelligence (AI) tools to improve operational efficiency.

2.2 Key messages

The key messages regarding efficient use of resources are presented and discussed below.

Submission predictability

Poor predictability of submission dates for applications makes efficient planning within NCAs complicated. This challenge is applicable to submissions of initial MAAs, responses to questions raised during assessment of the initial dossier and for variations. Planning is especially complex since assessors generally have multiple parallel tasks in ongoing MAAs, variations, scientific advice and clinical trials. Different measures to improve predictability of submissions have been introduced by the EMA (for the CP) and by CMDh (for the DCP and MRP). Further evaluation of the impact of these measures and optimization where necessary are advised.

Dossier maturity

The submission of immature dossiers for MAAs may lead to longer lists of questions. The applicant often needs more time to address those questions, which in turn leads to a delay in submission of responses. These responses frequently contain a large amount of new data, adding to the assessment workload, and affect resource planning. The revised EU pharmaceutical legislation includes mechanisms for an early rejection of dossiers that are incomplete or contain critical deficiencies that may prevent the evaluation. Efficient implementation of these mechanisms requires clear guidance on the identification of critical deficiencies. Involvement of relevant EMA scientific working parties and CMDh in the preparation of such guidance is essential for alignment of criteria to be applied.

Administrative burden

Within the EMRN several measures were introduced to reduce administrative burden in MAA handling, such as optimisation of assessment report templates and facilitation of collaboration between the different parties involved in the procedure. Further evaluation of the impact of those measures, and optimisation where necessary, is advised.

Post-approval activities

Post-approval activities (variations, renewals, PAMs) consume a significant amount of the available assessment resources. The amendment to variation Regulation (EC) No 1234/2008, which came into force in the beginning of 2025, aims to make post-authorisation changes more efficient and future-proof. The EMRN is invited to analyse whether this objective is fulfilled when sufficient data is available. In the revised pharmaceutical legislation, the per default obligation to apply for a renewal of the MA after 5 years is removed. This will mainly reduce administrative burden. Post-approval measures (PAMs), i.e. requirements for the company to provide additional data after obtaining the MA, constitute a significant burden in the centralised procedure. Further reflection on how PAMs could be handled more effectively is advised.

Multinational Assessment Teams (MNATs)

The system of MNATs contributes to efficient use of resources and strengthens collaboration in the network. The EMA has introduced measures to facilitate the formation of MNATs. Involvement in the on-the-job training, supported by IncreaseNET work package 6, provides assessors with insight in the handling of MAAs by other NCAs and may facilitate future collaboration in an MNAT. For efficiency gain, the MNAT system can be further optimised and can also be considered more broadly in the post-approval phase.

Involvement of external experts

Involvement of external experts in the assessment can contribute to capacity and competence building. NCAs mainly involve external experts to gain knowledge in complex and niche domains and to a lesser extent to handle resource issues. The EMA/HMA oncology pilot educational program aimed at making external experts familiar with the regulatory framework through a training program. Further information on the impact of this program would be welcome.

Availability and transparency of RMS capacity

There are challenges both, in NCAs and industry, regarding **a**vailability and transparency of RMS capacity, for which the CMDh is working on solutions. Increased transparency of availability for new RMS assignments, minimisation of the time for handling the RMS slot requests and further dialogue with industry are important aspects.

Reassement of dossier

Parts of the same dossier can be submitted in generic applications from different applicants. Different NCAs may be involved in the assessment, leading to the risk of repeated assessment of data. Development of a more extensive best practice guidance on how to identify similar, already approved, products would be welcomed. Different work-sharing procedures are already implemented by CMDh and the revised variation regulation has

made work-sharing for the assessment of variations obligatory. The revised pharmaceutical legislation introduces the Active Substance Master File (ASMF) certification enabling centralised assessment of drug substance documentation from a specific manufacturer to prevent parallel reviews. IncreaseNET task 7.5 focuses on the re-use of assessment reports on bioequivalence studies for generics. Appropriate information exchange between EMA and CMDh on generics with the same active substance being assessed in the DCP/MRP and CP is important.

Risk based approaches to assessments

Risk-based approaches increase the efficiency of regulatory procedures. Different measures are already introduced to strengthen the primary responsibility of the rapporteurs (in the CP) and the RMS (in the DCP and MRP) for the assessment. This could be further explored, for example, by sharing best practices between NCAs on criteria used to decide on the level of review of preliminary assessment reports. Guidance to focus the assessment on the main aspects relevant for the benefit-risk analyses is currently available, however, further elaboration and training on these are recommended. This would facilitate applicants to receive questions that are important to decide the outcome of the initial MAA or the variation.

Revision of the pharmaceutical legislation

Although the revised pharmaceutical legislation will facilitate tackling some of the existing challenges, it also brings new challenges. It is essential that the revised legislation is implemented in an efficient way, whilst maintaining the same level of advice, guidance, harmonization, training, etc. Strengthened requirements regarding Environmental Risk Assessment (ERA) require further expertise-building and collaboration in this area. The submission of raw data of clinical trials, as part of the MAA, requires expertise-building in the analysis of such data and, further, the necessary IT infrastructure at NCAs. The introduced phased review process for medicinal products, that are likely to offer an exceptional therapeutic advancement, should be less resource intensive and more predictable than the rolling review process that was in place during the COVID-19 period. The reduction of the scientific evaluation period for MAAs from 210 days to 180 days will also be a challenge for NCAs.

Scientific expertise and regulatory experience

Ensuring that assessor teams possess the necessary scientific expertise and regulatory experience for efficient work processes presents challenges for NCAs. The pharmaceutical sector is characterised by a broad range of products and rapid innovation, and assessors must keep pace with those advancements. The regulatory framework is complex and extensive. The EU Network Training Centre (EU NTC) provides tailored training materials for the regulatory network. In work package 5 of IncreaseNET, new training modules, which will be shared via EU NTC, are developed for identified needs. Work package 8 facilitates the involvement of academics in the training of assessors in innovative domains. In work package 6 of IncreaseNET, an on-the-job framework was developed to bring assessors to a level that allows them to independently assess new applications. It is important to ensure that the methodologies and framework developed in IncreaseNET can be consolidated for further on-the-job training of assessors in the EMRN.

Information and Communication Technology (ICT)

The use of ICT tools may improve efficiency during assessment, for example by reducing administrative burden, duplication of assessment work, improving co-ordination of assessment work and preventing different outcomes of assessment prepared by different NCAs. Important success factors for the IT tools are the interoperability between different systems, quality of the data in the systems and the search functions.

Artificial Intelligence (AI)

AI tools might increase efficiency in the regulatory processes. Examples of available tools includes tools for targeted data search and comparison, and for generating document and dossier summaries. It is important to ensure that no significant omissions or hallucinations occur when utilizing AI tools. IncreaseNET has expanded the scope of work package 7 with tasks 7.6, 7.7 and 7.8 that are focussed on expertise development and collaboration in the domain of AI.

2.4 Conclusion and Recommendations

Addressing the identified challenges faced by NCAs requires a multifaceted approach, involving improvements in several areas which includes submission predictability, dossier maturity, administrative efficiency, post-approval activities, MNATs, collaboration with external experts, RMS appointment, re-assessment and re-use of assessment reports. The impact of measures taken needs to be further evaluated and optimised. The use of digital solutions and AI tools may improve efficiency during assessment and in regulatory processes and reduce the administrative burden. The report provides specific recommendations for the European Medicines Agency (EMA), Heads of Medicines Agencies (HMA), Co-ordination Group for Mutual Recognition and Decentralised Procedures (CMDh), and NCAs to consider in addressing these challenges and enhancing the efficiency of the EU regulatory network.

2.5 Sustainability

Efficient resource utilisation is a key factor for assuring a sustainable regulatory network within the EU. Actions have been suggested by HMA/EMA (for the CP) and CMDh (for the DCP and MRP) to increase collaboration between national authorities as well as improving the predictability and maturity of submissions which have the potential to contribute to improved capacity planning and resource utilization in the network. Via HMA/EMA established working groups such as the Strategic Regulatory Oversight Group (SROG) and Focus Group on Submission Predictability (FGSP), identification of new actions can be proposed and surveillance performed on measures already taken. The Pre-Submission Interactions Group (Pre-SIG) pilot has been set up with the objective to optimize submission and compliance readiness, to better anticipate assessment issues and premature applications and to encourage alignment on submission timelines. Smoothing the evaluation process, by improving transparency of submission timelines and improving the quality of dossiers at submission, are necessary steps to take in connection to the implementation of the revised pharmaceutical legislation which requires agreement of submission dates and shorter timelines for assessment.

The revised legislation includes an option to reject immature application dossiers and this, together with EMA's pre-submission meetings, improves the ability to identify immature application dossiers within the CP. These tools will encourage better and more comprehensive application dossiers from applicants at the time of initial submission and thereby reduce binding of precious assessment resources and slowing down medicine approval times. However, it is important to assure sustainability guidance documents are provided.

The administrative burden for assessors has been reduced through improvement of templates and working procedures. However, administrative efficiency and sustainability require continuous improvements which can be assured through dedicated working groups at the EMA and CMDh. Use of digital solutions (ICT and AI) and a risk-based assessment approach should be evaluated as it may have an additional impact on efficient resource utilisation and sustainability within the EMRN.

3. Outline approaches with the potential to expand MNAT to DCPs (Task 7.4)

3.1 Introduction and background

MNATs are an important tool used to increase the overall assessment and Rapporteur capacity of the network, by filling gaps in expertise or resource constraints in national teams, that would otherwise be an obstacle for assuming the role as Rapporteur, with expertise available in other NCAs. They allow for the pooling of specialised expertise, flexibility in assembling the most appropriate scientific expertise, and the potential to speed up and strengthen scientific assessments. MNATs have been successfully used in the centralised procedures for assessing marketing authorisation applications since 2013. The MNAT initiative has broadened the involvement of NCAs across Europe in CPs, optimised the use of regulatory resources, and strengthened the scientific quality of assessments.

This task (7.4) explored the potential of applying the MNATs concept to the DCP for marketing authorisation of medicinal products in the European Union.

3.2 Feasibility analysis for use of MNATs in DCPs

The feasibility of using MNATs in DCPs, highlighting both pros and cons, was explored. The identified advantages are:

- Pooling scarce expertise across NCAs, potentially increasing the number NCAs stepping into the position of RMS and thus the number of procedures that can be handled. In other words - increasing the RMS capacity of the EMRN.
- Improving the quality of evaluations by bringing in niche scientific knowledge for complex products.

- Capacity balancing, as sharing assessment responsibilities can help distribute the workload more evenly.
- Serving as a tool for training and competence building, especially for smaller NCAs.
- Providing reassurance to stakeholders about the robustness of the evaluation process.

However, the following challenges were also identified:

- Legal and procedural fit, as the DCP is RMS-CMS driven without a formal coordination role for the EMA.
- Increased administrative and coordination burden and potential duplication of effort.
- Resource commitment concerns, as NCAs may be hesitant to participate without clear reimbursement or resource allocation.
- Risk of overcomplication for straightforward DCP applications.

Three options for implementing MNATs in the DCP were presented at the CMDh meeting. These options are:

1. **Option A: Voluntary MNATs Pilot Under CMDh Coordination**. Allows RMSs to request voluntary MNAT support from willing CMS NCAs for specific DCPs.
2. **Option B: RMS-led MNATs with Bilateral Memorandum of Understandings (MoUs)**: Enables the RMS to create an ad-hoc MNAT by contracting or seconding assessors from CMSs under bilateral MoUs.
3. **Option C: CMDh Procedure Change with CMDh Support**. Involves a formal CMDh procedure change to make MNATs an officially sanctioned part of the DCP.

3.3 Outcome and Recommendations

Following the CMDh discussions, it was concluded that while MNATs offer benefits in the centralised procedures, their direct application to the DCP faces structural limitations. Given that most DCP applications are for generic, hybrid, or well-established use products, the added value of sharing expertise is limited. The absence of a harmonised fee-sharing framework, increased administration and potential duplication of work are significant barriers.

The recommended approach is to allow voluntary, RMS-led MNATs under bilateral MoUs (Option B), which preserves RMS accountability, enables selective expertise sharing, and avoids unnecessary structural change. This approach keeps the door open for a more harmonised framework if the added value of MNATs in the DCP context becomes more evident in the future. Bilaterial MoU can also be established in advance and, when needed, a call for resources can be made allowing an efficient formation of an MNAT.

3.4 Conclusion

The potential of application of MNATs to the DCP has been explored. The benefits and challenges have been defined, and three options were discussed with CMDh. The outcome is a recommendation for a flexible and proportionate mechanism to enhance the DCP through voluntary, RMS-led MNATs. This approach is seen as a pragmatic way to leverage the strengths of MNATs in the DCP context while addressing the inherent limitations and complexities of the decentralised procedure.

3.5 Sustainability

The recommended approach to allow voluntary, RMS-led MNATs under bilateral MoUs (Option B) preserves RMS accountability, enables selective expertise sharing and avoids unnecessary structural change. This is the most flexible approach as it will allow RMSs to form an MNAT when needed. It will thereby be up to each MS to create agreements (MoUs) with other MSs, including the split of fees. Sustainability is achieved with the voluntary approach. Sharing of best practises and experience could increase the sustainability.

4. Possibility for work-sharing in assessment of BE studies (Task 7.5)

4.1 Introduction and objectives

The main objective of task 7.5 was to investigate the feasibility and advantages of implementing a well-structured work-sharing (WS) procedure for the assessment of BE studies. The intention was to harmonize the assessment of BE studies and thereby reduce the regulatory burden on NCAs. The feasibility analysis is based on the potential for usage of a WS procedure similar to the Active Substance Master File work sharing procedure (AMSF WS), which is already established.

4.2 Feasibility Analysis of a possible BE

In the feasibility analysis it was analysed if a well-structured WS, in line with the ASMF WS which is already established and in force for many years, could be set up.

The WS procedure would, as a first step, be intended to include BE studies submitted via the DCP/MRP procedures, where a full assessment report will be, or has been prepared, by the NCA acting as RMS. Therefore, the scenarios below only concern DCP/MRP procedures

In this context, a "Parent procedure" refers to the initial procedure where a complete BE study assessment report is prepared by the RMS acting as the lead assessor. "Daughter procedures" are subsequent procedures that use the same BE study, potentially with different RMSs or timelines. The assessment report from the Parent procedure would be

shared among the CMSs, allowing Daughter procedures to rely on this report, thus avoiding re-assessment and duplication of work.

Several scenarios for implementing a BE WS procedure were identified:

1. A new BE study in a single procedure:

   If a new BE study is used in a single procedure, the benefits of WS might be limited (if any). However, uploading the BE assessment report (BE-AR) to a common database would allow future procedures to access and potentially build upon this assessment. Thereby, there would not be a need for a complete re-assessment but rather, if needed, an update of the BE-AR in the new procedure.

2. When a new BE study is used simultaneously in more than one procedure:

   Where a new BE study is simultaneously used in more than one procedure with different RMSs, and/or different timetables, the BE study assessment could benefit from a WS procedure.

   The RMS of the Parent procedure prepares the assessment report, which can then be used by Daughter procedures, preferably with peer review from a daughter procedure to ensure robustness. A peer review process may reduce the risk of new critical points for the demonstration of bioequivalence.

3. Use of a previously assessed (in a WS procedure) BE study in a new procedure

   If a BE study has been assessed through a WS procedure and is later used in a new procedure, the final BE assessment report can be adopted without needing a new assessment, unless critical new information arises. However, changes in the product specific BE-guidance or a referral would require an update of BE-AR.

Advantages and disadvantages of the of the proposed WS procedure

The advantages of BE-WS procedure would include reduced duplication of assessments and regulatory burden, with the RMS/CMS managing the procedure.
However, BE is less complex than the ASMF because BE studies are typically assessed only once, during the initial application, and generally do not require updates like ASMFs do.

Concerns have been raised that the proposed structured WS approach might be too complex for practical implementation for BE studies.

4.3 Pharmacokinetic (PK) Master file procedure

The concept of a PK Master File, which would be a network-available master file on a product's pharmacokinetic properties to underpin BE study requirements, was explored. However, several challenges were identified, including who would be responsible for maintaining such a file, potential legislative needs, and the practicality of such a master file given the dynamic nature of BE studies and scientific progress.

In conclusion, the proposal for a PK master file procedure seems immature and is not recommended.

4.4 General Conclusion and Future Recommendation

The consensus is that, while the concept of WS for BE studies is supported, the proposed procedure, modelled in line with ASMF WS, may not be appropriate due to its complexity. BE studies have no further lifecycle, they are evaluated just once, while the ASMF needs a more complex procedure due to regular updates. Thereby a simpler, quicker solution is preferred for BE assessment reports.

The CMDh is exploring other feasible ways to avoid duplication of assessments, such as an improved functionality of the CTS-tool to share information on Contract Research Organisations (CROs) and number of BE studies, thereby enabling re-use of assessment in procedures based on the same studies or dossiers. Moreover, a living internal CMDh guidance document describing the handling of BE studies in CTS has been prepared.

In summary, the report concludes that while work-sharing for BE studies has potential benefits, the implementation of a complex procedure similar to the ASMF WS may not be the most practical approach. Instead, simpler mechanisms for sharing assessments and avoiding duplication of effort are being considered.

4.5 Sustainability

By adding a quick and simple solution for the BE WS procedure, duplication of work could be avoided and the need to conduct re-assessment of BE-studies could be limited. However, reassessment might be needed under special circumstances such as a revised guidance document, new data or a referral.

CMDh is in the process of developing the functionality of the CTS-tool and corresponding guidance for handling of BE-studies. This is also included in the CMDh workplan.

The ASMF WS procedure is proposed to be changed in the new revised human legislation, which further supports the recommendation to not implement the current ASMF WS process *as is*.

5. Overall conclusions

Work package 7 focuses on efficient use of resources and the specific objectives for tasks 7.3, 7.4 and 7.5, are to explore areas and possibilities for efficient use of resources, such as work-sharing and avoiding duplication of work, expansion of MNATs to DCPs and BE work-sharing, respectively. Challenges faced by NCAs in use of resources were identified with a multifaceted approach. Recommendations for measures for each of the challenges were presented.

For submission, predictability measures have been taken both by EMA and CMDh and the recommendation is to evaluate the impact of these measures and make further optimisations if needed. This recommendation is also applicable for measures taken to reduce the administrative burden. The amendment of the variation regulation was intended to improve the efficiency and future proof it. The recommendation to EMRN is, when more data and experience is available, analyse if this objective is fulfilled and propose improvements. Regarding availability and transparency of availability for new RMS-assignments there are challenges both in relation to NCAs and industry. NCAs and CMDh are working on solutions but further dialogue with industry is essential. Recommendations for improvements are made in connection to the development of digital solutions and AI tools to improve efficiency and reduce the administrative burden during assessment and in regulatory processes. Applying a risk-based assessment approach has the potential to further increase the efficiency. The revision of the pharmaceutical legislation will address some of the existing challenges, such as dossier maturity and post authorisation activities, but it will also bring new challenges. It is essential that the revised legislation is implemented in an efficient way, whilst maintaining the same level of advice, guidance, harmonization, training, etc.

The potential of application of MNATs to the DCP was explored. The benefits and challenges were defined, ending up with three options which were discussed with CMDh. The outcome was a recommendation for a flexible and proportionate mechanism to enhance the DCP through voluntary, RMS-led MNATs. This approach was seen as a pragmatic way to leverage the strengths of MNATs in the DCP context while addressing the inherent limitations and complexities of the decentralised procedure.

The potential to implement a BE work-sharing procedure was elaborated. It was shown that addition of a structured work-sharing procedure like the ASMF WS procedure for bioequivalence studies could have potential benefits, but the ASMF WS procedure is complex and may not be the most practical approach. Instead, simpler mechanisms for sharing assessments and avoiding duplication of effort are recommended. CMDh is in progress with the development/enhancement of the CTS-tool and corresponding guidance for handling of BE-studies, which would be a preferred solution and first step. Thereby duplication of work will be avoided and provide more efficient use of resources.

6. Abbreviations

AR	Assessment Report
ASMF	Active Substance Master File
BE	Bioequivalence
BPG	Best Practice Guidance
CMDh	Co-ordination Group for Mutual Recognition and Decentralized Procedures (human)
CMS	Concerned Member State
CoI	Conflict of Interest
CRO	Contract Research Organisation
CTS	Common Tracking System
DCP	Decentralised Procedure
EC	European Commission
EMA	European Medicines Agency
EMRN	European Medicines Regulatory Network
EU	European Union
FGSP	Focus Group on Submission Predictability
GCP	Good Clinical Practice
MAA	Marketing authorisation application
MAV	Marketing Authorisation Variation
MoU	Memoranda of Understanding
MNAT	Multinational Assessment Team
MRP	Mutual Recognition Procedure
MWP	Methodology Working Party
MS	Member State
NCA	National Competent Authority
PK	Pharmacokinetic
Pre-SIG	Pre-Submission Interactions Group
PSBG	Product Specific BE Guidance
RMS	Reference Member State
SROG	Strategic Regulatory Oversight Group
WP	Work package
WS	Work-sharing