TRENDS IN THE EVOLUTION OF THE ANNUAL CLASSIFIED LIST OF MEDICINES BETWEEN 1989-2012

ADRIANA-ELENA TĂEREL, VALENTINA SOROCEANU*, CRISTINA RAIS

Carol Davila University of Medicine and Pharmacy, Faculty of Pharmacy, 6th Traian Vuia Str., Bucharest 2, 02095
**corresponding author: valentina_soroceanu@yahoo.com*

Abstract

In this research we aimed to highlight trends in the development of medicinal products for human use in the transition and adaptation period of the Romanian health system to a market economy. The period analysed in the present study is 1989-2012.

Data on drugs in these lists (number of positions in the Annual classified list of Medicines, number of International Nonproprietary Names -INN, number of medicines having Marketing Authorization Holder in Romania or in foreign countries, number of prescription and over-the-counter medicines - OTC) were processed using the regression equation, the determination coefficient and Helmert-Pearson/chi-squared test.

Results indicated a continous increasing of the number of positions, occupied by medicines in the lists and confirmed that generic formulations, having foreign Marketing Authorization Holders, exceed the ones having Marketing Authorization Holders located in Romania. Also, this research showed that prescription medicines proved to be more numerous than OTC medicines.

Rezumat

În această lucrare am urmărit evidențierea unor tendințe în evoluția nomenclatorului medicamentelor de uz uman în perioada de tranziție și adaptare a sistemului sanitar românesc la economia de piață. Perioada luată în studiu este 1989-2012.

Date privind medicamentele înscrise în aceste liste (număr poziții în Nomenclator, număr DCI-uri, număr medicamente având Deținător al Autorizațiilor de Punere pe Piață situat în România sau în alte țări, număr medicamente eliberate pe bază de prescripții medicale și OTC) au fost prelucrate folosind următoarele metode statistice: ecuația de regresie, coeficientul de dependență și testul Helmert-Pearson.

Rezultatele obținute au indicat o creștere continuă a numărului de poziții ale produselor din nomenclator și a formulărilor generice având deținători de autorizații de punere pe piață în alte țări. De asemenea, cercetarea întreprinsă a arătat că medicamentele care se eliberează pe bază de prescripție medicală s-au dovedit a fi mai numeroase decât OTC-urile.

Keywords: drug, regression equation, determination coefficient, Helmert-Pearson/chi-squared test

Introduction

Two of the objectives of health policies around the world are to assure availability and accessibility for patients to treatments and medicines [6]. Also, the aim of any rules governing the production, distribution and

use of medicinal products must be to safeguard public health. The means used to attain this objective should not hinder the development of the pharmaceutical industry or trade in medicinal products [7-9].

Nowadays, the Annual classified list contains medical products for human use, authorized for marketing by the National Agency of Medicines and Medical Devices, which is the national regulator of medicinal products and by the European Medicines Agency [10].

This database includes human drugs which are authorized for use on the national territory.

Information available comprises the following parameters: brand name, international nonproprietary name (INN), pharmaceutical form, therapeutic classification (ATC code), number and date of release of the marketing authorization, classification for release (prescription or OTC), name, address and country of the marketing authorization holder, name, address and country of the manufacturer, type and number of packages.

This study aims to analyze the evolution of the Annual classified list of medicines between 1989 and 2012.

Materials and Methods

The materials used in this study were lists and databases of annual classified drugs between 1989 and 2012 [7,10].

The medicines were examined quantitatively by the following criteria: number of positions in the list, International Nonproprietary Name (INN), country of origin for the marketing authorization holders and the general drug classification (prescription medicines- noted in this paper with Rx, prescription medicines requiring special conditions as a hospital environment- noted with S and OTC medicine) [9].

Data were analyzed using three **methods: the regression equation** (in Excel program), **the determination of R squared** (R^2) coefficient and **the Helmert-Pearson/Chi-squared distribution test** (chi-squared coefficient - χ^2).

Regression equation is a statistical technique used to explain or predict the behavior of one variable (the dependent variable) using the value of another variable (the independent variable). Linear regression attempts to model the relationship between two variables by fitting a linear equation to observed data [1,5].

Between the two variables there must be a significant association. The strength of the relationship between the variables can be determined using a scatterplot [2]. The coefficient of determination describes the percent of the data that is closest to the line of best fit. R squared (takes values between -1

and +1) is a statistical measure of how well a regression line approximates real data points.

The Helmert-Pearson/chi-squared distribution test is used to investigate the agreement between observation and hypothesis. It compares frequencies observed at data that fall into a number of classes with the ones that are expected (from that data, upon some hypothesis) [3,4].

Results and Discussion

The collected data is presented in table I. As it can be seen, the number of positions in the database have varied between 1093 (in 1989) and 34438 (in 2012).

Table I

Number of positions in each year compared to the number of positions in 2012

Year	Number of positions per year	No. positions each year reported to no. positions in 2012
1989	1093	0.03
1991	1202	0.03
2003	7680	0.22
2004	8872	0.26
2005	8836	0.26
2007	12471	0.36
2008	17572	0.51
2009	23896	0.69
2012	34438	1.00

It can be seen that in 2003 the number of medicines increased over six times comparing with 1989 and 1991 years. This boost of the number of positions in the national drug database is due to new additional medical utility discovered for the same active ingredient, the multiplied number of presentation forms, and the numerous companies that import and distribute medicines.

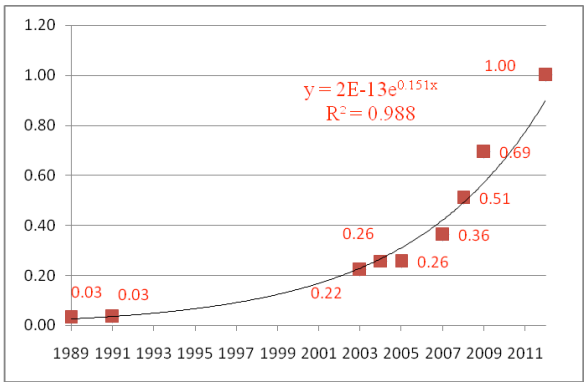

Figure 1

The increase in the number of positions in the National list from 1989 to 2012

The regression equation is $y=2E\text{-}13e^{0.151x}$ and indicates **an exponential growth** of the number of medicines, from 1989 to 2012. The value of determination coefficient R^2 (0.98) indicates a good dependence between the two variables (year and the number positions per year in the medicines list reported to number positions in 2012). A change of the year (x variable) explains 98% of the related variable (variance of y – the report of the positions).

Further on we have examined the number of INN in the total number of medicines registered between 2003 and 2012. The number of positions has increased from 7680 (2003) to 34438 (2012), while the number of INN varies from 1024 (2003) to 1331 (2012) with a slight increase in 2008 (2377).

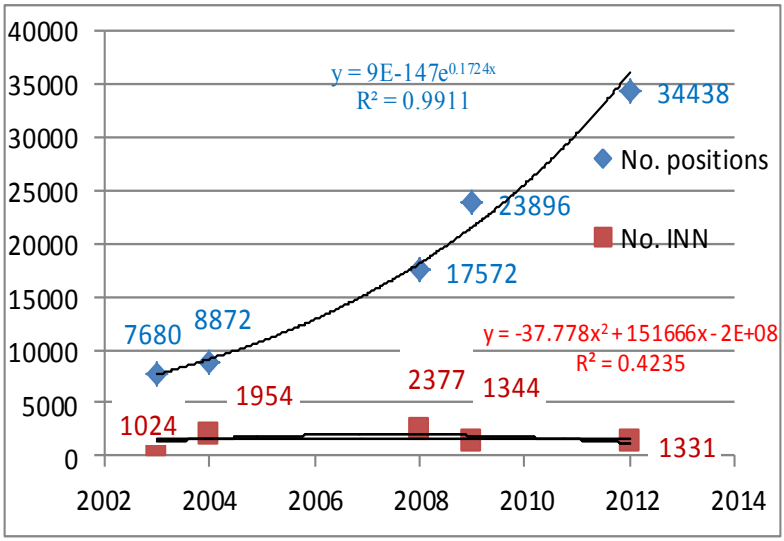

Figure 2
Trends of the no. of INN compared with the no. of positions in the Annual classified list

The regresion ecuation of polynomial form suggests that no major changes were made in the number drugs by international common name. The model has a low predictibility rate (R^2=0.42). Meanwhile only 0.01% of the total variation in number positions (y) remains unexplained.

Nevertheless, we can see an exponential increase in the number of positions compared to the stationary (little over 1000, with the exception of year 2008, when it was over 2000) number of INN. This suggests **an extending of generic formulations in relation to inovative medicines**.

Regarding the country of origin for the marketing authorisation holders (MAH), we collected the data concerning the foreing MAH and the ones that are situated in Romania, in the above specified period of time (tabel II).

Table II

Number of positions for medicines having the MAH situated in Romania or abroad

	1989	1991	2003	2004	2005	2008	2012
Foreign MAH	226	386	5711	6758	6395	15060	31030
MAH situated in Romania	867	816	1969	2112	2106	2512	3408

As it can be seen from this table, in the 90's the indigenous medicines production was higher (867) than the import (226), but over the years this raport has changed (31030 imported and only 3408 from Romania). With the multiplication of generic drugs, **the number of foreign medicines has also increasead significantly**.

In order to test this hypothesis we applied the logaritm function on the data. This way a trendline which indicates an exponential growth, becomes a straight line.

Table III

Logarithmic values of the data

	1989	1991	2003	2004	2005	2008	2012
Foreign MAH	5	6	9	9	9	10	10
MAH situated in Romania	7	7	8	8	8	8	8

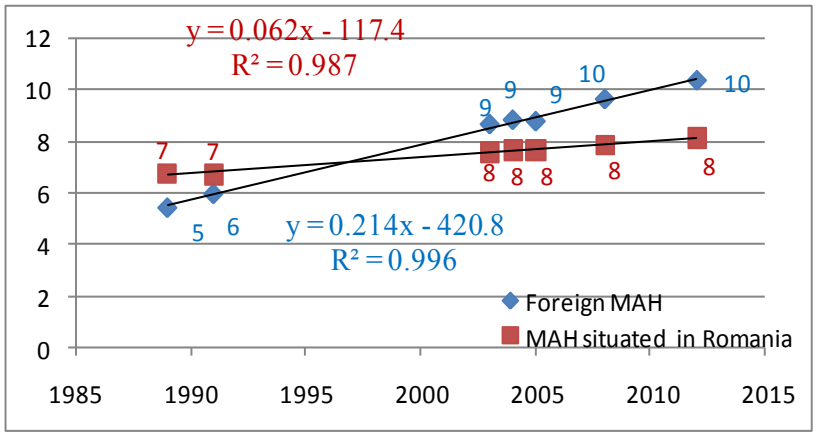

Figure 3

Log-value for medicines having MAH in Romania and/or abroad

As it can be seen from the scatter plot, the number of positions has increased significantly for both types of medicines (having MAH in Romania or elsewhere), with a probability of 99%.

Next, we used the Helmert-Pearson/chi-squared distribution in examining the following two hypothesis:

H_0: *There isn't a significant difference between the number of medicines having foreign and/or Romanian MAHs in 2003, 2004 and 2005*

H_A: *There is a significant difference between the number of medicines having foreig and/or Romanian MAHs in 2003, 2004 and 2005*

Data processing is shown in table IV. The symbols have the following significance: n_i – partial sums on every row; k_i-positions in 2004; l_i-positions in 2005;

n_i-k_i-l_i – positions in 2003; E_i-expected values; O_i –observed values.

Table IV

Applying Helmert-Pearson test

	Observed values (O_i)				Expected values (E_i)				$\chi^2_{(R-1)(C-1)} = \sum_{i=1}^{n} \frac{(O_i - E_i)^2}{E_i} = \chi^2_2 = 7,4$			
	$E_{i1} = \frac{(n_1 + n_2) - (k_1 + k_2) - (l_1 + l_2)}{n_1 + n_2} n_i;$ $E_{i2} = \frac{k_1 + k_2}{n_1 + n_2} n_i; E_{i3} = \frac{l_1 + l_2}{n_1 + n_2} n_i$								R-number of rows; C-number of columns			
	2003	**2004**	**2005**	**Total**	**2003**	**2004**	**2005**	**Total**	**2003**	**2004**	**2005**	**Total**
Foreign MAH	5711	6758	6395	**18864**	5783	6679	6401	**18864**	0.9	0.9	0.0	**1.8**
MAH situated in Romania	1969	2112	2106	**6187**	1897	2191	2100	**6187**	2.8	2.8	0.0	**5.6**
Total	**7680**	**8870**	**8501**	**25051**	**7680**	**8870**	**8501**	**25051**	**3.7**	**3.8**	**0.0**	**7.4**

The value calculated (7.4) is lower than the value in the chi-squared table (9.21) at 99% probability. Therefore, the null hypothesis (H_0) is confirmed, so **the number of medicines having foreign and/or Romanian MAHs in 2003, 2004 and 2005 does not differ significantly.**

Comparison of number of positions for medicines upon the releasing procedure revealed the following data.

Table V

Number of positions in the National list of approved drugs, by the release opportunities

Year	Over the counter (OTC)	With prescription (Rx)	Having Special Regimen (S)
2003	1240	4874	1566
2004	1339	6108	1423
2005	1196	6220	1420
2007	1483	7949	3039
2008	1562	14182	1828
2012	1803	29284	3350

The above data indicates a constancy of OTC medicines (around 1000) and an increasing number of prescription and special regimen drugs.

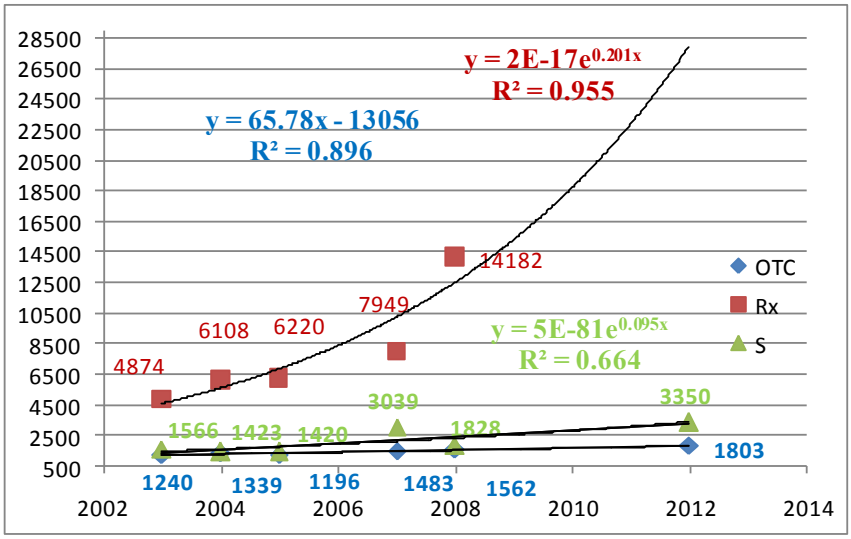

Figure 4

Evolution of number of positions for OTC, Rx and S

In the above chart the three trendlines show a continuous growth of medicines irrespective of the modality of release (over the counter, with a prescription or in special conditions).

The regression equations indicate two cases of exponential growth (for Rx medicines and special regimen medicines) and a linear one (for OTC drugs).

The values of the determination coefficient R^2 (0.955, 0.896 and 0.664 all over 0.5) show that all the regression lines offer a good representation of the data and can explain all the variation.

For the Rx medicines the goodness of fit is very good, so the model can be predicted by the x variable with 95% precision.

The mathematical model for the number of OTC positions (defined by y=65.78x-13056) is also a helpful reproductive model.

The trends of the medicines with a special regimen (S) are predicted with 66% accuracy.

Conclusions

The results obtained from this study indicate a continue increase in the number and type of medicines available for the patients and health professionals. The extendend number of positions in the Annual classified list for medicines indicates the diversity of pharmaceutical forms, types of use, presentation forms (packages).

The almost constant number of International Nonproprietary Names through the years with the increasing number of positions is showing the expansion of generic formulations. For well established active substances there have been discovered new therapeutic indications.

Many drugs came from abroad and the import increased at the expense of national research and production, as the number of foreign MAH exceeds the one in Romania.

Regarding the classification for release, an exponential growth was observed for the prescription medicines compared with the OTC medicines. This can be explained by the frequent changes (number, active substances, classification in lists A,B,C1-C3) in the lists of medicines approved by the Health Ministry for the Social Health Insurance System.

In conclusion, this paper demonstrates that the Annual classified list of medicines registers a sufficient number of drugs in order to assure the availability and accesibility for patients and health professionals as well as products on the European pharmaceutical market.

References

1. Beran T. N., Violato C., - Structural equation modelling in medical research: A primer, *BiomedCentral* 2010, 3:267 (2);
2. Chiang C.L., -Statistical methods of analysis, Danver USA, 2003, 329-335, 391;
3. Mircioiu Ctin., Sandulovici R.C., - Statistica aplicată în farmacie şi studii clinice, ed.aII-a, Ed. Universitară "Carol Davila", Bucureşti 2009, p.25, 217-222
4. Prasacu I., Miron D.S., Mircioiu Ctin. - Seminar de matematici aplicate în farmacie, ed. a II-a, Ed. Univ. "Carol Davila", Bucureşti 2010, 15-16
5. Rais C., Enăchescu D., Carată A., - Functional and structural modeling of the pharmacist's professional development process in Bucharest Faculty of Pharmacy. *Farmacia* 2011, 59 (4), 590-602;
6. Tăerel A.E., Ştiolică A.T., - Study on the range of drugs authorized in Romania- A determinant element for accessibility and availability of drugs, *Farmacia* 2009, 57 (2), 254-259;

7. Tăerel A.T. – Resursele sistemului farmaceutic-componente ale sistemului farmaceutic, Ed. Tehnoplast, Bucureşti, 2009, 243
8. xxx -Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 - Community code relating to medicinal products for human use (consolided version: 05/10/2009), OJ L 311, 28.11.2001, 67,129, 9-20;
9. xxx – Nomenclatorul de medicamente anii 1989 – 2012, www.anmdm.ro http://193.169.156.200/app/nom1/anm_list.asp.

Manuscript received: October 10th 2012