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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

REFLECTION PAPER ON THE EXTRAPOLATION OF RESULTS FROM CLINICAL STUDIES CONDUCTED OUTSIDE THE EU TO THE EU-POPULATION

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EXECUTIVE SUMMARY

Drug development is increasingly global and an increasing percentage of pivotal studies submitted to the European regulatory authorities are conducted outside the EU. Therefore, there is a need to understand the differences and concerns that may arise in the extrapolation of study results to the EU population. This reflection paper, including experience from a sample of applications, shows that in particular extrinsic factors, such as medical practice, disease definition and study population, may influence the applicability of foreign data to an EU setting.

These factors are also identified in the ICH E5, which highlights the importance of this guideline in the planning of worldwide clinical studies. The current paper identifies specific issues based on experience specific to the EU population and should be regarded as a reinforcement of the ICH E5 to be used when deciding whether certain clinical trials conducted in a specific area of the world would be relevant to the EU setting or if there are reasons to perform additional clinical trials within the EU.

1. INTRODUCTION

The ICH E5 guideline was adopted in 1998 with the purpose to facilitate the registration of medicinal products among different geographic regions by recommending a framework for evaluating the impact of ethnic factors upon the efficacy or safety of a product.

In the context of that guideline, the aim of this reflection paper is to highlight some current experience from pivotal clinical studies conducted outside the EU region and to discuss how different factors may complicate the evaluation of foreign data in an EU perspective. The current document does not replace any existing guidance and is mainly intended for regulatory assessors, even though the content could also be of interest for the industry in the planning of trials in different geographical areas.

Even though the purpose is to reflect the experience so far, it should be emphasised that the analysis do not include a random sample of studies submitted to the regulatory agencies and any conclusions should be considered as exploratory rather than confirmative.

2. SCOPE – PROBLEM STATEMENT

Up to a few years ago, the vast majority of pivotal clinical trials were conducted either in North-America, western parts of Europe, or in regions such as South-Africa or Australia. Recently this has changed, with an increasing number of trials being conducted in other parts of the world, e.g., Latin America, Asian countries and other European countries [1]. There are several reasons for this, including availability of patients, lower cost and increasing financial importance of these markets.

Due to potential environmental and patient-related differences between regions, extrapolation of clinical data between geographical areas may sometimes be difficult. In this context it should also be recognised that differences within the EU population (as well as within each member state) can probably sometimes be as large as between regions.

In ICH E5 the possible influence of ethnic factors on results and the interpretation of results are discussed [2]. Influences may be attributed to both intrinsic and extrinsic factors (Figure 1).

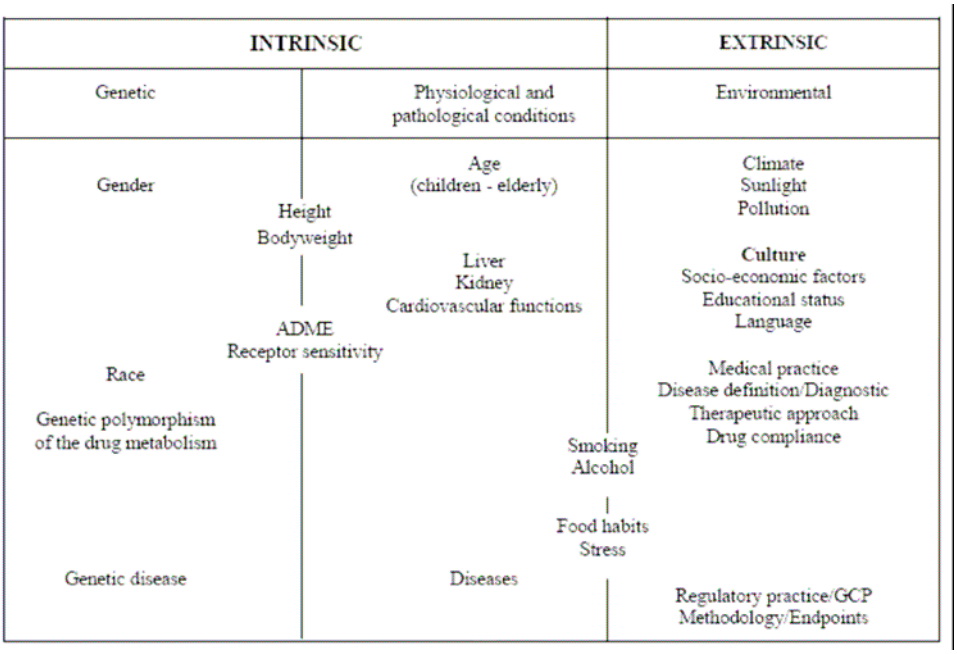

Figure 1: Shown is the classification of intrinsic and extrinsic ethnic factors (ICH e5)

The ICH E5-guideline defines these factors as follows: "*Intrinsic factors help to define and identify a sub-population and may influence the ability to extrapolate clinical data between regions. Examples of intrinsic factors include genetic polymorphism, age, gender, height, weight, lean body mass, body composition, and organ dysfunction.*
Extrinsic ethnic factors are factors associated with the environment and culture in which a person resides. Extrinsic factors tend to be less genetically and more culturally and behaviorally determined. Examples of extrinsic factors include the social and cultural aspects of a region such as medical practice, diet, use of tobacco, use of alcohol, exposure to pollution and sunshine, socio-economic status, compliance with prescribed medications, and, particularly important to the reliance on studies from a different region, practices in clinical trial design and conduct"

Considering that more clinical trials are performed in new regions in which social and cultural aspects may be different in comparison to the EU-population, the influence of extrinsic factors could be of particular interest. However, intrinsic factors are also of high importance, as specified in the ICH E5-guideline.

3. CURRENT EXPERIENCE

Background search methods:

To identify possible factors that may complicate the interpretation and extrapolation of clinical data, a background research was performed on a number of medicinal products for which extrapolation of study results to an EU population had been found to be difficult. It should be noted that these products were identified by questioning a limited number of regulatory assessors and do not represent a random sample of all products assessed in different regulatory procedures. Information was obtained from the EMEA European Public Assessment Reports (EPARs), including all studies submitted in the MAA file and Rapporteurs Assessment Reports for ongoing procedures and mutual recognition procedures.

This research focussed on the following characteristics:

Characteristics	Definitions
Disease group - indication	ATC-class; therapeutic indication
Population	Total number of subjects; Age; gender; ethnicity (geographical region)
Medical practice	Regional/country-specific treatment regimes
Co-morbidity	None; related; unrelated - disease group
Co-medication	None; co-prescribing; concomitant (time-interval)
Comparator	None; placebo; comparator drug
Endpoints	Primary endpoints
Results	*Subpopulation analysis of clinical data*

Table 1: Characteristics to identify intrinsic and extrinsic factors impacting the extrapolation of clinical data

Results:

The identified products included antithrombotic (n=4), antiviral (n=1) and antineoplastic agents (n=1), drugs affecting the nervous system (n=4) and insulin/insulin analogues (n=1).

Antithrombotic Agents

Four studies concerning antithrombotic agents were identified, including one marketing authorization application and three extensions of indications. In two of the studies there were beneficial effects in North American, but not in EU patients. It was speculated that this could have been due to a higher rate of early revascularisations and an earlier onset of treatment in North American centers.

Concerning the additional two studies, it was questioned whether the beneficial results seen in Asian patients (in one study only Chinese patients) could be extrapolated to the EU situation, considering the lack of positive results in subgroup analysis of patients with background therapies and interventions (e.g. beta-blockers, PCI) relevant to an EU setting.

Antiviral Agents

One application for an antiviral agent was examined. The vast majority of the population enrolled consisted of Asian patients. With respect to HBV baseline characteristics, as expected in patients of Asian ethnicity, the majority of patients were infected with HBV genotypes B (26%) or C (51%). Considering that genotype A is more frequent in the EU, there was a concern that the clinical data derived from EU patients were too limited.

Antineoplastic Agents

For the antineoplastic agent examined (for treatment of lung cancer), obvious differences in survival rates were found between Asian (predominantly Japanese patients) and Caucasian patients. The main reason for this difference was differences in tumor genetics (intrinsic factor) which may partly reflect differences in extrinsic factors such as smoking.

Nervous system (CNS)

Four applications were identified with drugs intended for the treatment of schizophrenia, manic episodes, vasomotor symptoms associated with menopause and fibromyalgia, respectively. For the two latter indications, results were more pronounced in the North American compared to the EU population. Potential explanations may have been differences in background therapy (e.g. higher use of anti-depressants in North American patients) and difficulties in defining heterogeneous conditions.

The difficulties concerning the schizophrenia study included findings of several aspects that threatened the validity of the data, such as dosing and different amendments found at monitoring at study sites in some parts of Europe. Furthermore issues were raised about the training of investigators and standardisation of scale including the use of local language in this regard.

In the application for treatment of mania, a beneficial effect was seen in Indian and Russian patients while North American patients had no benefit from the treatment. The reasons for this were unknown, but social environment could have been a contributing factor.

Insulin and analogues

This application concerned a new posology for the drug in question with the pivotal study being performed in China. The Chinese patients had lower BMI and a rather low rate of diabetes complications compared to what is usually seen in Caucasian patients. All patients were treated with at least one OAD. However, no measures were taken to make sure that the patients were true OAD failures such as having reached maximum or near maximum doses on current treatment. Due to these issues, it was considered questionable if the beneficial results seen in Chinese patients could be extrapolated to EU patients.

Discussion:

This reflection paper highlights examples of mainly extrinsic, but also intrinsic factors that may complicate the extrapolation of results from clinical studies between geographical areas worldwide, as well as within the EU population.

In the current overview of applications for initial MAAs or extensions of indications, several factors that could be of importance for extrapolation of data have been identified for different drug classes. Although the number of examples per drug class may be limited, they nevertheless give an overall impression of the kinds of factors that may need special attention in the planning of a study and in prospective analyses as well as in the interpretation of study results.

Following from the described cases three main extrinsic factors were identified that could have had an importance for the difficulties in extrapolation of the results: medical practice, disease definition and different aspects concerning the study population.

Concerning medical practice, one of the factors that can complicate the interpretation of the validity of the results in different geographic areas is differences in co-medications and invasive procedures. Especially in studies on conditions that require intensive medical care, standard of care can have an important impact on the outcome parameters. Transferability of the results of these studies might be impaired. To identify issues related to medical practice, regional treatment guidelines (where available) could be taken into account during a study design so that relevant proportions of patients enrolled in clinical trials will be subject to treatments that are relevant for the regions in which the drug will be used. Disease definition was identified as a factor that may influence the extrapolation of study data. Even thought disease definition and indication usually are well defined in clinical trial protocols, heterogeneous medical conditions may be defined differently throughout the world and this may also include different traditions concerning the medicalisation of some conditions. Patients available for clinical trials in different geographical regions may also differ with respect to the severity and clinical stage of the disease in question. Furthermore, insufficient standardization and validation of paper and/or electronically captured scores and scales will have the potential to induce biases in the evaluation of the results.

A good understanding of the patient population that will be subjected to a certain therapeutic treatment for a specific disease/condition is crucial. If the study population differs between geographical areas, this may affect the applicability of the results. Different interpretation of inclusion criteria will result in study populations that may not be representative from one region to another. Before the research protocol is final, epidemiological databases and statistics could provide an understanding of disease definition in the geographical areas in which trials will be performed as well as in the countries where the drug is to be licensed.

Apart from these three main identified factors, life style including medical and social environment, genetic factors and genotype pathogen strain were also found to be of potential importance for the extrapolation of results in the current examples.

In the current review of clinical files, it was also indicated that extrapolation of data within the EU population is not always straightforward. Factors such as background medical therapy, social environment and clinical practice can also differ between different geographical areas of the EU.

The identified factors in this paper, as well as other factors that may have an impact on extrapolation of data between different geographical areas, should be taken into consideration when planning and analysing clinical studies performed in different regions, and should also be addressed early , e.g. during Scientific Advice Procedures.

The studies included in the review were all phase III trials. However, the same ethnic factors should be taken into consideration when results from phase II trials are extrapolated between different geographic areas However, for generic and biosimilar drug development, the clinical trial setting may be different from that for new drug development as ethnic factors probably play little or no relevant role in these comparative clinical trials.

Conclusion:

Drug development is increasingly global – an increasing percentage of pivotal studies submitted to EU regulatory authorities are conducted outside the EU and there is a need to understand the differences and concerns that may arise in the extrapolation of study results to the EU population. Experience so far shows that intrinsic as well as extrinsic factors are important to consider when extrapolating data obtained in a study population to the EU setting. With an expanding EU, differences in terms of extrinsic and intrinsic factors also increase within the EU.

The current reflection paper indicates that in particular extrinsic factors, such as medical practice, disease definition and study population, may influence the applicability of foreign data to an EU setting. These factors are also identified in the ICH E5, which highlights the importance of this guideline in the planning of worldwide clinical studies. The current paper identifies specific issues based on experience specific to the EU population and should be regarded as a reinforcement of the ICH E5.

Global drug development does not necessarily support the approval of unrestricted indications in an EU population. On the contrary, a sponsor should take into consideration and discuss with key opinion leaders, ethics committees and competent authorities the possible influence of extrinsic factors on the interpretation of the results and ultimately the wording of relevant sections of the SmPC.

In conclusion, this paper speaks in favor of an in-depth, prospective analysis of potential extrinsic and/or intrinsic factors when conducting a clinical trial in a certain region. The outcome of such analyses may facilitate for regulatory assessors the decision whether certain clinical trials conducted in a specific area of the world are relevant to the EU setting or if there are reasons to perform additional clinical trials within the EU.

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