MARKET SURVEILLANCE AND CONTROL OF MEDICINAL PRODUCTS IN BULGARIA 2009 – 2015

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ABSTRACT

Manufacturing of medicines is one of the most regulated human activities and their production and distribution require public oversight and stewardship. It is very important from a public health perspective to perform appropriate quality control of medicines, independently from the manufacturers. This is done by the regulatory bodies which constantly monitor the quality of medicinal products to ensure that the specifications defined in the approved dossier are constantly met in routine manufacturing processes. The current publication analyzes the postmarketing surveillance in Bulgaria for the period 2009-2015 performed by the Bulgarian Drug Agency (BDA) on the grounds of risk based sampling plan. The analysis covers period of 7 years (2009 – 2015) and it is based on the desk study of relevant documentation, related to the performed analyses and annual reports of the two sub-directorates involved in the studied activities. Our study showed that the selection of products for market surveillance is in line with the risk based approach. Most frequently analyzed products (31%) were antihypertensive medicines. 12% of the analyzed medicines were analgesics excl. non-steroid anti-inflammatory analgesics (NSAIAs), 8% were NSAIAs, 7% - vasodilatators and 5% - antibiotics. The implemented market surveillance system is efficient and garantees that the medicines on the Bulgarian market are compliant with the specifications (96% of the tested products found compliant), and are effective and safe. Solid dosage forms – tablets and capsules are the most frequently analyzed medicines (64%), followed by parenteral solutions (12%), liquid pharmaceutical forms (9%) – syrups, suspensions, drops etc. and dermal solutions (8%)

Key words: *surveillance, medicinal products, control, analysis, pharmaceutical market.*

INTRODUCTION

The pharmaceutical industry is important for the public health, economic growth, trade and science and it is of an economic significance. [5,6] However, manufacturing of medicinal products is one of the most regulated human activities and the production and distribution of medicines require public oversight and stewardship. Unlike ordinary goods, an unregulated medicines market will fail: it will be not only inequitable, but also inefficient, and probably dangerous to public health.[12] Benefit/risk ratio based on safety and efficacy data derived from the clinical studies is determined and monitored for every authorized medicinal product and consistent quality is precondition for its safety and efficacy since changes in quality could alter the safety and/or efficacy profile. The manufacturers are obliged to have comprehensive pharmaceutical quality system which is fully documented and monitored for its efficacy on a regular basis and which ensures consistent delivery of products with appropriate quality attributes as well as establishes and maintains effective monitoring and control systems for process performance and product quality.[7]

Manufacturing, distribution and quality control procedures of medicinal products meet various problems such as inaccuracy of analytical methods, lack of identity, falsification, presence of impurities and others. One of solutions for dissolving the problems is the choice of analytical techniques [11]. Manufacturers utilize techniques to identify their products from the falsified ones. The usage of the

methods follows pharmacopoeia requirements and it includes validation procedures and determinations of analytical parameters. [8,9]. Analytical techniques find application in all tests – for identification, purity and assay.

Despite of the systems and methods applied by the manufacturers, it is very important from a public health perspective to perform appropriate quality control of medicinal products independently from the manufacturers. This is done by the regulatory bodies which constantly monitor the quality of medicinal products to ensure that the specifications defined in the approved dossier are constantly met in routine manufacturing processes.[1]

There are 5317 medicinal products authorized for sale in Bulgaria, distributed by 282 wholesalers operating in the territory, reaching the patients through 4195 pharmacies [13] and the postmarketing surveillance on a national level is done by the Bulgarian Drug Agency (BDA) [Закон за лекарствените продукти в хуманната медицина] which is given a status of Official Medicines Control Laboratory (OMCL).

The current publication analyzes the postmarketing surveillance in Bulgaria for the period 2009-2015 performed by the Bulgarian Drug Agency on the grounds of risk based sampling plan.

MATERIALS AND METHODS

The analysis covers period of 7 years (2009 – 2015) and it is based on the desk study of internal memos between the responsible directorates within the BDA (28 memos for the whole period), justifying the need of inclusion of particular products in the annual surveillance plan; 7 annual postmarketing surveillance plans for the studied period; relevant documentation related to the performed analyses (288 certificates of analysis) and 14 annual reports of the two sub-directorates involved in the studied activities. The following indicators were monitored: number of medicinal products by trade names, international non-proprietary name (INN) and pharmacological-therapeutic groups; pharmaceutical form; manufacturer (Bulgarian or foreign) and the conclusions of the performed analyses. In addition more specific parameters such as appearance, microbiological quality, average mass, assay, purity test, dissolution test, disintegration, hardness, pH, degree of coloration, molecular mass distribution, residual solvents, relative density and bacterial endotoxines were examined by their type and frequency of determination.

RESULTS AND DISCUSSION

Procedures for annual planning and implementation of national market surveillance are described in a standard operating procedure (SOP), part of the Quality Management System of BDA, according to which every year the choice of particular products for inclusion in the surveillance plan invloves a justification provided by heads of the folowing directorates: „Analysis of medicinal products“, „Market surveillance“, „Marketing authorization of medicinal products“ and „Pharmacovigilance and clinical trials". [4] The main principle applied is risk-based approach.[10] The following medicinal products are identified as high risk products: products imported for the first time to the Bulgarian market; products with non-conformities found during inspections; complex synthesis of the active substance or risk of presence of dangerous impurities; new manufacturing site introduced or complex manufacturing process; recalled medicines or medicines with more frequent adverse drug reactions; first generic medicine on the market; products used for chronic diseases; products with potential problems related to stability; new combinations of active substances; high daily dose products or low strength products; counterfeit products or in case of risk of falsification; medicines with wide usage etc.

The annual plan based on the above principles is cohered with the other OMCLs within the

European Union and then the final plan is approved by the Executive director of BDA. According to the plan, the inspectors are collecting samples from the market, following the requirements of the local legislation on sampling. [3] Samples are collected mainly from the pharmacies in order to test how the storage conditions there influenced the product characteristics. After the arrival of samples in the BDA, an analysis is performed within 2 months based on the requirements of BDS EN ISO/IEC 17025:2006. The results are documented, reviewed and in case of non-conformities further actions are foreseen. [2].

We have reviewed the trend concerning the number of analyzed medicinal products by their trade name as well as by their INN (Figure 1). After 2013, the number of INN decreased as the policy was changed and more trade names were included. The reason was that it was decided that all medicinal products with identical INN would be included in the market surveillance. This decreased the number of INNs and increased the number of trade names which reflected in increasing the number of monitored manufacturers.

Distribution of medicinal products according to the origin of the manufacturer (Bulgarian/foreign) is presented on Figure 2. As it is showed there the surveillance is mainly focused on the production of Bulgarian manufacturers.

Distribution of medicines according to pharmacological-therapeutic groups, presented on Figure 3 reveals that the most widely used products have been chosen for control of the market. [IMS] Most frequently analyzed products (31% of the tested medicines for the whole period) were antihypertensive medicines which enjoyed significant increase in sales. 12% of the analyzed medicines are analgesics excl. non-steroid anti-inflammatory analgesics (NSAIAs), 8% are NSAIAs, 7% - vasodilatators, 5% - antibiotics etc.

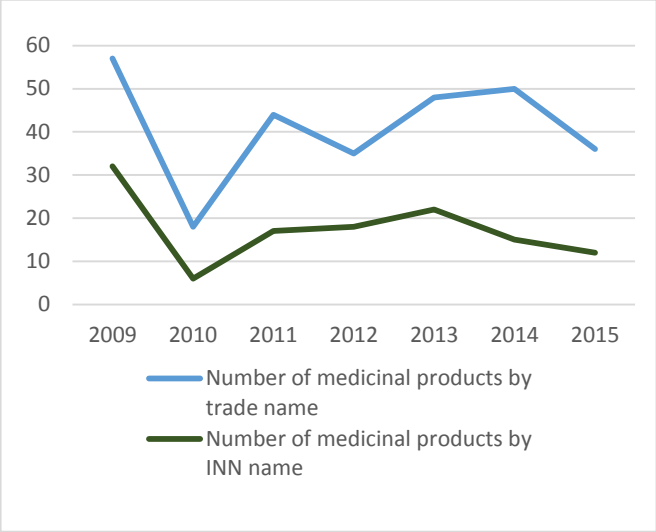


Fig.1 Number of medicinal products by trade name/INN name

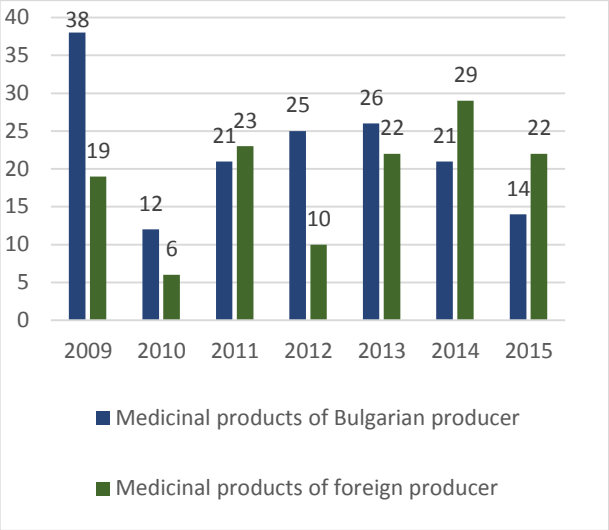
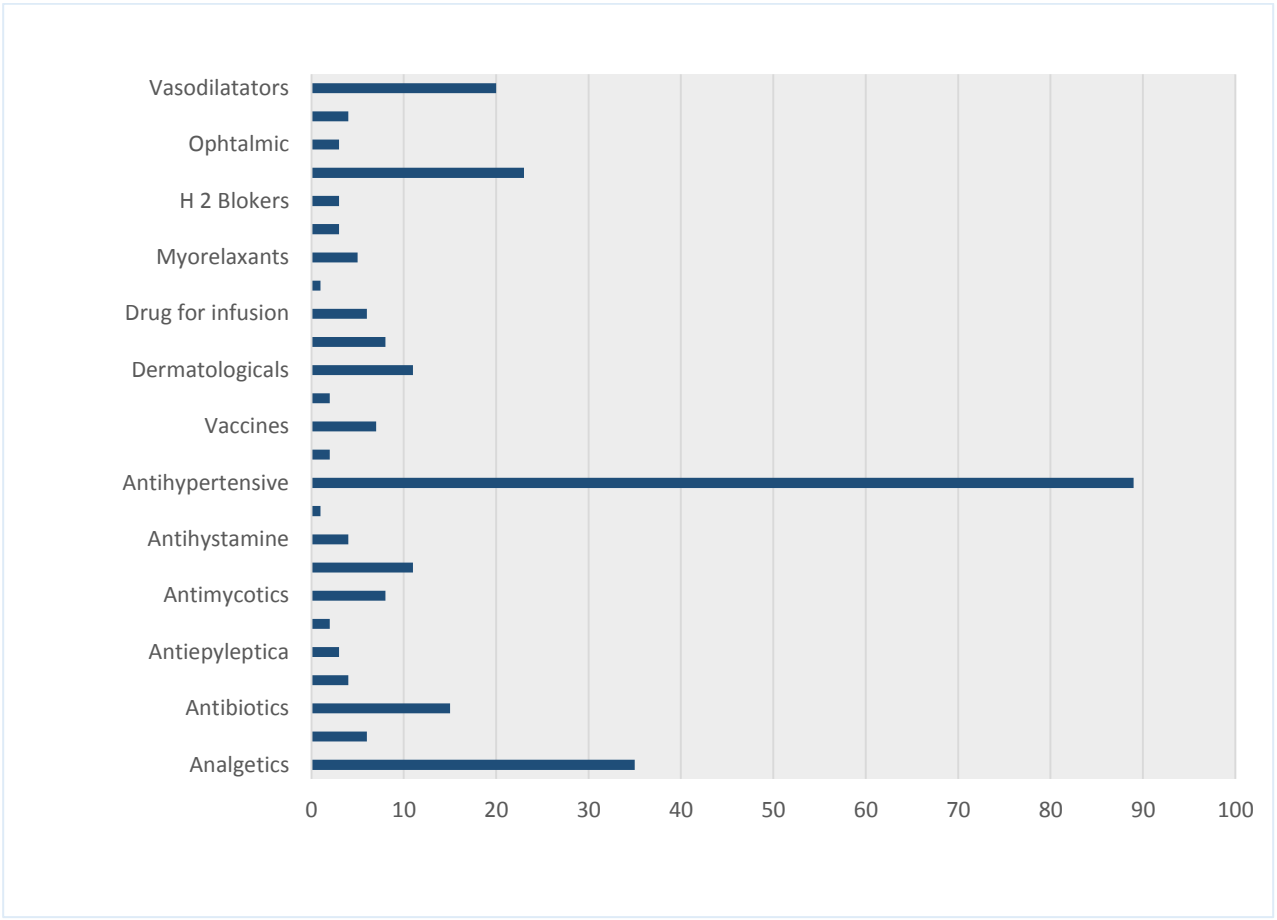


Fig.2 Medicinal products by type of producer

Solid dosage forms – tablets and capsules are the most frequently analyzed medicines (64%), followed by parenteral solutions (12%), liquid pharmaceutical forms (9%) – syrups, suspensions, drops etc. and dermal solutions (8%) (Figure 4). The rest pharmaceutical forms represents 7% in total.

All medicinal products were tested visually including the appearance, the condition of primary and secondary packaging materials. (Figure 5). Identity tests were performed for 89% of the products, of which for 88% quantitative analysis were performed and purity was determined for 68% of the collected medicines.

We have studied the analytical methods used as well as their frequency of use and found out that in 72% of the cases the identity tests were performed using high-performance liquid chromatography (HPLC) – Figure 6. In 25% UV spectrophotometry was applied, while the rest 3% are counted for thin-layer chromatography (TLC), gas chromatography, titrimetry or infrared spectroscopy (IR). This finding is directly related to the methods used for assays. This result corresponds with the methods used for assays (Figure 7). 69% of the assays were performed using HPLC, 22% - with UV spectrophotometry, and the rest 9% are for thin-layer chromatography (TLC). Gas chromatography, titrimetry (acid-base titrations, non-aqueous titrations, complexometry, redox titrations, potentiometric titrations and others), infrared spectroscopy (IR) and others are used rarely.


Vasodilatators
Ophtalmic
H 2 Blokers
Myorelaxants
Drug for infusion
Dermatologicals
Vaccines
Antihypertensive
Antihystamine
Antimycotics
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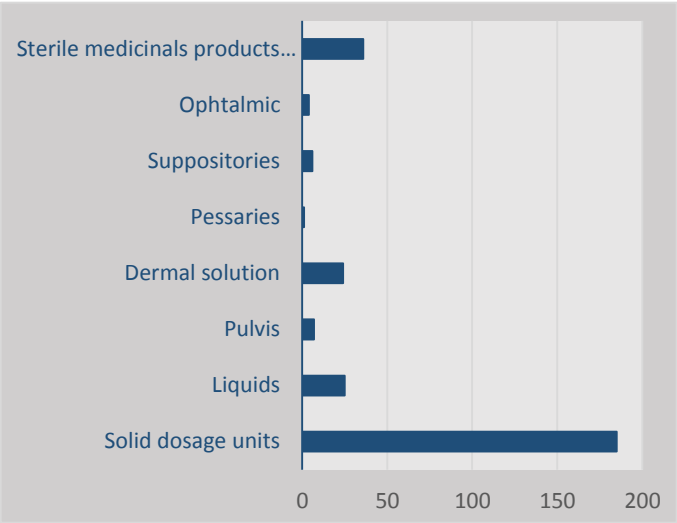

Fig.4 Distribution of medicinal products by formulation

Fig.3 Medicinal products by pharmacology groups

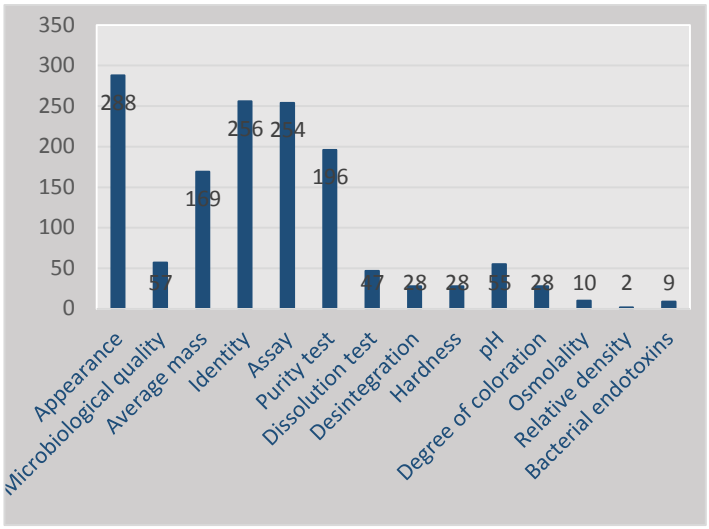

Fig.5 Analyzed parameters

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Purity tests are performed with 3 methods distributed as follows: HPLC (92%) with highest performance especially for determination of related substances and impurities, TLC – 5%, only to a certain degree and UV spectrophotometry - 3% for checking of degradation and oxidizing products as limitation of absorption values at fixed wavelength. (Figure 8). For the rest monitored parameters specific tests were applied. Undoubtedly the chromatography is the most frequently used analytical technique in quality control procedures. The system suitability tests attended every HPLC method allows the routinely monitoring of chromatographic performance.

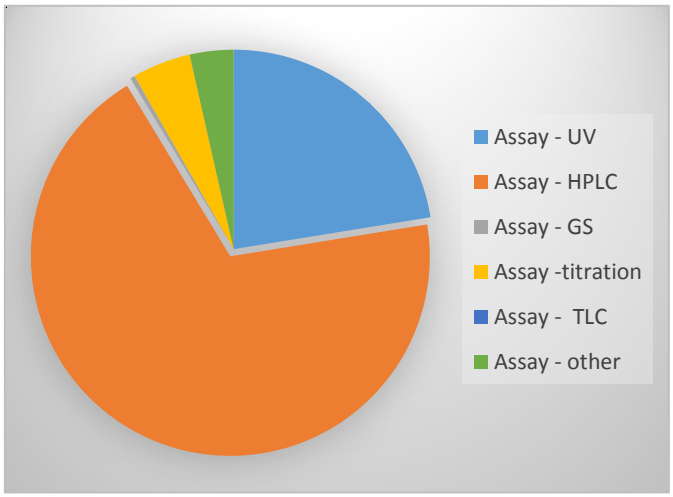

Fig.7. Methods for Assay

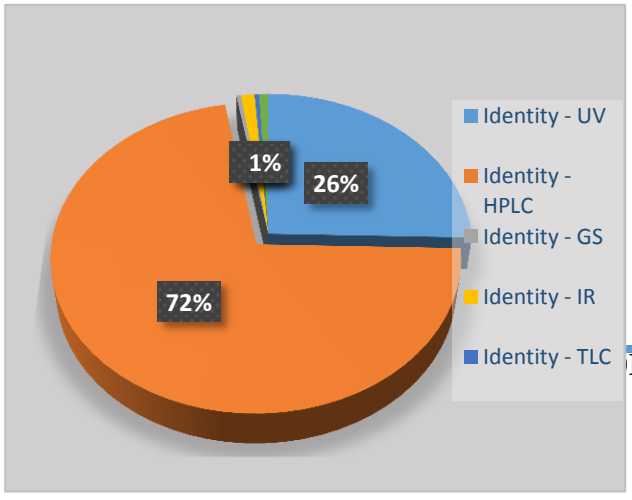

Fig.6. Methods for identity

In total 288 medicinal products were analyzed for the whole studied period (Figure 9). Out of them, 271 products (94 %) have been found to comply with the approved specifications, while 17 products (6%) were non-compliant with regard to microbiological quality (dermal solution), dissolution test (for a modified-release tablet), hardness etc.

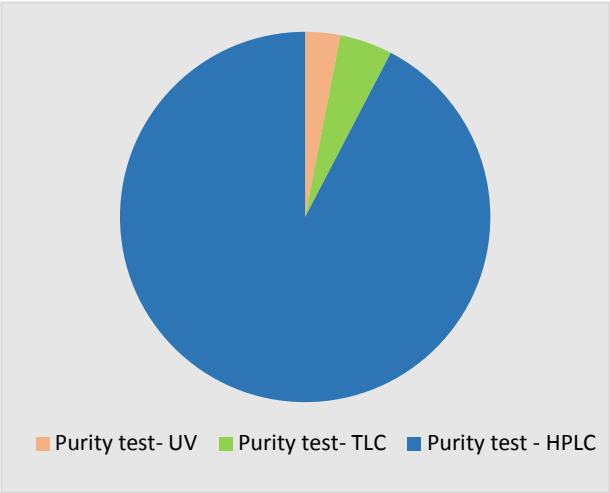

Fig.8 Methods for purity tests

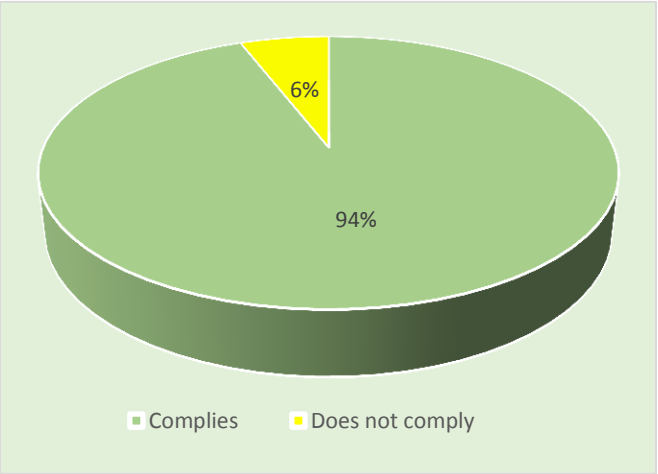

Fig.9 Results from analytical reports

CONCLUSIONS

Our study showed that the selection of products for market surveillance is in line with the risk based approach. Most frequently analyzed products (31% of the tested medicines for the whole period) were antihypertensive medicines which enjoyed significant increase in sales. 12% of the analyzed medicines were analgesics excl. non-steroid anti-inflammatory analgesics (NSAIAs), 8% were NSAIAs, 7% - vasodilatators and 5% - antibiotics.

The implemented market surveillance system is efficient and garantees that the medicines on the Bulgarian market are compliant with the specifications (96% of the tested products found compliant), and are effective and safe. Solid dosage forms – tablets and capsules are the most frequently analyzed medicines (64%), followed by parenteral solutions (12%), liquid pharmaceutical forms (9%) – syrups, suspensions, drops etc. and dermal solutions (8%).

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