A Model of European Medicine Agency (EMA)’s Decisions on Human Medicines

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ABSTRACT

This paper is aimed at examining the European medicine agency decisions in the field of human medicines. Different classes of human medicines approved in the last five years have been classified. They have been analyzed considering: i) the relation between non generic drugs and generic drugs, ii) time of approval, iii) objectives of the clinical trials, iv) criteria of efficiency, efficacy, safety. By using the Summary of the European Public Assessment Report for every human medicine in the period 2010-2015, a dataset has been arranged. A Structural Equation Model analysis was carried out. The degree of efficiency, the degree of safety, the tradeoff between efficiency and safety that lead to the EMA approval decisions are conditioned by the nature of the medicines and the characteristics of their class. Different degrees of benefits and risks underpinning the decisions have been identified together with the consequent guiding principles that lead to the EMA decision process. A latent general “safety” factor at the basis of EMA decision process was assessed.

Keywords: ATC Code, Efficacy, Efficiency, European Medicine Agency, Guiding Principle, Safety, Structural Equation Model

INTRODUCTION

Regulatory agencies play a crucial role in the approval of human medicines and, at the same time, in health care. The process leading to a regulatory outcome is guided by the benefit/risk assessment, which is a complex process based on the assessment of non-clinical, clinical and quality data submitted by the pharmaceutical manufacturer. In the case of authorized-for-use drugs, benefits must outweigh risks. A proper assessment of the risk/benefit ratio combines objective evidence and subjective elements, leading to decisions that should be reproducible and transparent. These are communicated to the various stakeholders (Trotta et al, 2011).

A huge literature has dealt with decision making processes adopted by regulatory authorities. The topics range from the criteria underpinning the decisions (Beyer, 2011; EMA, 2011; Leong et al, 2013; Tafuri et al 2014; Menon, 2015), to the design and the evaluation of different...
frameworks for decision making process (EMA 2007; C.I.R.S., 2011; Leong et al, 2015). Little
has been said about the outcome. To date, no theoretical account of when and in what circum-
stances decisions may be taken has been offered in the literature.

This paper is aimed at examining the European Medicine Agency (EMA) decisions in the
field of human medicines. The objective is twofold: on one hand three characteristics of human
medicine approved in the last five years have been classified: i) the relation between non generic
and generic drugs, ii) the time of approval, iii) objectives of the clinical trials – namely – mea-
ures of efficacy. Different degrees of benefits and risks underpinning the decisions have been
identified through different guiding principles. The development of these principles guides the
decision process. The last step has been to understand if and how these principles are implemented
uniformly considering the characteristics of the drugs. A dataset was assembled using the human
medicine reports on the EMA website. This work presents the first results.

MATERIALS AND METHODS

The EMA Framework

By checking EMA website, the public assessments about human medicines have been analyzed.
We limited our investigation to human medicines that were submitted for approval in the past
five years, accepting the EMA criteria of classification1. Terms like i) efficacy, ii) efficiency, iii)
effectiveness, for example, were used with their general meanings, respectively i) reproducing
an effect consistently, ii) measuring the performance of the process of conversion of inputs into
outputs, iii) measuring the degree to which the outputs satisfy requirements.

Three hundred and fifteen medicines were classified in different therapeutic groups accord-
ing to the organ or system on which they act. The classification was arranged on the anatomical
groupings which ATC Code2 takes into account. In this way we have considered 14 groups: 1)
Alimentary tract and metabolism, 2) Blood and forming organs, 3) Cardiovascular system, 4)
Dermatological, 5) Genitourinary system and sex hormones, 6) Systemic hormonal preparations
excluding sex hormones and insulins, 7) Anti-infective for systemic use, 8) Antineoplastic, 9)
Musculoskeletal system, 10) Nervous system, 11) Anti-parasitic, 12) Respiratory system, 13)
Sensory organs, and 14) Others not classified.

The Balance of Risks and Benefits that Leads to a
Decision. A Brief Review of the Literature

The assessment of the benefits and the risks associated with a medicine is defined as benefit-risk
assessment (BRA). Benefit-risk balance, or benefit risk ratio evaluation are different ways to
define the same kind of evaluation. BRA is an evaluation of two dimensions. The dimension of
benefits is measured primarily in terms of therapeutic efficacy, i.e. the successful treatment of
the condition for which the drug is indicated (Curtin, Schultz, 2011). There are other types of
benefits, such as improvement of quality of life or pharmaco-economic aspects. The dimension
of risks includes the safety profile: adverse event, severe adverse event, and discontinuation
rate due to adverse event. The potential risk of unobserved events should also be considered.
What we define as “balance” in theory does not indicate a real equilibrium in practice, nor does
it have comparable measures. Cheung and Kumana (2001), for example, argued that a minimal
benefit can never be attractive, even if there is a 99% chance of occurrence. On the other hand,
a tiny risk, say 1%, cannot always be ignored, especially if the penalty is something unpleasant.
Similarly, Herxheimer (2001) stated that benefits and risks have completely different dimen-
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