Some Directions of Pharmaceutical Industry Development in the Republic of Moldova

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Direcţii posibile de dezvoltare a industriei farmaceutice în Republica Moldova

Industria farmaceutică este una dintre ramurile prioritare în economia mondială. Pentru Republica Moldova, ţară cu un potenţial ştiinţific adaptat modest la elaborarea şi la implementarea în practică a medicamentelor, aceasta este o ramură strategică. Cinci direcţii de dezvoltare a industriei farmaceutice sunt prioritare în Republica Moldova şi în alte state, cu un potenţial economico–financiar similar. Elaborarea, producerea şi implementarea în practica terapeutică a medicamentelor originale, care necesită alocaţii financiare impunătoare şi un potenţial ştiinţific înalt–calificat, în prezent depăşeşte posibilităţile ţărilor în curs de dezvoltare. Fabricarea produselor generice constituie 90% din producţia de medicamente autohtone. Noile combinaţii de substanţe active cunoscute prezintă un aspect cost/eficienţă/ inofensivitate actual pentru terapeutica modernă. A patra direcţie de perspectivă în industria farmaceutică este elaborarea unor principii active, cu proprietăţi fizico-chimice modificate, care ar micşora riscul efectelor nedorite (alergizarea) şi, prin urmare, ar ameliora tratamentul. O importanţă indiscutabilă prezintă implementarea în practica medicală a produselor destinate terapiei personificate, cu folosirea realizărilor moderne din domeniul farmacogeneticii.

Cuvinte–cheie: medicament original, medicament generic, medicament combinat.

Возможные направления развития фармацевтической промышлености в Республике Молдова

Фармацевтическая промышленость является одной из приоритетных отраслей в мировой экономике. Для Республики Молдова, при существующей квалификации научного потенциала в области разработки и внедрения лекарственных средств, данная отрасль является стратегически важной. Были выявлены пять возможных направлений развития фармацевтической промышлености в Молдове и в странах с аналогичным финансово-экономическим положением. Производство и внедрение в терапевтическую практику новых оригинальных лекарств, требующих значительных финансовых капиталовложений и высококвалифицированного научного потенциала, является важным направлением. Производство генериков составляет около 90% фармацевтической продукции в Республике Молдова. Новые комбинации активных веществ с их терапетическим потенциалом – это многообещающее направление в развитии лекарственного производства. Весьма перспективной представляется и разработка новых активных препаратов с измененными физико–химическими свойствами, позволяющих уменьшить риск побочных эффектов (аллергизации) и, как следствие, повысить эффективность лечения. Несомненную роль сыграет внедрение в медицинскую практику лекарственных средств, предназначенных для персонифицированной фармакотерапии с использованием достижений в области фармакогенетики.

Ключевые слова: оригинальное лекарство, генерическое лекарство, комбинированное лекарство.

Introduction

A drug is defined as a chemical substance or psychogenic factor which after being introduced into the human or animal body in an adequate dose, cures and/or ameliorates particular symptoms of an illness or medical condition, or which may be used as preventive medicine which does not treat existing or pre-existing diseases or symptoms, or which can be used for diagnosis of a disease, or used to otherwise enhance physical or mental well-being. The drug should be licensed for production and authorized for medical use and placed on the pharmaceutical market in several countries which are members of WHO [1].

Some governments define the term drug by law. In the United States the definition of "drug" in the Federal Food, Drug, and Cosmetic Act includes "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals" and "articles (other than food) intended to affect the structure or any function of the body of man or other animals." Consistent with that definition, the U.S. separately defines narcotic drugs and controlled substances, which may include non-drugs, and explicitly excludes tobacco, caffeine and alcoholic beverages.

A medicinal product is defined in amended Directive 2001/83/EC as:

'… any substance or combination of substances presented as having properties for treating or preventing disease in human beings… [or] any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis'[2].

"Drug" is thought to have originated from Old French "drogue", possibly deriving later into "droge-vate" from Middle Dutch meaning "dry barrels", referring to medicinal plants preserved in them.

Three major demographic trends in the developed world-aging population, increased life expectancy, and increased incidence of chronic diseases-make for ideal conditions for increased used of medicines (Table 1).

The increased used of medicines will have important consequences for consumers. First, morbidity and mortality will be reduced. According to a study by the London-based

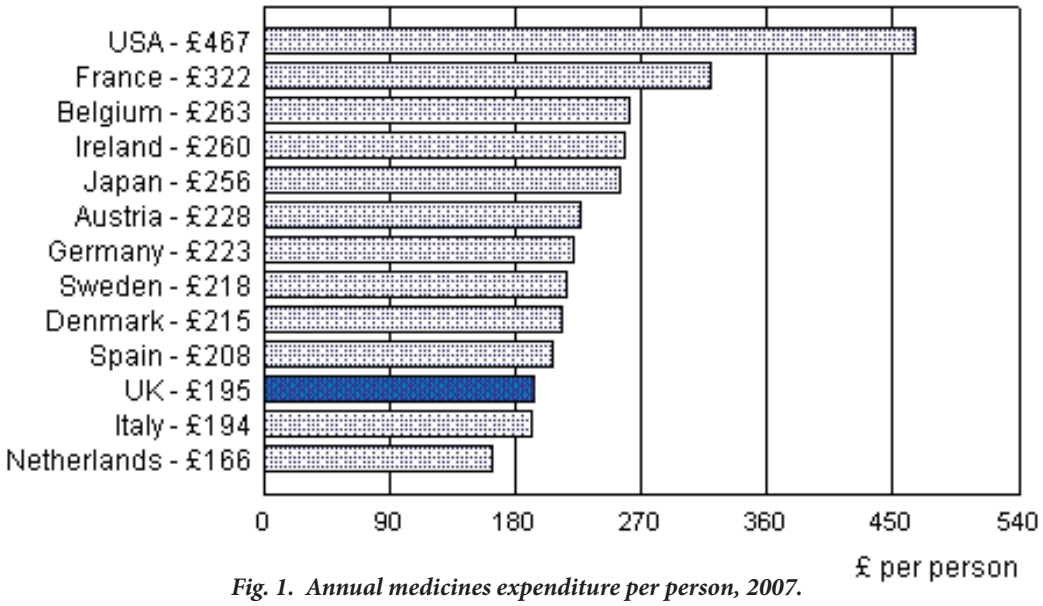

Fig. 1. Annual medicines expenditure per person, 2007.

Notes: £ per person, Includes prescription and hospital medicines**; Source:** IMS (Intercontinental Marketing Services) World Review, United Nations, World Population Prospects, Office for National Statistics

Office of Health Economics, pharmaceuticals will account for 10 to 40 percent of future reductions in heart disease mortality, 15 to 40 percent in cerebro-vascular disease, 28 to 65 percent in breast cancer, and 3 to 26 percent in lung cancer. Second, medical costs will be reduced. According to estimates by the National Bureau of Economic Research, based in Cambrige, MA, USA, replacing older medicines with newer ones increases drug spending by an average of $18 but reduces other health-care costs by $129, resulting in a net saving of $111 per person. Finally, greater use of medicines will create an increased quality of life for consumers (Fig. 1).

Table 1

World trade in pharmaceuticals, 2007, billion £

Country	Exports £	Imports £	Balance £
Switzerland	20,206	9,336	10,870
Ireland	9,664	1,520	8,144
Germany	24,395	18,810	5,586
UK	14,567	10,291	4,276
France	13,675	10,135	3,540
Sweden	4,726	1,731	2,995
Netherlands	7,439	7,276	0,163
Italy	7,607	8,466	-859
Spain	4,142	5,227	-1,085
Japan	1,736	4,625	-2,889
USA	17,491	35,801	-18,310

Source: EFPIA – European Federation of Pharmaceutical Industries and Associations, JPMA – Japan Pharmaceutical Manufacturers Associations, US Census Bureau,UK Customs and Excise

Industry studies claim that newer medicines contribute to reduced hospitalizations and surgery, fewer adverse effects from medication, decreased complications of disease, and increased worker productivity [3].

In a global industry such as pharmaceuticals, it is important to be among the top group of the world's pharmaceutical producers (Table 2).

Table 2

Top world pharmaceutical corporations, 2007

Company	Country	Sales billion £	Growth* %	Market share** %
Pfizer	USA	22,292	-2	6.7
GlaxoSmithKline	UK	18,847	1	5.6
Novartis	SWI	17,154	9	5.1
Sanofi Aventis	FRA	16,788	8	5.0
Astrazeneca	UK	15,010	9	4.5
Johnson & Johnson	USA	14,478	5	4.3
Roche	SWI	13,814	18	4.1
Merck & Co	USA	13,631	8	4.1
Abbott	USA	9,570	8	2.9
Lilly	USA	8,335	13	2.5
Leading 10		149,920	6	44.9
Amgen	USA	8,188	1	2.5
Wyeth	USA	7,949	8	2.4
Bayer	GER	7,020	13	2.1
Bristol-Myers Squibb	USA	6,519	6	2.0
Boehringer Ingelheim	GER	6,277	11	1.9
Schering-Plough	USA	6,181	10	1.9
Takeda	JAP	5,479	9	1.6
Teva	ISR	5,300	12	1.6
Novo Nordisk	DEN	3,336	18	1.0
Daiichi Sankyo	JAP	2,925	7	0.9
Leading 20		209,093	7	62,6

Notes: By worldwide sales value, *calculated in US$, ** IMS (Intercontinental Marketing Services) audited markets;
Source: IMS (Intercontinental Marketing Services)

An analysis of the world's top 100 medicines reveals that, after the USA, Britain's pharmaceutical companies' market share is more than all its European competitors combined (Fig. 2) [3].

There are five development pathways in the pharmaceutical industry.

I. The synthetic or classical development pathway of drug development

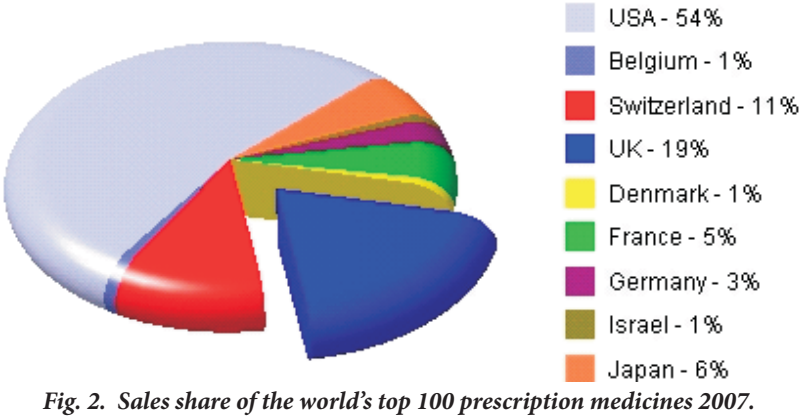

Fig. 2. Sales share of the world's top 100 prescription medicines 2007.

Source: IMS (Intercontinental Marketing Services)

The classic paradigm of synthetic drug development consists of four steps: drug discovery and design, preclinical and clinical studies. This paradigm results in a drug-development process that is high risk, time-consuming, and expensive. The process requires screening an average of 10,000 active compounds to find a single compound that successfully makes its way through validation to drug approval and the marketplace.

The potential of new molecules in drug development is judged on the basis of the benefit/risk ratio. Preclinical safety – which includes the classical toxicology disciplines and safety pharmacology, immunotoxicology, drug metabolism and pharmacokinetics –is an important dimension for comparing similar molecules and helps in the selection of molecules with superior chance for a successful development. New in silico or in vitro methods are available or are under development which makes possible a much more rapid assessment of a series of compounds for major liabilities (e.g., genotoxicity, major organ toxicities, teratogenicity, immune system perturbations, drug-drug interaction potential). Early safety evaluation takes advantage of these new tools to build a testing strategy which begins with target assessment and extends to lead compound optimization and the selection of clinical candidates. Starting with in silico techniques (verification of databases to detect structural alerts; and also modeling, etc.) and in vitro methods (enzymatic or cellular models, preferably with humanized cell lines) applied methods become more complex (e.g. in vivo imaging) and as result the selection of potential drug candidates in a project narrows. These tests are intended to support science-based decisions and target the nature of the molecule under consideration taking all previous experience with a compound class into account. Today in vitro methods are not ready to replace in vivo testing entirely because results are limited by the uncertainty of extrapolation to a whole organism and the human species. However, they allow to focus in vivo evaluations to the relevant questions, support selection of the most promising clinical products, help in refining study designs and overall allow to reduce the amount of required in vivo animal and human testing.

Pharmaceutical R&D is a highly complex set of processes in which uncertainty and risk persist throughout long cycles of discovery and development. On average the development of safe and effective medicines takes 12 -15 years at a total cost that is now approaching $1 billion per product. Productivity for the industry as a whole, as measured as total cost per approved drug, has declined. Although many internal and external factors contribute to this lowered rate of productivity clearly one approach to address this issue is redesigning the R&D engine to increase the rate of innovation and development of new products at a lower cost to meet medical needs [4,5,6,7].

The highly expensive development process of original drugs makes it unaffordable for pharmaceutical industries of CIS countries, including Republic of Moldova. There will be fewer originators of new therapeutic classes of drugs such as Morton's Ether, Sir Fleming's Penicillin, Domagk's Prontozile, Sertürner's Morphine, Banting and Best's Insulin. It is only with some skepticism that we consider the domestic drugs Izoturone, Pacovirine, Pimistimuline-3, BioR etc. as original products.

II. Generic production

The ongoing need to provide the population of the Republic of Moldova with cost-effective pharmacological therapies has led to an emergent public health initiative in this country for the production of generic versions of therapeutic products. Generics have historically afforded considerable savings to the consumers in need of prescription and OTC medication. A recent report issued by the US Department of Health & Human Services estimates that generic drugs constitute 63% of the total prescription medicines sold in the US. The report also stated that generic drugs cost approximately 11% of the total cost of branded pharmaceuticals (on a per – dose basis) [8]. According to the Congressional Budget Office, generic drugs save consumers an estimated $8 to $10 billion a year at retail pharmacies. Even more billions are saved when hospitals use generics [9].

Therefore, generic drugs can save patients and insurance companies substantial costs. The relatively low price of generics is determined by the fact that:

- Manufacturers do not incur the cost of drug discovery;
- Manufacturers do not have to prove the safety and efficacy of the drugs through clinical trials (although they have to conduct bioequivalence study);
- Manufacturers do not incur marketing efforts, including media advertising, presentations by drug representatives, and distribution of free samples;
- Many generic drugs are already well-known to patients and providers (although under their branded name);
- Competition increases among producers when drugs no longer are protected by patents.

As manufacturers incur fewer costs in producing the generic drug and are therefore able to maintain profitability while

offering the drug at a lower price to consumers. The costs of the majority of generic drugs are quite low and many developing countries can easily afford their manufacturing. For example, the Republic of Moldova manufactures a number of generic products, amoxicilline, azitromicin, captopril, carbamazepin, ceftazidime, clotrimazole, diclofenac, metoprolole, lisinopril, indapamid, ranitidin, spironolacton, tramadol, etc.

The pharmaceutical drug production process is easily replicated and a generic drug product is virtually identical to the original. According to the legislation of many countries, generic drugs are identical or bioequivalent to the brand name counterparts in their pharmacokinetic and pharmacodynamic properties. By extension, therefore, generics are identical in their indented use, dose and strength, route of administration, safety, and efficacy. The drug's sponsor must show that a generic drug delivers the same amount of its active ingredient in the same amount of time as the trade-name counterpart. This bioequivalence is critical for proving that both the original and generic drugs will produce similar therapeutic results [9].

In most cases, generic products are available once the patent protections afforded to the original developer have expired. When generic products become available the market competition often leads to substantially lower prices for both the original brand name product and the generic forms. The time it takes a generic drug to appear on the market varies. In the US, drug patents give twenty years of protection, but they are applied for before clinical trials begin, so the effective life of a drug patent tends to be between seven and twelve years. The expiration of a patent removes the monopoly of the patent holder on drug sales licensing. Actually, there is no way to renew a patent after it expires. A new version of the drug with significant changes to the compound could be patented but this requires new clinical trials. In addition, a patent on a changed compound does not prevent sales of the generic versions of the original drug unless regulators take the original drug off the market. This allows the company to recoup the cost of developing that particular drug. After the patent on a drug expires it can be manufactured and sold by any pharmaceutical company. Since the drug has already been tested and approved the cost of simply manufacturing the drug will be a fraction of the original cost of developing that particular drug.

Generally, the people of the Republic of Moldova have more confidence in imported brands which are more expensive than locally produced pharmaceuticals, but with the growing economic uncertainties and budgetary constraints more consumers are expected to turn to local brands.

Meanwhile, increasingly health-conscious Moldavians are contributing to the growth of herbal and traditional medicines, a desire that is undeterred by the current economic environment. This trend is attributed to consumers' preference for self-administered healthcare, the prevalence of chronic illnesses that cannot be cured by conventional drugs, and the high pace of life which induces higher levels of stress. Consumers are increasingly turning from synthetic allopathic drugs (conventional drugs) to herbal products to maintain health and prevent illnesses. The rich biological heritage of Republic of Moldova presents a potential for the local pharmaceutical industry to lead in the herbal market. Many local players have already ventured into this arena, especially with the encouragement from the Government through various grants and incentives for R&D in the use of herbal products. Some of these are: Amniocen, Coriocen, Todicamp, Pimistimulin–3, Pacovirin, BioR, Fibrofit, Imupurin, Medicas E, Enoxil, etc.

III. New combinations

The concomitant use of medicinal products may trigger the development of a fixed combination product which manufacturers believe will be more convenient for the consumers and ultimately improve compliance. Four main scenarios can be identified: the combination of well-known compounds already approved/used in combination; the combination of approved/well known compounds not previously approved in combination; the combination of one or more new chemical entity(ies) [NCE] with one or more well known compound(s); and the combination of two or more NCEs.

Almost half of marketed drugs are fixed combination preparations. Advantages of fixed combination preparations include: increased compliance, synergy, increased efficacy, reduced side-effects and lowered cost. Potential disadvantages include an inflexible fixed dose ratio and the possibility of incompatible pharmacokinetics and increased toxicity. Moreover, the physician or pharmacist – or both – may be ignorant of the totality of the medicine's contents. Some combinations of undisputed value are oral contraceptives, levodopa with decarboxylase inhibitors, pyrimethamine with sulphadoxine, etc. In other cases fixed-dose combinations may have value in strictly specified circumstances, but probably in some cases are over-prescribed. There is also widespread, unjustified use of combinations in over-the-counter preparations which may have unforeseen adverse effects. Combinations should only be used if each component is necessary for the desired effect and if the advantages outweigh the added risks of using 2 or more drugs. Before prescribing combination drugs, clinicians should always ask themselves a series of questions, of which the most important is whether the patient needs each drug in a particular combination, or if 1 component alone would suffice. In general, government regulatory bodies in developed countries are attempting to curb the use of combination drugs, but a better approach might be to better educate doctors on both the advantages and disadvantages of fixed combination preparations which would lead to improved methods of prescribing these drugs.

Neamon–hepa, taken in capsule form, is a pharmaceutical combination now being studied at The Scientific Center of Medicines of the Republic of Moldova. The drug is used in hyperammonemic conditions (the high concentration of ammoniac in the blood and especially in the brain). It is well–known that the main toxin in severe hepatic dysfunction (active chronic hepatitis, cirrhosis, encephalopathy and hepatic coma) ammoniac is not metabolized into urea due to albuminous failure. Neamon–hepa is prescribed in general conditions of physical and mental weariness associated with an albuminous failure, in specific asthenic conditions during convalescence. Capsulated Neamon–hepa is a pharmaceutical combination containing Spironolactone, Arginine aspartate and BioR. Spironolactone is a well-known K+ saving diuretic; Arginine aspartate a tonic substance used in hyperammonemic conditions, mental and physical asthenia; and also in certain memory disturbances; and BioR a spiruline micro-algae extract (extremely rich in vitamins, minerals and enzymes). The new pharmaceutical composition is intended to provide a combination of active substances which is super-additive and synergistic. Nevertheless, no additional side-effects are experi-

enced. The therapeutic effect of the combination corresponds approximately to the maximum achievable improvement. The principal advantage of the combination is the improved adherence to treatment due to the simplification of the regimen. This, in turn, should result in higher levels of efficacy. The main disadvantage is the inflexibility of the dosage.

The issues to consider when initiating a new regimen are potency, tolerability, convenience, coburdens, long-term toxicities, and future therapeutic options. Each participant (patient, physician and pharmacist) should be involved in determining the balance of these questions. Actually, these are the questions that play a large role in determining how patients accept new therapies that is the patient's ability to tolerate the drug and its overall convenience while physicians must consider potency, long-term toxicities, and future treatment options.

Also on the horizon is the issue of patients' co-payments for fixed-dose combinations. Obviously it is simpler for patients with third-party payers to make one co-payment for 3 drugs than separate co-payments for each. Finally, it is more convenient and economical for the provider to explain one instruction to the patient than several – one aspect of the growing issue of cost-effectiveness doctors must face in consulting with their many patients.

IV. Reducing the incidence of adverse reactions by modifying the drug's physical and chemical properties (e.g. allergenic properties of xenobiotics).

Many new drugs are expected to be developed in the coming years. Advances in technology and the knowledge of how cells and xenobiotics inter-react will allow pharmaceutical manufacturers to become more efficient in the R&D process. New technology allows life scientists to test drug candidates far more rapidly than in the past. Based on empirical observations, a correlation has been established and an index proposed to relate the physical properties of medicinal substances and their allergenic potentialities. This index, based on the physical properties of the substance (melting point, solubility, molecular weight, dose, etc.) has been verified on a series of commonly known drugs.

The allergenic index (indicating the probability of allergic reactions) directly correlates the molecular weight, dose and melting point of the substance, and indirectly with its solubility in water and/or lipids.

The formula of allergenic index is:

$I = (0{,}001M + 0{,}5d + 0{,}01T) / 0{,}1S$

where: I – allergenic index,

M – molecular weight of the substance,

d – dose in grams,

T – melting point in degrees Celsius, and

S – solubility in water or lipids g/100 ml.

The parameter I may have a wide range of variations, in which values lower than 1,0 indicate low allergenic character while values higher than 1,0 indicate the opposite.

Substances were selected in order to establish values for M, d, T, and S included at certain intervals and they were then separated into two groups, each of about 300 active substances. The average index I and the percentage showing the allergenic properties are presented in Table 3.

The allergenic index calculated from the proposed formula gives 0,44 for the first group and 3,24 for the second.

Table 3

Allergenic index of drugs with the melting point up to 100^{0}C compared to those with melting point higher than 200^{0}C

M	d	T	S	I	% with allergenic properties
106 ± 16,9	0,35 ± 0,078	48,8 ± 3,92	19,7 ± 3,92	0,44	3
352 ± 40,1	0,42 ± 0,01	245 ± 5,4	9,3 ± 2,44	3,24	70

Table 4

Allergenic index for nicotinic acid and its derivatives

Substance	M	d	T	S	I	Allergenic
Nicotinic acid	123	0,1	236-238	70	19,6	Strong
Nicotinamid	122	0,1	130-132	10	1,5	Weak
Nicotinic acid dimethylamide	132	0,5	20-25	0,1	0,14	No

The proposed formula allows a pharmaceutical manufacturer to estimate the potential of the drug/substance to develop allergenic properties.

Another example was chosen for nicotinic acid and two of its derivatives (Table 4).

We can see that the higher the value of I the higher are the allergenic properties of the drug. The allergenic index correlates well with the allergenic effects of different compounds; therefore, if the index is higher than 1,0 the xenobiotics have a potential to produce allergic reactions[12].

The characteristics of substances with a high allergenic index show that they tend to have high molecular weight, a high melting point and low solubility. These factors indicate the strong possibility that these compounds will be found in the body as solid particles, possibly as molecule associations or microcrystals, not as molecular solutions. As a result the antigen processing and presenting cells (such as macrophages or dendritic cells) will react more actively and increase the immune response of the body. Certainly, the chemical composition of xenobiotics is essential in manifesting allergenic potential. The solubility, melting point, and aggregation state of xenobiotics greatly influence the "recipient's" reaction. Substances with melting points higher than 2000C have enhanced allergenic properties compared to those substances with melting points lower than 1000C. Drugs with high allergenic potential are approximately 180 times less soluble in water than substances which do not manifest allergenic properties. Liposoluble substances behave similarly. Macromolecular compounds (proteins, mucopolysaccharides), large molecules presenting associations of molecules which are not ionized in organisms, also manifest a higher allergenic potential. Pharmacodinamic properties of drugs are influenced by the aggregation state of the substance. Crystalline substances are more allergenic; amorphous powders, liquids and gases, especially, are not. The stronger the intermolecular power the higher the possibility of allergic reactions. The formula shows that the allergenic index is dose - dependent – a larger amount of substance may act as a stronger allergen [13].

V. Personalized healthcare possible through the achievements of modern pharmacogenetics

The rapidly growing understanding of the molecular bases of disease pathology, aided by progress in genomics and

genetics, provides medical sciences with numerous new insights into the differences among patients and a more informative and accurate taxonomy of the states of a disease. Large population differences with small individual differences are consistent with the role of heredity as a determinant to a patient's response to a given drug. It is estimated that genetics can account for 20 to 95 percent of the variability of the drug's disposition and effects [14, 15]. Medical professionals are able to develop appropriate tests and drugs for specific diseases and disease subgroups to create medicines that are more effective and safe. This is "personalized healthcare" or "personalized medicine". With the knowledge of the individual characteristics of patients and their diseases, personalized healthcare professionals are able to target medicines more precisely. This personalized medicine can help professionals avoid prescribing patients medicines from which they are unlikely to benefit, and from exposure to the side-effects of a particular treatment. In some cases it will also be possible to identify patients who have a higher likelihood suffering side-effects who can then be treated with less risky therapies. In 2004, Pirmohamed et al. published an analysis of the impact of adverse drug reactions (ADRs) on two large Merseyside NHS (National Health Service) hospitals over six months. They found that 6,5 % of over 18.000 admissions were due to ADRs, and projected that the annual cost to the NHS was around £ 466 m. Most of these events were thought avoidable with the main culprits being low-dose aspirin, warfarin, other non–steroidal anti–inflammatory drugs and diuretics [16].

This approach to healthcare promises many benefits:

• Patients and physicians will benefit by being able to make safer, more effective and more rational therapy choices. (Example: drugs such as 6-thioguanine are widely used in oncology, dermatology and other specific fields of medicine. These have a number of potentially serious side effects, including fatal myelosuppresion. Metabolism of these drugs is performed primarily by the enzyme thiopurine S-methyltransferaze (TPMT), although others are involved, including methylenetetrahydrofolate reductase. A number of common polymorphisms in the TPMT gene determine the level of enzyme activity. Individuals with low or intermediate activity are at risk of drug toxicity unless the drug dose is reduced, usually to about 10 per cent of standard doses) [17]. The reduction of uncertainty related to the potential danger of adverse side-effects will likely improve patient compliance and the patient-physician relationship, and shorten the duration of the therapy.

• Healthcare systems will benefit by reducing the burden of administering therapies to patients who have little or no chance of deriving benefit and by reducing the impact of avoidable adverse drug reactions. Pre-treatment genetic tests have been carried out in the U.S. for approximately 10 years, and there is evidence to suggest that it is cost-effective in certain health care settings. One of the difficulties of transferring testing to other countries is that there are around 13 known alleles associated with reduced TMPT activity, first identified in predominantly Caucasian patients. However, these variants have different frequencies in different population groups as well as variations in functional effects between heterozygous and homozygous individuals, suggesting that other genetic or environmental factors have a role in determining the response to particular drugs [17]. Whether or not this will lead to net cost savings by healthcare systems is difficult to say as they will have to incur the cost of testing in order to reap these benefits – but personalized medicine does represent a more rational and cost-effective approach to healthcare.

The discovery and development of new drugs is expensive and risky. Most fail in early clinical trials, with a common failure rate of around 97-99 %. Pharmacogenetics could help in reducing high failure rates and development costs by identifying potential responders and non-responders to a drug at an early stage by using genetic variants that are markers of drug efficacy [17].

There is a direct relationship between gene discovery and identification of new drugs — the more genes identified the more paths available for drug discovery. Data obtained from the mapping of the human genome can be compared with known gene sequences to identify the proteins produced by each gene and the effect of those proteins on the body. The study of these gene sequences and the varieties of proteins they produce contributes to the development of new medicines, both biotechnological and chemical. Among other uses, new genetic technology is being explored to develop vaccines to prevent or treat diseases such as AIDS, malaria, tuberculosis, etc., the cures of which have eluded traditional vaccines.

In order to draw health professionals and patients attention to the importance of pharmacogenetics issue, we have proposed to complement patient information leaflet with a facultative component: elements of personalized pharmacotherapy.

The pharmaceutical industry of Republic of Moldova is far from being the leading manufacturing sector either in this country or in the global pharmaceutical industry. For Moldovian pharmaceutical companies to become significant manufacturers requires many steps in development, flexibility, and the willingness to undertake risks, all necessary if it is to build a strong, growing and globally successful pharmaceutical industry.

References

1. Parii B. Medicamentul şi antimedicamentul. Curierul medical. 2008, Nr 5 (305), pp. 51 - 57
2. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. Official Journal, 28 November 2001, no. L 311, pp. 67 – 128.
3. Facts and statistics from the pharmaceutical industry. http://www.abpi.org.uk/statistics/section
4. Adams, Christopher P., and Van V. Brantner, "Estimating the Cost of New Drug Development: Is It Really $802 Million?" *Health Affairs,* vol. 25, no. 2 (March/April 2006), pp. 420 - 428.
5. DiMasi, Joseph A., Ronald W. Hansen, and Henry G. Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics,* vol. 22, no. 2 (March 2003), pp. 151 - 185.
6. Rowberg, Richard E., *Pharmaceutical Research and Development: A Description and Analysis of the Process,* CRS Report for Congress RL30913 (Congressional Research Service, April 2, 2001).

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