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Position paper on the non-acceptability of replacement of pivotal clinical trials in cases of GCP non-compliance in the context of marketing authorisation applications

Introduction

The aim of this position paper is to inform applicants and Marketing Authorisation Holders (MAH) on the position of the European Medicines Agency (EMA) concerning the non-acceptability of replacement of pivotal clinical trials during the assessment of an application in the context of a marketing authorisation in cases of GCP non-compliance.

GCP Requirements

Good clinical practice (GCP) is an international ethical and scientific quality standard for designing, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and wellbeing of trial subjects are protected and that clinical trial data are credible and reliable.

As per Annex I to Directive 2001/83/EC (point 8 of the 'Introduction and general principles'), 'All clinical trials, conducted within the European Community, must comply with the requirements of Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. To be taken into account during the assessment of an application, clinical trials, conducted outside the European Community, which relate to medicinal products intended to be used in the European Community, shall be designed, implemented and reported on what good clinical practice and ethical principles are concerned, on the basis of principles, which are equivalent to the provisions of Directive 2001/20/EC.'

In turn, Article 1(4) of Directive 2001/20/EC provides that "All clinical trials, including bioavailability and bioequivalence studies, shall be designed, conducted and reported in accordance with the principles of good clinical practice".

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Moreover, applicants submitting a MAA to the EMA declare in the application form "that all existing data which are relevant to the quality, safety and efficacy of the medicinal product have been supplied in the dossier, as appropriate" (Module 1.2: Administrative Information)[1]. The Common Technical Document (CTD) Module 2.5 (Clinical Overview) "include[s] a statement regarding GCP compliance"[2].

As per Article 57(i) of Regulation (EC) No 726/2004, the Agency is in charge of coordinating the verification of compliance with the principles of good clinical practice.

GCP inspections are conducted in accordance with Article 15 of Directive 2001/20/EC ('Clinical trials' Directive).

Directive 2005/28/EC ('GCP' Directive) lays down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use.

Clinical trials included in any marketing authorisation application (MAA) in the European Union (EU) and in any subsequent application to the initial one are required to be conducted in accordance with GCP.

GCP-non compliance

Based on the above, GCP compliance is an essential prerequisite for the CHMP scientific assessment of the safety and efficacy of a medicinal product[3].

In case a study is found to be GCP non-compliant during an inspection, the applicant/MAH may comment on the inspection findings, provide a re-analysis of the data (excluding the non-GCP compliant data) and/or present a justification why, in their view, the data can be relied upon.

The CHMP will formulate their opinion on the benefit/risk taking into account the data from the remaining studies included in the same application as well as the applicant's/MAH's response, as applicable and detailed above.

In case the application contains only one pivotal study which is found to be GCP non-compliant and reanalysis is not provided or not possible, this means that the application no longer contains any pivotal clinical data that can be used to support the safety and efficacy of the medicinal product in the context of the application in question.

Article 7(c) of Regulation (EC) No 726/2004 provides that, in order to prepare its opinion, the CHMP may allow the applicant to "supplement the particulars accompanying the application within a specific time period", but this does not mean that the applicant is allowed to replace pivotal studies on which the application is based, in case of GCP non-compliance. When submitting the application, MA applicant declares that the clinical studies supporting the application were performed in compliance with GCPs. If at any time during the assessment of the medicinal product a pivotal study were found to be non-GCP compliant, this would be at odds with the applicant's obligation to meet the legislative requirements and would also contradict the applicant's own declaration of conformity. As indicated above the CHMP will formulate their opinion on the benefit/risk taking into account the data from the remaining studies and the applicant's/MAH response. In case the application contains only one pivotal study which is found to be GCP non-compliant and reanalysis is not provided or not possible, this means that the application no longer contains any pivotal clinical data that can be used to support the safety and efficacy of the medicinal product in the context of the application in question.

[1] http://ec.europa.eu/health/files/eudralex/vol-2/2015-06_caps-human.pdf
[2] http://ec.europa.eu/health/files/eudralex/vol-2/b/update_200805/ctd_05-2008_en.pdf
[3] Other cases of non-compliance may be examined in due course.

In cases where the GCP non-compliance of a pivotal study is detected after the relevant medicinal product has been authorised and placed on the market, action on the marketing authorisation may be required as reliability of the data submitted is essential for the benefit/risk assessment of the medicinal product, however this would require additional considerations. Some other elements should be properly evaluated to respect the principle of proportionality, amongst others the patients' interest to continue to use the medicinal products at stake and the harm that discontinuing the treatment would entail for them and the possibility for the MAH to provide relevant information confirming the quality/safety/efficacy of the product and the persistence of a positive risk/benefit ratio.

Conclusion

Based on the above, the EMA position is not to allow replacement of GCP non-compliant pivotal studies by other pivotal studies during the assessment of an application. This position highlights the importance for the applicants and MAHs of being able to demonstrate compliance with GCP standards, which provides public assurance that the rights, safety and wellbeing of trial subjects are protected and that generated data are robust. In the primary interest of public health, adherence to the legislative requirements is required for the reliability of the data submitted in support of the application.

This position is without prejudice to the possibility for the applicant to resubmit an application supported by appropriate pivotal data in compliance with the legal requirements including GCP.

Applicants for marketing authorisation applications/MAHs in the EU are reminded of the importance of compliance with GCP standards and of their responsibility for the quality of the data submitted in the context of their application.