

BIOEQUIVALENCE IMPLIES THERAPEUTIC EQUIVALENCE. II. ECONOMIC AND SOCIAL APPROACH

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ABSTRACT: In spite of the fact that bioequivalent drugs are therapeutically equivalent, following a lot of apparent scientific disputes which traduce in fact the contradictions between different groups of interest, the sharing of the market between brand and generic drugs differs from country to country, which implies finally great differences in expenses and efficiency of health systems. Generic drugs account for 88% of all prescriptions filled USA and only 23 % in Romania. Authors consider that this situation decreases the availability for assurance of fundamental right to health for poor people and propose two solutions for entering of Romania on the right. First is the modification of the curricula at universities of medicine and pharmacy by including biopharmacy and pharmacokinetics, GMP, GCP and QAS essential information. Second proposal is the renaissance of the public control of drugs starting from the model of Institute for State Control and Research of Drugs based on the facilities and specialists of the faculties of pharmacy and National Institute for Chemico-Pharmaceutical Research and Development. Such an institution could convince medical doctors and patients that really Romanian generics drugs have the same quality as brand drugs.

Keywords: health politics, generic drugs, bioequivalence, therapeutic equivalence, public drug control

INTRODUCTION:

Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments) imposed to Food and Drug Administration (FDA) a general frame for generic drug introducing the abbreviated new drug application (ANDA) approval process, more simple and rapid than the new drug application (NDA) procedures, for drugs with same safety and effectiveness as previously approved and "listed" drugs.

Two drugs assuring similar concentrations in blood for active substance were called bioequivalent and it was accepted that their effect is essentially the same, being "therapeutically equivalent". NDA was restricted to proving good manufacturing practice and bioequivalence. Statistical prove of bioequivalence is based on only two parameters, maximum concentration C_{max} and area under plasma level curves (AUC) at healthy volunteers. This is really sufficient to prove rigorously bioequivalence (Gherghiceanu et al., 2016) in practically all cases.

Since the costs of generic drugs are significantly lower (50%-70%) in comparison with their branded correspondents, governments from all over the world, confronted with continuously increasing of costs of drugs and aging populations, encourage and develop politics for increasing their use. In 2015 generic drugs account in US for 88% of all prescriptions filled and predictions, generics will represent some 91%-92% of prescription volumes by 2020. (Nasdaq, 2016). Retrospectively it was appreciated that application of the mentioned law permitted an easier access to poor

people to cost and life savings generic drugs. For example in the period 2003 through 2012, proved that generic substitution generated more than \$1.2 trillion in savings to the health care system in USA and contributed to well-being of innumerable lives. (Hamburg, 2014)

In spite of their huge advantages the problem of using generics remains under dispute, first of all due to economic interest of innovator companies in maintaining high prices to drugs but also following real concerns of medical doctors regarding the effect of some classes of generics, (Atif et al., 2016), (Benet, 2003) mainly highly variable drugs (HVD) and narrow therapeutic index (NTI) drugs.

Following these disputes and balance of forces between different groups of interest, the sharing of the market between brand and generic drugs differs from country to country, which implies finally differences in expenses for health systems.

There are some dosage forms for which definition of active components and determination of plasma levels meet difficulties, named "non biological complex drugs" (NBCDs) such as drugs obtained using nanotechnologies (Crommelin, 2015) colloidal iron carbohydrate drugs (Borchard, 2012) (EMA, 2011) for which proving of bioequivalence is not sufficient or even impossible to perform such as inhalatory powders or drugs acting in the gastrointestinal tract. For topical drugs were conceived other methods (SHAH, 2015) using qualitative and quantitative (Qs) criteria. In rest, for almost drugs,

proving of bioequivalence and therapeutic equivalence is a feasible and scientifically robust task.

In case of NTI and HVD there are concerns of clinicians about possible risks associated to change from brand to generic drugs. A lot of research was performed to verify if some drugs as for example antiepileptics (Crawford et al., 2006), (Zachry et al., 2009), warfarin (Wysowski et al., 2007). In these category also, there is no one example of drugs approved as bioequivalent and presenting suspicions of non therapeutic equivalence.

The aim of present paper is to present the huge difference between Romanian and American

distribution of money between the two categories and implicit between efficiency of health systems and to propose measures to correct this situation.

Generic drugs market in USA

Beyond exceptions connected to evaluation of bioequivalence, today, almost all drugs that go off patent could be replaced by alternative generic drugs and the opinion is favorable toward actual prescription of generic drugs. Their market is continuously increasing in the last years and, for example in 2012, about 84 percent of all prescriptions filled in USA were for generic versions. (Boehm et al., 2013)

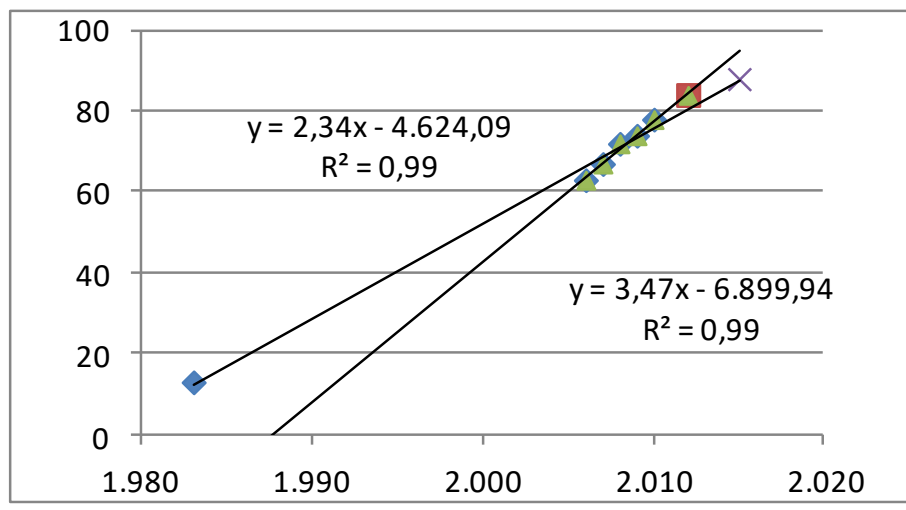


Fig. 1. Evolution of the proportion of generics in prescribing drugs in US in 1983 – 2016 period ($y = 2.34x - 4624$ the regression line for the period 1983 - 2014, $y = 3.47x - 6899$ the regression line for the period 2010 – 2014 , x estimated value for 2016 by the regression line for the entire period 88 % face to 88.1 % actual found value

Putting together, representing graphic and modeling data from different documents concerning evolution of generic market un US in different periods included in the last 33 years can be drawn some interesting conclusions. First of all is that the linear evolutions on different periods can be joint in a linear evolution between 1983 and 2016. Though in the period 2006 – 2010 it was an acceleration (slope increased from 2.34 to 3.47) the prediction concerning value for 2012 and 2016 was excellent using the long term 1983 – 2010 model). Surely the line have to change in the future toward a saturation portion since the increase cannot attain 100 % since the research for innovative drugs have to and really will survive. Innovative companies will compensate the loss of volume in market by the increasing of prices of new drugs. The prediction of the linear model for 2020 is 96 % and prediction of FDA (Nasdaq, 2016).

Going further from medical doctor to pharmacy, pharmacists are interested in release of generic drugs. The high prices for branded drugs reduce the pharmacy profit margins. On the contrary, the cheaper generics permit a higher markup by the pharmacy (Cook, 1998).

In United States is permitted “switching” from a brand drug to a generic equivalent by the pharmacist,

even in case when prescription is written as a brand name product. (Greenberg, 2001). In 2012 for example, generics reached 84% of dispensed prescriptions, with an increase of cost by \$8 billion (IMS 2013).

Finally, in spite of great reduction of expenses following generic substitution, in a meeting with great drug companies, Donald Trump, the new president of USA appreciated In a "pharma" meeting in the Oval Office with executives from companies such as Merck & Co. and Johnson & Johnson that they have done a "terrific job over the years" but that prices for drugs must come down, that the prices of drugs are abnormally high and have to be significantly reduced (Landers, 2017).

Generics drug market in Europe

Despite the maturity of the European generic pharmaceuticals market, the president of the EGA, Nick Hagggar, sees substantial opportunities for further growth. “Generic medicines currently represent 54% of medical prescriptions in Europe by volume, but that figure could reach 80%”, he told *Correo Farmaceutico* in an interview during the 20 Annual General Meeting of the EGA in Madrid last week in Spain, where the generic penetration rate is 38% .

In United Kingdom the proportion of prescriptions that are filled by generics remains among the highest in Europe. The key driver for this remains the acceptance by physicians (unique among European countries) of writing prescriptions by generic name without specifying the brand or manufacturer (open prescribing).

In other countries in Europe, politics concerning supporting generics are not uniform and less effective than in U.S. In Germany, Poland, Denmark, the Netherlands, etc. where generic drug consumption in 2006 was 40% and in 2012 reached 50%. In 2006, countries like Austria, Belgium, Italy, Greece and Switzerland, selling a generic drug increased for supporting national drug industry (Simoens, 2013). Austria has introduced policies for pricing and reimbursement of generic drugs and part of money are used for to develop research in the field. (Hassali et al., 2010). In Norway pharmacists must inform

patients on the lowest price generic drug type (Mohamed et al., 2009).

ROMANIA

In Romania the fate of generic drugs is completely different to that in US. The most in depth analysis of this situation was performed by the Council of Concurrence (Consiliul Concurentei, 2015).

Essentially, in spite of a lot of specific regulations intended to increase the use of generics, the situation goes from bad to worse. Though prices of generic drugs are lower with 35 % than that of brand drugs, many years after authorization, their part on the market remain low.

An evolution of the drug market in Romania in the period 2011 – 2015, starting from data provided us by Centre de Gestion et de Documentation de l'Information Médicale (CEGEDIM) is presented in figures 2a and 2b.

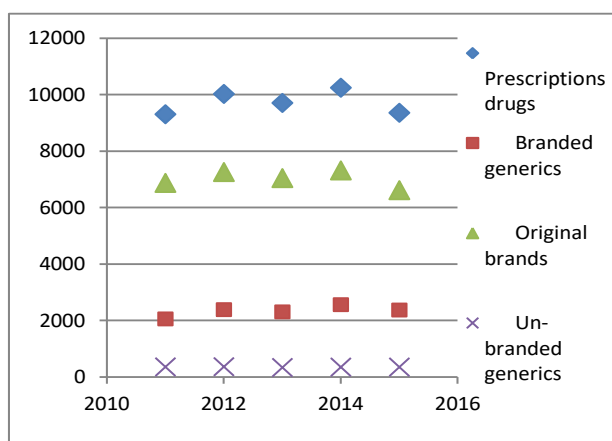
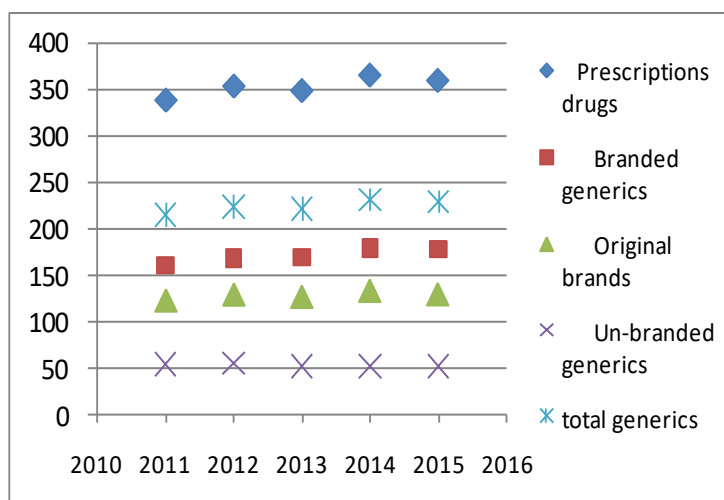


Fig. 2. Number (millions) of units of drugs (2a) and value (millions of RON) on the market (2b)

It can be seen that the number of units (millions) of original brand drugs is much higher than that of generic drugs. Since the prices of original brand drugs are higher the situation is more dramatic if we examine the millions of RON paid by Romanians

for different categories of drugs, as can be seen in figure 2b. If we sum the two generic categories and calculate the percent of the value of generics in the total value, as can be seen in figure 3. Appears a linear increase of the proportion of generic drugs but

the long term effect is rather insignificant. From 26.1 % to 29.3 % means $(29.3\% - 26.1\%) / 5 = 0.62\% / \text{an}$. An

increase to more than 80 % could be obtained in approximately 80 years.

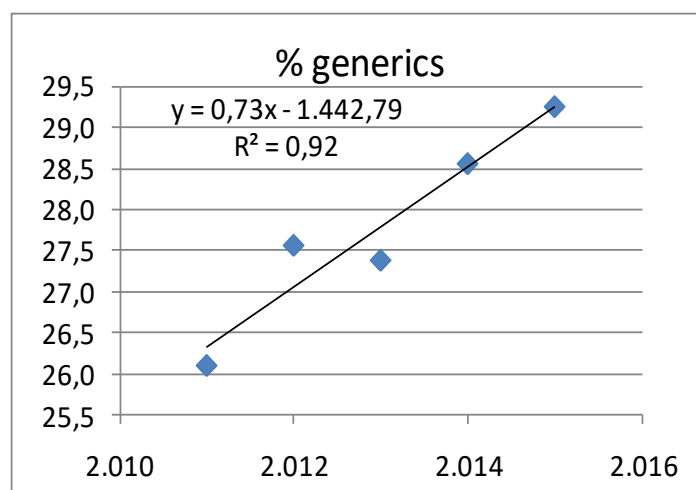


Fig. 3. Sum of two generic categories and the percent of the value of generics in the total value

In a poetic expression, Romania is the “gold sponsor” of multinational drug companies.

It concerns the roots of such a situations, we mention some, starting from the excellent analysis and reports of Council of Concurrence in the last years. (www.consiliulconcurentei.ro)

Contributions to this situation are coming from all directions: medical doctors, pharmacists, patients, authorities.

Prescribers. First of all medical doctors don't know the definition of bioequivalence, don't know what does mean Good Manufacturing Practice, Good Laboratory Practice and Quality Assurance Systems in pharmaceutical industry. Their information on this subject is based essentially on advertise and symposia organized by innovator companies. Even many large scientific congresses are sponsored for organization and assurance of participants mainly by innovator drug companies. Sponsorization of medical doctors for participating to congresses in Romania in 2014 was 5.271.635 RON from the part of generic companies and 49.235.079 RON from innovator companies. It concerns congresses outside Romania expenses were 1.396.440 and respectively 18.483.095 RON (CC report).

It was found by the Council of Concurrence that frequently, when the protection of a brand drug A ended and appeared generic bioequivalent with that drug, prescriptions move immediately to another brand drug B, and A as well its equivalents are no more prescribed.

Patients. Further, part of this bias in information of medical doctors is transferred to patients. Although the prescription have to recommend the active substance and not a trade name, 57 % of patients, influenced by medical doctors, ask in pharmacy the brand name drug.

It is interesting to note that lower prices, even in cases of poor people, are not attractive in all cases. A business experiment performed a few years ago in company Labormed Pharma led to surprising

conclusion that reduction of prices didn't implied an increase in size of selling. People, both medical doctors and patients think sometimes that lower prices mean lower quality and never heard about research, development and quality systems in pharmaceutical industry.

Pharmacists. It concerns pharmacists, the situation is inverse to that in US: financial advantage come from selling brand drugs since these are more expensive and part of pharmacy is proportional with the price. They are better informed than medical doctors following courses of biopharmacy and pharmacokinetics in their graduate education cycle, and they have legal right to interchange drugs. But domination of chains of pharmacies which are strongly oriented toward maximization of profit by owners, they play only a still minor part in generic politics.

Sometimes appear some strongly anti-concurrence less moral associations between producers, prescribers and pharmacists. Council found many such cases. For example (CC report pag. 254) in September 2014 it was found the following situation. In Iasi county there are 368 pharmacies. In the frame of National Program for Transplant first pharmacy released 43 % of the drug released in entire county, the second 18 and the third 13. In the National Program for Oncology, the first pharmacy released 69 % of drugs, the rest of pharmacies releasing between 0 and 7 %. In Constanta county, first three pharmacies released 63 % of the drugs of drugs in the Program for Transplant. Similar situations appeared practically in many national programs and in many places.

These types of association as well a lot of very incisive promotion politics of brand companies could explain unbelievable, highest level disequilibria between brand drug and generics particular drugs. For example, drug Tertensiv had its protection expired more than 10 years ago. Its part on the market increased from [55 – 65 %] in 2009 to [65 – 75 %] in 2014 although there are many authorized generic alternatives. Sermion has a aliquot of [65 – 75 %] in

the market in spite of appearance of generics starting with 2003. And in the same report there is presented a long, long list of this type.

Strategy for reverse the evolution

The conclusion of the above presentation is that the in Romania situation is bad. A lot of measures taken by governments in the last years had no perceptible effects. But the problem is what to do for reversing the situation? Response of authors inside a more large group of specialists from Romanian Academy, Academy of Medical Sciences and “Carol Davila” University is that it is necessary a change in mentality in this domain and this change could be performed using deep scientific arguments and politics. In parallel, at governmental model, it is necessary to understand that access to drugs as a fundamental human right, idea presented by V. Voicu and C. Mircioiu at the Eighth Session of the Intergovernmental Bioethics Committee (IGBC), Paris, 5 – 6 September 2013 .

Reverse of the Marginalization and Elimination of the Institute for State Control of Drugs and Pharmaceutical Research (ICSMCF) of university clinical trial laboratories, of National Institute for Chemico-Pharmaceutical Research and Development

The opinion of authors is that the greatest mistake of post-december authorities was the renouncement to the American model of a drug authority FDA doubled by a methodological authority Center for Drug Evaluation and Research (CDER) and its replacement by a rather bureaucratic institution National Agency for Medicine and Medical Devices following European model based rather on the control of papers about quality to scientifically based regulation and control of quality. Disappearance of ICSMCF, had a devastating effect on the public control on drug quality and on the trust of medical doctors, pharmacists and patients, in all drugs.

Two laboratories for research and bioequivalence studies were created joint to Bucharest and respectively Cluj faculties of pharmacy. But, after some years activity, laboratories have to be closed in context of the entire world strangling of the universities participation in clinical trials, regulatory authorities preferring formal quality face to in depth analysis. Romanian companies were encouraged to develop their own bioequivalence laboratories. Justified or not, the mistrustful in the selfcontrol of companies exists.

National Institute for Chemico-Pharmaceutical Research and Development is still alive but, following continuous politics for approximately 25 years to allocate to research the lowest % of income in Europe and salaries rather symbolic, all pharmacists left the institute migrating to pharmacies or to jobs at multinational companies. So that, without enough specialists, without duties at national level, without perspective in the frame of health politics the institute is less and less „national”.

Changes in curricula at universities of medicine and pharmacy level.

Analysis and discussions concerning European curricula and competences in pharmaceutical education involving the authors of the present paper were undertaken in the frame of the Erasmus project **PHAR-QA QUALITY ASSURANCE IN PHARMACEUTICAL EDUCATION AND TRAINING 2012–2016**. (Anuta et al., 2014), (Prasacu et al., 2014).

Important knowledge and competences connected with research, development, control, quality assurance of drugs, after a questionnaire addressed to some two thousand specialists from all European countries were defined to be (Atkinson et al., 2016) knowledge and ability to apply good manufacturing practice (GMP), good laboratory practice (GLP) and good clinical practice

- ability to work as qualified persons, responsible for quality of batches in industry,
- information about guidelines for marketing authorization of drugs.

Set-up of a public Drug Control and Research Institute.

All these are valid for entire Europe. Special for Romania is the acute problem for setting up of the public national institute for replacing the destroyed ICSMCS. Proposal of the “Carol Davila” University of Medicine and Pharmacy “LABTEST - University, Research and Drug Control Laboratory. „, submitted to Ministry of Research

Industrial Platform „**Innovative Medicine Initiative**” (IMI), which is starting in 2008, underline the essential role in the future of **Academia-Research - Industry institutional integration** and scientific integration.

The project try to be the embryos of a such integration of the university with industry and National Institute for Chemico-Pharmaceutical Research

The concrete objectives of the project are as follows:

- building of central laboratory for research and development of drugs, integrating in vitro and in vivo research,
- endowment of the central laboratory of the faculty with equipment necessary for performing in vitro and in vivo complex drug evaluations,
- set up of new fields of biopharmaceutical research, which are not existing in this time in Romania.

Achievement of these primary objectives will further permit to solve other, more large objectives :

- improvement of the quality and efficiency of the research development activities in the faculty,
- consolidation of the partnership “Carol Davila” University – Industry – Governmental institutions established in previous projects,
- identification of innovation perspectives and their application in increasing the competitiveness of Romanian drug producers,
- implementation of Good Laboratory Practice (GLP) and Good Clinical Practice in development, production and therapeutic utilization of drugs in the such as to can assimilate Central Laboratory as a

- reference laboratory, able to undertake studies and perform different tests as part of research development and/or evaluation of drugs produced by industrial partners,

- improvement of the quality of education for master and doctorate cycles for people coming from industry following the possibility to use modern techniques and equipment in research and evaluation of drugs.

- The scientific activity will stretch from theoretical estimations *in silico* to effective formulation and evaluation of drugs, including mainly three research fields:

A. Evaluation of biological activity, pharmacokinetics and metabolism of chemical entities:

- *in vitro* using cell cultures, isolated organs or other experimental methods,
- *in vivo* on animals and
- correlation of *in vitro* and *in vivo* experiments.

B. Evaluation of drugs

- *in vitro* evaluation concerning release of active substances from pharmaceutical formulations, their transfer across interfaces and absorption by membranes,

- *in vivo* evaluation, on healthy volunteers, it concerns pharmacokinetics and relative bioavailability,

- *in vitro in vivo* correlation and elaboration of predictive models.

C. Preformulation and pharmaceutical development in order to optimize the biopharmaceutical properties. Evaluation of new formulations using the methods mentioned at A and C. and pharmaceutical development targeting the optimization of biopharmaceutical properties. Testing the new formulation *in vitro* and *in vivo* in the context of the activities mentioned at A and B.

Building will be projected in compliance with Good Practice Rules (Laboratory, Manufacturing, Clinical, Animal etc) such as to permit authorization and certification of laboratories from three departments with 9 sub departments, each one being practically an independent laboratory:

- pharmaceutical availability with sub-departments
 - pre-formulation
 - *in vitro-in vivo* correlation
- experimental pharmacokinetics with sub-departments
 - *in vitro* pharmacokinetics
 - *in vivo* pharmacokinetics
 - physiological pharmacokinetics
- clinical pharmacokinetic and toxicokinetics
 - clinical tests laboratory
 - bioanalytical laboratory
 - bioavailability sub-department
 - biostatistics

CONCLUSIONS:

Crisis and the ageing of Romanian population means that larger volumes of high quality cost-effective medicines impose a pro-generic politics in Romania, similar to all independent countries. (USA,

Canada and Japan as well as India, China and South Korea and, in the last years, almost EU countries also).

First cause for preference of brand face to generic drugs in Romania is the missing of education and information of both health care professionals and patients about therapeutic equivalence between brand and generic medicines. This missing information have to be corrected by an addition of appropriate courses in the university curricula both in pharmacy and medicine faculties.

Politically imposed lower prices for generics could undermine the sustainability of generic production. A correct approach is to support, in this context, in the same time reduction of expenses of government and patients, and increase the income of both generic producers and pharmacists.

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