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

Roberta Troisi, University of Salerno, Salerno, Italy

Carmine Garzillo, University on Naples "Federico II", Naples, Italy

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

DOI: 10.4018/IJPPHME.2015010101

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 circumstances 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 – measures 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 classification[1]. 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 according to the organ or system on which they act. The classification was arranged on the anatomical groupings which ATC Code[2] 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-

sions: a benefit is a material or experiential good thing, while a risk is a probability, the chance that something bad will happen. Therefore 'benefit' should be weighed against 'harm', along with the probability of benefit against the probability of harm. Edwards et al. (1996) went one step further and argued that the phrase 'benefit–risk' is clumsy and has been used in too many different contexts. By examining several attempts to quantify BRA, they argue that no method provides a fully satisfactory solution regarding BRA, because it is difficult to reduce its multi-dimensional aspect to simple metrics, in a context where other therapeutic alternatives play a role. The preferred term was therefore 'merit assessment' since it unambiguously indicates the determination of the worth of a medicine in a given context.

As a matter of fact, perceptions of risks versus benefits are influenced to a great extent by the context in which they occur, and may be different to actual risk. In any given situation, the acceptable risk-to-benefit balance is an individual judgement on the part of the patient or the prescriber.

Benefit–harm balance is a more general and therefore more appropriate term, which is used for example in the new EU pharmaceutical legislation. Benefit-harm is defined as 'an evaluation of the positive therapeutic effects of the medicinal product in relation to the risks', with risks being defined as 'any risk relating to the quality, safety and efficacy of the medicinal product as regards the health of patients' (Council of the European Union, 2003). In the European Union, medicines must meet the three exclusive criteria laid down in the Community Law which are: quality, safety and efficacy, for a marketing authorization to be granted (Brunet, 1999). In Directive 2001/83/EC of the Community Code relating to medicinal products for human use, it is stipulated that a marketing authorization shall be refused if: (a) the risk–benefit balance is not considered to be favorable, or (b) its therapeutic efficacy is insufficiently substantiated by the applicant, or (c) its qualitative and quantitative composition is not as declared by the common core elements upon which all the frameworks are based .

Therefore, it is clear that the regulatory decisions are the outcome of a balancing the benefits: e.g., the effectiveness of the drug and the risk; and the safety that the medicines bring. At the same time, it is clear that effectiveness and safety are variable values depending on the kinds of medicines and the kinds of care which medicines are aimed at.

Approval decisions for public safety are made considering different levels of efficacy or different levels of safety, until the low levels of ineffectiveness and unsafety lead to denial of authorization.

Within the range where benefits are greater than risks there are many possible combinations. High levels of efficiency may be combined with high, medium and low levels of safety, and vice-versa.

Structural Equation Model (SEM) Analysis

SEM analysis (Pugesek, Tomer, von Eye, 2003) supplies information as a causal modeling of the processes under study, represented by a series of structural (*i.e.*, regression) equations, which can also be pictorially modeled to enable a more clear conceptualization of the theory. Unlike most other multivariate procedures that are essentially descriptive by nature, this process is confirmatory (i.e., hypothesis-testing), rather than exploratory in terms of data analysis. The hypothesized model can then be tested statistically in a simultaneous analysis of the entire system of variables to determine the extent to which it is consistent with the data.

Whereas traditional multivariate procedures are incapable of either assessing or correcting for measurement error, SEM provides explicit estimates of these error variance parameters. Methods such as those rooted in regression, or the general linear model, assume that errors in

the explanatory (i.e., independent) variables vanish; so errors in the explanatory variables are ignored, leading to serious inaccuracies.

A good fitting model is one that can reproduce the original variance-covariance matrix (or correlation matrix) from the path coefficients, in much the same way that a good factor analytic solution can reproduce the original correlation matrix with little error. Parameters were estimated by maximum likelihood, an iterative procedure which attempts to maximize the likelihood that obtained values of the criterion variable will be correctly predicted.

The IBM_SPSS_22 and AMOS software packages were used for the statistical analyses.

RESULTS

The Amount of Generic and non-Generic Medicines

We examined the percentage of drugs approved for every therapeutic area, distinguishing between generic and non-generic medicines according to ATC Code. As shown in Table 1, the percentage of antineoplastic medicines (ATC Code 8) is the highest (23.1%). The treatment of cancer and other degenerative diseases, such as multiple sclerosis, is included in this group. Both medicines for the alimentary tract and metabolism (ATC Code 1) and anti-infective for systemic use (ATC Code 7) have the same percentage in the field of non-generic medicines (11.4%), but different percentages in the field of generic medicines (respectively 3.5% vs 1.2%). Among others, the treatment of obesity and diabetes mellitus are included in the first group, as the treatment of HIV and HCV are included in the second one.

The percentage of non-generic medicines compared with generic ones is mainly modest or even zero. A reverse distribution concerns medicines grouped in Musculoskeletal system (ATC Code 9), and in Nervous system (ATC Code 10), where the percentages of generic drugs are,

Table 1. Percentage distribution OF APPROVALS between generic and non-generic medicines by ATC Code

ATC Code	NOT GENERIC	GENERIC
1. Alimentary tract and metabolism	11.4	3.5
2. Blood and forming organs	4.3	0.0
3. Cardiovascular system	6.3	1.6
4. Dermatological	2.0	0.0
5. Genitourinary system and sex hormones	2.0	0.4
6. Systemic hormonal preparations excluding sex hormones and insulins	1.2	0.0
7. Anti-infective for systemic use	11.4	1.2
8. Antineoplastic	20.0	3.1
9. Musculoskeletal system	1.6	4.3
10. Nervous system	7.9	6.8
11. Respiratory system	5.5	0.0
12. Sensory organs	2.7	0.0
13. Others not classified	2.7	0.0
TOTAL	78.8	20.8

respectively, higher (4.3 vs 1.6) and just lower (6.7 vs 7.8) than the percentages of non-generic drugs. In both cases the percentages are the highest in absolute terms, among generic drugs. To name but a few, treatments for bone metastasis (ATC Code 9), Parkinsons and Alzheimer diseases (ATC Code 10) are included in these groups. This should be of particular concern.

Today long-established treatments for diseases like Parkinson and Alzheimer are out of date and, as EMA reports, in both cases non-generic drugs aim at reducing the numbers of symptoms and at slowing down the progress of the disease, so that, when medicines able to recovery lack, the result is an abundant supply of generic drugs. Moreover, when the patents of the routine drugs are probably expired, the outcome is certainly a greater number of corresponding generics. On the contrary, with more recently discovered diseases, grouped in anti-infective drugs (ATC Code 7) such as Hepatitis C or HIV, drug patents may still be exclusive. In this case the approval of a greater number of generic forms would be premature. With time the recovery target should reduce the drug request and the market intake of generic medicines.

But, in the class of antineoplastic drugs, for example, where, though treatments aim at the care of old diseases, the target of medicines is, in many cases, to extend life of the patients or just to improve the quality of their life, statistics are different. In fact, even if circumstances are favorable to a market intake of generic drugs, in this case the number of generic drugs in comparison with not generic ones is only one-sixth.

Another explanation is also possible. In the case of musculoskeletal group (ATC Code 9) the high number of generic drugs is not counterbalanced by non-generic ones: probably little has been invested in research for new drugs.

Something of analogous occurs for what concerns drugs grouped in the nervous system category (ATC Code 10). Although generic drugs are 7% on the total of non-generic medicines, representing the third category in absolute terms, the corresponding generic medicines are just as many, representing the most significant category in the corresponding group. Such as high proportion of generic drugs may indicate that new treatments of certain diseases are currently missing. New medicines probably show the same efficiency degree of the older ones which are replicated in the generic medicines.

Despite the interesting considerations about generic medicines, our analysis was limited to the consideration of the amount of generic drugs with respect to the non-generic ones. The other characteristics we take account of, refer to non-generic drugs, inasmuch they show different level of risk/benefit ratios in their approval process. As a matter of fact the approval procedure of generic drugs consists in a bioequivalence comparison with the non-generic ones and with the risk/benefit ratio evaluated for the last ones. Table 2 shows the diseases contained in the most representative ATC Code classes for generic and non-generic medicines.

Time of Approval

Table 3 shows the EMA's approval trends of the non-generic medicines. Columns from 1 to 5 refer to the lapse of time from submission to approval: 1 means 6 months from submission, 2 means a time from 6 months to 1 year, 3 means a time from 1 year to 1 and a half year, 4 means a time from 1.5 year to 2 years, 5 means a time beyond 2 years. It should be noted that for EMA 2 years is the deadline time and so approval time beyond this period is considered a guilty delay.

The majority of drugs (42.08%) is approved in a medium time (column 3), during a time from 1 year to one and an half year. Comparing column 2 and column 4 it results that EMA authorizes more drugs in minor time (22.8 vs. 19.3) and that there are more authorizations within 6 months (column 1) from submission than beyond the deadline (column 5, 8.9 vs. 6.9). Excluding ATC Code 10 (2.5% in column 1), both authorization dates in column 1 and in column

Table 2. Diseases included in the most representative ATC Code classes with percentages of Generic / non Generic drugs

ATC Code	Disease	Generic	Not Generic	Total
2. Alimentary tract and metabolism	Total	2.55	14.85	17.40
	Diabetes Mellitus type 2	1.86	7.42	9.28
	Obesity	0.46	4.18	4.64
	Others	0.23	3.25	3.48
3. Cardiovascular system	Total	0.46	7.42	7.89
	Heart Failure	0.00	0.46	0.46
	Pulmonary Hypertension	0.00	0.93	0.93
	Dysplidemias	0.00	0.46	0.46
	Hypercholesterolemia	0.00	1.39	1.39
	Hypertension	0.46	4.18	4.64
7. Anti-infective for systemic use	Total	0.70	18.09	18.79
	Cystic Fibrosis	0.00	1.39	1.39
	C Epatithis	0.00	4.64	4.64
	Hiv infection	0.23	4.64	4.87
	Influenza	0.23	1.39	1.62
	Meningite	0.00	1.86	1.86
	Tubercolosis	0.00	1.39	1.39
	Others	0.23	2.78	3.02
8. Antineoplastic	Total	2.09	37.12	39.21
	Lymphoma non Hodgkin	0.00	2.32	2.32
	Breast Neoplasm	0.00	1.86	1.86
	Carcinoma Small Cell	0.46	4.18	4.64
	Colorectal Cancer	0.00	0.93	0.93
	Glaucome	0.00	1.86	1.86
	Graft Rejection	0.00	1.86	1.86
	Leucemia	1.16	3.25	4.41
	Melanoma	0.00	2.32	2.32
	Multiple Sclerosis	0.00	1.86	1.86
	Myeloma	0.00	2.32	2.32
	Neutrophenia	0.00	2.78	2.78
	Ovarian Cancer	0.00	1.86	1.86
	Pancreatic Cancer	0.00	0.93	0.93
	Prostatic Cancer	0.00	3.25	3.25
	Pulmonary Fibrosys	0.00	0.46	0.46
	Rheumoatoid Arthris	0.23	0.93	1.16
	Soft Tissue Sarcoma	0.00	0.93	0.93

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Table 2. Continued

ATC Code	Disease	Generic	Not Generic	Total
	Stomach Cancer	0.00	1.39	1.39
	Uterine Neoplasm	0.23	0.00	0.23
	Others	0.00	1.86	1.86
10. Nervous system	Total	4.18	12.53	16.71
	Alzheimer	1.39	1.39	2.78
	Epilepsy	1.86	1.86	3.71
	Multiple Sclerosis	0.70	1.39	2.09
	Parkinson	0.23	2.78	3.02
	Schizophrenia	0.00	2.32	2.32
	Others	0.00	2.78	2.78
Total		9.98	90.02	100

5 are homogeneously distributed. ATC Code 12 is almost integrally concentrated in the second semester (column 2, 4%), whereas ATC Code 7 has the same percentage (4.95%) in column 2 and column 3, more than in column 4 (3.5%). A similar trend can be observed for ATC Code 8: the value is 7.9 in column 1, greater than the value in column 4 (4.5%) and little minor than that in column 3 (10.9%).

Measure of Efficacy

By means of efficacy we intended to quantify the primary objectives pursued by the trials of the pharmaceutics industries to obtain the approval of EMA. Items were ranked taking account of the trial reports and in the majority of cases they coincide with the primary endpoints. They consist of five groups (Table 4), building up a hierarchically scale: 1 stands for cure rate, 2 for the disease progression rate, 3 for overall survival, 4 represents the percentage of reduction of the number of the symptoms, 5 stands for the quality of life. Considering subtotals, the major percentage of drugs was found in the group 2 (disease progression rate), and ATC Code 1 (Alimentary tract and metabolism) has the greatest value: 9.47%. It is not surprising to find the major percentage, 9.47, of antineoplastic drugs (ATC Code 8) in the group 3 standing for the overall survival. Anti-infective drugs for systemic use (ATC Code 7) have the greatest percentage, 6.51, in the group 1, measuring the care rate. On the contrary, drugs belonging to the ATC Code 10 (nervous system) have both the subtotal and the total greatest percentage in the group 4. The cure of symptoms is a less ambitious objective than the reduction of the disease or at least making it stationary. There are not many drugs pursuing the improvement of quality of life (QoL). Drugs that do improve QoL are mainly concentrated in the ATC Code 1 (column 6, 1.78%).

Identifying Efficiency: Recognizing the Value of the Benefits

Approval decision involves, above all, an efficiency evaluation of the medicine. Consulting the summaries of the European Public Assessment Report (EPAR) for every human medicine in the period 2010-2015, we went back to evaluation methods by which European Agency assessed the medicine to recommend its authorization in the EU and its conditions of use. Answering to

Table 3. Items by authorization date distributed according to the ATC Code

Atc Code	Authorization Date (Percentages)					Total
	6Months	6 Months To 1 Year	1 Year to 1.5 Year	1.5 Year to 2 Years	Beyond 2 Years	
1. Alimentary tract and metabolism	1.0	2.0	8.9	1.5	1.0	14.4
2. Blood and forming organs	0.0	0.0	4.0	1.5	0.0	5.4
3. Cardiovascular system	1.0	1.0	2.5	2.0	1.5	7.9
4. Dermatological	0.0	0.0	1.5	0.0	1.0	2.5
5. Genitourinary system and sex hormones	0.5	0.0	0.5	1.0	0.5	2.5
6. Systemic hormonal preparations excluding sex hormones and insulins	0.0	0.0	0.0	1.5	0.0	1.5
7. Anti-infective for systemic use	1.0	5.0	5.0	3.5	0.5	14.9
8. Antineoplastic	1.0	7.9	10.9	4.5	1.0	25.2
9. Musculoskeletal system	0.0	0.5	1.0	0.5	0.0	3.0
10. Nervous system	2.5	1.5	3.5	2.0	0.5	9.9
12. Respiratory system	1.0	4.0	1.5	0.0	0.5	6.9
13. Sensory organs	0.0	0.5	2.0	0.5	0.5	3.5
14. Others not classified	1.0	0.5	1.0	1.0	0.0	3.5
Total	8,9	22.8	42.1	19.3	6.9	100.0

the question "why medicine has been approved", EMA says: 1) the medicine is effective, 2) the medicine has a modest/limited in time/effectiveness, 3) the medicine has a relevant efficiency/ more than another medicine/ or evaluated without a comparison, 4) in case of generic drug: the medicine is in line with a similar product, 5) in case of non-generic drug: the medicine has a comparable efficiency with others, 6) the medicine can be used as alternative to other medicines, 7) the medicine represents a second line treatment to other medicines, 8) improvement efficiency has been demonstrated when used in combination with other medicines, 9) the medicine is not sufficient in efficiency.

We assembled the answers in four levels of efficiency: 1) high level of efficiency/high level of benefits that includes answers 3, 6, 8; 2) medium level that includes answers 1,4,5; 3) low level that includes answers 2, 7, and finally 4) less than low level of efficiency/ benefit that includes answer 9.

Identifying Safety: The Kind of Risks

Moreover, approval decision involves an identification and an evaluation of the drug safety. Also in this case it has been utilized the Summary of the European Public Assessment Report (EPAR) for every human medicines in the period 2010-2015, and the corresponding list of items useful to understand the value given to every risk that can prejudice the safety of the medicine. From

Table 4. Items for the measure of efficacy distributed (percentages) according to the ATC Code

ATC Code	Efficacy					Total
	Cure rate	Disease Progression Rate	Overall Survival	Reduction of the Number of the Symptoms	Quality of Life	
1. Alimentary tract and metabolism	4.14	9.47	0.59	0.00	1.78	15.98
2. Blood and forming organs	0.59	2.96	0.59	1.18	0.00	5.33
3. Cardiovascular system	1.78	1.78	0.59	1.78	0.00	5.92
4. Dermatological	1.78	0.59	0.00	0.59	0.00	2.96
5. Genitourinary system and sex hormones	0.59	0.00	0.00	0.59	0.59	1.78
6. Systemic hormonal preparations excluding sex hormones and insulins	0.59	1.18	0.00	0.00	0.00	1.78
7. Anti-infective for systemic use	6.51	5.92	1.18	1.18	0.00	14.79
8. Antineoplastic	4.73	8.88	9.47	2.96	0.00	26.04
9. Musculoskeletal system	0.59	1.78	0.00	0.00	0.00	2.37
10. Nervous system	1.18	1.78	0.59	4.73	0.59	8.88
12. Respiratory system	1.18	5.33	0.00	0.59	0.00	7.10
13. Sensory organs	1.18	1.18	0.00	0.59	0.00	2.96
14. Others not classified	0.00	2.96	0.59	0.59	0.00	4.14
Total	**24.85**	**43.79**	**13.61**	**14.79**	**2.96**	**100**

the answers to the questions "why medicine has been approved" and "what are the risks of the medicines", we caught the following degrees of safety, mainly linked to the side effect risks[3]. They are standardized, as for the efficiency assessment: 1) side effects are totally manageable, 2) side effects are largely manageable, 3) there is some concern for some side effect, 4) side effect are well tolerated, 5) side effects are acceptable, 6) side effects are local, 7) (specifically for generic) side effects are comparable with the original medicine, 8) lack of comparable medicine side effects, 9) as combination of two or more medicines, side effects are well known, 10) easily/ resolving in short time, 11) side effects or some side effect is toxic, 12) side effects are unmanageable.

We also assembled the answers in four levels of safety: 1) high level which includes answers 1, 7, 8, 10; 2) medium, including answers 2, 4, 6, 9; 3) low, including answers 3, 5; 4) less than

low, including answers 11, 12. Safety furthermore may be divided in Safety 1 and Safety 2, because EMA definitions of security about risks are duplex, so each level of safety splits in two.

Table 5 shows the relation between Efficiency and Safety 1, expressed as percentages according to the ATC Code, meanwhile Table 6 shows the analogous relation with Safety 2. Efficiency levels 1, 2, 3 agree with the approval of the drug, whereas level 4 stands for the refusal of the drug because of its substantial inefficiency. In Table 5 at the highest levels of Efficiency and Safety 1 corresponds a percentage of 13.04, lesser than that of low level of Safety 1 (14.13%). On the contrary, as shown in Table 6, the highest level of Efficiency corresponds to the highest level of Safety 2, 17.58%, even though the low level of Safety 2 shows a value of 13.58%. Generally, at the other levels of Efficiency the percentages of low Safety noticeably decrease.

In both Tables it is shown that approval decisions with high Efficiency evaluations are in the same percentages of approval decisions with medium Efficiency, even though the last one is related to highest levels of Safety that then decrease to medium level, low level, and in less than low level, in the approval decisions with low Efficiency. From Table 5 and Table 6 it can be maintained that the higher is the Efficiency level, more side effects are admitted, and then the lesser Safety. The First Guiding Principle of EMA decision can be deduced:

1. Raising the benefits, major risks can be tolerated.

And as a corollary:

2. Decreasing the benefits, risks must decrease too.

Moreover, for what concerns ATC Code 8 (antineoplastic drugs), its behavior is like aggregate data: a lesser Safety for a higher Efficiency. Table 5, at high Efficiency level shows 5.43% for low level of Safety, vs 0.54 of high level of Safety. In Table 6 high Safety and low Safety are respectively 7.41% and 6.17%. Moreover, from both Table 5 and 6 Safety increases in high and medium levels for decreasing levels of Efficiency. On the contrary, the distribution of ATC Code 7 (anti-infective drugs) is different: for high Efficiency level, Safety 1 is decreasing in the high, medium and low levels, whereas Safety 2 increases in the same levels, showing an opposite behavior. Interestingly, ATC Code 10 (nervous system) and ATC Code 3 (cardiovascular system), are mainly concentrated in the medium level of Efficiency, with medium and low levels of Safety. A possible explanation may derive from data in Table 2. As a matter of fact, anti-infective drugs are not versus fatal diseases as instead are antineoplastic drugs. So, probably the Safety level for approval is necessarily higher on average. We, therefore, can update the above guiding principles including these ones:

1. High levels of benefits are related to high levels of risk especially in case of fatal diseases;
2. With high benefits and not fatal diseases, the risks should not be very high.

As a corollary we can add a third principle:

3. For drugs of medium level of efficacy, reference diseases should not be fatal.

Other inquiries are probably necessary to explain the trends of the medium-low levels of Safety and Efficacy Level 3 (Overall survival), and of nervous system drugs.

Table 5. Relation (in percentages) between Efficiency and Safety 1 according to the ATC Code

	Efficiency																			
	High					**Medium**					**Low**					**Less than low**				
	Safety 1					**Safety 1**					**Safety 1**					**Safety 1**				
ATC Code	High	Medium	Low	Less than low	Total	High	Medium	Low	Less than low	Total	High	Medium	Low	Less than low	Total	High	Medium	Low	Total	Total
1. Alimentary tract and metabolism	1.63	1.63	1.09	0.00	4.35	3.80	2.72	1.09	0.00	7.61	0.54	1.63	1.09	0.00	3.26	0.00	0.00	0.00	0.00	15.22
3. Cardiovascular system	0.00	0.54	0.54	0.00	1.09	1.63	0.00	1.09	0.54	3.26	0.00	0.00	0.00	1.09	1.09	0.00	0.00	1.09	1.09	6.52
4. Dermatological	0.54	0.00	0.00	0.00	0.54	0.00	0.54	0.54	0.00	1.09	0.54	0.00	0.00	0.00	0.54	0.54	0.00	0.00	0.54	2.72
5. Genitourinary system and sex hormones	0.00	0.00	0.54	0.00	0.54	1.09	0.00	0.00	0.00	1.09	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.63
6. Systemic hormonal preparations excluding sex hormones and insulins	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.54	0.00	0.54	0.00	0.54	0.54	0.00	1.09	0.00	0.00	0.00	0.00	1.63
7. Anti-infective for systemic use	4.35	3.80	2.17	0.00	10.33	2.17	1.09	0.54	0.00	3.80	0.00	0.00	0.00	0.54	0.54	0.00	0.00	0.00	0.00	14.67
8. Antineoplastic	0.54	3.26	5.43	0.54	9.78	4.89	2.72	2.17	0.54	10.33	1.09	0.00	2.17	0.00	3.26	0.00	1.63	0.54	2.17	25.54
9. Musculoskeletal system	0.00	0.00	0.54	0.00	0.54	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.54	0.00	0.54	1.09
10. Nervous system	1.63	1.09	0.54	0.00	3.26	2.72	1.09	1.63	0.00	5.43	0.00	0.00	1.09	0.00	1.09	0.00	0.54	0.54	1.09	10.87
12. Respiratory system	2.17	0.00	1.09	0.00	3.26	0.54	0.54	0.00	0.00	1.09	1.63	0.00	1.09	0.00	2.72	0.00	0.00	0.54	0.54	7.61
13. Sensory organs	1.09	0.54	0.00	0.00	1.63	0.00	0.00	0.00	0.00	0.00	0.00	1.09	0.00	0.00	1.09	0.00	0.00	0.00	0.00	2.72
14. Others not classified	1.09	0.00	1.09	0.00	2.17	1.09	0.00	0.00	0.00	1.09	0.54	0.00	0.00	0.00	0.54	0.00	0.00	0.00	0.00	3.80
Total	**13.04**	**10.87**	**14.13**	**0.54**	**38.59**	**19.02**	**9.78**	**8.70**	**1.09**	**38.59**	**4.35**	**3.26**	**7.61**	**1.63**	**16.85**	**0.54**	**2.72**	**2.72**	**5.98**	**100**

Table 6. Relation (in percentages) between efficiency and safety 2 according to the ATC Code

	Efficiency																	
	High					Medium					Low				Less than low			
	Safety 2					Safety 2					Safety 2				Safety 2			
ATC Code	**High**	**Medium**	**Low**	**Less than low**	**Total**	**High**	**Medium**	**Low**	**Less than low**	**Total**	**High**	**Medium**	**Low**	**Total**	**Medium**	**Less than low**	**Total**	**Total**
1. Alimentary tract and metabolism	1.23	0.00	1.23	1.23	3.70	4.94	3.70	0.00	0.00	8.64	0.00	0.00	2.47	2.47	0.00	0.00	0.00	14.81
3. Cardiovascular system	0.00	0.00	0.00	0.00	0.00	2.47	0.00	0.00	0.00	2.47	0.00	1.23	0.00	1.23	0.00	0.00	0.00	3.70
4. Dermatological	0.00	1.23	0.00	0.00	1.23	1.23	3.70	0.00	0.00	4.94	0.00	0.00	0.00	0.00	0.00	2.47	2.47	8.64
5. Genitourinary system and sex hormones	1.23	0.00	0.00	0.00	1.23	1.23	0.00	0.00	0.00	1.23	0.00	0.00	0.00	0.00	1.23	0.00	1.23	3.70
6. Systemic hormonal preparations excluding sex hormones and insulins	1.23	0.00	0.00	0.00	1.23	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.23
7. Anti-infective for systemic use	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.23	0.00	1.23	1.23	0.00	1.23	2.47	0.00	0.00	0.00	3.70
8. Antineoplastic	1.23	2.47	4.94	0.00	8.64	2.47	1.23	1.23	0.00	4.94	0.00	0.00	0.00	0.00	0.00	0.00	0.00	13.58
9. Musculoskeletal system	7.41	2.47	6.17	0.00	16.05	4.94	0.00	1.23	1.23	7.41	1.23	0.00	0.00	1.23	0.00	3.70	3.70	28.40
10. Nervous system	0.00	0.00	1.23	0.00	1.23	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.23	1.23	2.47
12. Respiratory system	1.23	1.23	0.00	0.00	2.47	0.00	3.70	1.23	0.00	4.94	1.23	0.00	0.00	1.23	0.00	2.47	2.47	11.11
13. Sensory organs	1.23	0.00	0.00	0.00	1.23	1.23	0.00	0.00	0.00	1.23	1.23	1.23	0.00	2.47	0.00	0.00	0.00	4.94
14. Others not classified	2.47	0.00	0.00	0.00	2.47	0.00	0.00	0.00	0.00	0.00	0.00	1.23	0.00	1.23	0.00	0.00	0.00	3.70
Total	**17.28**	**7.41**	**13.58**	**1.23**	**39.51**	**18.52**	**12.35**	**4.94**	**1.23**	**37.04**	**4.94**	**3.70**	**3.70**	**12.35**	**1.23**	**9.88**	**11.11**	**100**

Further Indication about Safety/Efficiency

EMA supplies further indications about the efficiency and the safety of the drugs. Its content is negative or at least dubitative, that is to say that EMA approving a drug singles out grounds for caution. It is a case of conditional approval, with very low percentages, as shown in Table 7. It has been utilized the Summary of the European Public Assessment Report (EPAR) for every human medicines in the period 2010-2015, and the corresponding list of items useful to understand the value given to every risk that can prejudice the safety of the medicine. Here are the answers to the question "why the drug was approved": 1) not sure it works with a particular subgroup, 2) not proved its efficiency when combined or compared, 3) not proved efficiency in secondary use, 4) only to use in specialized centers of control, 5) not proved the efficiency on the progress of the disease or in long time, 6) data is partial, 7) some particular side effect should be further investigated or limited the use. 1-2-3-5- were grouped in a hierarchical way under the heading 1 "partial efficiency", 6 under the heading 2 "partial data", 4-7 under the heading 3 "partial safety". This means that Efficiency and Safety values, up to now considered, cannot have an absolute value. As shown in Table 7, just the 3.5% of drugs were conditional approved, whereas Table 8 shows the percentages of Further Indication Levels according to the ATC Code.

Table 9 is very interesting. It shows that the major percentage of Further Indication is related to high levels of Efficiency, decreasing at low levels of Efficiency.

Then we need once more to update the Guiding Principles. The first one will sound like this: High levels of Efficiency, whether partially or scarcely proved, can come with low levels of Safety, in a few cases also partially or scarcely proved. And the second one: Safety increases with medium levels of Efficiency, meanwhile decreasing the conditions under which Efficiency and Safety are partially and scarcely proved.

Table 7. Conditional approval percentages of drugs

	Conditional Approval		
ATC Code	**YES**	**NO**	**Total**
1. Alimentary tract and metabolism	0.00	14.43	14.43
2. Blood and forming organs	0.00	5.47	5.47
3. Cardiovascular system	0.00	7.96	7.96
4. Dermatological	0.00	2.49	2.49
5. Genitourinary system and sex hormones	0.00	2.49	2.49
6. Systemic hormonal preparations excluding sex hormones and insulins	0.00	1.49	1.49
7. Anti-infective for systemic use	0.50	13.93	14.43
8. Antineoplastic	1.99	23.38	25.37
9. Musculoskeletal system	0.00	1.99	1.99
10. Nervous system	0.50	9.45	9.95
12. Respiratory system	0.00	6.97	6.97
13. Sensory organs	0.50	2.99	3.48
14. Others not classified	0.00	3.48	3.48
Total	**3.48**	**96.52**	**100**

Table 8. Percentages of further indication levels according to the ATC Code

ATC Code	No Further Indication	Further Indication			
		Partial Efficiency	Partial Data	Partial Safety	Total
1. Alimentary tract and metabolism	9.50	2.00	1.00	1.50	14.00
2. Blood and forming organs	4.00	0.50	0.00	1.00	5.50
3. Cardiovascular system	6.50	0.50	1.00	0.00	8.00
4. Dermatological	1.50	0.00	0.50	0.50	2.50
5. Genitourinary system and sex hormones	1.50	0.50	0.00	0.50	2.50
6. Systemic hormonal preparations excluding sex hormones and insulins	0.50	1.00	0.00	0.00	1.50
7. Anti-infective for systemic use	8.50	3.50	0.50	2.00	14.50
8. Antineoplastic	15.50	5.50	1.50	3.00	25.50
9. Musculoskeletal system	1.00	0.50	0.50	0.00	2.00
10. Nervous system	8.00	1.50	0.50	0.00	10.00
12. Respiratory system	3.00	2.50	1.00	0.50	7.00
13. Sensory organs	2.50	0.00	1.00	0.00	3.50
14. Others not classified	1.50	1.50	0.00	0.50	3.50
Total	**63.50**	**19.50**	**7.50**	**9.50**	**100**

Low levels of Efficiency now come with low levels of Further Indication (differently from the Safety trend): low Efficiency cannot get worse because of "partial data" or "partial safety", otherwise the drug should be not approved.

ATC Code 7, 8 and 10 have the higher percentages of further indication that come with high levels of efficiency.

SEM Analysis

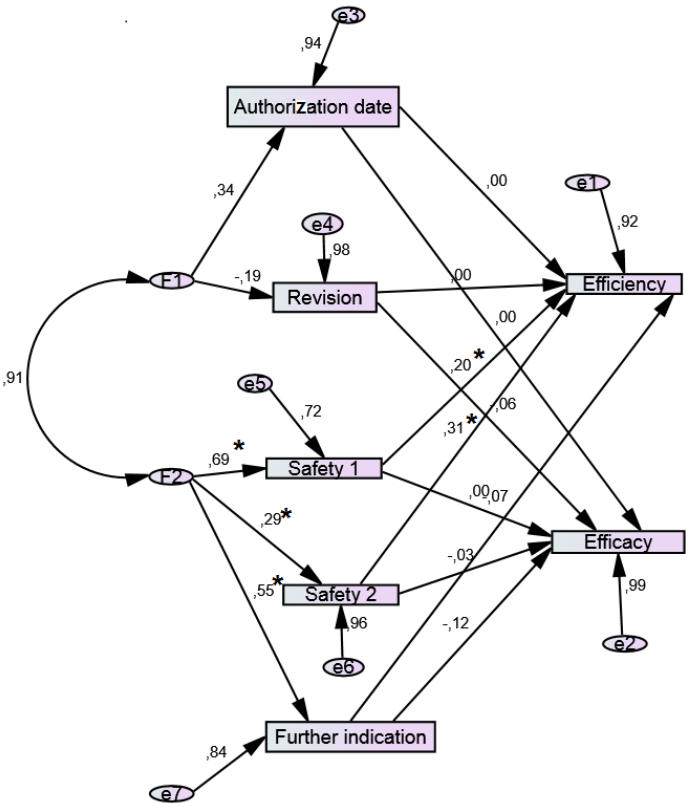
SEM analysis was carried out by taking into account seven observed variables: Efficiency, Efficacy, Safety 1, Safety 2, Further Indication, Authorization Date, Revision, as endogenous variables, and two unobserved exogenous variables F1 and F2.

We hypothesized that there were two unobserved latent factors (one for timing, F1, and one for safety, F2) that underlay the observed variables as described in Figure 1. Authorization Date and Revision load on F1 (with loadings (a.k.a. Regression Weights), see Table 10, 0.34 and -0.19 respectively). Safety 1, Safety 2, Further indication, load on F2 (with loadings 0.69, 0.29, and 0.55 respectively). The double headed arrow indicates the covariance between the two latent factors (F1 and F2). e1 through e7 represent the residual variances (variance in the observed variables not accounted for by the two latent factors). We set the variances of F1 and F2 equal to 1 so that the parameters will have a scale. This will result in F1 and F2 representing the correlation between the two latent factors (.91).

Table 9. Percentages of further indication levels correlated with levels of efficiency

	Efficiency														
	High				**Medium**				**Low**				**Less than low**		
	Further Indication				**Further Indication**				**Further Indication**				**Further Indication**		
ATC Code	**Partial efficiency**	**Partial data**	**Partial safety**	**Total**	**Partial efficiency**	**Partial data**	**Partial safety**	**Total**	**Partial efficiency**	**Partial data**	**Partial safety**	**Total**	**Partial efficiency**	**Total**	**Total**
1. Alimentary tract and metabolism	1.37	2.74	0.00	4.11	2.74	0.00	2.74	5.48	1.37	0.00	1.37	2.74	0.00	0.00	12.33
2. Blood and forming organs	0.00	0.00	0.00	0.00	1.37	0.00	1.37	2.74	0.00	0.00	1.37	1.37	0.00	0.00	4.11
3. Cardiovascular system	0.00	0.00	0.00	0.00	1.37	1.37	0.00	2.74	0.00	1.37	0.00	1.37	0.00	0.00	4.11
4. Dermatological	0.00	0.00	0.00	0.00	0.00	0.00	1.37	1.37	0.00	1.37	0.00	1.37	0.00	0.00	2.74
5. Genitourinary system and sex hormones	0.00	0.00	1.37	1.37	1.37	0.00	0.00	1.37	0.00	0.00	0.00	0.00	0.00	0.00	2.74
6. Systemic hormonal preparations excluding sex hormones and insulins	0.00	0.00	0.00	0.00	1.37	0.00	0.00	1.37	1.37	0.00	0.00	1.37	0.00	0.00	2.74
7. Anti-infective for systemic use	4.11	0.00	4.11	8.22	4.11	1.37	0.00	5.48	0.00	0.00	1.37	1.37	1.37	1.37	16.44
8. Antineoplastic	5.48	1.37	5.48	12.33	2.74	2.74	1.37	6.85	5.48	0.00	1.37	6.85	1.37	1.37	27.40
9. Musculoskeletal system	1.37	1.37	0.00	2.74	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.74
10. Nervous system	0.00	1.37	0.00	1.37	2.74	0.00	0.00	2.74	1.37	0.00	0.00	1.37	0.00	0.00	5.48
12. Respiratory system	6.85	1.37	0.00	8.22	0.00	0.00	0.00	0.00	0.00	1.37	1.37	2.74	0.00	0.00	10.96
13. Sensory organs	0.00	1.37	0.00	1.37	0.00	0.00	0.00	0.00	0.00	1.37	0.00	1.37	0.00	0.00	2.74
14. Others not classified	2.74	0.00	1.37	4.11	0.00	0.00	0.00	0.00	1.37	0.00	0.00	1.37	0.00	0.00	5.48
Total	**21.92**	**9.59**	**12.33**	**43.84**	**17.81**	**5.48**	**6.85**	**30.14**	**10.96**	**5.48**	**6.85**	**23.29**	**2.74**	**2.74**	**100**

Figure 1. Path Diagram. Significant Standardized Regression Weights are asterisked.



The path coefficients of the SEM model show that Efficiency is significantly affected by Safety1 (path coefficient = 0.20) and Safety2 (path coefficient = 0.31). Moreover, the three safety criteria: Safety 1, Safety 2, Further indication, are significantly affected by the latent factor F2 (path coefficients = 0.69, 0.29, 0.55, respectively).

DISCUSSION

With the help of Table 11 we can now integrate the guiding principles that are likely to have oriented EMA decisions:

1. Higher efficiency agrees with lower safety. This is true i) even if efficiency is partial, as described above, ii) particularly when the medicines belong to an ATC Code class (i.e. 8, antineoplastic drugs) including fatal diseases. Low life expectancy is typical of those ATC Codes whose main measure of efficacy is level 3: "overall survival".
2. If efficiency is equally high and eventually partial but the medicines belong to ATC Codes with a major life expectancy, safety is typically medium-high. This is particularly true for those medicines whose main measure of efficacy is level 1: "care rate".

Table 10. Standardized regression weights estimations, presented with their p-values as appearing in Path Diagram

Determinants			Standardized Regression Weights	p
Authorisation date	<---	F1	.342	.090
Revision	<---	F1	-.189	.133
Safety1	<---	F2	.692	.002
Safety2	<---	F2	.295	.048
Further indication	<---	F2	.550	.002
Efficiency	<---	Authorization date	.005	.944
Efficiency	<---	Safety1	.199	.020
Efficiency	<---	Revision	-.005	.945
Efficacy	<---	Further indication	-.120	.334
Efficacy	<---	Safety2	-.029	.787
Efficacy	<---	Revision	-.057	.428
Efficacy	<---	Authorization date	-.005	.947
Efficiency	<---	Further indication	-.066	.585
Efficiency	<---	Safety2	.305	.002
Efficacy	<---	Safety1	.004	.965

3. When efficiency is medium, safety has to be high and increasing with the lack of further indications. As said above, as a matter of fact, medium efficiency is incomplete in itself to be effected by further limits. When efficiency is medium, it is typically related to classes of ATC Code with low risk of life threatening conditions and with a high life expectancy: i.e. hypertension, obesity, in ATC Code 1 and 3.

The condition of medium-low efficiency related to a low level of safety is particularly true for ATC Code classes 1 and 10, where treatments are intended to be used for psychiatric and neurological disorders (i.e. epilepsy, schizophrenia), elderly diseases (Alzheimer, Parkinson) and diseases with a major mortality among older peoples (diabetes, obesity).

From the results of the SEM model (see Figure 1 and Table 10) we can surmise that at the basis of EMA's decisions there is a latent "safety" factor (inasmuch it significantly affects Safety 1, Safety 2 and Further Indication) as a determinant of the efficiency criterion.

CONCLUSION

A general model of the determinants of efficiency and efficacy criteria that lead to the EMA approval decisions was assessed. Different degrees of benefits and risks underpinning the EMA decisions have been identified together with the consequent guiding principles that lead to the decision process. Our findings give evidence of a latent general "safety" factor in the background of EMA's decision process.

Table 11. Main characteristics of medicines whose ATC Code has a percentage distribution up to 6

ATC Code	Generic vs non Generic	Approval time	Measure of Efficacy	Efficiency/ Safety	Low Efficiency/ Safety	Further Indication vs No Further Indication	Further indication / Efficiency
1. Alimentary tract and metabolism	3.54 vs 11	third semester	disease reduction progress rate	2nd class- medium efficiency/ safety with high-medium safety related	the highest among percentges in class 3rd -low efficiency	4.5 vs 9.5	1st and 2nd class high and medium efficiency
3. Cardiovascular system	1.57 vs 6.27	fifth semester and beyond	care rate, disease reduction progress rate, reduction of symptoms	2nd class- medium efficiency/ safety with high-medium safety related	low percentage in class 3rd- low efficiency	1.5 vs 6.5	2nd class medium efficiency
7. Anti-infectives for systemic use	1.18 vs 11.37	first and second semester	care rate	1st class -high efficiency with high- medium safety related	no data in class 3rd- low efficiency	6.0 vs 8.5	1st and 2nd class high and medium efficiency
8. Antineoplastic	3.15 vs 20.08	first and second semester	overall survival	1st -high efficiency with low safety related	low percentage in class 3rd- low efficiency with related safety omogeneously distributed in high-mediun-low	10.0 vs 15.5	1st and 2nd class high and medium efficiency
10. Nervous system	6.69 vs 7.87	first semester	reduction of symptoms	2st -medium efficiency with medium -low safety related	low percentage in 3rd class- low efficiency with related high and low safety.	2.0 vs 8.0	1st and 2nd class high and medium efficiency

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ENDNOTES

1 Authors thank one referee for having stressed this aspect.

2 The **Anatomical Therapeutic Chemical (ATC) Classification System** is used for the classification of active ingredients of drugs according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. It is controlled by the World Health Organization Collaborating Centre for Drug Statistics Methodology (WHOCC)

3 We just reported EMA term of classification (side effect), without further investigating the nature of adverse reactions. This was deemed sufficient at this stage of analysis.