The International Society for Pharmacoepidemiology's Comments on the Core Recommendations in the Summary of the Heads of Medicines Agencies (HMA) - EMA Joint Big Data Task Force

The International Society for Pharmacoepidemiology (ISPE) appreciates the work done by the HMA/EMA Task Force and the importance of ensuring that the European regulatory network can evaluate evidence generated by new and emerging data sources and methods. The successful integration of real-world evidence (RWE) into the regulatory decision-making process will ultimately benefit patients, both within Europe and globally.

We note that the summary report highlights that "a prioritisation and focusing of activities is required, which should build on ongoing actions and, where possible, link to existing structures". In this response, we point to such ongoing actions, and to areas that, in ISPE's view, are most likely to provide useful insights for regulatory decisions.

To make optimal use of the many exciting new digital data sources and methods to ensure effectiveness and safety of licensed medical products, regulatory agencies will have to articulate the use cases they wish to address. The population-level effectiveness and safety can be demonstrated by studying the causal relationship between drugs and relevant health outcomes using randomized and non-interventional studies.

More than 2,000 members of ISPE undertake studies with non-interventional digital data that are generated by the routine operation of healthcare systems. While pharmacoepidemiology has been mostly working with and developing causal inference methods for data from insurance claims, registries, and electronic health records, the increasing availability of digital health data generated from sources like wearable devices and social media, provides an unparalleled opportunity to improve and accelerate causal inference on medical products. Key ingredients are clear temporality, and accurate measurements of exposures, outcomes, confounding factors and markers of patient groups with varying susceptibility. Regardless of where the data originate, the application of the robust causal inference models developed in pharmacoepidemiology over decades is necessary to generate the RWE that can inform regulatory decision-making.

As also pointed out by the HMA/EMA Task Force, we consider a strengthened collaboration between academia, pharmaceutical companies, professional organisations and regulators essential to further this progress. In addition, and as also highlighted in previous EMA work [1–3], strong emphasis on the transparent reporting of designs and methodological choices and the application of best pharmacoepidemiologic practices will be essential in evolving the field further [4,5]. Of note, this applies regardless of the specific nature of the real world data (RWD) used.

ISPE strongly supports the Task Force's recommendation to initiate studies comparing evidence generated through randomized trials and non-interventional data sources for the same safety or effectiveness questions. Such studies, based on the multitude of curated healthcare databases already available throughout Europe, will be essential to expand our understanding of the value from RWD analyses in generating RWE supporting regulatory decision making. At the same time, we wish to emphasise that RCTs and non-interventional studies can each be used to address different questions, all equally important for public health.

We also note that the HMA/EMA Task Force points to standardization of data sources. While increasing harmonization would indeed help to facilitate their use, the diverse structure and scope of RWD data is inherent to the healthcare system and healthcare providers generating the data. With RWD, more so than with other sources of data, local expertise and understanding of the particular data source is crucial. Such knowledge, including data breaks, changes in coding practices etc., is difficult to fully capture by meta data. For this, and other reasons, full harmonization of datasets is not always the best solution. Rather, continued

work is needed on setting up distributed data networks based on various levels of data harmonization, including collaborations supporting distributed analyses. Considerable experiences have already been accrued in this developing field, as was summarized in a recent ENCePP survey of methodologies for EU publicly funded multi-database safety studies [6]. Irrespective of which RWD is used, including emerging data streams, ensuring sustained access to data, with transparent processes around data collection, curation, storage, access and analysis is essential for credible continual RWE generation that is essential for public health [7].

ISPE fully agrees with the HMA/EMA Task Force that the era of Big Data offers immense opportunities. Machine learning and all aspects of predictive modelling, natural language processing, and the many techniques to structure massive longitudinal data streams are important tools to process such data and feed them into subsequent analyses. However, addressing this primarily as a technical data science exercise will not realize its full value for regulatory decisions. A profound understanding of epidemiological concepts including confounding, design, measurement and inferential analyses will be vital to avoid being misled by the inevitable spurious, non-causal associations. The ISPE community has nearly four decades of experience in addressing such issues scientifically [8] and would gladly offer its assistance in incorporating this perspective into the future work of the Task Force.

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ISPE is a multi-national voluntary professional and scientific society. It has adopted no official position on these matters.

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