Recommendations on a new model for the provision of scientific advice

Safe and effective medicines that benefit patients

Drug development requires appropriate scientific standards to ensure safe and effective medicines that benefit patients and a high level of human health protection required by the article 168-1 of Treaty on the functioning of the European Union. These requirements should be defined and made available to drug developers via a public debate.

To inform drug developers about scientific and procedural requirements, the European Medicines Agency (EMA) provides scientific advice (SA) to companies. This activity is supported by European regulation[1]. However, the current model of confidential SA to individual companies does not seem to be the best use of this instrument, but rather results in a number of problems.

At present, only very limited information is available on the content and outcome of SA by EMA. Due to this lack of transparency, it is unclear to what extent EMA achieves the objectives of SA and to what extent individual companies make appropriate use of the SA provided.

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1. Article 57-1 (n) of Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004.
2. Scientific advice and protocol assistance adopted during the CHMP meeting 11 – 14 September 2017 http://www.ema.europa.eu/docs/en_GB/document_library/Annex_to_CHMP_highlights/2017/09/WC500234818.pdf

The current model of scientific advice

Currently, SA is offered to individual companies and is conducted behind closed doors. Besides general information about the number of SAs by substance type (chemical, biological, advanced therapy) and therapeutic indication, very little information on SA is available in the public domain[2]. Specifically, the scientific and procedural questions discussed during the individual advices and any answers by EMA are unknown and are thus not available to generally inform drug development.

Confidential SA to individual companies poses a number of potential problems:

- Neither the questions raised nor comprehensive information on the advice given are made public: therefore neither the purpose of the SA nor its utility can be assessed publicly.
- Individual confidential SA to companies inherently bears the risk of regulatory capture. Current arrangements might allow for a bargaining process which may be a way to negotiate confidential waivers to existing guidelines. As a consequence, individual confidential SA could be used as a driver towards lowering the regulatory bar.
- Confidential SA does not allow a public debate on the scientific requirements of drug development and approval.
- Confidential SA could undermine trust in the impartiality of the regulatory decision making process.
- Confidential SA including contact between drug assessors and the regulated pharmaceutical company has the potential to compromise the overall independence of the regulatory agency. This is particularly critical under the current fee-for-service model and in the context of possible revolving door effects.
- Provision of SA on the development of a drug by the same person who later in the process assesses the drug leads to a potential conflict of interest of this person, which may influence the decisions on drug approval.
- Provision of SA on drug development by the same organisation that later assesses the drug leads to a potential conflict of function of the organisation, which may influence decisions on drug approval.
- Confidential SA to individual companies represents an inappropriate use of the sparse resources of regulatory agencies and other scientific experts[3]. Additionally, individual SA misses the opportunity to set transparent, uniform standards for therapeutic areas which could be applied to all companies and publicly scrutinised. These uniform standards would moreover contribute to a more efficient management of limited resources and would improve the comparability of evidence available for different treatment options.

A new model for scientific advice

To avoid detrimental effects of confidential SA and simultaneously ensure clarification of scientific and procedural requirements, SA should be conducted in a transparent way. As such, SA would include:

- General guidelines on scientific principles for conducting randomised clinical studies, including comparative trials against standard treatments using patient-relevant endpoints, assessing efficacy as well as harms. Indeed, current EU regulation does not rule out marketing applications containing

3. In the first 8 months of 2017 alone, according to EMA's report adopted during the CHMP meeting 11-14 September 2017, EMA has provided 462 SA and protocol assistance procedures (http://www.ema.europa.eu/docs/en_GB/document_library/Annex_to_CHMP_highlights/2017/09/WC500234818.pdf). These advices must have used substantial resources. The fact that the outcome of these advices is only available to the individual company involved in the advice does not seem to be an appropriate use of resources of the agency, the scientific community, and at the companies.

such comparative trials that are essential to help patients and professionals choose the best options.

- Disease-specific guidelines to clarify disease-specific requirements (e.g. on patient populations, interventions and comparators, outcomes and study duration). These guidelines are partly already available.
- Public general or disease-specific workshops to clarify upcoming questions at shorter notice. Guidance developed by means of these workshops could then be used to update existing guidelines or develop new guidelines. To avoid any inappropriate influence on the workshop outcomes, clear guidance about how to conduct these workshops should be developed.
- Written questions of individual companies to EMA (and/or HTA bodies or payers), which are also answered in writing (without confidential meetings), with both questions and answers made publicly available at the time the answers are issued. EMA services should prepare publicly available frequently asked question and answer documents. New requests for SA should be limited to questions which are not yet covered in the available question and answer documents. This procedure would substantially reduce the number of questions to be answered. In this context, EMA should refrain from collecting fees for SA.
- SA processes should be public to avoid confidential waiver negotiations to existing guidelines.
- SA should be given by independent advisors, being not part of the marketing approval nor the pharmacovigilance process as well as being independent from industry.

Shifting SA to the public domain is possible without disclosing commercially confidential information because clinically relevant information is not commercial but scientific information, in the public interest.

The components of SA described above would allow a public debate on scientific requirements for drug approval while simultaneously providing drug developers with timely advice on questions arising during the drug development process. Public discussion and availability of scientific requirements would not only allow inclusion of broad expertise but would also ensure appropriate use of sparse resources. Any outcomes of these discussions would inform the overall drug development process, rather than an individual pharmaceutical company as is the case with the current confidential, individual SA model. This would improve the conduct of clinical studies overall, which in turn would provide more meaningful results. Study outcomes could be compared better across different drugs which would support decision making. The substantial resources used within the current confidential process should be sufficient to provide an appropriate and timely public process.

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