Prescrire comments

**on the core recommendations of the summary report of the
HMA-EMA Joint Big Data Taskforce**

We would like to thank the HMA-EMA Joint Big Data Taskforce for having opened a public consultation on their summary report outlining a set of recommendations and associated actions on what needs to be addressed.

Current discussions and debates on the use and utility of "real life data" and "big data" take a prominent place in the organization of healthcare including the regulation of pharmaceuticals and health products. Great hope is put in the utility and opportunities of "big data" for the health sector including greater capacities, cost-efficiency and fast results.

Some "big data" can and could be useful for enhancing people health when their reliability is secured in order to avoid numerous and major bias. This use of "big data" is probably of most importance after drug approval to enrich the drug's harm-benefit balance assessment.

We consider that regulation on the authorization and supervision of health products cannot be based on hope and promises but needs to rely on facts, trustworthy evidence and transparency. The current gold standard for marketing authorization relies on data from randomized double-blind comparative trials. It is also recognized that in addition to these clinical trial data, phase IV clinical trials, observational studies and other data from clinical daily practice are helpful for the post-market safety surveillance and the monitoring of drug use as well as compliance with guidelines.

Indeed, the conduct of unbiased robust RCTs are costly, going through a complex and long process but this is the price for their utility for patients and caregivers who rely on these data to make the best possible therapeutic decisions[i].

RCTs are not fit for purpose to identify rare adverse events. As in the case with RCTs, "big data" weaknesses and limitations have to be addressed as well. We are often faced with multiple sources of data of great heterogeneity and fragmentation sometimes without any quality control. Building up meaningful patient registries is time and human resources consuming, very costly and requires a sustainable framework in the long run. A recent OECD study on the use of routinely collected data and evidence from clinical practice highlighted the lack of analytical capacity, of legislation to safeguard patient privacy, of inadequate information technology infrastructure as well as poor data quality among the main barriers for greater uptake[ii].

We strongly invite EMA and HMA's to consider very carefully the source and quality of "big data" and their internal validity and utility for new approaches in the regulatory context. According to a study, co-authored by EMA staff on EU-funded initiatives for real world evidence "...*the immediate utilization of their outputs to support regulatory decision-making is limited, often due to insufficient available information and to discrepancies between outputs and objectives*"[iii] . A study on electronic healthcare databases in Europe noticed "*the fragmentation, heterogeneity and lack of transparency existing in many European electronic healthcare databases*"[iv]. Some experts[v] already pointed out that observational studies and data (like registries[vi]) are not suitable for a benefit assessment[vii].

The current debate on "big data" should not be used to further weaken the current drug approval process; instead, it needs a critical review. We urge European and national regulators not to weaken marketing authorization requirements by shifting the provision of evidence to real world data after marketing authorization. Experience showed that once marketing authorization has been granted, years can go by before studies of sufficient methodological quality are obtained[viii] and that even once a drug is proven to have severe or even fatal effects, it often takes months, if not years, to withdraw its marketing authorization[ix].

We urge the "big data" taskforce to focus their research into the clinical effectiveness and related cost and cost-efficiencies of wider use of big data in health products regulation. They should address the major methodological challenge of bias in real life data, that historically led to the development of RCT designed to avoid major biases thanks to randomization and blinding. Pragmatic RCT is probably a priority to advocate for. It should clearly state which problems are intended to be solved. We request that, like clinical studies, research and studies using "big data" (including protocols) be registered in a publicly accessible and centralized European Registry that complies with reporting requirements. Reproducibility, validated statistical analyses and transparency throughout the whole process (from data collection to data use) also need to be addressed carefully[x]. Transparency on conflicts of interests of interested parties has to be ensured. Recommendations should be based on robust evidence generated through independent rigorous evaluation free from vested financial conflicts of interests.

The taskforce rightly identified the need for standardization and data quality as key prerequisites for data analyses. Due to data heterogeneity, and the many local and regional initiatives of data collections, standardization is already a challenging task at national level not to mention at EU or international level. As stated, implementation of standards is expensive, requires concerted and harmonized action and is a lengthy process. Priorities should be fixed considering which "big data", if any, might be helpful to improve the regulatory and decision-making process.

As regards the membership of the taskforce we are surprised that next to the EMA only 14 of the 28 National competent authorities participate in the joint taskforce.

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