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ANALYSIS OF THE CHANGES IN PRICING REGULATION ON LEADING ANALGESICS MEDICINES PRICES AND UTILIZATION IN BULGARIA

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ABSTRACT

In 2004, the new pricing regulation was enforced in Bulgaria. It liberates the OTC medicines pricing procedure from reference pricing to registration according to marketing authorization holder proposal. The goal is to analyse the changes in the pricing regulations concerning OTC and its impact on prices and utilization of analgesic medicines. Two main hypotheses are tested in the study. H1: The changes in the price regulation liberate the market in terms of increase in the analgesics utilization; H2: The changes in the regulation lead to the decrease in prices. Regulatory and market analysis were performed focusing on procedures for price settlement and their changes for 4 international non-proprietary names (INNs) of analgesics on the local market – methamizole sodium, paracetamol, ibuprofen, acetylsalicylic acid for the period before and after the changes in the regulation. The descriptive statistic, z-test for proportions, and one way ANOVA analysis were performed to evaluate the statistical significance of the changes in utilization and prices. An increase in the analgesics utilization has been observed in 2006 compared to 2003. Increase in utilization was found to be statistically significant for all INN and thus confirms our first hypothesis. After the changes in the regulatory control we observe the increase in the mean official and market prices of methamizol and paracetamol in 2006 and decrease in 2009. The prices of ibuprofen decrease in 2006, but in 2009 the officially registered price increased while the market one remains lowest. For acetylsalicylic acid the mean prices decreased slowly in 2003 and then increased in 2009. All changes in the prices were not statistically significant even when we compare the prices in 2009 with the ones in 2003. Thus our second hypothesis is not confirmed. The liberalization of the price control led to increase in utilization but also to increase in prices.

INTRODUCTION: Over-the-counter (OTC) medicines are dispensed without prescription directly to consumers. They are intended to treat self-limiting conditions easily recognized and manageable by the general public. The non-prescription status of OTC medicines is determined by medicines regulatory

agencies. OTC medicines usually contain active ingredients, which are well known, long term established on the market, and safe in recommended dosages¹. The therapeutic group of non-prescription analgesics comprises of 4 active ingredients and some of them have been known for more than 150 years.

Those are acetylsalicylic acid (on the market since 1889 under the brand name Aspirin), paracetamol (introduced in clinical practice in 1886 as Antifibrin), methamizol (on the market since 1922), and ibuprofen (discovered in 1960 and introduced on the market in 1969)^{2, 3, 4, 5}. All of them are used as analgesics, antipyretics and anti-inflammatory agents. Acetylsalicylic acid in triple smaller dosages possesses also anti platelet effect.

In most of the countries, the prices of OTC medicines are not regulated by the governmental authorities because they are not reimbursed by the health insurance systems and the cost of treatment of minor ailments is lower than that for chronic and debilitating conditions^{6, 7}. In contrast there are many other countries where the OTC prices are or were under regulatory control for ensuring peoples affordability⁸. In Europe the opinion that the price control of OTC medicines is not necessary because it is an obstacle in front the competition prevails⁹. Some countries like Bulgaria liberate the OTC price control but evidences for the effect of this measure are still controversial.

The goal of this study is to analyse the major changes in the pricing regulations concerning OTC medicines and its impact on prices and utilization of leading analgesic medicines.

Two main hypotheses are tested in the study.

H1: The changes in the price regulation liberate the market in terms of increase in the OTC analgesics utilization;

H2: The changes in the regulation lead to a decrease in prices.

MATERIALS AND METHODS: Regulatory and market analysis of prices and utilization changes were performed in years 2003, 2006 and 2009. The regulatory analysis focuses on the procedures for price settlement and their changes before and after the endorsement of the new price regulation. Analysis includes two price regulation regiments that were in force before and after year 2004^{10, 11}. The requirements for price regulation or registration were evaluated as well as the time lines of both procedures.

The OTC analgesics were chosen as an object of observation due to the fact that they belong to a small therapeutic group, well established on the market and all the products possesses the same therapeutic action. All 4 international non-proprietary names (INNs) of analgesics are available on the local market. Methamizole sodium (500 mg dosage form), paracetamol (500 mg dosage form), ibuprofen (200 and 400 mg dosage form), and acetylsalicylic acid (500 mg dosage form) were included in the study. The antiplatelet dosage form of acetylsalicylic acid was excluded from the analysis because it is usually recommended by the physicians. For the same reason we also exclude the products for paediatric practice as solutions, as well as the injection forms. On total 10 dosage forms of ibuprofen, 6 of methamizol, 6 of acetylsalicylic acid, and 6 dosage forms of paracetamol were included in the analysis.

Information on all authorized for sale trade names, dosage forms, and their prices was collected, as well as on their utilization in number of tablets and value on the local market in 2003, before the new regulation come in force, and in years 2006 and 2009. The market share of every INN was calculated as part of the utilization of all INN under consideration. For every dosage form found on the market two price variables were collected – the officially registered ceiling retail price and the one on the market. The prices were recalculated per dosage form (tablet) and per defined daily dose (DDD) that is the average recommended dose, established by the World health organization (WHO)¹².

The descriptive statistic, z-test for proportions, and one way ANOVA analysis were performed to evaluate the statistical significance of the changes in utilization and prices.

RESULTS AND DISCUSSION:

Regulatory Analysis: In 2000, the Ministry council accepted an Ordinance for medicines price regulation¹⁰. According to the ordinance all medicines prices, including OTC medicinal products, were regulated by the pricing committee established at the Ministry of health. The price control focused on producers' prices and mark ups within the distribution channel.

Producers' price was regulated through the external reference price comparison with European countries and the lowest price was approved as a reference price per product. Using the regressive marginal scale, the maximum possible mark ups were endorsed and depending on the producer price, the ceiling retail prices including VAT of 20% were calculated and officially published (**Table 1**).

Near the end of 2004 the new ordinance was endorsed¹¹. The changes affect mainly the OTC medicines prices. With the new ordinance the medicines were divided by prescription status and the previous system for price

regulation remained only for prescription only medicines. The price registration regiment of the OTC medicines was established. Producers have to declare only the ceiling retail price in local currency. This ceiling retail public price was announced by the Ministry of Health in a dedicated public register, and on every 3 months in the private section of the State Gazette. In light of the new ordinance, the pharmacy (retailer) is obliged to sell the OTC product at a price not higher than the approved maximal retail price. Thus the OTC medicines could be found within the pharmacies with different prices – the officially registered, and “market” price (Table 1).

TABLE 1. MAIN CHARACTERISTICS OF THE TWO REGULATIONS

	Ordinance 130 (2000) [10]	Ordinance 257 (2004) [11]
General conditions	Equal price formation and registration rules for all medicines.	Division of two groups POM and OTC with different price control and registration regiments
Price registration regiment	Ceiling retail price registered in the MoH for all medicines (35+14 days by regulation)	Ceiling retail price registered in the MoH for POM and maximal retail price registration for OTC (35+20 days and 20+7 days, respectively)
Producer price establishment	External reference price comparison and lowest price approval (reference countries – all in the Council of Europe)	The same external price comparison for POM, but with focused reference countries – Romania, Russia, Czech republic, Slovakia, Hungary, Poland, Portugal, Spain, Austria. Lack of control on producer and dispensers for OTC medicines.
Distribution channel regulation	Regressive mark-up scale	Regressive mark-up scale for POM. OTC medicines are free of mark up control.
Final price establishment	Ceiling retail price calculation for all medicines with 20% VAT	Registered maximal retail price.
Public information	Approved price is published with all elements (producer price, wholesale and retail margins, VAT) at the Ministry of health website.	MoH created dedicated prices register and announcement in the State Gazette: for POM not late than one months after the approving ordinance; for OTC – official updated list published on every 3 months

After the endorsement of the new ordinance in 2004 producers started to register their ceiling retail prices and this process took near 1 year. Thus, the market changes started to be observed in 2006.

Due to the longer period of introduction enforced by the new regulation, in the current study we observe 2003 as a year before the changes, 2006 as the first year, when the registered prices appear on the market for all products and 2009 as the year when we can reveal some long term consequences. The regulatory changes shorten the process of access to the market and decrease the necessary evidences for price regulation of the OTC medicines.

OTC Analgesics Utilization: A tremendous increase in the OTC analgesics utilization has been observed in 2006 compared to year 2003. For all INN the general increase in utilization of tablets is from 2.34 for methamizol to 3.68 fold times for acetylsalicylic acid (**Table 2**). The increase in utilization of tablets leads to a comparable increase of utilization in value terms. In 2009 observation points to a relatively smaller increase in the utilization measured in number of tablets and value terms for methamizol (2% and 8%, respectively), ibuprofen (21% and 37% respectively) and paracetamol (9% and 17%), while for acetylsalicylic acid, a decrease in tablets consumed is performed with 17% and increase in utilization in value terms with 7% in comparison with 2006. Increase in utilization was

found to be statistically significant for all INN during all years (Table 2). Thus our first hypothesis is confirmed.

Methamizol is the market leader with 43.4% (2006 year) to 45.7% (2009 year) relative share of utilization in tables among the 4 INNs observed, followed by acetylsalicylic acid with 31.3% (2009 year) to 36.4% (2003 and 2006), then paracetamol and ibuprofen (Table 3). Similar are the proportions in value terms. No statistically significant changes in the market share

of the INNs have been observed, which means that the leader during the whole period remains methamizol.

OTC Analgesics Prices: In terms of new product entrance, the market of analgesics is stable. Only for ibuprofen 5 new dosage forms were introduced, which led to 10 dosage forms available on the market in 2009. Methamizol, acetylsalicylic acid, and paracetamol were presented with 6 dosage forms each in 2009 (Table 4).

TABLE 2: OTC MEDICINES UTILISATION PER INN IN VALUE AND NUMBER OF TABLETS WITH ANOVA SINGER FACTOR ANALYSIS

INN	Utilization in value (BGN)			ANOVA for changes of utilization in value	Utilization in tablets			ANOVA for changes of utilization in value
	2003	2006	2009		2003	2006	2009	
Metamizol 500 mg	3 986 772	12 486 428	13 574 260	p<0.05	71 279 340	167 321 790	171 246 120	p<0.05
Ibuprofen 200 mg, 400 mg	835 715	3 276 061	4 502 787		2 675 956	9 860 944	11 936 586	
Acetylsalicylic acid 300 mg	2 523 511	5 751 458	6 184 628		57 882 680	140 493 300	117 482 140	
Paracetamol 500 mg	1 185 896	5 085 141	5 961 269		27 327 580	67 635 148	74 320 082	

TABLE 3: Z-TEST ANALYSIS OF THE CHANGES IN PROPORTIONS OF UTILIZATION

INN	Utilization in value (%)			z-test analysis for proportion changes in value						Utilization in tablets (%)			z-test analysis for proportion changes in tables used					
	2003	2006	2009	2006/2003	Stat	2009/2006	Stat	2009/2003	Stat	2003	2006	2009	2006/2003	Stat	2009/2006	Stat	2009/2003	Stat
	%	%	%	z-test value	sign	z-test value	sign	z-test value	sign	%	%	%	z-test	sign	z-test	sign	z-test	sign
Metamizol 500 mg	46.7	46.9	44.9	-0.063	No	0.066	No	0.059	No	44.8	43.4	45.7	0.031	No	-0.076	No	-0.029	No
Ibuprofen 200 mg, 400 mg	9.8	12.4	14.9	-0.146	No	-0.127	No	-0.292	No	1.7	2.6	3.2	-0.101	No	-0.077	No	-0.169	No
Acetylsalicylic acid 300 mg	29.6	21.6	20.5	0.317	No	0.046	No	0.261	No	36.4	36.4	31.3	0	No	0.186	No	0.186	No
Paracetamol 500 mg	13.9	19.1	19.7	-0.242	No	-0.026	No	-0.262	No	17.1	17.6	19.8	0	No	-0.097	No	-0.120	No

TABLE 4: DESCRIPTIVE STATISTIC FOR OTC ANALGESICS PRICES

INN	2003				2006				2009						
	N dosage forms	Mean price per tablet (SD)		Mean price per DDD (SD)		N dosage forms	Mean price per tablet (SD)		Mean price per DDD (SD)		N dosage forms	Mean price per tablet (SD)		Mean price per DDD (SD)	
		official	market	official	market		official	market	official	market		official	market	official	market
Metamizol	5	0.794 (0.336)	0.689 (0.329)	0.272 (0.078)	0.239 (0.087)	5	1.236 (0.411)	1.22 (0.60)	0.408 (0.071)	0.405 (0.154)	6	1.19 (0.55)	1.18 (0.69)	0.404 (0.117)	0.387 (0.195)
Ibuprofen	5	5.412 (3.203)	5.164 (3.436)	1.664 (0.664)	1.531 (0.712)	9	5.187 (3.668)	4.372 (3.447)	1.756 (0.722)	1.309 (0.524)	10	6.095 (3.425)	4.911 (3.277)	2.141 (1.135)	1.717 (1.052)
Acetylsalicylic acid	6	3.594 (5.146)	2.18 (4.444)	0.328 (0.214)	0.298 (0.182)	6	3.325 (4.664)	3.138 (4.717)	0.273 (0.177)	0.228 (0.162)	6	2.893 (2.115)	2.188 (1.526)	0.439 (0.229)	0.332 (0.146)
Paracetamol	6	1.568 (1.410)	1.319 (1.216)	0.740 (0.732)	0.619 (0.630)	6	2.345 (0.888)	1.803 (0.486)	1.045 (0.648)	0.794 (0.437)	6	2.341 (0.905)	2.002 (0.794)	0.996 (0.763)	0.854 (0.663)

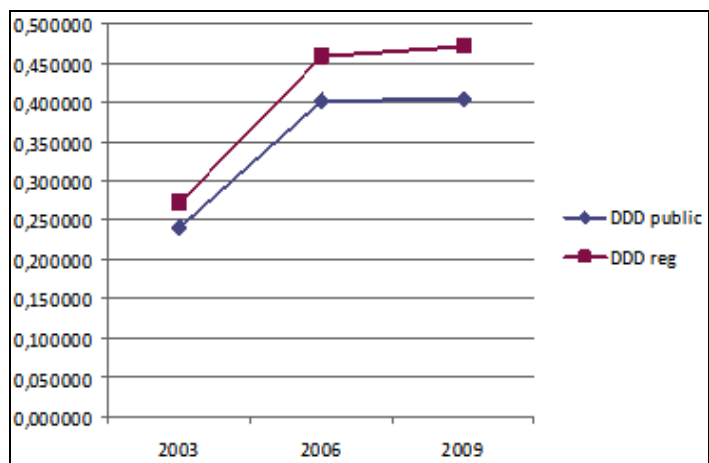
The officially registered mean prices were higher than the "market" ones for both price variables (tablets and DDD) and performed a steady increase – Figure 1. It is logical because the official prices are ceiling ones but medicines could be sold at lower

prices on the market. All manufacturers benefit from this regulatory provision and register higher prices but sold at lower ones. The difference among the official prices per DDD and the market ones was not found to be statistically significant (Table 5).

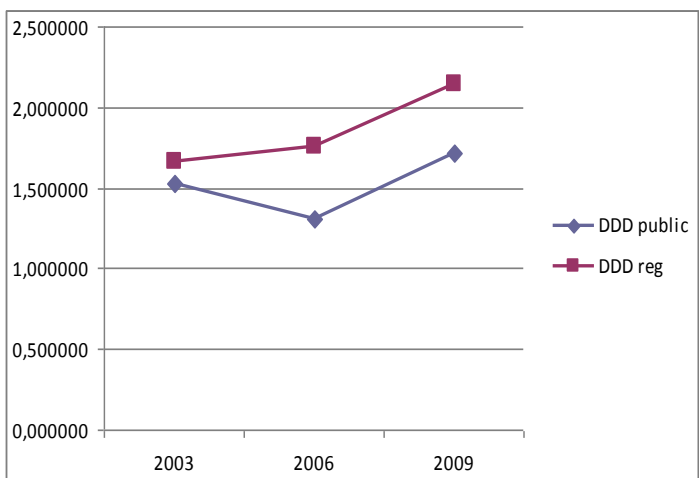
TABLE 5: ANOVA SINGLE FACTOR ANALYSIS FOR PRICE DIFFERENCES AND CHANGES

INN	Price difference 2003	Price difference 2006	Price difference 2009	Changes in prices during 2003-2009
	Official vs Market price	Official vs Market price	Official vs Market price	Market Prices per DDD
	per DDD	per DDD	per DDD	
Metamizol	p < 0.05	p < 0.05	p < 0.05	p < 0.05
Ibuprofen	p < 0.05	p > 0.05	p > 0.05	p < 0.05
Acetylsalicylic acid	p < 0.05	p < 0.05	p < 0.05	p < 0.05
Paracetamol	p < 0.05	p < 0.05	p < 0.05	p < 0.05

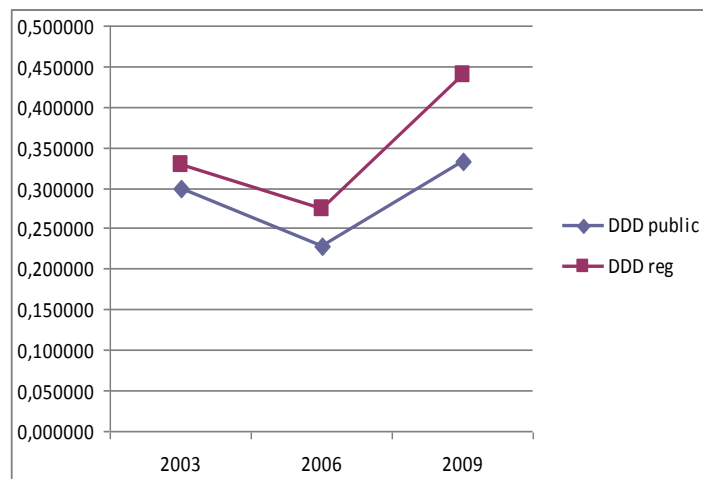
After the changes in the regulatory control we observe the increase in the mean official and market prices of methamizol and paracetamol in 2006 and slow decrease in 2009, but prices remain higher in comparison to 2003 (Figure 1, Table 4). The mean price of ibuprofen decreased in 2006, but in 2009 the officially registered price increased, while the market ones remain lower. For acetylsalicylic acid the mean price decreased slowly in 2003 and then increased in 2009. All changes in the prices were not statistically significant, even when we compare the prices in 2009 with those in 2003.



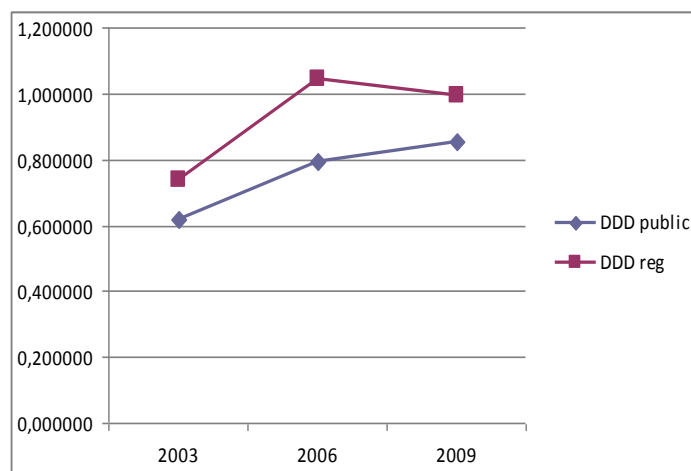
a) METHAMIZOL PRICES PER DDD



b) IBUPROFEN PRICES PER DDD



c) ACETYLSALICYLIC ACID PRICES PER DDD



d) PARACETAMOL PRICES PER DDD

FIG. 1: CHANGES IN PRICES PER DDD DURING 2003 AND 2009

Thus, our second hypothesis is not confirmed.

The result that the prices of the observed products increase after the liberalization of the regulatory procedure is not a surprising one. Similar results have been observed in Norway after the changes in the OTC prices regulation¹³.

It is a well-known theoretical postulate that the pharmaceutical market is not a common market and competitive rules don't seem to work even when patients could recognize their symptoms and choose alone the necessary product¹⁴. We can suppose that the competition plays more important role - that is the case of ibuprofen, but other factors like market campaigns may also play an important role. The number of ibuprofen dosage forms increased twice on the market and the mean prices became lower. Similar results have been reported in other studies for cardiovascular medicines¹⁵. Lluch and Kanavos consider that the liberalization of the distribution of OTCs could stimulate competition and hence improve access to medicines¹⁶.

It is evident that the mean prices rose insignificantly for all other product. It could be supposed that the market is sensitive to sharp price changes and manufacturers are careful. Thus the liberalization of the price regulation did not benefit people. On the other side the tremendous increase in the utilization probably influenced from advertising campaigns led to the sharp increase in market values, which benefits manufacturers.

The leading place of methamizol in comparison to other European markets could be explained with well-established habits of usage during the longer period of national production. The leading Bulgarian manufacturers have produced methamizol for more than 50 years.

CONCLUSION: The regulatory changes shorten the process of access to the market and decrease the necessary evidences for price regulation of the OTC medicines.

Manufacturers register higher prices but medicines are available in lower ones on the market. The liberalization of the price control led to the increase in utilization but also to an increase in prices.

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