Response to the European Commission Consultation on the Delegated Act on Post-Authorization Efficacy Studies

General comments

In general Teva welcomes this initiative which is an important step in ensuring gathering adequate information about marketed products, and we have the following comments:

- This initiative should be applicable only to new innovative medicines and not to generics and/or biosimilar products for which, by their nature, there is enough long term efficacy data. All comments made are, therefore, related only to innovative products.

ITEM 1

- It must be clear that in general a post-authorisation efficacy study is not a mandatory requirement for any application, but only where *"concerns relating to some aspects of the efficacy of the medicinal product are identified and can be resolved only after the medicinal product has been marketed"*.

- The study(ies) needs, design, time frame etc should be discussed and agreed with the applicant and not imposed unilaterally by the agency. Applicants should have the right and opportunity to argue the merit of post-authorisation efficacy studies in each case. A mechanism for discussion and agreement between the applicant and the agency should be established, including the process for the delivery of the final decision along with the right to appeal the agency's decision to CHMP.

- As a follow up of the point above, post-authorisation efficacy studies should not be included in the clinical development review with EMA at early stage such as end of phase II. This is because it will usually not be clear at that stage whether there will be a need for post-authorisation efficacy studies. That should be part of the discussion between the agency and the applicant at the dossier submission stage.

- The request for post-authorisation efficacy studies in general should be raised at the approval process stage. Such studies should not be imposed after the grant of the Marketing Authorisation, unless there are very serious concerns about the efficacy of the product.

- Post-authorisation safety studies and post-authorisation efficacy studies should be combined as much as possible (and it could be done in most, if not all, cases) and not to impose a separate studies, which will increase significantly their burden and cost.

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ITEM 2

- Post-authorisation efficacy studies should generate efficacy data and indeed the emphasis should be on "real life" effectiveness data or "relative efficacy" and not extending and repeating the Randomised Clinical Trials that were part of clinical development plan.
- The studies should be limited for efficacy data and NOT for health economic, pricing and reimbursement or for HTA (health technology assessment) purposes.
- The obligation to generate post-authorisation efficacy data for new products could, if treated as obligatory by the agency, lead to a higher burden on companies (and higher costs) to get products authorised on the EU market.

ITEM 3

In general: for all points mentioned, there should be dialogue between the competent authorities and the marketing authorisation applicant/holder to decide if additional studies should be conducted or not. Otherwise, marketing authorisation holders could be forced to conduct large, expensive and time-consuming studies in situations where this would not be justified based on commercial considerations. As a further general point, any measure which jeopardises the commercial viability of authorised products risks resulting in the withdrawal of that product leading to a reduction in patient choice.

Point 5.1- Clinical outcome is the desired endpoint; however that may be almost impossible in long term chronic disease and mortality data. Transferring surrogate outcome (for example in multiple sclerosis from annual relapse rate and disability progression to mortality) will be untenable in terms of length and cost of studies and will materially hinder development of medicines in unmet medical needs conditions. Therefore Teva does not agree with the assertion of the document that "*Given that the generation of such data in many instances is expected to require a large sample size and/or long term follow-up, a post-authorisation efficacy study may be considered appropriate to alleviate any concerns relating to the efficacy of the medicinal product."* In addition, Teva repeats its submission that such studies should only be requested where valid concerns exist over the adequacy of efficacy data submitted. These studies should not become the norm where benefit:risk as been assessed by the agency as being positive and the product recommended for approval.

Point 5.2- Combination with other medicines is an important issue, but as mentioned, there are numerous and unlimited possible combination. Combinations are a huge and important area of many possible interactions (based on PK or PD) with a lot of room for discussion and different interpretations. A clear distinction should be set between combinations that might result in clinically relevant/significant effects and those where no clinically significant interactions (or no interactions at all) are expected based on known scientific facts. If included in the Delegated Act, it should be clear that the need for post-authorisation efficacy studies should be judged on a case-by-case basis, and there will be the possibility for dialogue, in which MAHs can justify or defend its own position for situations when they think post-authorisation efficacy studies are not necessary. However, the main and important clinically relevant interactions will have been already studied during the development stage, so Teva is not convinced this needs to be included in the Delegated Act.

Point 5.3- there are 2 issues:

- the hint "*but there might be situations in which the request could arise later in the product life cycle based on availability of new data*.", indicates there is no limitation to time of request for a post-authorisation efficacy study. This refers to our concern raised in bullet 4 at item 1
- the most relevant sub-population has been studied before the application and is part of the dossier. It should be limited to cases in which the applicant wants to submit a variation for an additional indication (paediatric, renal, pharmacogenetic etc), but this should not be imposed if there is no such intention to vary a marketing authorisation without good reason.

Point 5.5- Teva has the same concern that there is no limit of time and the marketing authorisation holder will be requested to conduct studies throughout the life cycle of the product with significant cost unforeseen at time of application

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Point 5.7- Teva agrees that this is an important topic, but it needs to be left to the marketing authorisation holder to decide.

ITEM 6

Teva does not agree with the assertion "*Interventional studies are expected to represent the majority of cases and would be the preferred option*", because, as intended in this proposal, normal practice evaluation by registries or observational studies should be the main route and interventional studies will be required only in very few defined specific circumstances.