Received: 20 September 2019 | Accepted: 23 September 2019

DOI: 10.1002/pds.4911

COMMENTARY

WILEY

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

Anton Pottegård[1] | Olaf Klungel[2] | Almut Winterstein[3] | Krista Huybrechts[4] | Jesper Hallas[1] | Sebastian Schneeweiss[4] | Stephen Evans[5] | Andrew Bate[6,7] | Lisa Pont[8] | Gianluca Trifirò[9] | Meredith Smith[10,11] | Alison Bourke[12]

[1] Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, Odense, Denmark

[2] Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, The Netherlands

[3] Pharmaceutical Outcomes and Policy and Center for Drug Evaluation and Safety, University of Florida, Gainesville, Florida

[4] Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts

[5] Department of Medical Statistics, London School of Hygiene & Tropical Medicine, London, UK

[6] Epidemiology, Pfizer, Tadworth, UK

[7] Epidemiology, New York University, New York City, New York

[8] Pharmacy Department, Faculty of Health, University of Technology Sydney, Sydney, New South Wales, Australia

[9] Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina, Messina, Italy

[10] Global Patient Safety, Amgen Inc., Thousand Oaks, California

[11] School of Pharmacy, University of Southern California, Los Angeles, California

[12] Real World Solutions, IQVIA, London, UK

Correspondence
Anton Pottegård, Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, Odense.
Email: apottegaard@health.sdu.dk

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 noninterventional studies.

More than 2000 members of ISPE undertake studies with noninterventional 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 organizations, and regulators essential to further this progress. In addition, and as also highlighted in previous EMA work,[1-3]

 © 2019 John Wiley & Sons, Ltd.

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 noninterventional data sources for the same safety or effectiveness questions. Such studies, based on the multitude of curated health care 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 emphasize that RCTs and noninterventional 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 are inherent to the health care system and health care providers generating the data. With RWD, more so than with other sources of data, local expertise and understanding of the particular data source are 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 data sets 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, noncausal 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.

Text box

This comment was submitted by the authors on behalf of the International Society for Pharmacoepidemiology as a response to the European Medicines Agency (EMA) and Heads of Medicines Agencies (HMA) Joint Big Data Taskforce Summary Report made public in February 2019. The report is available from https://www.ema.europa.eu/en/documents/minutes/hma/ema-joint-task-force-big-data-summary-report_en.pdf.

CONFLICT OF INTEREST

While Dr. Meredith Y. Smith is a full time employee of Amgen, Inc. and owns shares in the company, the contents herein represent herpersonal opinions and not necessarily those of Amgen. She is also an adjunct professor, School of Pharmacy, University of Southern California. While Andrew Bate is a full time employee of Pfizer and holds stock and stock options the contents herein represent his personal opinions and not necessarily those of Pfizer. The remaining authors report no conflicts of interest.

ORCID

Anton Pottegård https://orcid.org/0000-0001-9314-5679
Krista Huybrechts https://orcid.org/0000-0001-5805-8430
Jesper Hallas https://orcid.org/0000-0002-8097-8708
Andrew Bate https://orcid.org/0000-0003-3151-3653
Alison Bourke https://orcid.org/0000-0002-0005-9016

REFERENCES

1. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). The ENCePP Code of Conduct. 15 March 2018. EMA/929209/2011.
2. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Guide on Methodological standards in Pharmacoepidemiology (Revision 5). EMA/95098/2010.
3. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). The European Union electronic Register of Post-Authorisation Studies (EU PAS Register).
4. Berger ML, Sox H, Willke RJ, et al. Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making. *Pharmacoepidemiol Drug Saf*. 2017;26(9):1033-1039. https://doi.org/10.1002/pds.4297
5. Wang SV, Schneeweiss S, Berger ML, et al. Reporting to improve reproducibility and facilitate validity assessment for healthcare database studies V1.0. *Pharmacoepidemiol Drug Saf*. 2017;26(9):1018-1032. https://doi.org/10.1002/pds.4295
6. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Survey of methodologies for European Union publicly funded multi-database safety studies. 21 October 2014. EMA/651167/2014.
7. Bourke A, Bate A, Sauer BC, Brown JS, Hall GC. Evidence generation from healthcare databases: recommendations for managing change. *Pharmacoepidemiol Drug Saf*. 2016;25(7):749-754. https://doi.org/10.1002/pds.4004
8. Public Policy Committee, International Society of Pharmacoepidemiology. Guidelines for good pharmacoepidemiology practice (GPP). *Pharmacoepidemiol Drug Saf*. 2016;25(1):2-10. https://doi.org/10.1002/pds.3891

How to cite this article: Pottegård A, Klungel O, Winterstein A, et al. 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. *Pharmacoepidemiol Drug Saf*. 2019;28:1640–1641. https://doi.org/10.1002/pds.4911