NATIONAL CENTER OF PUBLIC HEALTH AND ANALYSIS

ANELIA HRISTOVA NIKOLOVA

STUDY AND ANALYSIS OF THE HEALTH TECHNOLOGIES ASSESSMENT PROCESS AND ECONOMIC ASPECTS SINCE THE INTRODUCTION IN BULGARIA

PhD DISSERTATION SUMMARY

SCIENTIFIC SUPERVISORS:

Prof. Ilko Getov, Ph.D.
Assoc. Prof. Evgeni Grigorov, Ph.D.

SOFIA, 2020

The dissertation contains 152 pages, including 8 tables, 95 figures, 1 appendix. The bibliography consists of 142 literary sources, in Cyrillic and Latin.

In connection with the dissertation, 4 articles have been published.

The dissertation was discussed, accepted, and directed for defense by an extended joint Collegium of the Classification Systems, Standards, and Innovations Directorate and the National Health Data and e-Health Directorate at the National Center for Public Health and Analysis held on 16.10.2020 based on Order № RD-387/15.10.2020 of the Director of NCPHA.

Contents

Abbreviations

GDP - Gross Domestic Product
EMA - European Medicines Agency
EU - European Union
LMPHM - Law on Medicinal Products in Human Medicine
BDA – Bulgarian Drug Agency
HTAC - Health Technology Assessment Commission
KK - Cochrane collaboration
MP - Medicinal product
WEG – Working expert's group
MH - Ministry of Health
NHIF - National Health Insurance Fund
NCPR - National Council on Prices and Reimbursement for Medicinal Products
NCPHA - National Center of Public Health and Analysis
HTA – Health Technologies Assessment
PDL - Positive drug list
MAH - Marketing Authorization Holder
AETMIS - Agency for evaluation of technologies and modes of intervention in health
APOR - Association for Pharmacoeconomics and Outcomes Research
BIA - Budget Impact Analysis
CBA - Cost-benefit analysis
CEA - Cost-effectiveness analysis
CETS - Council for the Evaluation of Health Technologies
DALY - Disability-Adjusted Life Year
EUnetHTA - European Union network for Health Technology Assessment
HEOR - Health economics and outcomes research
INN - International non-proprietary name
IQWiG - Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
ISPOR - International Society for Pharmacoeconomics and Outcomes Research
JA - Joint Action
MEDLINE - Medical Literature Analysis and Retrieval System Online
NHS - National Health Service
NICE - National Institute for Clinical Excellence
PBAC - Pharmaceutical Benefits Advisory Committee
PBS - Australian Pharmaceutical Benefits Scheme
QALY - Quality-adjusted life year
REA - Relative effectiveness assessment
SBU - Swedish Agency for Health Technology Assessment
CUA – Cost-utility analysis
CMA – Cost-minimization analysis

1. Introduction

In recent years, the growth rate of health care spending has been significantly higher than the growth of the gross domestic product in most countries. There is a lasting tendency for government expenditures to increase annually in value and as a relative share of the total state budget. As a result, even developed economic countries are finding it increasingly difficult to finance their health systems. Such an increase in total health care funds, incl. drug treatment is also observed in Bulgaria.

The increase in the cost of medicinal products is a natural process depending on many factors which can be summarized in 2 main groups:

- the aging population, increasing number of patients with chronic diseases, growing expectations of society (striving for modern and more effective treatments) and more needs of the population;
- The presence of innovative therapies, increased and in many cases irrational use, polypragmatism, insufficient adherence to therapy, and ineffective management of drug costs.

The resources for pharmacotherapy should be managed to ensure available access to it by all patients who have a genuine need.

Public resources allocated to medicines should be distributed as fairly as possible, ensuring a balance between the interests of society and the individual patient, while maintaining the interest of the pharmaceutical industry in the specific national drug market.

Expenses for medicinal products are constantly increasing in all European countries and measures for their arrest are increasingly more the focus of attention of the politicians who in turn should ensure a smooth rate of increase and/or reduce costs without compromising with the quality of healthcare. Actions that managers and regulators take into connection with this, aim to ensure rational drug use and to control public costs for medicinal products. These activities and initiatives are aimed at all participants in the system, ensuring a fairer distribution of the risk of overspending on the already limited financial resources. Such an effective mechanism for ensuring cost-effectiveness is the introduction of the process of health technology assessment (HTA).

Health technology assessment (HTA) is an established scientific methodology. It serves health managers and politicians to make informed decisions about

the reimbursement of new diagnostic and therapeutic approaches, drugs, and medical devices. Based on data from clinical trials, in line with the proposed price, the number of target patients, and potential costs, information can be obtained on the relative value (cost) effectiveness of new health technologies, such as medicines, devices, and medical services. In most cases, a comparison with existing standards (or opportunity) for treatment and care for patients. HTA is conducted using analytical frameworks, based on clinical, epidemiological, and health-economic information, to determine how best to allocate limited health resources.

The HTA process in Bulgaria has started since the beginning of 2016, and it applies only to medicinal products (MP).

Normatively, the process is regulated by Ordinance No 9 of 01.12.2015 on the terms and conditions for performing health technology assessment (revoked).

In Bulgaria, the process of HTA occurs at an intermediate step after the issuance of marketing authorization and before the inclusion of medicinal products in the PDL. This process is mandatory.

According to the changes in Art. 259, para. 1, item 6 of LMPHM (SG No. 102/2018, effective 01.01.2019), as of 01.04.2019, the national body for performing HTA in Bulgaria has been changed. Art. 259 of the LMPHM states that the National Council for Prices and Reimbursement of Medicinal Products (NCPR) undertakes the activity of assessing the health technologies of medicinal products, as the procedure is part of the process of inclusion in the PDL.

Accumulated tons of experience more than three years in the period February 2016 - March 2019 gives reason to be carefully examined and analyzed the reported benefits, weaknesses, and errors in the introduction of process in the country to formulate conclusions and actions targeted, effective and rational use of the HTA instrument in the payment of drug and non-drug therapy, diagnostic and other treatment and rehabilitation procedures in the future.

At this stage, it is important to take into account and highlight the key points and problems in the implementation of HTA in Bulgaria for these 3 years and to serve for further development, improvement, and expansion of the scope of evaluations.

2. Hypothesis, aim, tasks, materials, and methods of the studies

2.1. Scientific hypothesis

The introduction of the process of health technology assessment leads to support and optimized decisions on reimbursement of medicines in Bulgaria, as well as savings in public funds for health care.

2.2. Aim and tasks

The present study aims to make a comprehensive analysis of the introductory stage of institutionalization, organization, and implementation of HTA in Bulgaria and the economic aspects of the application, deriving the key factors for development and effective management.

To achieve this goal, the following tasks are set:

1. To be done with a historical review and an analysis of the process of HTA worldwide.

2. To follow the process of performing HTA - from the submission of an application by the Marketing authorization holder (MAH) of the medicinal product to the approval of the HTA report, defining the key stages, obstacles, omissions, and weaknesses.

3. To analyze the prerequisites for the successful preparation of a draft report on HTA, incl. provision with experts and their opinion, organization of the work of the working expert's group, and the terms for carrying out the evaluation.

4. To investigate reports of working expert's group to establish compliance with the requirements and procedures, presenting it in a report, making a final decision, and formulate factors affecting the process of HTA.

5. To analyze the economic aspects of the introduction of the HTA process in Bulgaria.

6. To formulate guidelines and recommendations for the improvement of the HTA process at the national level and in the context of the EU legislative initiative.

2.3. Object and subject

Objects of the study are the organization and activities of the Department of Health Technology Assessment at NCPHA, the Commission on Health Technology Assessment, and the Working expert's group under Article 10 of Ordinance No 9 of 01.12.2015 for the period 02.2016-04.2019 г.

The paper studies the structure, organization, processes, and results of operations of separate WEG of experts, Commission and Department HTA. Extensive and intensive indicators such as security of the process with experts, technical security, intensity and sustainability of the process, final results of the procedures, etc. have been studied and analyzed.

To analyze the economic aspects of the introduction of the process of HTA in Bulgaria, as a research tool are used HTA reports of medicinal products that have been approved and published on the NCPHA internet site in the study period.

2.4. Materials and methods of the research

Historical and sociological (survey, observation, documentary) methods were used to collect the data. Statistical methods (alternative, variational, graphical), economic analysis, and expert evaluation were used in the processing and analysis of the information.

The PhD student is directly professionally involved in the overall process of HTA in Bulgaria from the very beginning of its implementation in our country, which provides the necessary access to valid and reliable information and ensures the adequate application of research methods. The quantitative results of the study are presented schematically and graphically.

Historical and sociological methods have been applied to extract data and interpret information from the following research materials:

- foreign and Bulgarian scientific publications concerning the nature, procedures, and methods of HTA, incl. the experience of other countries in this field;
- normative documents regulating the implementation of HTA in Bulgaria and the activity of the objects of the research - law, ordinance, procedures, and rules;
- database of submitted applications, which are analyzed according to various criteria for completeness and duration of the procedure;
- databases for selection of experts for working commissions in connection with the assessment of security with specialists from different fields - doctors, dentists, pharmacists, economists, statisticians, lawyers, and others;
- reports from the working groups and minutes from the meetings of the HTA Commission at NCPHA on the results of the procedures;
- international and Bulgarian databases with statistical indicators on the consumption and costs of medicines;

- reports from international and Bulgarian institutions and organizations in connection with data concerning the pharmaceutical market and the process of HTA at home and abroad.

The method of expert assessment is applied in summarizing the key factors influencing the development and effective management of the HTA process at the national level and for formulating recommendations for its improvement in Bulgaria.

Regarding the survey for knowledge and attitude to the HTA process by experts and outsiders, a method of a direct individual anonymous online-based survey with a questionnaire is used.

A survey was conducted among stakeholders: academics, doctors, experts in the field of HTA, representatives of the pharmaceutical industry and the media, patients. The survey was developed in the "google forms" platform, and the results were extracted and subsequently processed with MS Excel.

Economic analysis and comparison of treatment costs were performed.

No personal data, sensitive and company information was collected and processed for all surveys, as well as no expert opinions and opinions were commented.

Limitations of the study:

PhD thesis does not address all aspects of HTA, but only those, which concern the organization of the process in Bulgaria and the economic impact on the budget of the institutions that paid agents with public funds.

Time range:

The period is three years and covers the period from the introduction and net of HTA in Bulgaria since the beginning of 2016 to March 31, 2019

3. Results analysis

3.1. Analysis of the HTA process in Bulgaria

3.1.1. Organizational structure and course of the HTA process

Objective: To describe and analyze the organization of the HTA process in Bulgaria, the main participants, and compliance with regulatory requirements.

HTA is introduced in Bulgaria with the promulgation of Ordinance № 9 of 01.12.2015 (Promulgated SG No. 97 of 11 December 2015) on the terms and conditions for conducting an assessment of health technologies, issued by the Minister of health, hereinafter "regulation". At the end of 2018, with the incoming and final provisions of the Budget Act of the National Health Insurance Fund for 2019, many changes are introduced in the process of HTA in Bulgaria. The law stipulates that health technology assessment after 03/31/2019, will be done by the National Council on Prices and Reimbursement of medicinal products (NCPR), thus we consider the analysis of the experience gained over more than four years to be very necessary and useful.

The functions of NCPHA and the Commission on HTA, which it supports, are transferred and to NCPR and so have created new frameworks for assessment and decision making to support the selection of drugs that are reimbursed.

This paper analyzes the achievements, gaps, and experience gained in the process of HTA for a period of 3 years - from the introduction in Bulgaria to March 31, 2019, incl.

According to the Ordinance, the assessment of health technologies is mandatory for medicinal products belonging to a new international non-proprietary name, which is not included in the relevant annex of the Positive Drug List (PDL).

The process of performing HTA in Bulgaria, which has more than 4 years of history, has been established in our country. Its effectiveness depends on many factors, such as technical equipment, availability of experts, their training and expertise as well as experience and awareness of companies marketing authorization holder (MAH) the nature, administrative procedures, terms, and requirements for assessments of health technologies.

The ordinance establishes an HTA Commission, which is an advisory body to the Director of the NCPHA and is composed of 13 members, including the Chairman. It involves representatives from different institutions (Figure 1) as follows:

- three representatives of the Ministry of Health;

- two representatives of the National Health Insurance Fund;
- three representatives of the National Council on Prices and Reimbursement of Medicinal Products;
- two representatives of the Bulgarian Drug Agency;
- three representatives of Nacional Center of Public Health and Analyses.

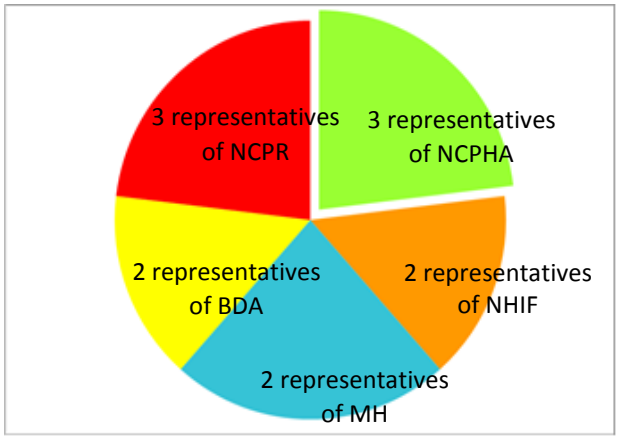
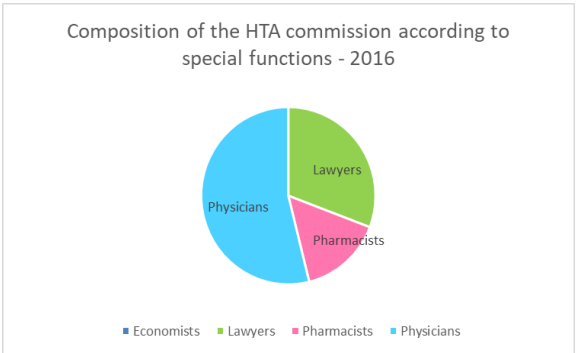


Figure 1. Structure of the HTA Commission in Bulgaria.

Initially, the nominal composition of the HTA Commission was determined on 25.02.2016 by Order of the Minister of Health and since then nine more orders have been issued to change its composition. According to the Ordinance, the Commission must include the Director of NCPHA.

The members of the Commission do not receive remuneration for their work. Various specialists were involved in the composition of HTAC change over the years, with the issuance of the respective change orders.

When the Commission was established in 2016, its specialists were divided into three groups - physicians, pharmacists, and lawyers. Not one economist is included, but at the expense of the share of jurists, which is unjustified - 30% or 4 people out of 13 are jurists.



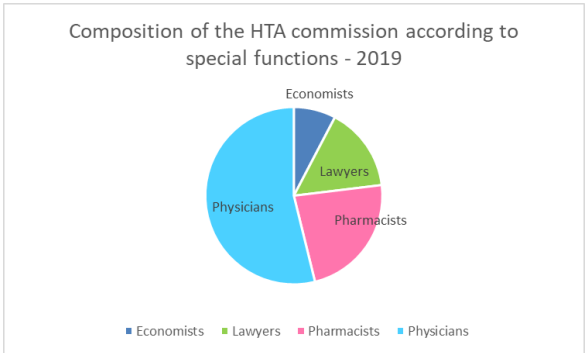


Figure 2. and figure 3. The composition of the HTA Commission presented according to the specialties of the individual members as of March 2016 and as of March 2019.

The graph shows that the HTAC by 2019 is composed of 4 (four) separate groups of specialists: doctors, master pharmacists, lawyers, and economists. The number of pharmacists is increasing and there is 1 new member with a degree in economics.

The work of the Commission is supported by a secretary and technical assistants who are employees of the NCPHA. They shall not be members of the Commission and shall not vote in meetings. Their nominal composition is also determined by an Order of the Minister of Health.

The duties of the Secretary of the Commission are regulated in the Ordinance and they include:

1. Organizing the work of technical assistants.
2. Organization and preparation of Commission meetings;
3. Preparation and proposals for the agenda for the meetings to be approved by the Chairman of the Committee;
4. Keeping minutes of Commission meetings.

In order to carry out the activity of the Commission, working expert's group are established under the Director of NCPHA, which include doctors, dental specialist, master pharmacists, economists, statisticians, lawyers and other specialists. The working groups carry out a preliminary assessment of the documents submitted by the MAHs and the analysis of HTA, after which they prepare a draft report for assessment of the health technology.

In order to administer the process, a special department "Health Technology Assessment" has been established in the structure of the NCPHA, which serves the work of the Health Technology Assessment Commission. The establishment of the department takes place after the Rules for the structure and activity of the National Center of Public Health and Analysis approved by the Ministry of Health, in which a new structure of the NCPHA is adopted.

The HTA Commission considers and resolves issues within its competence in open or closed meetings. Only members of the Commission and its Secretary shall attend a closed meeting. By Commission decision, other persons may be present at a closed meeting.

In order to organize and regulate the work of the Commission, *"Rules on the Terms and Conditions for the Work of the Health Technology Assessment* Commission" have been established, which the Commission voted on and adopted at its meeting. This internal document correlates with Ordinance № 9 of 01.12.2015

and has been prepared by the HTA Department and approved by an order of the Director of NCPHA. These rules are not publicly available.

According to the Rules, the Commission is convened at least once a month at a regular meeting and the initiative of the Chairman of an extraordinary meeting.

Proposals for convening an extraordinary meeting may also be made by the members of the Commission to the Chairman through the Secretary of the Commission. No extraordinary meetings were convened during the period under review. There were 38 regular meetings with an average quorum of 10 people and there were 9 failed meetings due to lack of quorum. For all meetings held, the full composition of the HTAC met only once.

The Secretary of the Commission shall prepare a draft agenda for each meeting, which shall be approved by the Chairman and published on the NCPHA website. Three working days before each meeting, the Secretary of the Commission shall send the approved agenda to all members of the Commission.

The Commission meetings shall be regular if at least 2/3 of the members are present and the decisions shall be taken by open vote and again by a majority of 2/3 of the members or 9 votes.

The Chairman and the members of the Commission shall not take part in the voting on the evaluation of a medicinal product if they have participated in activities related to its development, production, marketing, wholesale and retail trade, which each declares in person before the meeting.

Minutes of each meeting of the Commission shall be kept and signed by the Chairman of the Commission, the Secretary, and all members present at the next meeting at the latest. A personal name sheet signed by each of the members present shall be attached to the minutes of the Commission.

Stages of the process

In general, the HTA process goes through the following 3 distinct stages:

1. The marketing authorization holder or his authorized representative shall apply for authorization of HTA with accompanying documents:
   - a copy of the authorization for use of the medicinal product under Art. 1, para. 2 following the requirements of the LMPHM, where the marketing authorization has been granted in accordance with Regulation № 726/2004, Annex I "Summary of Product Characteristics", Annex II "Holder of the manufacturing authorization responsible for batch release. the marketing authorization "and Annex III" Indications on the packaging and package leaflet "; the applications are submitted on electronic media;

- information on the unique identification code of the company or cooperative from the commercial register, and for companies registered in a Member State of the European Union or in a state party to the Agreement on the European Economic Area - a copy of a document for current registration under national law issued by a competent authority of the respective state of the persons under para. 1 not later than 6 months before the submission of the application;
- explicitly notarized in full power, in case the application is submitted by a representative of the marketing authorization holder; when the power of attorney has not been issued in the Republic of Bulgaria, a translation into Bulgarian shall be submitted for the same, performed by a translator who has concluded a contract with the Ministry of Foreign Affairs for official translations;
- evidence regarding the representative power of the person, who has signed the power of attorney under item 3;
- prepared analysis in accordance with the manual under Annex № 2 of the Ordinance

2. The documents go through an eligibility check by employees in the HTA Department.

Provided that the submitted application or the documents to it do not meet the requirements, a letter is prepared to the applicant, which NCPHA requires remedial documentation and additional information. In this case, the term of the procedure shall cease to run until the date of elimination of the deficiencies in the documentation and submission of the additionally required documentation.

If within 30 days from the date of notification, the applicant fails to rectify the deficiencies found or if there is a negative assessment of the health technology for the evaluated medicinal product carried out by a government institution of Great Britain, France, or Germany, the assessment procedure is terminated.

3. In case the documentation meets the requirements of the Ordinance, the procedure is started:

- the dossier shall be provided to all members of the Commission. For this purpose, there is a specially created common server space in the NCPHA.
- The Chairman of the Commission prepares proposals for the composition of a working expert's group (WEG) under Article 10 of the Ordinance, which is voted at the next meeting of the Commission. The decision is reflected in the minutes of the meeting.

- The director of NCPHA issues an order to approve the list of members of the WEG, as decided by HTAC.
- The members of the WEG are notified, they are given complete sets of HTA documents submitted to the NCPHA and they fill in declarations following the Rules for declaring, preventing, and establishing conflicts of interest in the HTA process.
- The WEG carries out a preliminary assessment of the documents and prepares a draft report for assessment of the health technology according to Annex № 3 of the Ordinance.
- The draft report of the WEG is adopted at its meeting, after which it is submitted to the office of the NCPHA with an incoming number to the Director of the NCPHA. The director of NCPHA defines resolution tabled a report to the Secretary of HTAC for inclusion in the agenda of the meetings.
- The chairman of the WEG presents the draft report for assessment of the health technology at a meeting of the HTAC. The Commission shall adopt by decision the draft health technology assessment report or return it to the WEG with instructions. The Commission may or may not accept the recommendation of the WEG.
- The adopted report is sent by the Chairman of the Commission to the Director of the NCPHA for approval.
- The Director of the NCPHA approves by order the report for assessment of the health technology adopted by the Commission.
- The Director of the NCPHA notifies the MAH by letter of the decision taken and sends a copy of the report.
- The order and the letter to the MAH are prepared by the HTA Department. It informs the MAH of the decision taken; the application is issued and sends an invitation to consent to the publication of the report on the NCPHA website.
- A summary of the report is published on the website of NCPHA. The full report can be published after obtaining the explicit consent of the MAH.

Internal documents relevant to the procedure:

1. Regulations for the documents and the document turnover, corresponding to the specifics and peculiarities of the activity and structure of the National Center for Public Health and Analysis (NCPHA), approved by Order № RD-25 / 18.01.2016 of the Director of NCPHA. It determines the general rules regarding the document circulation, record keeping, and archival activity of the NCPHA, in order to ensure speed, efficiency, traceability, and control in the processing of documents in the

NCPHA and to ensure the work of all structural units in the center. The regulations regulate:

- The acceptance and registration of incoming documents by external legal entities and individuals, the movement of internal documents, as well as the registration of contracts, and the movement of outgoing documents.
- The distribution and organization of work with documents.
- The requirements for the preparation of outgoing documents.
- Control over compliance with deadlines.
- The rights and obligations of the employees of NCPHA when working with the documents.
- Archiving and storage of documents.

2. Procedure on the conditions and order for the evaluation of health technologies medicinal products belonging to the new international non-proprietary name, which is not included in the relevant Annex of the Positive Drug List (PDL). This is a Standard Operating Procedure that indicates how the department works and the stages the process goes through (described above).

3. Rules for the conditions and the order of work of the Commission for an assessment of the health technologies (HTAC) under art. 5 of the Ordinance. They were adopted at its first meeting and indicate how the Commission works and takes decisions.

4. Rules for determining the composition and the manner of work of a working commission (WEG) at the NCPHA under Art. 10, para. 1 of Ordinance № 9 of 01.12.2015 on the terms and conditions for carrying out an assessment of health technologies approved by Order № RD-167 / 29.03.2016 of the Director of NCPHA. They indicate the procedure, conditions and rules for determining the composition and manner of work of the WEG, as well as the deadlines for preparing a draft report on HTA. The rules regulate what specialists should be included in the WEG, as well as the requirements for the education and professional experience of the experts. Relevant additional documents to these rules are the minutes of at least 2 regular meetings of the WEG. The minutes describe the decisions taken and the discussions made by the members of the WEG, after which they are signed and submitted to the NCPHA. A model form of such a protocol is approved as Annex 3 to the Rules. The rules are given to each expert at the beginning of his work when he is included in a certain WEG.

5. Rules for declaring, preventing, and establishing conflicts of interest in the process of health technology assessment. They are approved by the Director of

the NCPHA and regulate the procedure and manner for establishing and preventing conflicts of interest of the persons participating in HTA activities. These persons include the members of the HTAC, the members of WEG, and all persons involved in the process. According to the Rules conflict of interest arises, when the person is involved in activities related to development, production, marketing, and wholesale and retail assessments of the medicinal product. For this purpose, declarations are signed, and NCPHA is obliged to maintain a register of these declarations for a period of 10 years. The director of the NCPHA appoints by order an official to keep the register and to make the entries in it.

6. Rules for determining the procedure for concluding civil contracts, assigning activities according to an order of the Director, and reporting them to the NCPHA. They settle the issue of the payment of fees to experts for participation in WEG. Initially, this was done based on a civil contract, for which purpose it was prepared and signed with each member of a WEG. In the latter with nascent to facilitate the work and the volume of documentation it was decided that fees be paid based on an order issued by the Director of NCPHA. For this purpose, a transceiver protocol is signed for the work performed between the Director of the corresponding Directorate in NCPHA and the Chairman of the WEG. After that, a technical assistant prepares a report and an order for payment of remunerations, which are forwarded to the Accounting Department for implementation. The payment of the remunerations may not precede the adoption of the draft report by the HTAC.

Conclusion: The review and analysis of the process and the related rules and documentation show that although in a relatively short period a functioning administrative procedure and a team for inspection, management, reporting, and control of the HTA process in the country have been established. The committed administrative, technical, expert resources and financial resources guarantee the timely, impartial, and quality conduct of the evaluations.

3.1.2. Analysis of the deadlines for carrying out an HTA procedure.

Objective: To track and analyze the average duration of HTA procedures and the factors influencing, as well as to indicate indicative examples in a positive and negative direction.

The deadlines for performing health technology assessments vary in different European countries and depend on the type of assessment that is performed - single, multiple, rapid assessments, etc. (Table 1).

Table 1. Deadlines for HTA implementation in selected countries

<= 90 days	90-220 days	> 220 days
Austria, Belgium, Bulgaria, France, Hungary, Ireland, Malta, Lithuania	Czech Republic, Finland, Netherlands, Portugal, Spain, Sweden, United Kingdom, Norway,	United Kingdom (NICE - for specific assessments)

Source: Mapping of HTA national organizations, programs and processes in EU and Norway, European commission, Written by Julia Chamova, Stellalliance AB –May -2017

For Bulgaria, the normatively determined term for carrying out the HTA procedure is 90 days from the date of submission of the application by the MAH.

In the general case of conducting HTA, the practice shows that this term is extremely insufficient. The leading reason for going beyond the time frame is the interval for convening and holding regular meetings of the HTAC. According to the legal regulation they are made once a month, in some cases, it takes about 20-30 days until employment WEG. Technically, after the voting of the composition of the WEG, all members of the HTA Commission shall prepare and agree on the minutes of the meeting. The time for technical preparation and signing of the orders by the Director of NCPHA is 3 days. Subsequently, the notification of the appointed experts and the distribution of working materials also require technical time - moreover, they are not always in the same city and the administration of the process is carried out by two employees in the "HTA" department, who have other duties and technically serve several RCs simultaneously

The analysis of the terms of the procedures shows that the share of procedures completed on time is very small and decreases over the years:

- 2016 - 14%
- 2017 - 8%

- 2018 - 5%

The next figure 4 shows the number of procedures with met/ have not met the deadline by years. The average duration in days of all completed procedures by years was also studied.

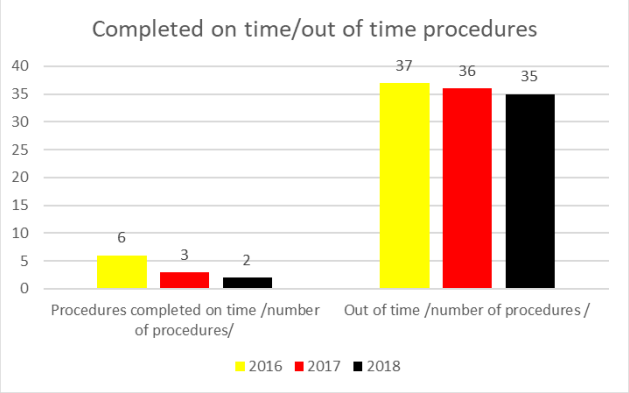


Figure 4. Completed on time / out of time procedures

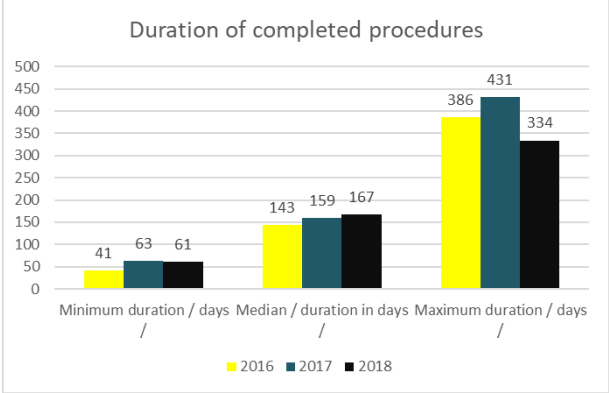


Figure 5. Duration of completed procedures.

The longest period in 2016 is a procedure in the field of oncology, 2017 in urology, and 2018 in the field of hematology.

The shortest possible time for procedures was in 2016 - in the field of dermatology, 2017 in rheumatology, and 2018 in endocrinology.

For 2019, due to the relatively short period of operation of the HTA process in its current form - three months, there is only one started and completed procedure.

In general, the completion of procedures in the shortest possible time is observed in the fields of dermatology, rheumatology, cardiology, and endocrinology, and the longest is considered procedures in the field of oncology and hematology.

The main problem in the process of evaluation and preparation of a draft report is the communication between the individual members of the WEG. This is most often done through emails and phone calls. Most WEG, despite the need for a face-to-face meeting to discuss the individual details of the HTA process, communicate entirely remotely.

Expert refusals often occur for various reasons - personal and official workload, participation in marketing activities with the specific drug, etc. This requires re-amendment of the order and re-notification of the other members of the WEG, which further delays the process.

At a later stage, the procedure is delayed further due to delay making it a decision already submitted and presented a report from HTAC return or report processing. The percentage of draft reports returned for processing ranges from 35% to 41%, with a tendency to increase the number of revisions over the years.

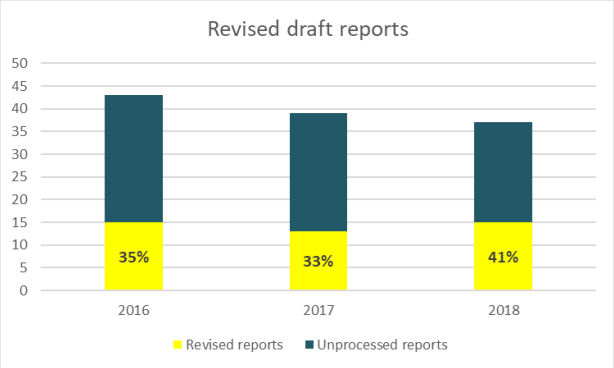


Figure 6. Draft reports returned for revision.

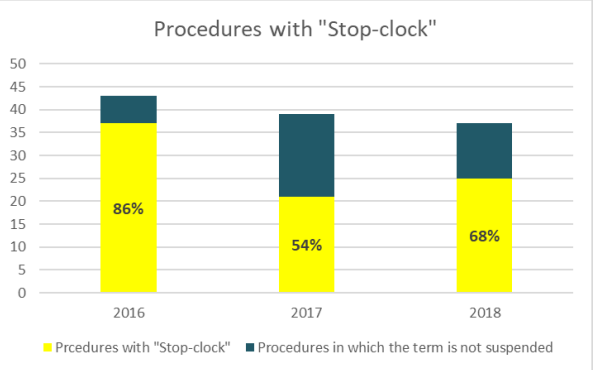


Figure 7. Procedures in which the term is suspended.

In case additional documents are required from the company in the process of work, this period stops running until the date of elimination of inaccuracies. These "suspensions" of the HTA procedure can be at different stages of the evaluation:

- At the stage of legal assessment and admissibility of the submitted documentation;
- At the stage of additional questions from the WEG;
- At the stage of application for revision of the draft report by the HTAC.

The most suspensions of the procedures were observed in 2016. During this period, the remarks most often concern the legal part and the initial preparation of the MAH documentation. This is logical and understandable, as the process started this year and the Applicants were not yet familiar with the requirements in detail and do not have accumulated experience and routine for the HTA process.

Over the next two years of the analyzed period, the percentage of procedures in which the term was suspended fell sharply. During these years, as a result of the accumulated experience and knowledge among the experts in the field of HTA, the additional questions from the working commissions become more frequent.

Summary: The normatively set term of 90 days turns out to be insufficient and, regardless of the efforts made, is not observed in 90% of the implemented procedures. The average duration of an HTA procedure in Bulgaria in the analyzed period is about 156 days or 73% more than allowed. The established practice shows that in the country the duration of HTA is close to the group of EU countries with a set deadline for HTA of 90-220 days.

3.2. HTA experts

3.2.1. Analysis and evaluation of the provision with HTA experts

Objective: To review and analyze the register of HTA experts, to conclude its specifics, the availability of potential and competence for the implementation of HTA in the country, and the quality of the experts' conclusions.

WEG in Health Technology Assessment under Article 10, paragraph 1 of the Ordinance are advisory bodies to the Director of NCPHA which consist of at least 4 (four) members including a chairman.

With the start of the HTA process in the country, a procedure for recruiting experts from various fields - physicians, dental specialists, master pharmacists, economists, statisticians, lawyers, other specialists to join as members of the working expert's groups.

A register of experts has been set up, and the procedure for inclusion in it requires the applicant to submit an application to the Director of the NCPHA with personal and professional data, including a professional autobiography.

To start the process of recruiting experts, the HTA Department prepared and sent letters to all universities, national consultants (at that time), university hospitals, the non-governmental sector, and other institutions in order to issue invitations and promote the process. Over a period of 1 month, more than 800 units of official correspondence were sent on paper.

Those wishing to join as external experts at the NCPHA for HTA should meet the following criteria:

- to have the educational qualification degree "master";
- for physicians to have acquired a

clinical specialty, which in consequence correlate with the scope of assessments medicinal product;

- to have at least 5 (five) years of experience in the specialty.

An advantage in determining an expert in the WEG has the persons, who:

- have the Ph.D. degree;
- is a habilitated person;
- have scientific publications in the field of HTA;
- have publications in foreign scientific journals with impact factor;
- have additional specializations or qualification courses in the field of clinical trials, pharmacoeconomics, health technology assessment, etc., relevant to the activity of the WEG;

As a result of the sent letters, 382 applications for participation were submitted by specialists from different fields, all of which were approved and the people were included in the specially created register.

A chairman or a member of a WEG may not be a person involved in activities related to the development, production, marketing, wholesale and retail trade of the evaluated medicinal product. In this regard, each member of the WEG must fill in and submit a declaration of conflict of interest in a form approved by the Director of NCPHA.

The composition of each WEG must include a person with a master's degree in medicine and a specialty in the profile of the disease for which the HTA is performed.

WEG carried out a preliminary assessment of the documents and prepares a draft report for Health Technology Assessment in accordance with the applicable № 3 by the Ordinance. In the process of work, additional documents may be required from the company, incl. revision of the analysis, which suspends the procedure.

The draft report contains four main sections concerning the different areas - health problem analysis, comparative analysis of therapeutic efficacy/efficacy and safety, pharmacoeconomic indicators analysis, budget impact analysis. The structure of the report requires in each WEG, as a rule, to participate: one or two doctors, at least one master pharmacist, economist and lawyer.

The information on all experts included in the register is summarized in a table (excel file) and is updated periodically. Almost a year after the launch of the process NCPHA already had a base with 258 experts in various fields.

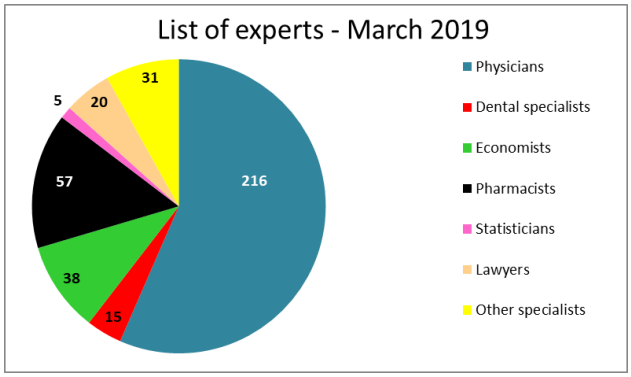


Figure 8. Register of experts as of January, 2017

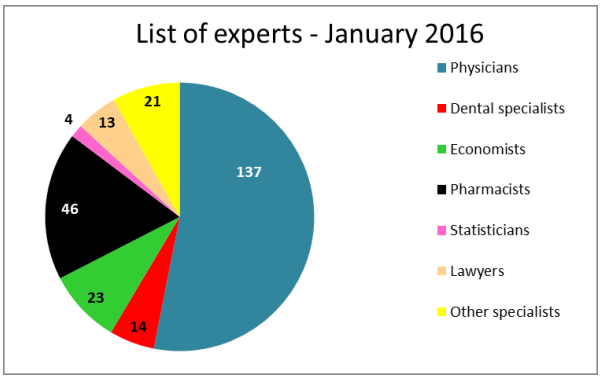


Figure 9. Structure of experts by specialties as of March 31, 2019

As of March 2019, the number of experts included in the register is already 382. Physicians from various specialties predominate. The number of statisticians and economists is relatively small and does not cover the needs of the process, so the same expert has to be involved at the same time and work in several committees at the same time.

A significant part of the experts are habilitated persons and their number has increased over the years. The large number of habilitated persons who have applied for inclusion as experts in the WEG is dictated by their scientific interest in the specific field and the topicality of the HTA process in Bulgaria. As chairman always is appointed a habilitated person and shall always be appointed the person responsible, preferably a physician with a profile of specialty for the specific disease.

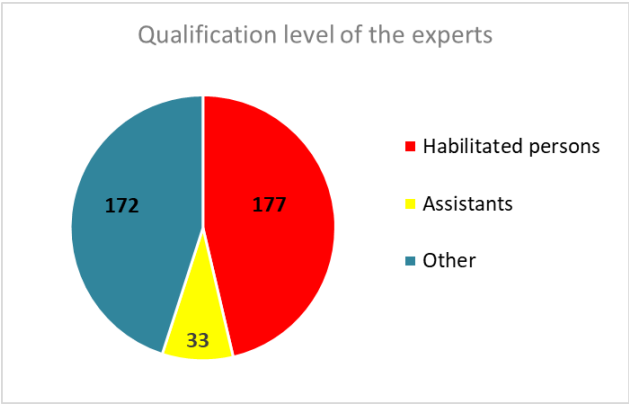


Figure 10. Qualification level of the experts included in the NCPHA register as of January 2017

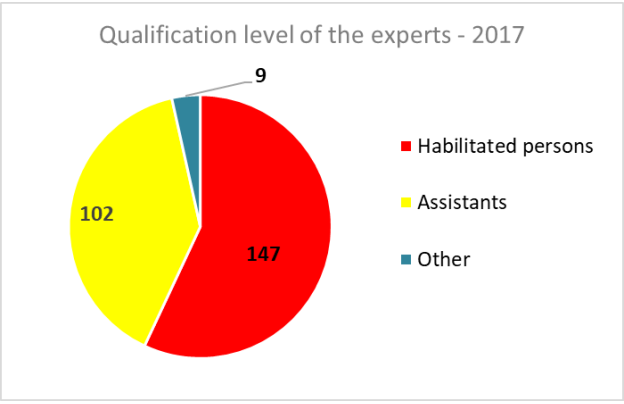


Figure 11. Structure of the experts by qualification level as of 31.03.2019

The largest share of habilitated persons is among dentists and doctors, while the persons holding the academic position of “assistant” predominate in the group of

pharmacists (Figure 12). In general, the relative share of habilitated persons increases with each passing year.

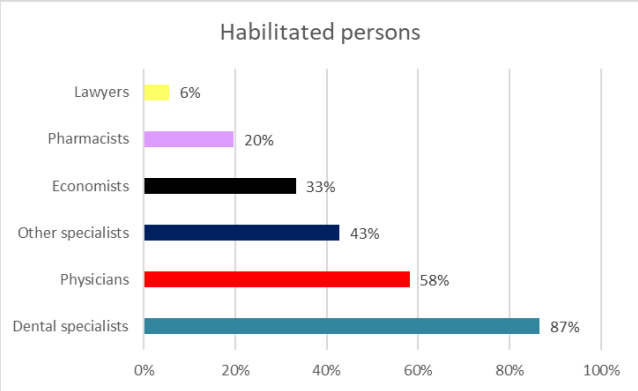


Figure 12. Share of habilitated persons in the different groups of specialists.

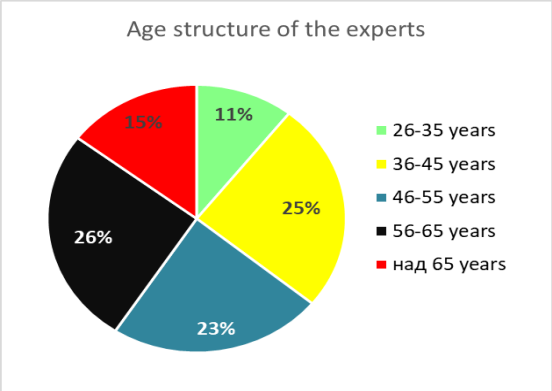


Figure 13. The age structure of the experts.

The age structure of the experts is based on a representative sample of 250 people from the register of experts. The youngest expert who submitted an application for inclusion in the WEGs on HTA is 28 years old, and the oldest is 82 years old and he works actively in the analyzed period. The age structure of the experts shows interest on the part of specialists from different generations, interest in the process, and their desire to contribute to the development of HTA in Bulgaria. There are no significant differences in age groups.

The number of experts in the register is traced in the dynamics of the following figure 14.

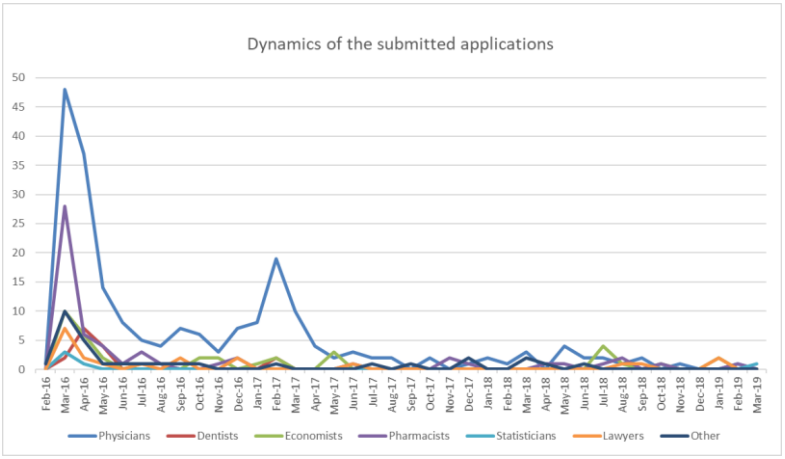


Figure 14. Dynamics of the applications submitted by experts

There is a pronounced peak at the beginning of the process in March, April and May 2016, which is linked o the campaign of NCPHA recruitment experts and sending letters to the different institutions. An increase in the submitted applications was

also observed at the beginning of 2017 when a large number of information letters were again sent to the national consultants and patient organizations.

Summary: The collected information and studies show the presence of significant expert potential and interest in conducting HTA by specialists with different levels of education, position, and specialty. It can be concluded that the system for conducting HTA in Bulgaria is provided with experts and the human resources and potential guarantee the quality performance of the tasks regarding HTA of medicinal products. All internationally recognized and comparable standards for clinical, economic, epidemiological and legal assessment, quality, and avoidance of conflicts of interest and completion of procedures on time have been introduced.

3.2.2. Analysis of the compositions of the job they committees

The composition of each WEG is compulsorily voted on at a meeting of the HTAC after the documents submitted by the MAH have been reviewed for admissibility and the procedure under the HTAC has been initiated. As a rule, each WEG includes specialists from different fields - physicians, pharmacists, economists, lawyers and a group of others. Required in the composition of the WEG includes physicians with a specialty on the profile of the disease, which is carried HTA. It is recommended that he be appointed Chairman of the WEG and accordingly submit a draft report to the HTAC, as it is assumed that he is best acquainted in detail with the specifics of the disease, the number of patients, therapeutic practice, pharmacotherapeutic action, guidance, recommendations of international and national professional societies, the need for the medicinal product, ADRs, etc.

Due to the nature of the work, it is necessary to include in the composition of each WEG:

- Two physicians and a one and one health professional group of "others" to prepare the clinical part of the pro is KTA report - the first two sections "Analysis of the health problem" and "Comparative analysis of therapeutic efficacy/effectiveness and safety"
- At least one Master of Pharmacy, who should prepare a section "Analysis of pharmacoeconomic indicators"
- At least one economist competent in preparing a 'Budget Impact Analysis'
- If necessary, no more than one lawyer is appointed in the WEG, who prepares an opinion on the administrative part of the submitted documentation,

observes compliance with the deadlines of the procedures, and assists and records the meetings of the WEG.

- At the end of 2017, the decision was made to the composition of each WEG to be determined and a technician from NCPHA, which supports communication so between members of the WEG to prepare and submit materials to the members of the WEG to provide technical assistance in case of questions, preparation of minutes of meetings, entry of documents on the spot, forwarding of emails, etc.

The average number of experts in a commission over the years is from 5.25 to 5.59 (Figure 15).

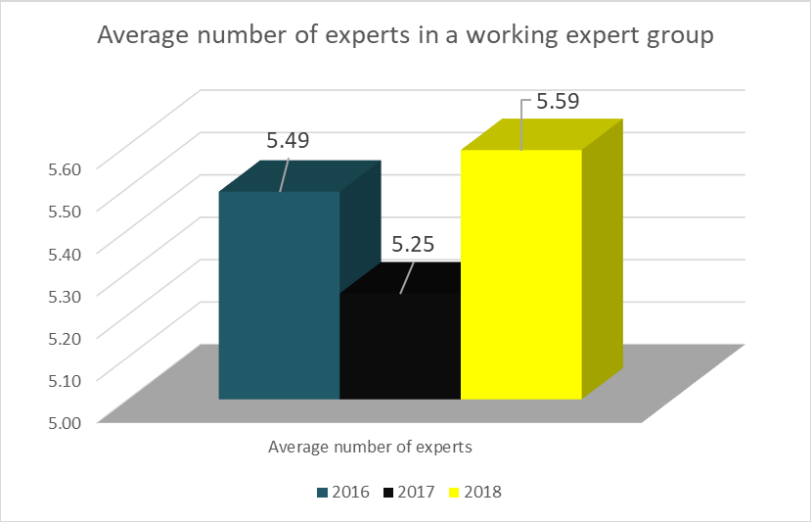


Figure 15. Average number of experts in a working expert group by years

The largest share is physicians followed by pharmacists and economists. Lawyers and specialists from group 'others' were not included in any committee, as this is why their average number is less than 1.

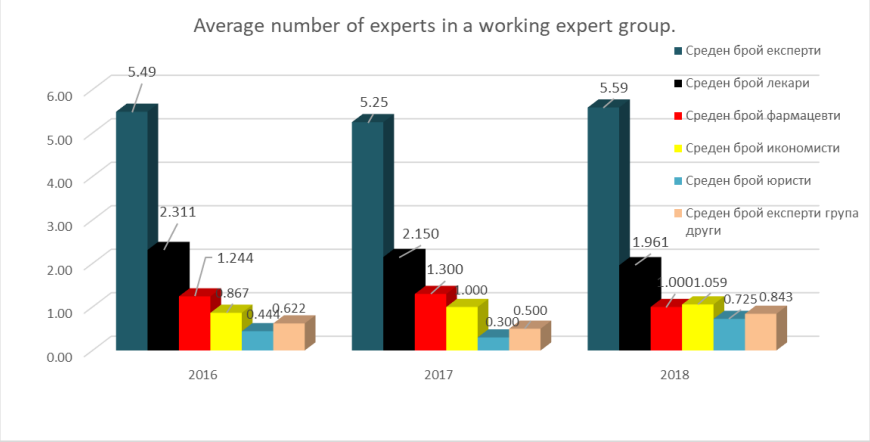


Figure 16. Average number of experts in a working expert group

The ratio of men/women in the composition of the WEG was followed.

The number of appointed experts is dominated by women and the difference is most noticeable in 2016.

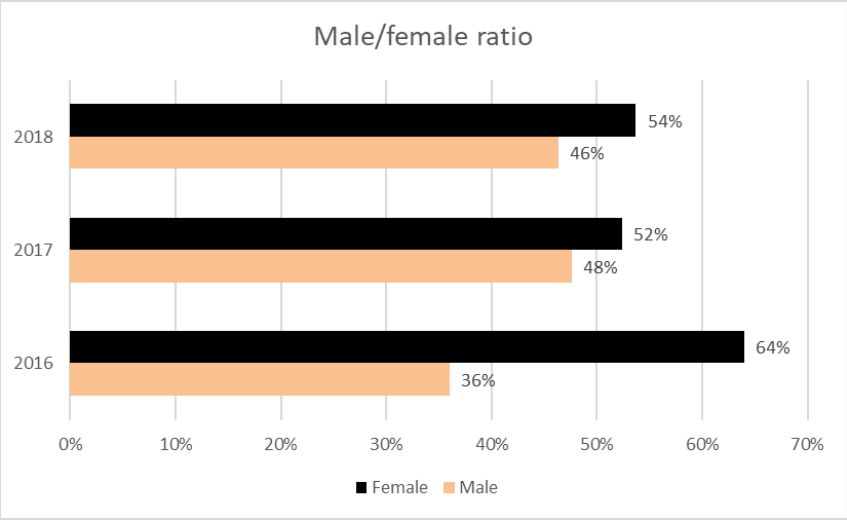


Figure 17. Male/female ratio in the composition of the WEG.

The ratio of women to men in each committee was also examined as the most common value.

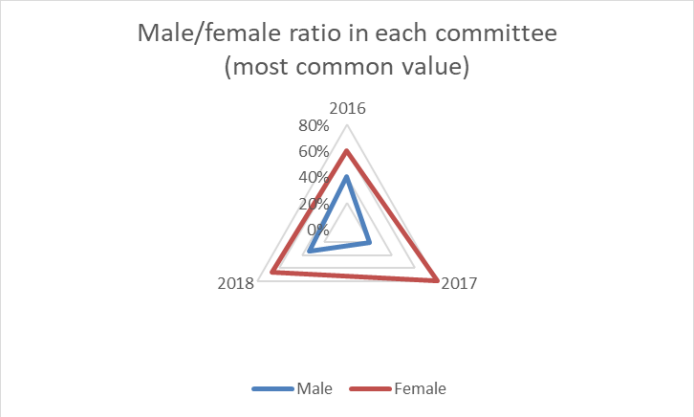


Figure 18. Male / female ratio in each committee / most common value /

Male / female ratio in each committee / most common value /	**2016**	**2017**	**2018**
Men	40%	20%	33%
Women	60%	80%	67%

Due to refusal by experts, the compositions of the WEG are often changing. Analysis of the number of issued orders to determine the nominal composition of the WEG and subsequent orders to displacements of the composition shows that in almost half of the cases the compositions are changed at least once.

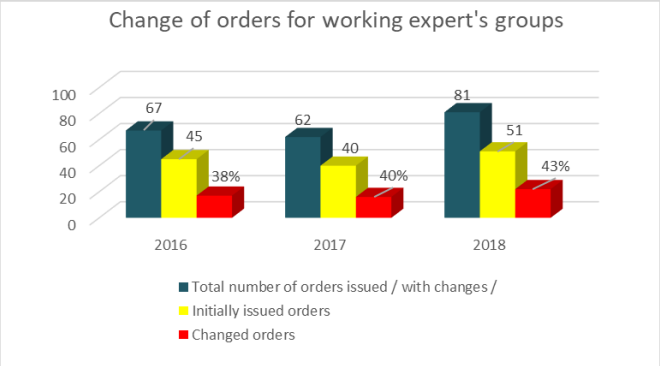


Figure 19. Change of orders for the determination of the memorial composition of working commissions.

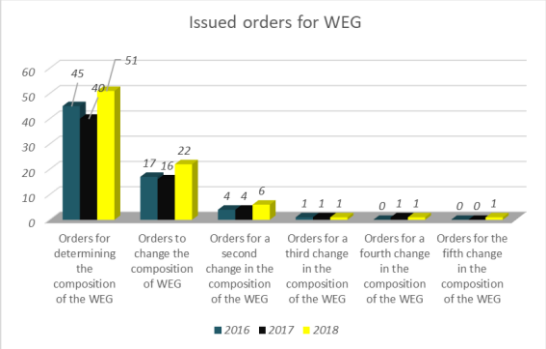


Figure 20. Issued orders for determining and changing the composition of the WEG.

Among the main reasons for refusing experts so by participating in WEG is a great pressure of work, participation in a clinical trial with this medicinal product which assesses long-term absence from the country or illness.

Dropping out of the WEG shall be certified by submitting a letter of application to the Director of NCPHA.

An upward tendency of increasing the number of refusals over the years is observed.

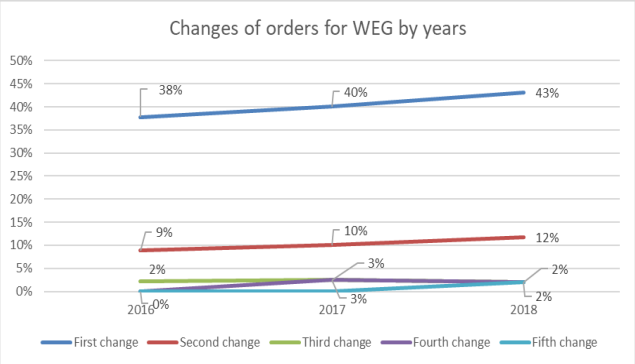


Figure 21. Changes of orders for WEG by years.

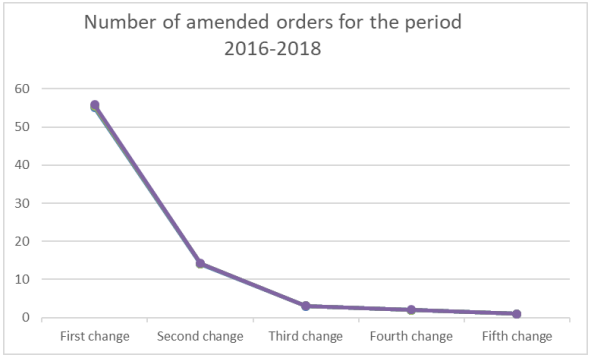


Figure 22. Number and amended orders for the period 2016-2018

Out of a total of 136 issued orders for the analyzed three-year period, 55 (40%) have been changed at least once.

An analysis of the therapeutic areas in which most often is altered the composition of the WEG is presented.

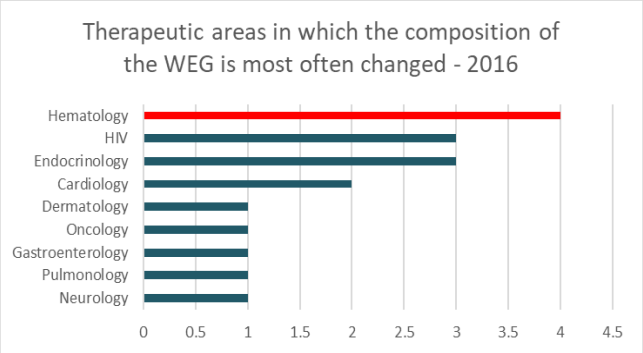


Figure 23. Therapeutic areas in which the composition of the WEG is most often changed - 2016

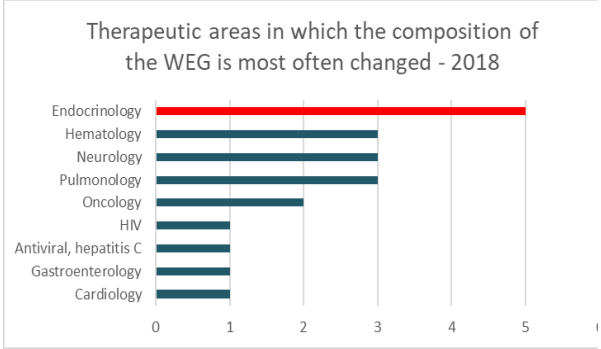


Figure 24. Therapeutic areas in which the composition of the RC is most often changed - 2018

Most changes in the number of orders issued in 2016 are in the fields of dermatology, hematology, HIV, and in 2018 - Antiviral and Pulmonology

Summary: The presented data show that the WEG follows the requirements of the regulatory framework, is dominated by medical professionals, predominantly physicians, followed by pharmacists and the participation of other professionals is rather due to the specific need for the scope of the assessment. The variability of the composition of the WEG is a common practice, which prolongs and delays the performance of the assessments.

3.3. Research and analysis of awareness about the process of health technology assessment in Bulgaria

Objective: To study the level of awareness about the HTA process, as well as to collect and analyze data from the opinion of experts, representatives of pharmaceutical companies, media, patients, and the public on the organization of the HTA process until 31.03.2019 and to assess the regulatory changes introduced after that date.

In the period from the introduction of the process of health technology assessment to March 31, 2019, more than 370 experts from various fields were involved – physicians, pharmacists, economists, lawyers, and other specialists with higher education.

To collect data on the objectification of knowledge about HTA, in 2017 for the first time in Bulgaria, a survey was conducted on the awareness of the public

and professionals about this new process for our country. The performed primary analysis was published and gave an idea of the awareness related to the HTA process and the procedures that accompany it, based on the experience gained for 2016-2017.

In 2019, a second study was conducted to collect and analyze data on changes and trends in the opinion and assessment of experts, representatives of pharmaceutical companies, media, patients, and society on the organization of the HTA process until 01.04.2019 and the introduced regulatory changes after that date.

The respondents answered a total of 150 questions. They cover the various stakeholders - media, industry (pharmaceutical), patients, physicians, and experts in the field of HTA.

Question № 1 shows to which group the respondents are assigned. The largest share of the expert's in total (47 answers), followed by physicians (38 answers) and representatives of academia (35 answers). The surveyed representatives of the industry are 16, the representatives of the media - 4, patients - 2 and 8 of the respondents have identified themselves in the category "others".

The following graph shows the distribution of respondents.

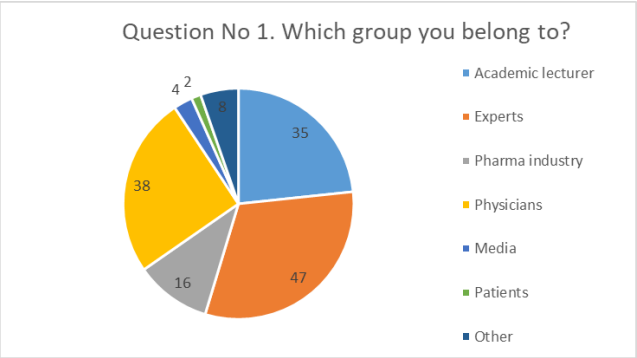


Figure 25. Question No 1. Regarding the group to which the respondents belong.

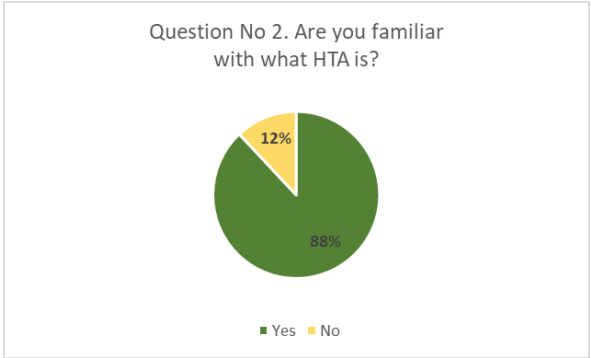


Figure 26. Question No 2. Are you familiar with what HTA is?

Question No 2 on knowledge of the nature of HTA was answered by all 150 respondents, with only 12% answering that they were not familiar.

For comparison, 2 (two) years ago the respondents who were not familiar with the process were 20% or by about 40% the share of those unaware of HTA in the target sample decreased. From these data, it can be logically concluded that awareness has almost doubled over the past period.

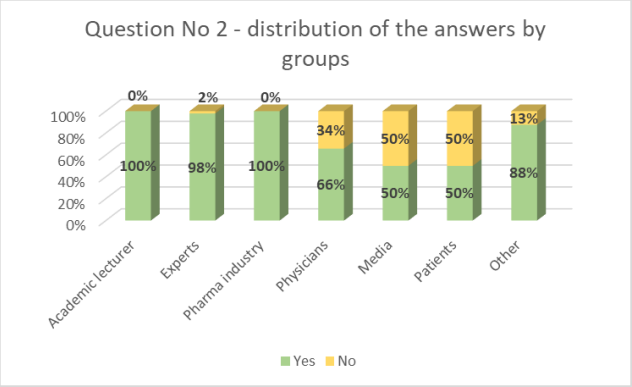


Figure 27. Distribution of the answers to question No 2 by groups.

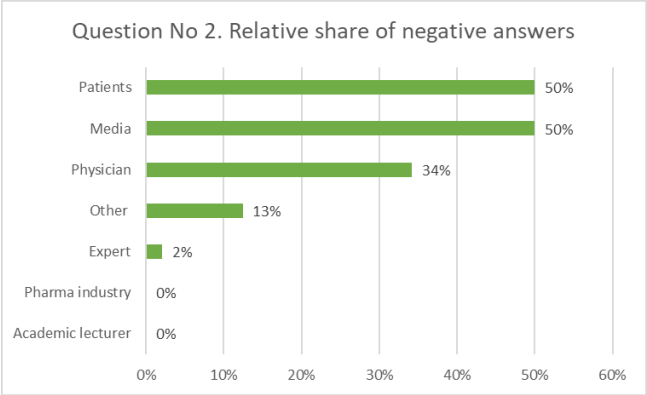


Figure 28. The relative share of negative answers to question No 2.

The results show that in the group of academics, experts, and industry, almost everyone is familiar with the HTA process.

Of the 18 respondents with "no", the highest relative share is patients, followed by the media and physicians.

In the previous study, the largest share of those unfamiliar with the process was among patients. This is explainable and understandable because of the specifics.

We can see an increase in the share of physicians who are not familiar with the process. The explanation is probably due to the larger number of surveyed physicians who are not included in the register of NCPHA experts and have not participated in WEG. Experts who state that they are not aware of what constitutes HTA sharply decreased, compared to 2017 from 15% to 2%. This is an expected consequence of the accumulated experience, but also evaluates the actions taken to ensure continuing education in this area, as well as the inclusion of this topic in the training of students and graduates.

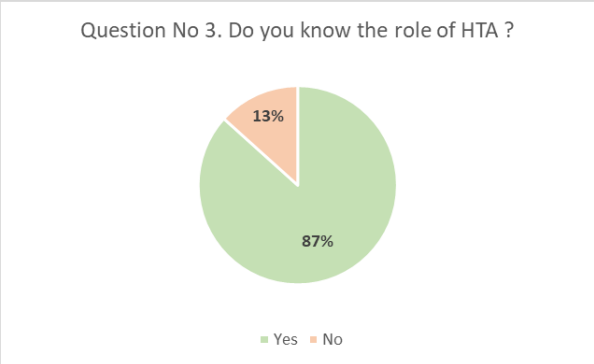


Figure 29. Question No 3. Do you know the role of HTA?

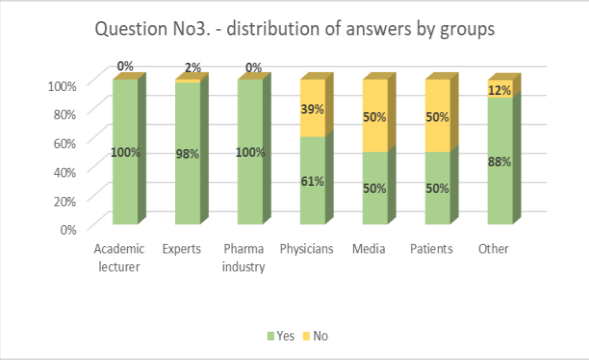


Figure 30. Distribution of the answers to question No 3 by groups.

Only 20 of the respondents (13%) do not know the role of HTA in the healthcare system, drug policy, and, accordingly, decision-making for access to new technologies. A comparison with the previous survey, (25% as of 2017), shows that their number has almost halved.
The distribution of respondents shows that patients and the media are again the least familiar with the role of HTA, which is to be expected, but it is worrying that 39% of those who answered "no" are physicians.

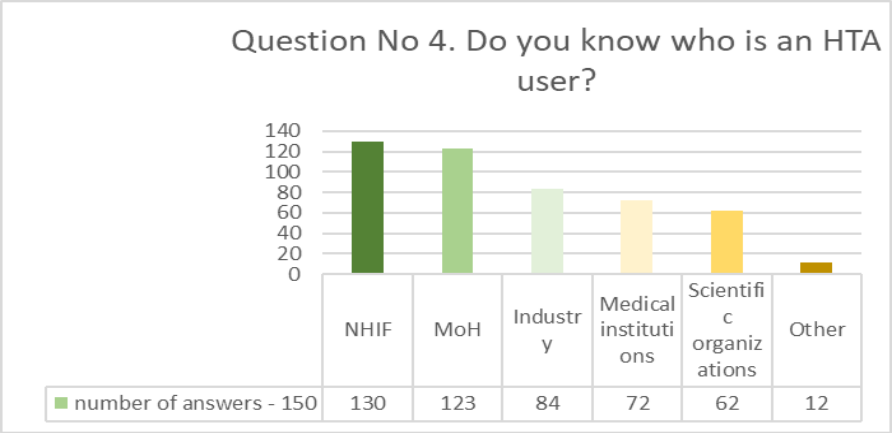


Figure 31. Question № 4. Do you know who is a user of HTA?

The respondents indicated the National Health Insurance Fund and the Ministry of Health as the main users of HTA. About 41% of the respondents indicated that the users of HTA are the scientific organizations and so this answer ranks last. This is too small, as, in addition to regulators, the main beneficiaries of HTA are mainly scientific organizations and research societies.
The answers of the respondents to 2017 to the same question do not show a significant difference.
As other possible users of HTA, the respondents indicated patient organizations, NCPR, patients, and the public.
Question № 5 was developed in order to obtain information about the respondents' opinion on the organization of work and the start of the process in our country in 2016.

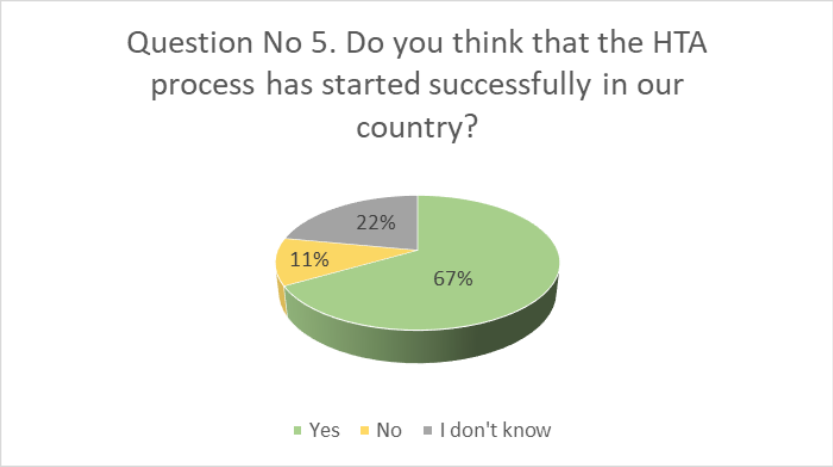


Figure 32. Question № 5. Do you think that the HTA process has started successfully in our country?

A large part of the respondents (67%) answered "yes" to the question, which gives a predominantly positive assessment of the activity carried out so far. Approximately a quarter (22%) of the respondents answered "I do not know" and only 11% believe that the HTA process has not started successfully in our country.

The following graph shows the distribution by groups of respondents who answered in the negative.

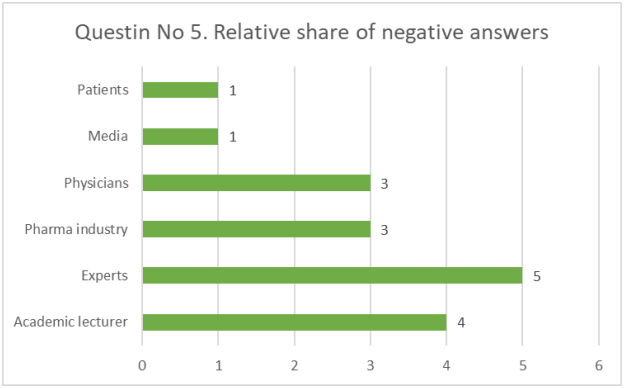


Figure 33. Distribution of negative answers to question No 5.

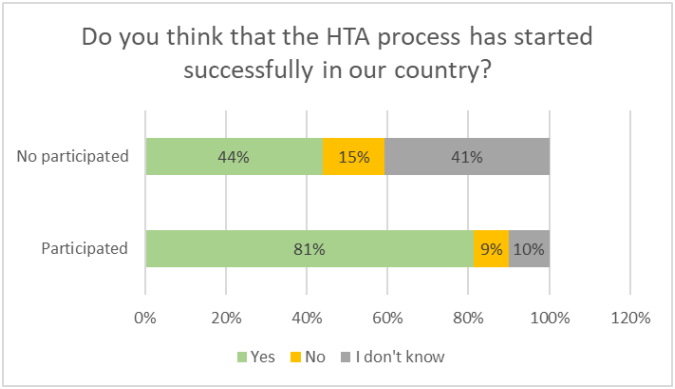


Figure 34. Distribution of the answers to Question No 5 according to the criterion for participation in RC.

To be able to obtain an objective assessment, it is important to study and summarize the opinion of the experts who have participated in WEG on HTA, as they have experience and a direct view of the process.

The results show that 81% of the respondents who participated in WEG believe that the HTA process has started successfully, compared to 44% of those who did not participate. Among those who did not participate, the share of answers with "I

do not know" is also high, which is expected, as in this group the respondents are less familiar with the process.

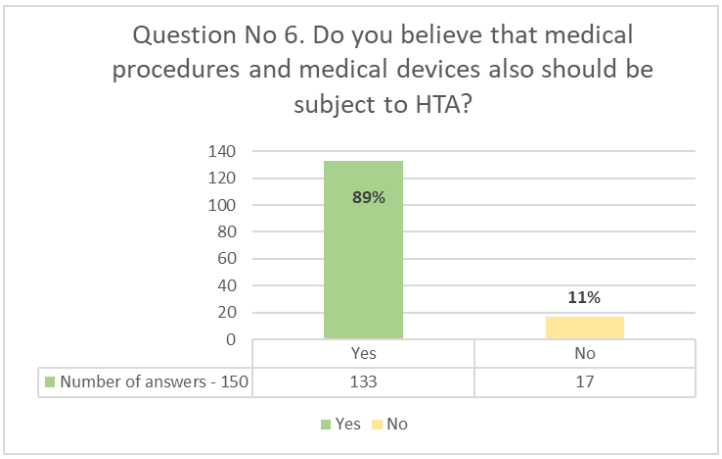


Figure 35. Question No 6. In addition to medicines, do you consider that medical procedures and medical devices should be subject to HTA?

The majority (89%) of respondents believe that HTA should be applied not only to medicinal products but also to cover other aspects of health and medical activities such as procedures and medical devices. However, the positive answers are less than in 2017 (then over 94%). This is probably due to the better acquaintance of the experts with the process, the problems with the lack of epidemiological data and the practical difficulties encountered in conducting HTA.

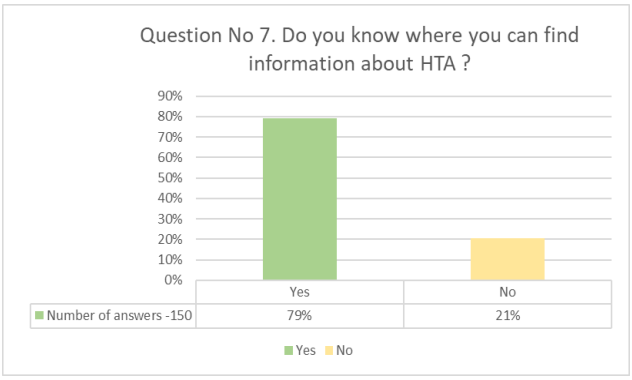


Figure 36. Question No 7. Do you know where you can find information about HTA?

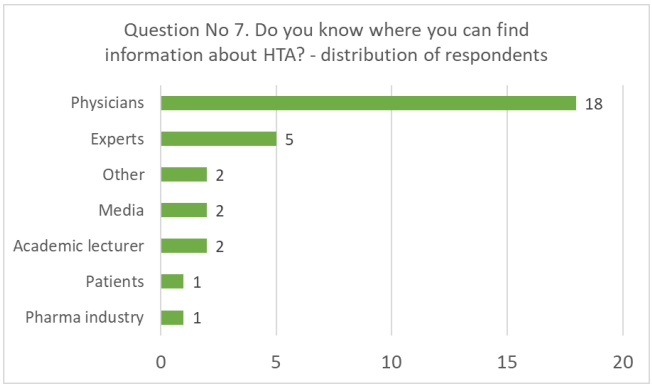


Figure 37. Question No 7. Do you know where you can find information about HTA - distribution of respondents?

The share of respondents who indicated that they do not know where to find information about HTA is 21%. This share is 12% less than in 2017, which speaks of greater public awareness after 3 years of experience. The distribution of respondents with "no" is presented in the following graph.

The share of physicians who answered negatively to this question is alarmingly high.

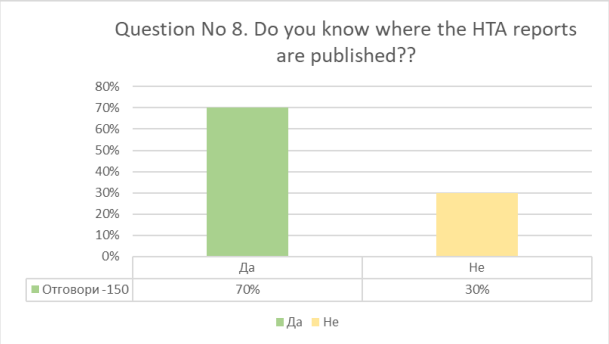


Figure 38. Question No 8. Do you know where the HTA reports are published?

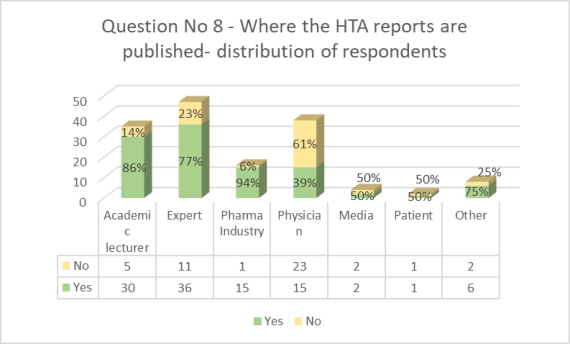


Figure 39. Question No 8. Do you know where the reports on HTA are published - distribution of respondents?

Almost 2/3 of the respondents know where the reports (summaries) with the performed assessments on HTA are published, which speaks for significantly better awareness compared to the previous survey in 2017 (59% of positive answers). As many as 94% of industry representatives expect to know where HTA reports are published, from which it can be concluded that the information published in the summaries of the reports is mostly used by pharmaceutical companies.

The next question concerns the depth of knowledge about the nature of the HTA performed.

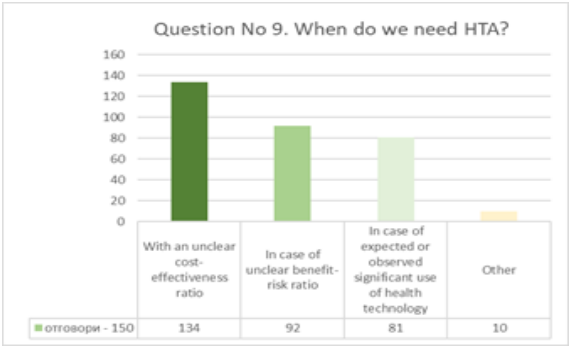


Figure 40. Question No 9. When do we need HTA?

Answers from a 2017 survey	
With an unclear cost-effectiveness ratio	77,56%
In case of unclear benefit-risk ratio	59,51%
In case of expected or observed significant use of health technology	59,51%

Figure 41. When we need HTA - answers from a previous study in 2017

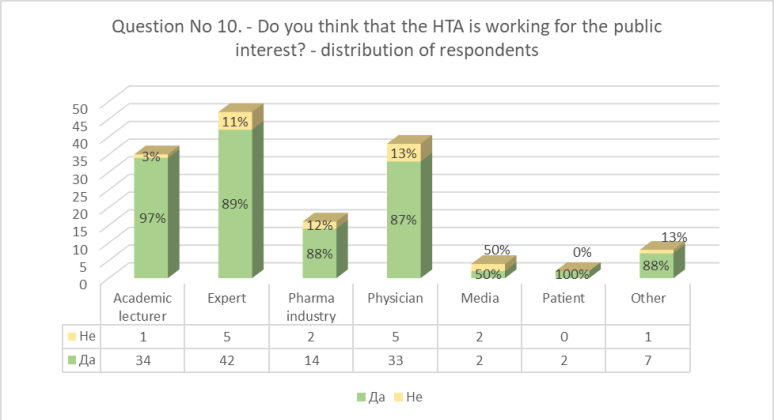


Figure 42. Distribution of respondents to question No 10.

The share of respondents who believe that HTA works in favor of the public interest is 89%, which is 7% more than in 2017. This indicates greater confidence compared to the previous period and a positive assessment of the work done, as well as better knowledge of the process in society.

The distribution of the answers in the different groups of respondents is shown in the following graph. Patients are most interested in the introduction of HTA and this group, 100% of the respondents answered "yes". The share of positive responses is increasing compared to 2017 in the group of industry, physicians, and experts.

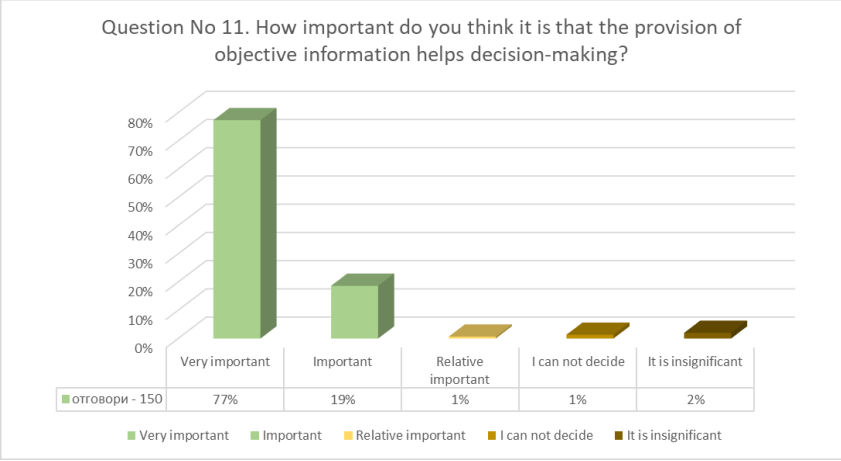


Figure 43. Question No 11. How important do you think it is that the provision of objective information helps decision-making?

The share of respondents is extremely high, who believe that the provision of objective information helps to make decisions about access to innovative medicines and new technologies. Respondents' answers to this question did not differ significantly from the previous survey in 2017.

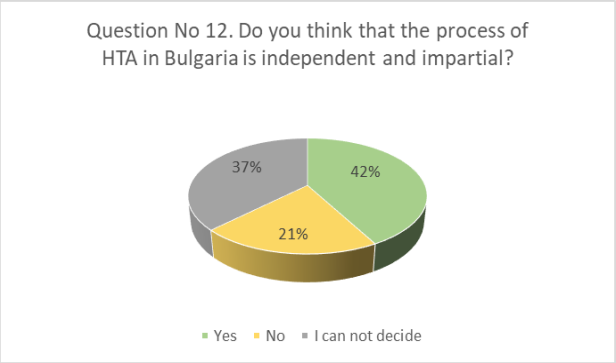


Figure 44. Question No 12. Do you think that the HTA process in Bulgaria is independent and impartial?

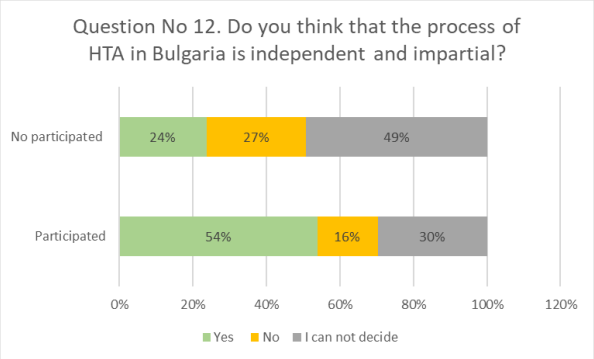


Figure 45. Distribution of the answers according to the criterion for participation in the RC to the question of whether the HTA process in Bulgaria is independent and impartial.

To take into account, the opinion of the experts who have worked on specific procedures (participated in WEG); the following graph shows the distribution of responses according to this criterion.

All respondents	**Number**	**Title**
Excellent	22	15%
Very good	65	43%
I cannot decide	17	11%
I have no opinion	25	17%
Not very well	10	7%
Definitely not good	11	7%
Total	**150**	**100%**

Figure 46. Question № 13. How do you evaluate the process and the implementation of HTA until now?

More than half of the respondents (58%) rate the HTA process excellently or very well, 28% have no opinion or cannot judge, and only 14% rate the process negatively.

The following graph shows the distribution of respondents by groups.

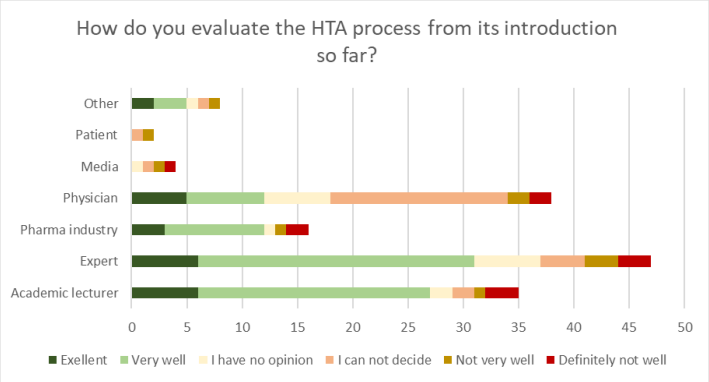


Figure 47. Distribution of the respondents' answers by groups of Question No 13

It is noteworthy that in the group of patients, media and physicians the predominant responses are neutral or negative, while in the other groups the responses are largely positive (industry, experts, and academics).

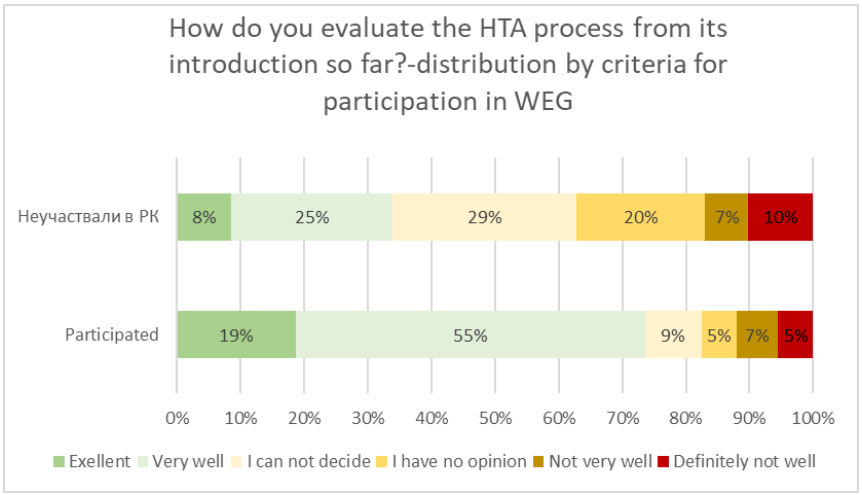


Figure 48. Distribution of the answers to Question No 13 according to the criterion for participation in the WEG.

In the group of respondents who did not participate in the WEG on HTA, the answers “I have no opinion” and “I cannot judge” prevail, which is logical and normal, as they do not know the organization of the process in detail.

Of the respondents who indicated that they had participated in WEG, 74% rated the process as excellent or very good.

The next question concerns the qualification of the experts.

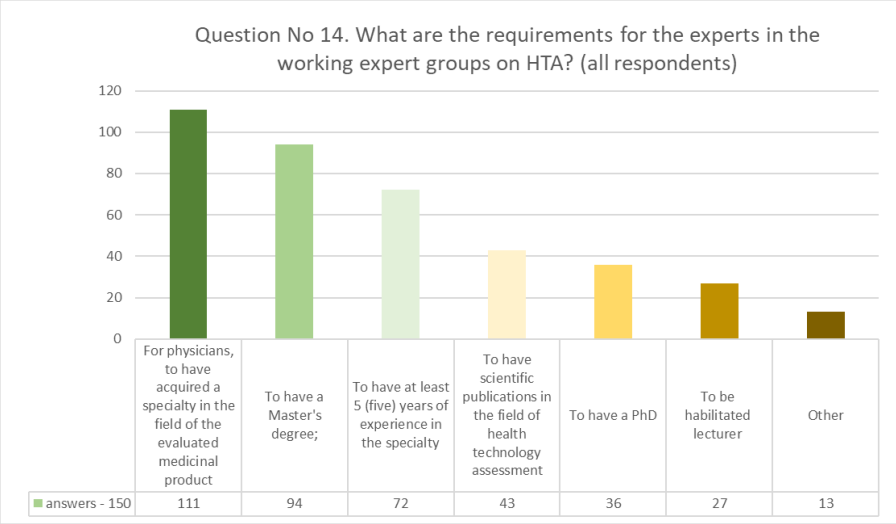


Figure 49. Question No 14. What requirements do the experts in HTA working groups have to meet?

Respondents assess as the most important the acquired specialty in the field of the evaluated product, as well as the experts to have a master's degree.

In the category "other" the respondents indicated professional experience from the point of view of the industry, personal qualities such as honesty, integrity, independence, teamwork, to have international experience, and others.

Out of 150 respondents, 91 (61%) of the participants have participated at least once in a WEG on HTA.

To be able to examine the main problems in the preparation of draft reports by the WEG, the respondents who participated in the WEG were asked additional questions, which provide an opportunity to look at the problems and difficulties that are most common when performing an assessment.

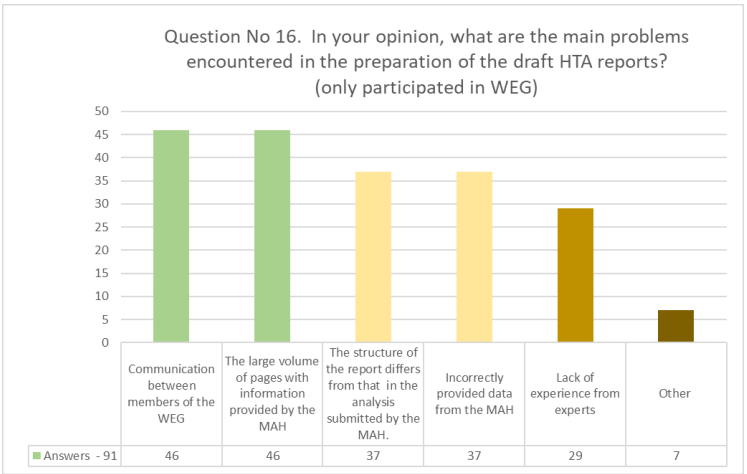


Figure 50. Question No 16. What do you think are the main problems encountered in drafting a report on HTA?

On this issue, the experts point out in the first place as a problem the poor communication between the members of the WEG and the large volume of pages of information (dossier) provided by the MAH, which need to be analyzed.

The lack of experience on the part of the experts is pointed out last, which speaks of the experience gained during the analyzed period and the greater confidence in the expertise of the participants in the HTA process.

As additional problems in the column "other", the respondents indicated the lack of clear criteria, lack of data; repetition of the same information in different parts of the reports submitted by the MAH and the WEG; insufficiently clear and complete description of the analyzes performed by the MAH (presentation of the results only, often without the initial data and the methodology of the analysis), the need for independent access to international publications, as well as the fact that no critical analysis of the submitted documentation is made but instead, the data submitted by the MAH is transcribed literally.

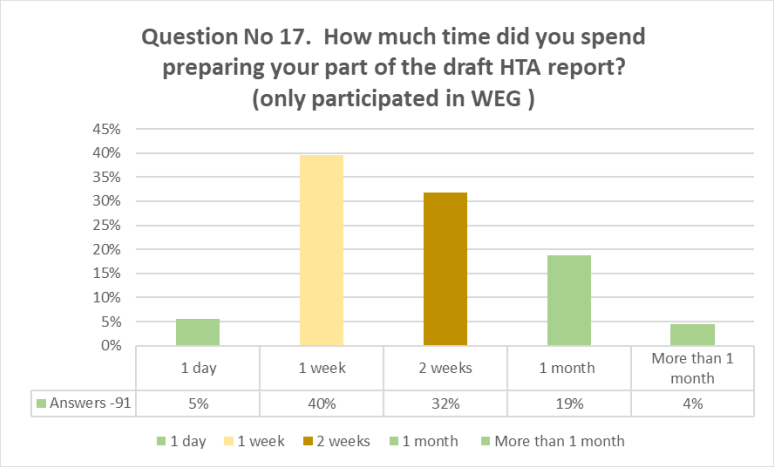


Figure 51. Question No 17. How much time did you take to prepare your part of the draft HTA report?

The normatively determined term for carrying out a procedure for HTA is 90 days (Art. 17, para. 7 of Ordinance № 9 of 1 December on the terms and conditions for assessing health technologies)

Further detailed analysis of the procedures shows that this deadline is in most cases hard to meet. On the other hand, the term for completion of the work of the WEG is set at 40 days from the issuance of the order of the Director of NCPHA.

Most of the experts claim that they have managed to prepare their part of the draft report within one or two weeks. Only 4% indicated a period longer than one month. This gives grounds to conclude that the 40-day deadline set for the prepa-

ration of the draft HTA report is sufficient and does not need to be changed. However, the practice shows that the period from the start of the work of the WEG to the submission of the finished draft report to the NCPHA is much longer. This speaks of poor communication and coordination between the individual members of the WEG, as each member manages to work out his part (section of the report) on time, but the subsequent assembly and technical preparation of the report takes an unforeseen time. This indicates a lack of coordination and requires attention to be paid to the organization of work within the WEG itself.

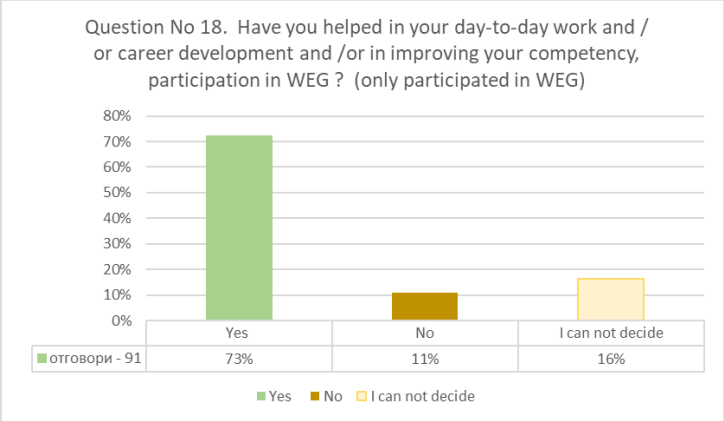


Figure 52. Question № 18. Did participation in HTA WEG help you in your daily work and/or in your career growth and/or in improving your competence?

The last question is open and aims to summarize information about the opinions of academics, physicians, experts, industry and others of the introduced normative changes, according to which the assessment of the health technologies will be performed by NCPR, as of 01.04.2019.

As the answers received were varied, some of them short and clear, others more comprehensive and wordy. In order to summarize and systematize the information, they were grouped into several categories.

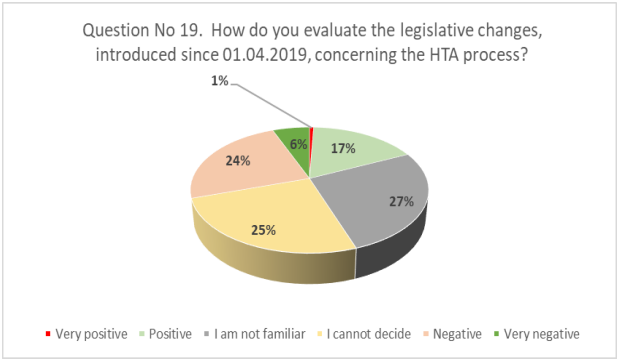


Figure 53. Question № 19. How do you evaluate the normative changes introduced on April 1, 2019, concerning the HTA process?

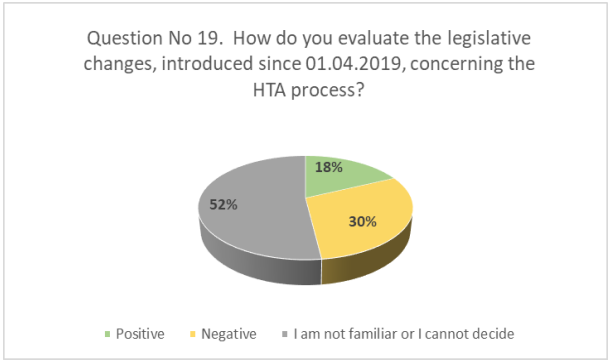


Figure 54. Grouped answers to Question № 19.

In order to present the information in an even more generalized form, the answers were reduced to three groups:

- Positive
- Negative
- I'm not familiar or I can't judge

The analysis made in this way shows that more than half of the respondents are not aware of the changes or cannot evaluate them.
This confirms the insufficient publicity and awareness of the public about the changes in the organization of the HTA process.
Only 30% of the respondents give a categorically negative assessment of the introduced changes.
Among the answers are opinions that criticize the way the legislative changes take place, pointing out the lack of argumentation, non-transparency, the concentration of the possibility of influence in only one body, lack of public interest due to difficulties in accessing medicines. Some respondents find the changes ineffective, as there is no sense in restructuring an already functioning structure and the need to start over.

The vast majority of respondents are unaware or give the answer "I cannot judge" because they consider the changes unclear, do not have enough information, or think that more time is needed to be able to assess what is happening.
The following graph shows the answers within the groups of respondents.

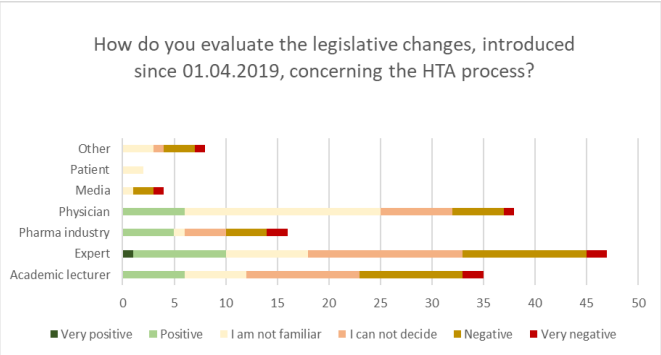


Figure 55. Distribution of respondents by groups of Question № 19.

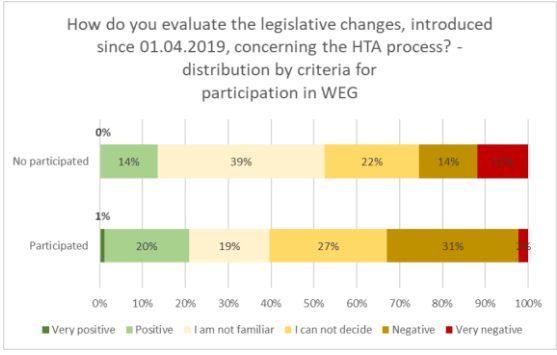


Figure 56. Distribution of the answers to Question № 19 according to the criterion for participation in the RC.

The results show that the majority of experts who participated in the WEG gave a negative assessment compared to those who did not participate. The share of ex-

perts who cannot give an assessment is alarmingly high (46% in the group of participants and 61% in the group of respondents who did not participate in WEG on HTA).

Summary and conclusions: From the data from the conducted survey it is necessary to conclude that the process of HTA after the accumulated three years of experience is already sufficiently known to the Bulgarian public. This awareness has doubled in two years. It can be logically concluded that the HTA process is best known to the experts who participated in WEG. The share of respondents who report the positive aspects of the introduction of HTA in Bulgaria is high.
In the two compared studies on the same methodology and largely overlapping issues, a high share of supporters of the provision of objective information in decision-making on new technologies is observed. The share of respondents who believe that HTA does not work in the public interest has decreased significantly.
A large part of the respondents generally positively assess the organization of the HTA process and what has been done so far, and nevertheless, some of the respondents believe that the HTA process in Bulgaria is not sufficiently independent and impartial.
The need for a broader explanation of the changes and their impact on the HTA process in the country was taken into account.

3.4. Analysis of the results of the HTA activities

3.4.1. Activity volume indicators

Objective: To analyze, according to the available data, qualitative and quantitative indicators of the results of HTA activities in the study period.

From the very beginning of the process in NCPHA until 31.03.2019, a total of 146 cases have been submitted by 56 MAH (pharmaceutical companies) for conducting Health Technology Assessment. 127 procedures were completed (Figure 57).

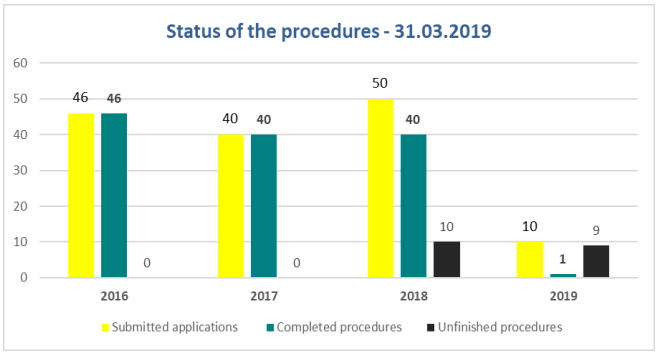


Figure 57. Status of the procedures - March 31, 2019

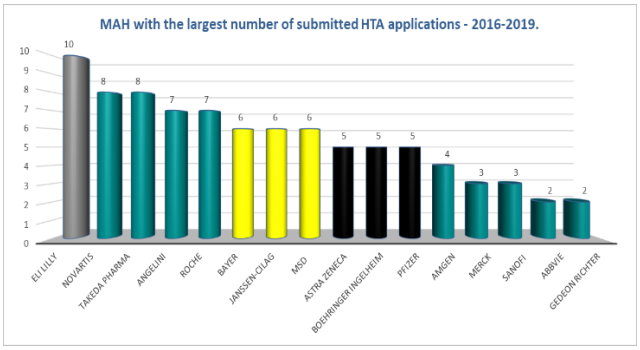


Figure 58. The MAH with the largest number of submitted HTA Applications.

The dynamics of submitting applications for health technology assessment by months was also monitored (Figure 59).

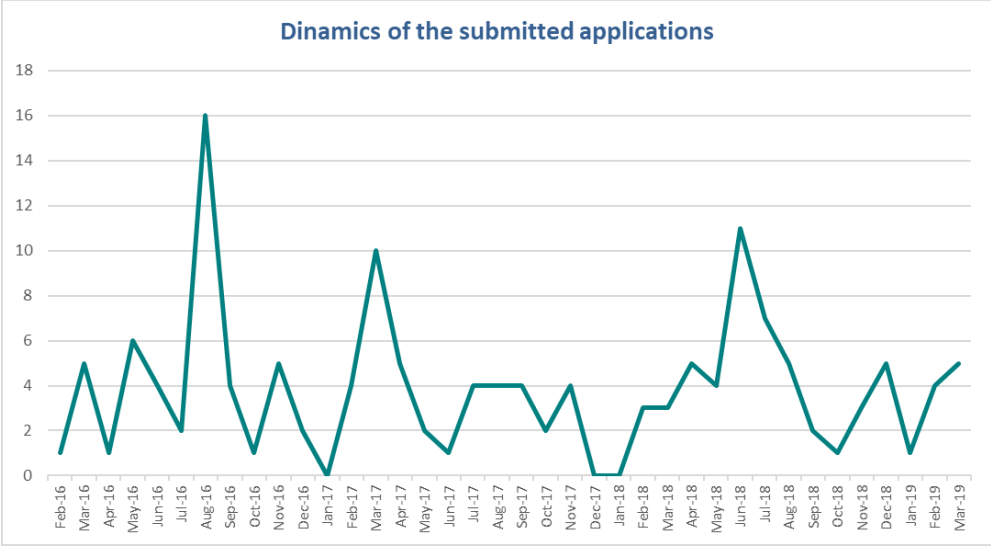


Figure 59. Dynamics of the submitted applications by months for the period February 2016-March 2019

The analysis of applications MAH record indicates that the medicinal products in the field of endocrinology, cardiology, hematology and antivirus products are predominant (Figure 60 Figure).

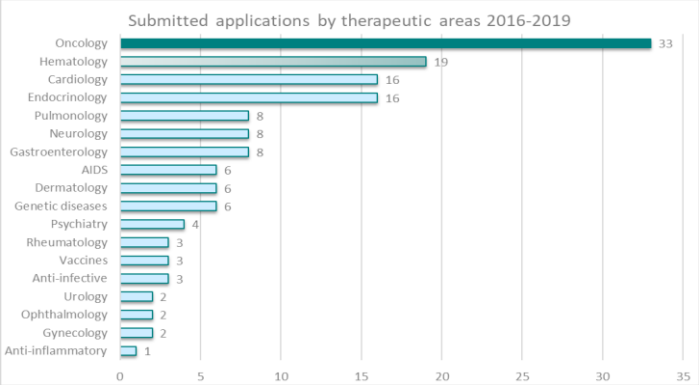


Figure 60. Number of dossiers submitted according to the field of application of the medicinal products.

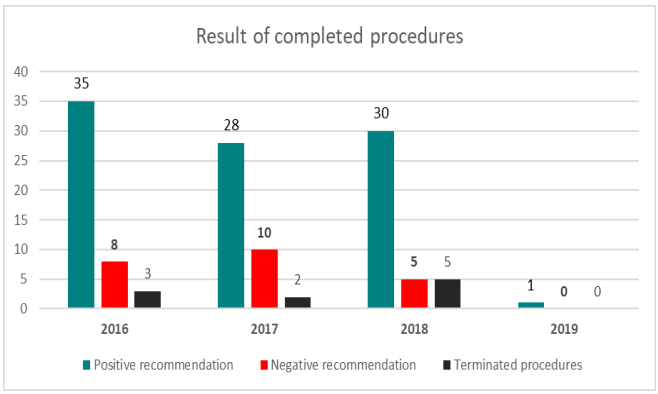


Figure 61. Result of completed procedures.

A total of 94 procedures ended with a positive recommendation (74%), 23 with a negative one, and 10 were terminated. Among the motives of the HTAC for a negative recommendation the most common are:

- The medicinal product is not cost-effective.
- Lack of convincing efficacy data.
- Administrative barriers, the specified ICD code does not correspond to the disease for which HTA is requested and does not correspond to the indications of the medicinal product.
- The preliminary analysis of the MAH is remarkably low quality and does not meet the requirements of Ordinance № 9 and its applications, although several have requested revisions to BC in accordance with these requirements.
- The inclusion of the medicinal product in the PDL would lead to an additional financial burden for patients.

The reasons for termination of the procedure most often with poor quality of submission by the applicant of analysis for HTA and failure to eliminate incomplete notes in time or omissions from the administrative part of documents, incl. and the presence of a negative recommendation in one of the reference countries.

The higher share of positive recommendations indicates the availability of innovative, non-alternative and effective technologies, most of which have already been reimbursed in other countries.

A large part of the medicinal products are intended for rare diseases, which as a rule have a lighter regime for obtaining a marketing authorization and reimbursement. The following chart shows the number of orphan drugs compared to

the total number of applications submitted. An analysis of the applications submitted for HTA combined medicinal products already available in the PDL INN.

The use of the term new international non-proprietary name to some extent distorts the HTA process. This definition in the Ordinance gives rise to a phenomenon, expressed in the assessment of dossiers of old, already existing molecules or combinations between several old molecules, combined in a new form, resp. with a new international non-patent name. The reason for this is legal prerequisites, not a real necessity. In these circumstances, as required by the Ordinance these products must undergo re h process and of HTA. Such situations lead to negative consequences and unnecessary complication of the system.

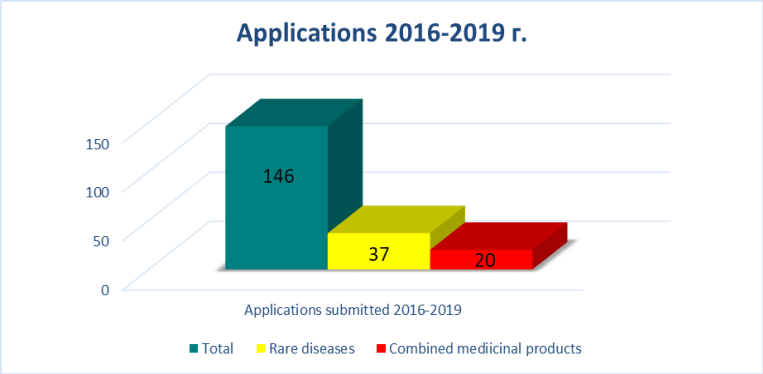


Figure 62. Applications for HTA for rare diseases and combined medicinal products submitted.

25% of all submitted applications are for medicinal products intended for rare diseases, most of which are in the field of hematology (Figure 63).

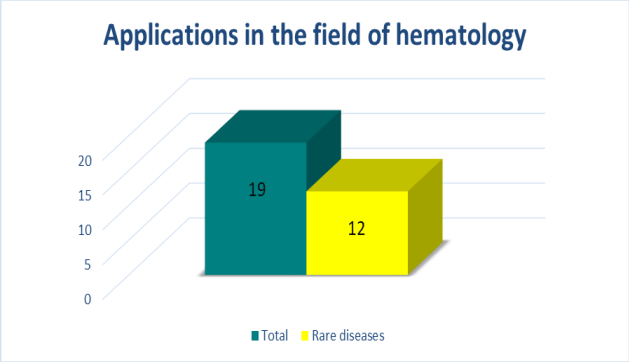


Figure 63. Applications in the field of hematology.

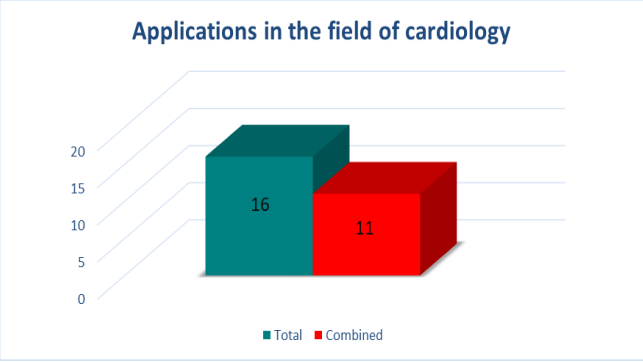


Figure 64. Combined medicinal products in the field of cardiology.

More than half of the medicinal products in the field of hematology are intended for rare diseases - from 19 applications over the analysis period, 12 were for rare diseases.

Combination medicinal products have previously been available in the fields of cardiology and endocrinology, as in the cardiology field they account for over 69% of the received applications (Figure 64).

Orphan drugs are still observed in the fields of gastroenterology, pulmonology, and oncology. In the field of genetic diseases, 100% of medicinal products are intended for rare diseases.

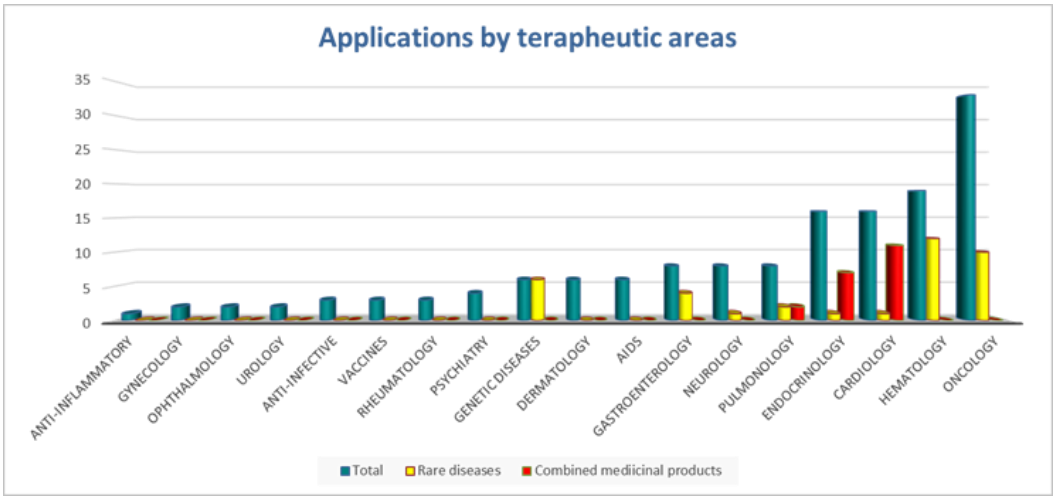


Figure 65. Therapeutic areas - rare diseases and combined MP.

For the entire analyzed period, the procedures that received a negative recommendation were 23 (18% of the total number of completed procedures). Since there is no statutory limit to the same application be resubmitted, most of these negative recommendations are being considered again.

This phenomenon is also a result of the absence of an introduced fee for performing HTA until the end of the analyzed period. This fee was passed legally in 2018, but until the applications process in NCPR was not introduced.

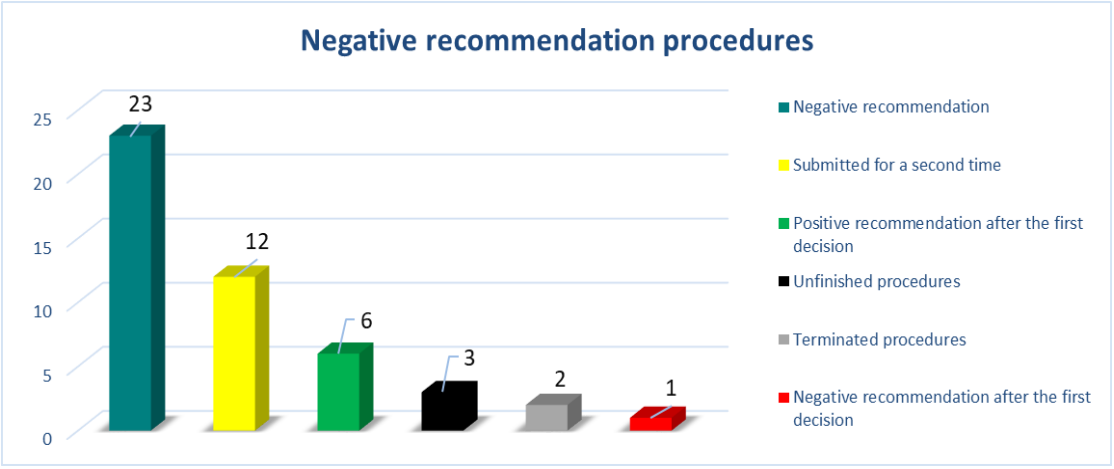


Figure 66. Negative recommendation procedures.

The figure shows that about half of the procedures with negative recommendation are in re-submitted applications and half of them have received a positive opinion on the second consideration. There are three unfinished, two suspended and only one is a procedure that has a negative recommendation and in consideration of the resubmitted application.

This can be explained in several ways: MAH applicants have made significant and sufficiently serious changes in the content and scope of the analysis, which speaks to the role and place of HTA in the process of clarifying the importance of drug documentation and study data; or the quality of the re-evaluations by the WEG and the attention of the HTAC was lower. Regardless of the direction of reasoning, this fact requires in-depth further analysis and comparison.

The therapeutic area in which the most negative recommendations are observed is also the area with the most combinations of existing INNs, namely cardiology (Figure 67).

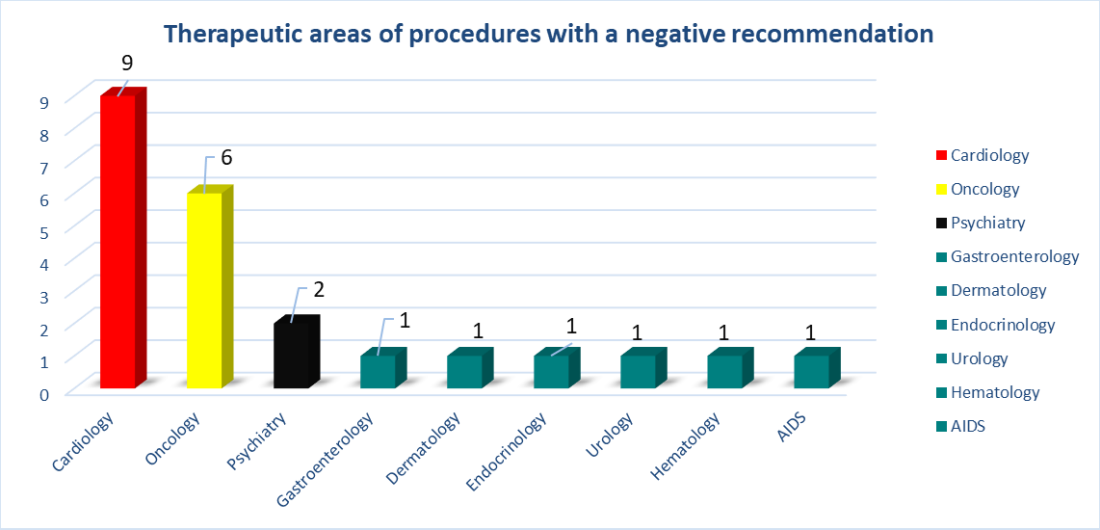


Figure 67. Therapeutic areas of procedures with a negative recommendation.

The difference with the other therapeutic areas is noticeable - 39% of all drugs with a negative recommendation are in the field of cardiology. The next therapeutic area with the most negative recommendations is oncology, but this is logical and understandable, as most applications have been received in the field of oncology, while for cardiology the negative evaluations are disproportionately high.

Medicinal products that received a negative recommendation were also tested as a percentage of the total applications submitted in the specific therapeutic area. This makes it possible to obtain a more realistic picture of the medication but

refused tons veins products and in which therapeutic area they dominate because such analysis takes into account not only the number of rejected but the number of applications.

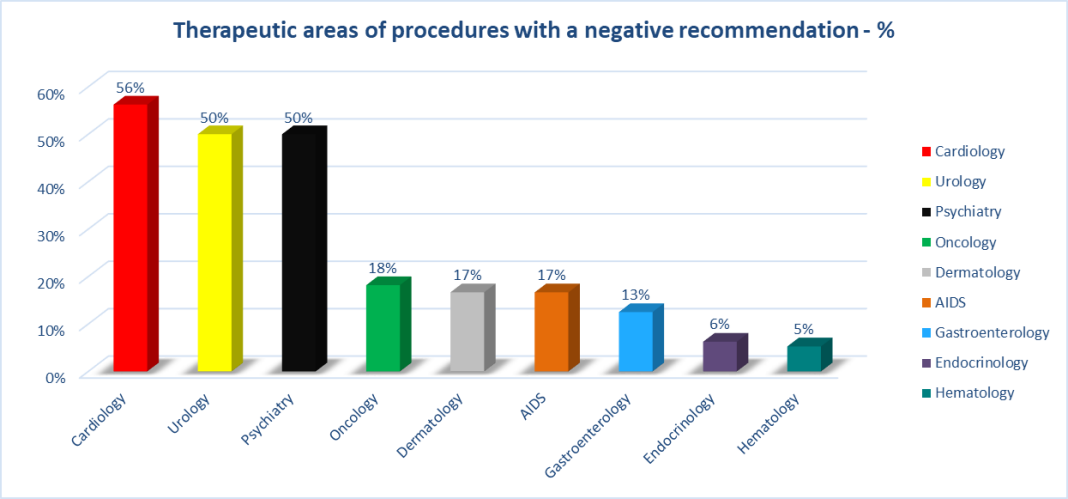


Figure 68. Therapeutic areas of the procedures with a negative recommendation – as a percentage of the submitted

Here it can be observed that in fact, the failures in the field of oncology are not so much as a percentage of the applications submitted in the same field. Negative recommendations in the field of cardiology remain predominantly high.

Summary and conclusions: The presented data have an in-depth analytical, substantive and confirmatory nature, showing the preferred areas of the industry for innovation, the results in the practice of gaps and oversights in regulation, and serious and quality work on administering a large number of HTA procedures in relatively short deadlines and without the presence of serious experience and capacity for this.

3.4.2. Analysis of the quality of the activity

A key element of any health technology assessment is a comprehensive, transparent, and reproducible pharmacoeconomic analysis that contains all relevant data from health outcomes. Although the need for flexibility is recognized, a consistent approach is required to facilitate comparisons between technology and disease areas, changes over time in therapeutic and economic parameters.

In Ordinance № 9 of the Ministry of Health of 1.12.2015 in Annex №3 to Art. 17 para. 5 the structure of the Health Technology Assessment Report is published. Based on this structure, the NCPHA team under the leadership of Prof. Dr.

Petko Salchev, MD developed a methodology for evaluating the reports, subsequently, it was adopted at a meeting of the HTA Commission and included as an element in the decision to adopt the report.

3.5. Economic indicators and impact

3.5.1. Budget impact analysis by therapeutic areas

The budget impact analysis is part of the basic requirements for HTA and includes basic components, part of the general analysis of the health problem. Key points are epidemiological surveillance and treatment of the disease, clinical impact, economic impact; design analysis and methods of analysis: patient population, therapeutic mix horizon, perspective, description of the analytical framework, incoming data collection and sources of data, analysis, evaluation of the safety, evaluation of the annual number of the target population, an estimate of the annual number of patients in whom the new health technology will be applied, an estimate of the current expenditures of public budget funds for the treatment of patients for five years. The results of each of the analyzes, their statistical processing (graphical and tabular presentation of the results) and subsequent conclusions are essential for determining the budget impact.

According to the requirements of Appendix №1 of Decree № 9 Applicants prepare an analysis of the budgetary impact in terms of payer - NHIS (the time is 5 years and the costs are discounted by 5% annually). The budgetary impact analysis presents two scenarios - the first in which health technology is introduced into the healthcare system and reimbursed with public funds and the second - in which the new technology is not reimbursed. The difference between the two scenarios is the budgetary impact. It can be:

- Positive budget impact - when the introduction of the new technology leads to additional costs of public funds;
- Negative budget impact - when introducing new technology leads to savings in the budget;
- Neutral or zero budget impact - when no change in costs is expected after the introduction of the new technology.

This section examines and summarizes budget impact data from validated HTA reports, supplemented by information from analyzes provided by applicants where necessary.

A total of 146 HTA reports were reviewed and analyzed. Due to the specifics of some drugs and the impossibility of standardly calculated indicators, they are excluded and in order not to distort the results.

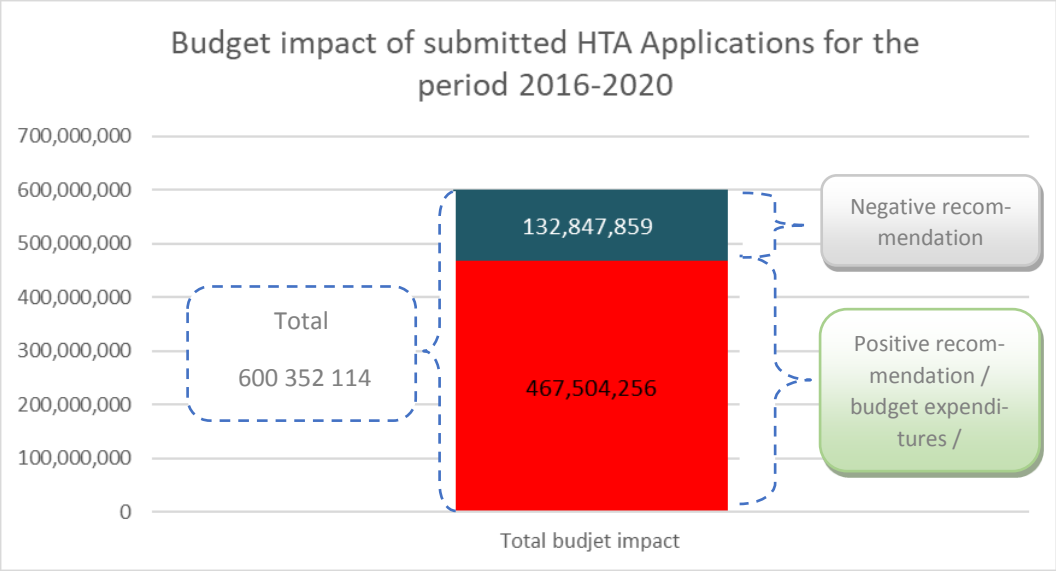


Figure 69. Budget impact of submitted HTA Applications for the period 2016-2020

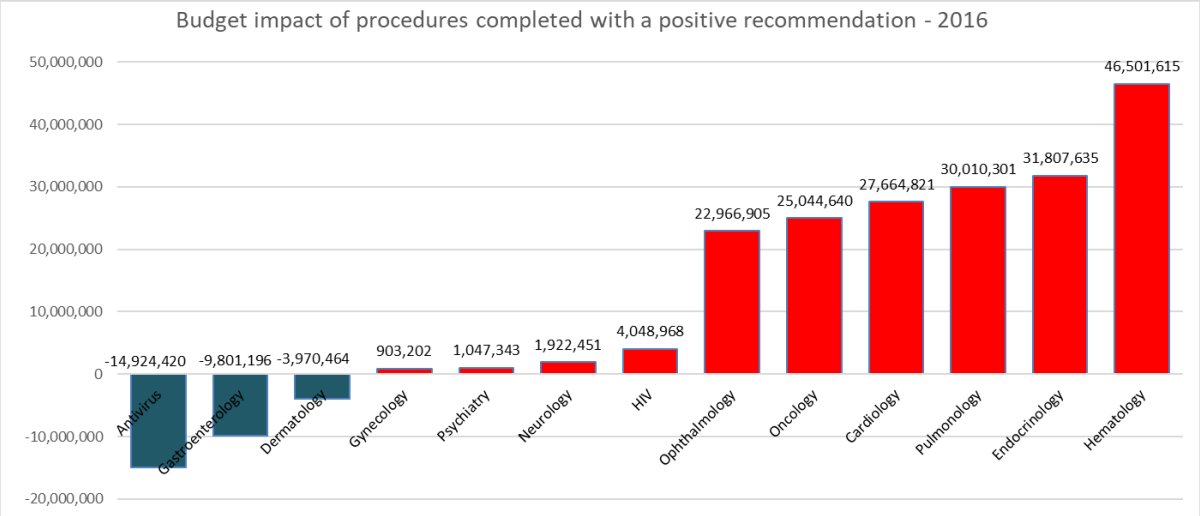


Figure 70. Budget impact of procedures completed with a positive recommendation - 2016

In three therapeutic areas introduction of assessed MP will result in a savings to the budget -antivirus, gastroenterology and dermatology. The therapeutic area that generates the highest cost is hematology, and the biggest savings are in antiviral drugs.

It is interesting to note that out of a total of 6 drugs in the field of hematology, 5 have the status of orphan drugs. The average estimated budget impact of MP in

the hematology therapeutic area is 1, 550,054 BGN and the average price for one year of treatment in one patient is 134,894 BGN; all 6 medicinal products with a positive Budget effect.

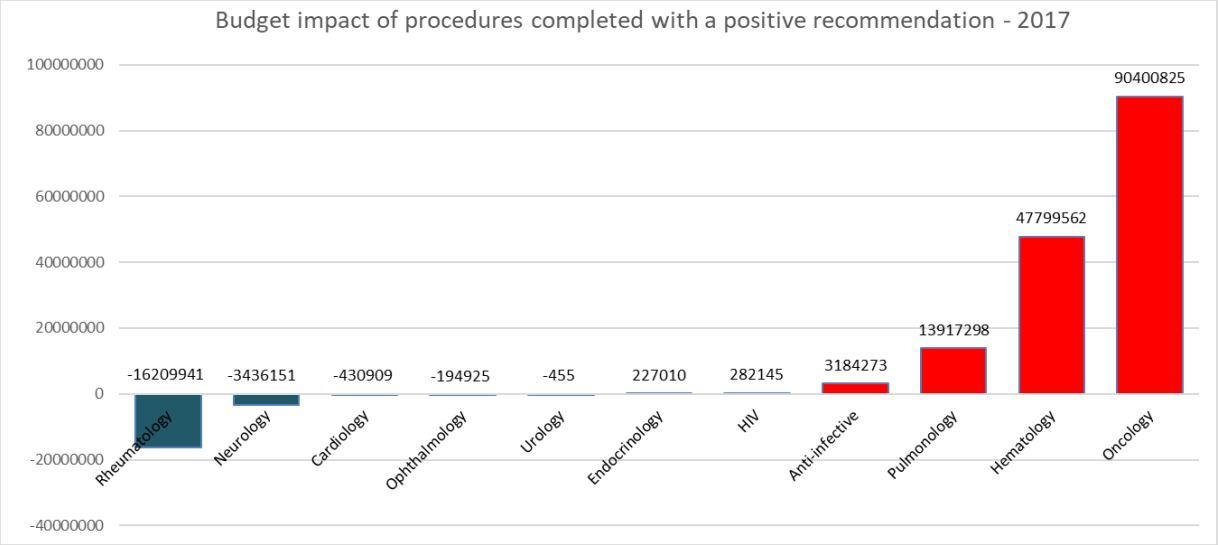


Figure 71. Budget impact of procedures completed with a positive recommendation - 2017

For 2017 the largest expense is generated by the new medicines in the field of oncology. General Budget effect for five years is predicted at a rate of 90, 400, 825 BGN the majority of which again spent on drugs for rare diseases (Figure 72).

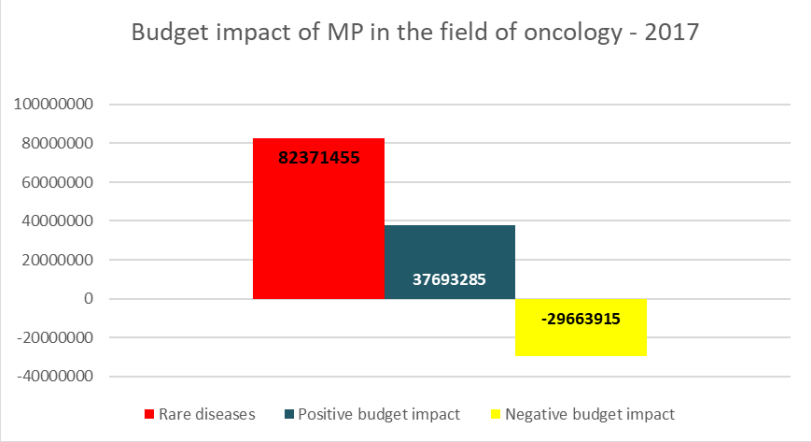


Figure 72. Budget impact of MP in the field of oncology - 2017

Table 2. COSTS in the "Hematology" - 2017

	Total MP oncology	Rare diseases	MP with negative BI	MP with positive BI
Number of applications	8	3	3	2
Budget impact - total for 5 years	90, 400, 825 BGN	82, 371, 455 BGN	-29, 663, 915 BGN	37,693,285 BGN
Average budget impact per year	2,441,667 BGN	5, 975, 820 BGN	-1, 977, 594 BGN	3, 769, 329 BGN

Average cost per 1 patient per year	126,721 BGN	231, 959 BGN	63, 578 BGN

From the comparison, it is clear that almost all the fuel in the oncological field is generated from medicinal products intended for treatments of rare diseases. The average cost per patient for orphan drugs is almost twice as high as the average measured for all products in total and almost four times higher than the average cost for drugs in oncology, which are not for rare diseases.

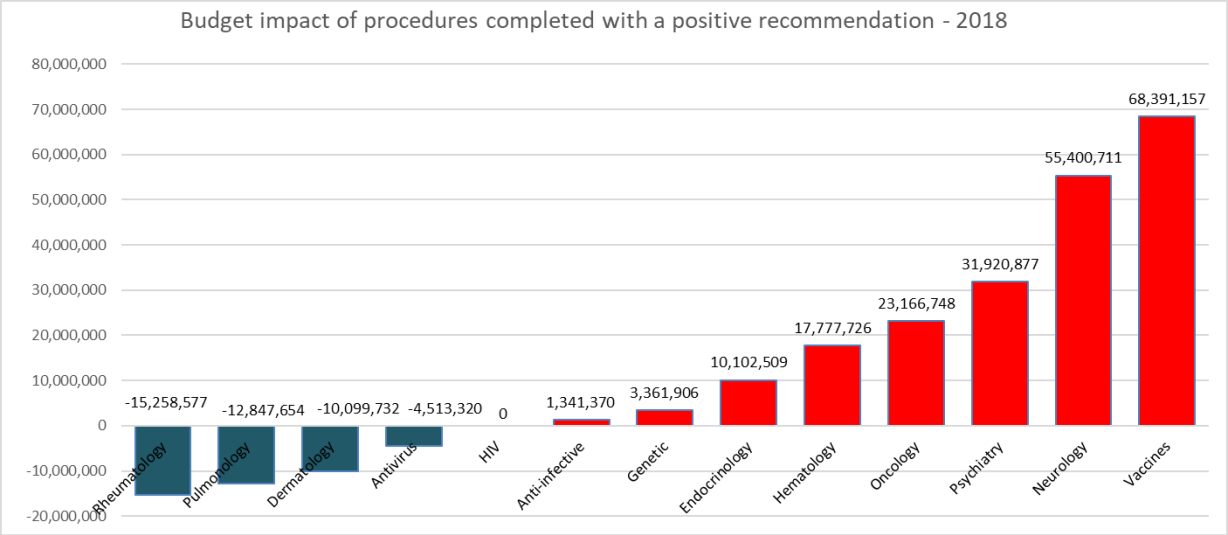


Figure 73. Budget impact of procedures completed with a positive recommendation - 2018

3.5.2. Cost analysis - an average price of medicinal products.

The cost analysis was performed based on the submitted applications by comparing the average annual cost of treatment in the different therapeutic areas by years.

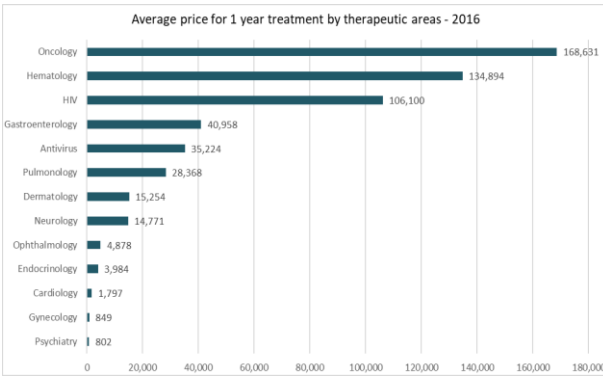


Figure 74. Average price for treatment by therapeutic areas - 2016

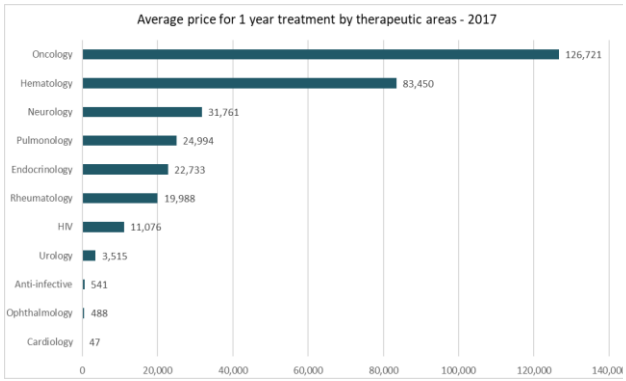


Figure 75. Average price for treatment by therapeutic areas - 2017

The highest costs are for treatment in the fields of oncology, hematology, genetic diseases (rare diseases). The fields of psychiatry, cardiology, and endocrinology have the lowest annual treatment costs per patient.

3.6. Review and comparative analysis of the changes in the legislation concerning HTA after 01.04.2019

According to changes in Art. 259, para. 1, item 6 of LMPHM (SG No. 102/2018, effective 01.01.2019), as of 01.04.2019, the national body for performing HTA in Bulgaria has been changed. Art. 259 of the LMPHM states that the National Council on Prices and Reimbursement of Medicinal Products (NCPR) undertakes the activity of assessing the health technologies of medicinal products, as the procedure is part of the process of inclusion in the PDL.

The following table is comparable in two stages of development, application and content of the HTA process; they are drawn basic similarities and differences, the implementation of new regulatory requirements, as well as their advantages and disadvantages.

Table 3. Review of legislation concerning HTA

	NCPHA - until March 31, 2019.	**NCPR - after April 1, 2019**
Applicable normative and sub-normative documents:	·Law on Medicinal Products in Human Medicine ·Ordinance № 9 of 1 December 2015 on the terms and conditions for carrying out health technology assessment ·The procedure of NCPHA the conditions and procedures for the evaluation of health technologies of medicinal products ·Rules for the terms and conditions of work of the Commission on Health Technology Assessment (HTAC) ·Rules for determining the composition and the manner of work of a working expert's group at the NCPHA under Art. 10, para. 1 of Ordinance № 9 of 01.12.2015 ·Rules for declaring, preventing and establishing conflicts of interest in the process of health technology assessment.	·Law on Medicinal Products in Human Medicine ·Ordinance on the terms and conditions for regulation and registration of the prices of medicinal products ·Tariff for fees and commissions collected under the Law on Medicinal Products in Human Medicine ·Structural regulations of the NCPR. ·Guide regarding the requirements to the content of the analysis for HTA (Appendix № 6 to Art. 35, para 3 and 6 to the Ordinance on the conditions, rules and procedure for regulation and registration of the prices of medicinal products)
Disclosure of HTA procedure	Separate procedure - the MAH submits an Application to the NCPHA Advantages: - An independent scientific organization performs the evaluation. The decision is taken by an independent advisory body (HTAC) Disadvantages:	The procedure is part of the procedure for inclusion of the medicinal product in the PDL Advantages: - MAHs do not have to submit documents for two separate procedures in different institutions Disadvantages:

	- Probability of delay in the deadline, which prevents the submission of documents to the NCPR for the procedure for inclusion in the PDL.	- The same institution is responsible for the evaluation (positive or negative) and the inclusion of the MP in the PDL.
Fee for performing HTA	There is no fee for performing HTA Advantages: - Cost savings for business operators (MAHs) Disadvantages: - There are no revenues from the activity for the budget, the costs for carrying out HTA are covered by the budget - No additional costs can be provided for administrative and technical support of the work of experts, etc. - Some applications are submitted 2 or even 3 times after receiving a negative evaluation on the principle of "chance"	- To include an MP with a new INN, for which HTA is also performed; - BGN 3,000 for the first therapeutic indication indicated in the application; - BGN 1,500 for each subsequent therapeutic indication; - To include an MP with a new INN for which HTA is performed in another application of the PLC: - BGN 2,300 for the first therapeutic indication indicated in the application; - BGN 1,650 for each subsequent therapeutic indication; - To perform HTA: - BGN 1,500 for the first therapeutic indication indicated in the application; - BGN 750 for each subsequent therapeutic indication; Advantages: - Additional revenues in the budget of the Ministry of Health - Thorough review and verification of the MAH documentation before submission and higher quality of the analyzes Disadvantages: - Upon termination of the procedure, the fee or part of it is not refundable and cannot be used improperly
Term of the procedure	90 days	90 days for a new indication (expansion of therapeutic indications) and 180 days for the inclusion of MP in PDL belonging to a new INN (incl. Performing HTA)
Subject to HTA **Advantages / disadvantages of changes**	1. Medicinal products belonging to the new INN incl. combined MPs already included in PDL INN. 2. Maintenance of reimbursement status of MP under Art. 259, para. 1, item 7 of LMPHM. - not required to expand therapeutic indications when INN is included in PDL Advantages: - Prevention in PDL of old products with dubious qualities, dropped out of PDL for various reasons, as well as the deterrence of MAHs from the withdrawal of MP Disadvantages: - Consumption of "unnecessary" resources in the implementation of HTA on combined MP - Lack of objective assessment of the benefits and costs of paying for new therapeutic indications for the same drug	1. MPs belonging to a new INN that is not included in the PDL 2. MPs are included in PDL, for which an extension of the therapeutic indications has been requested, for which it has not been paid so far. - not performed on combined MPs from existing ones in PDL INN. - HTA of substances with well-established use in medical practice is not performed Advantages: - Saving time and effort to evaluate substances with well-established use in medical practice or combination medicinal products Disadvantages: - Lower potential for access to innovation, due to stimulating the search for

	- Unclear definition of new INN	opportunities from the MAH to include "old" products
Conditions for HTA in other reference countries	No negative assessment in Germany, France or the United Kingdom. According to the Ordinance - on paper and electronic media. Advantages: - Possibilities for use in case of "doubtful" conclusions and referral if necessary Disadvantages: - Sometimes the unclear interpretation of the recommendations of other European agencies - Incomparable assessments - e.g. MP product received a negative rating in another country due to its high price, but the data could not be adapted for Bulgaria. - Incomparable population and medical characteristics between Bulgaria and the indicated countries	Existence of at least one positive assessment in Germany, France, Great Britain, and Sweden. Advantages: - Opportunity to borrow from other people's experience - Greater security - Avoiding the possibility for other countries to refer to the first and only assessment performed in Bulgaria Disadvantages: - Restriction of the entry into the Bulgarian market of MP, which has not been evaluated so far in any of the reference countries.
Necessary documents	According to Ordinance № 9 - on paper and electronic media. Additionally required: - Declaration in free text for the absence of a negative assessment in one of the reference countries; Advantages: - Strict observance and clarity of the texts in the ordinance - Lack of additional administrative burden for the MAH Disadvantages: - Very often this declaration is forgotten by the MAH, which leads to a delay in the procedure - Even a small discrepancy between paper and electronic media is a reason to suspend the procedure	Additionally required: - Document for paid state fee; - Files in Excel format of models for the prepared analyzes - CEA and BIA; Advantages: - The files provide the decision-makers with additional information on how the calculations were performed in the analyzes. - The procedure does not start before the fee is paid Disadvantages: - The submission of the detailed models reveals a trade secret of the Applicants - This allows for borrowing ideas and a way of performing analyzes
Structure of the HTA analysis (provided by the MAH)	Appendix № 2 to Art. 16, para. 1, item 5 of Ordinance № 9 of 1 December 2015 on the terms and conditions for performing a health technology assessment	Annex № 6 to Art. 35, para 3 and 6 of the Ordinance on the conditions, rules, and procedure for regulation and registration of the prices of medicinal products

Process administration:	NCPHA - Classification systems standards and innovations Directorate, HTA Department - 4 full-time positions	NCPR - "Directorate of Regime Management and Health Technology Assessment" - 15 full-time positions
External experts / working groups for the implementation of HTA /	They are appointed on each submitted application	They are appointed on each submitted application
Experts	Physicians specializing in the profile of the disease being evaluated, pharmacist, economist, lawyer Advantages: - Mandatory participation of a clinician with a profile of the disease is assessed - Participation of a lawyer who supports the work of the commission and the preparation of proper accompanying documentation Disadvantages: - Participation of 5-7 experts in one RC of different specialties and sometimes difficult communication between them.	Experts majoring in Medicine, Pharmacy and Economics, representative of the National Health Insurance Fund and the Ministry of Health Advantages: - Fewer experts - Participation of a representative of the institutions Disadvantages: - Lack of motivation and financial commitment of the representatives of the institutions, opportunities for delay and "overloading" of external experts
Working groups	Prepare a draft report on HTA	Prepare a clinical and pharmacoeconomic evaluation of MP
Presentation	The Chairman of the WEG presents a draft report to the HTAC Advantages: - A medically familiar person presents the case in detail (in most cases it is a clinician who has the direct observation of patients and the health problem) Competent to answer questions Disadvantages: - The physical presence of the Chairman is related to an additional commitment for him, quite often the date of the meeting of the HTAC coincides with urgent commitments or trips of the Chairman of the WEG.	A member of the council shall submit an expert report prepared by him on each requested procedure. The chairman of the working group takes part in the meeting, as well as a representative of the Ministry of Health / NHIF. An opinion of the National Health Insurance Fund is required for MP intended for the treatment of malignant diseases. Advantages: - The report is prepared and presented each time by certain people in the council, which leads to the unification of the style of preparation and presentation, and hence to facilitate its discussion. Disadvantages: - Representatives of the Ministry of Health and the National Health Insurance Fund do not have the right to vote

Making a decision	HTA Commission - 13 members incl. Chairman, representatives of NHIF, MH, NCPR, BDA, NCPHA. Advantages: - Decisions are based on the expertise of at least 9 people (due to the minimum quorum for decision making). - Representatives of different institutions participate, which allows discussing the specifics of the individual procedures - e.g. specifics of coding diseases, non-existent ICD codes, drugs for the treatment of AIDS, vaccines. Disadvantages: - Difficult quorum	NCPR - 7 members, incl. Chairman. Advantages: - Faster decision making Disadvantages: - There are no representatives of external institutions and independent experts, the principle of institutional encapsulation has been introduced - It is not possible for those who know the medical problem, will apply the MP and/or have a broader expert opinion - representatives of professional and patient organizations to participate in the discussion.
A quorum for meetings and decision making	More than 2/3 of the total number of members of the HTAC Advantages: - Decisions based on more expert votes - More detailed discussion and comments on issues. Disadvantages: - Difficult decision-making and majority achievement.	More than half of the total number of members Advantages: - Ability to make decisions with less fighting votes, which speeds up the process - Less failed due to lack of quorum meetings Disadvantages: - Possibility to influence the votes of the members of the council because the chairman is also their leader
Publication of summaries	On the NCPHA website Advantages: - Publicity and transparency - Opportunity for other countries to refer to the approved reports Disadvantages: - Additional administrative work for the employees in NCPHA - Need for careful censorship of data in HTA reports	According to the Ordinance - on the website of the NCPR In practice - as of April 2020 there **is no** published summary of the report on HTA on 25 issued decisions * Advantages: - Preservation of the principles of transparency, traceability, and upgrading Disadvantages: - Lack of published summaries due to lack of external control over the competent authority
Appeal	Before the Minister of Health, through the Director of NCPHA. The order of the Director of NCPHA is appealed by administrative order. Advantages: - Opportunity for a politician and senior state administration to participate in the process - The HTAC may rule ugly in the same procedure and confirm/change its decision Disadvantages: - Appeal procedure through the administrative body issuing the HTA Order and controlling the procedure	Before the Transparency Commission. It can be appealed as appropriate. The whole decision of the NCPR is being appealed, not only the HTA procedure. Advantages: - Possibility for an independent body to rule on the procedure - Two-instance procedure for HTA and appeal outside the competent authority Disadvantages: - Delay in the decision, expansion of the circle of experts involved in the evaluation, access of a wide range of persons to trade secrets

Re-application	There is no restriction on re-submitting an application after a negative assessment has been received. Advantages: - Opportunity for the MAH to re-apply in case of change of circumstances - e.g. lower price. - Ensuring faster access to innovation in compliance with the MAH's comments and concerns from previous procedures Disadvantages: - The same analyzes are submitted several times without a significant change in circumstances	There is no explicit possibility, which means that the MAH can submit new documents, pay a fee, at any time.

** Source: NCPR website https://www.ncpr.bg*

Concerning combined medicinal products and the changes according to which they are not subject to HTA, there are explicit requirements in the legislation as to what conditions they should meet.

3.7. Summary of key problems

3.7.1. Summary of key problems in initiating and organizing process by HTA in Bulgaria

- Insufficient availability of reliable and accessible data on the epidemiology of diseases;
- Insufficient number of experts to participate in the HTA WEG;
- Insufficient training of experts in the field of HTA, especially pharmacoeconomic part and budget impact analyses;
- High refusal rate among the nominated specialists for participation in the WEG;
- Lack of clear and sustainable communication with and between the experts in the WEG;
- Technical problems in submitting the necessary documentation and receiving the draft reports from the WEG;
- Multiple suspensions of the procedure and submission of additional documents, data, analyzes, etc .;
- Weak resource security of the process of organization and introduction of HTA;
- Need for additional funds for the functioning of the processes and specific training of experts;
- Diversity of the way of formation and scope of prices of health services;

- Lack of systematic and standardized local data on quality of life;
- Problem with access and or lack of data from patient registers.

3.7.2. Problems in preparing the HTA dossier by the MAH Company

- Non-compliance with the instructions according to the current regulatory framework - structure and required data - the content is not arranged, there is no numbering of tables and figures or it does not correspond to the text, missing whole points and sections of the report, frequent errors in spelling the INN of the medicinal product.
- Parts of the dossier contain a description of the full characteristics of the new technology without an analytical part, as well as the mixing of the copied parts (in Bulgarian and English), as well as poor translation from English.
- There is insufficient data or data transfer for the relevant population.
- There is no exact description of the target group for the new technology (number of patients) - often only patients who have been treated by the NHIF or all patients with the given disease are described.
- Missing and/or insufficient data on product safety.
- Very often presented analyzes contain data for comparison with placebo and not with available technology currently used in practice;
- There are no clearly defined methodologies for the application of the assessment - insufficiently clear description of the epidemiology of the respective disease, the risks and the risk groups;
- No distinction is made between incidence and prevalence;
- Pharmacoeconomic analyzes are incomplete and inaccurate, leading to incorrect budgeting.
- The data are not adapted for Bulgaria. Frequent mistakes are made in determining the patient population and the courses of treatment. Errors in cost calculations are often found that are significant and require a complete overhaul of the analysis. There are no data on sensitivity analyzes. No discounting is applied and the time horizon of the analysis is often too short (1 year). No information is provided on the additional (indirect) costs.
- Technical imperfections - the information is often not sufficiently illustrated, the tables are illegible, mixing text in Bulgarian with figures, diagrams and tables in English.
-

3.7.3. Problems in preparing the draft report by the WEG

- The reports do not follow the structure specified in the current regulatory framework, which complicates the process of preparing the evaluation tables according to the established methodology and leads to gaps and missing information in the report, which is necessary for decision making.
- Omissions in certain parts of the report.
- Analytical parts and conclusions are often missing, with only a description of the point.
- Recommendations to the reports include elements that are not part of HTA - eg. proposals for a new level of reimbursement, in which application of PDL to include the medicinal product, etc.;
- The most common weaknesses in the reports are related to pharmacoeconomic analysis and budget impact analysis;
- There is no critical assessment of the submitted data, as well as with public conclusions of the WEG. The information is often copied from the analysis prepared by the MAH.

Discussion: The problem of the lack of data is main to the whole country. This makes it difficult for the MAH to develop an epidemiological model with accurate and clear estimates of the target population for HTA purposes. It also makes it difficult for the HTAC to make decisions, as it is difficult to predict the exact costs of introducing a new medicinal product. For a small proportion of diseases, such data are available from the NHIF or national registries, but in most cases, they are not comprehensive enough.

The huge amount of work that requires an assessment is a factor that makes experts give up due to lack of sufficient time and heavy workload. In most cases, the Chairman of the WEG are prominent in their field physicians, clinicians, charged with a large number of patients and management activities in the medical institution where they work. The lack of adequate payment and the opportunity to cover travel expenses are another factor that leads to reluctance to commit to participation in the WEG. Each procedure is also accompanied by a considerable amount of administrative work and documents, which accumulates additional time. This problem is partly avoided by the decision to appoint by order of a technical assistant from the NCPHA for each procedure.

The lack of experience in preparing the analysis by the MAH, as well as its review by the experts who prepare the draft report, is a problem that gradually decreases over time with the accumulation of experience. Gradually, the Applicants learned what the requirements are for the type and quality of the analyzes, and the experts

participating in the working committees to extract the information they need, to critically evaluate and, if necessary, request additional data and ask targeted questions that arose in the evaluation process.
The need for funds for the functioning of the process is an issue that is at the forefront among the managers involved in the HTA process. The introduction of a fee to be paid by the MAH is a matter of paramount importance. With the new changes and the implementation of the HTA by the NCPR, the storage of the fee is already a fact.
As a result of the experience gained over the years, it can be concluded that most of the problems gradually decrease and disappear. This speaks of the readiness of society, industry, and government and a good acceptance of the process as a whole. There is a noticeable increase in the qualifications and experience of all participants in the process.

4. Conclusions and recommendations

The health technology assessment considers the benefits and risks of introducing a medicinal product from all points of view - clinical evaluation, safety profile, pharmacoeconomic indicators, budgetary impact assessment, and ethical aspects. It is a more in-depth analysis, which is necessary for the introduction of innovative technologies and their payment with public funds.

Assuming that the positive budget impact of non-inclusion medicinal products that have received a negative recommendation is a cost-saving, the scientific definition should be supplemented in this direction, namely that: " Health technology assessment leads to optimization of decisions to reimburse health services as well as to save public funds".

The optimization of decision-making is a fact because through HTA it is possible for a more complex view and assessment of all the benefits and risks of introducing technology.

Cost savings are realized on the one hand by stopping the access of cost-ineffective medicinal products and on the other hand by the possibility to set certain conditions that MAHs must comply with - e.g. cost reduction, reduction of the number of patients, or payment based on the result of the therapy. The recommendations in the HTA report may also include conditions for the MAH to pay for specific tests or additional costs and concomitant medications.

On the other hand, with the introduction of cost-effective medicines, current therapies are being replaced, competition is being created and prices are falling.

In the present study, a complete analysis and assessment of the organization and process of HTA in Bulgaria is made. The key factors for the further development and management of the process can be summarized as follows:

Based on the large volume of successfully completed work, it can be concluded that in general, the organization of the process is very good, despite the low resource security. As a key factor for the development of the process, the awareness of the need to perform HTA should be brought to the fore, incl. from Applicants, leading specialists in the respective fields, institutions, and citizens.

After the introduction of a fee for submitting an Application, it is necessary to revise the budget in the part of the payment of the experts included in the WEG, as well as providing business trips - travel, living, and accommodation for the experts who are not from Sofia.

The attraction of highly qualified specialists to be involved in the HTA process must continue.

A training system for experts needs to be set up. As there are frequent participations of the same experts in different WEG, it would be very useful to organize regular workshops for exchange of experience. Such meetings and training would be useful and businesses as it will be able to exchange information with each other, which ultimately lead to improved quality of the submitted analyzes and adjoining documentation.

MAHs should be involved in the establishment, financing and maintenance of disease registries. Currently in Bulgaria for most diseases there are no registers and retrospective statistics, the problem with data collection and adaptation of such is brought to the fore by experts involved in the preparation and evaluation of dossiers.

It is necessary to increase the administration for servicing the process, as well as to provide a software product to facilitate and track the voluminous documentation, deadlines, etc.

5. Yields

Scientific and theoretical:

For the first time in Bulgaria, the organization of the implementation, the expert and administrative potential and the difficulties in the assessment of the health technologies have been studied and analyzed in detail.

Based on a thorough review of the modern scientific literature, the features, advantages, difficulties and challenges in the assessment of health technologies, as well as the prospects for the future are highlighted.

An algorithm has been developed and presented for a detailed description of the organization and stages of the process, procedures and rules for work, the importance of expert potential and resources, and the experience gained related to the assessment of health technologies.

Applied and practical:

The main factors that affect the duration of the procedures, the quality of the reports are defined and a comprehensive assessment of the organization of the HTA process in Bulgaria for the first three years of implementation.

Opinions and attitudes about the motivation for participation and the most common problems and difficulties of the experts in WEG for evaluation of health technologies are studied and summarized.

The expected economic aspects of the introduction of post-HTA medicinal products by periods, rate of increase of costs, therapeutic areas, saved costs of rejected drugs, the average cost of treatment with new drugs by years, and others are shown that can serve as a starting point of further studies of the effect of HTA in the country.

A critical analysis and commentary were made on the advantages, disadvantages, and the expected impact of the changes concerning the legislative framework, introduced after 31.03.2019.

6. Conclusion

The study and analysis of the state of the process of introduction and application of health technology assessment in Bulgaria showed the main steps, difficulties, leading factors and participants that can provide a unique contribution of HTA in decision-making processes in the health care system. The application of the principles and scope of HTA should be used to assess the potential consequences not only for medicinal products and medical interventions but also of organizational measures and policies for health system reform.

The main task of HTA is to provide decision-makers with an in-depth and summary assessment of the potential effects and outcomes on health, the implications for medical practice, the health system, the economy, and society. Valid conclusions in the HTA process make it possible to make an informed decision on whether to introduce or reject a technology, to accelerate or slow down its spread, and to take various measures to accelerate the development of existing practice.

In recent years, in the EU member states, processes of introduction and harmonization of HTA and establishment of specialized agencies have been accelerated in order to ensure transparency and efficiency in the process of evaluation of new health technologies. Bulgaria is one of the first countries with a nationally competent, regulatory body and a normatively introduced process on HTA, at this stage only for medicinal products. As described, this tool uses several complex criteria that should be taken into account when assessing and deciding on public payment. The evaluation and access to innovative technologies, including therapies, should be outside the debate on political priorities but should lead to the expansion of the resources of the health system and to respond to public attitudes.

In addition to the shortcomings, omissions, and expectations of the experts listed in the study, it should be noted that the main problem for Bulgaria is the lack of solid and systematically developed and maintained clinical, epidemiological, and economic data and evidence, which in itself to be a prerequisite for making informed and adequate decisions for access to innovative health technologies. Filling this gap is an important and fundamental moment for supporting the rational conclusions in the assessment of health technologies, their validity for medical practice and their transfer to/for other countries. The introduction of e-health and the system of registers is expected to have a strong impetus in this direction.

7. Publications and participation in scientific forums:

1. Nikolova, A., E. Grigorov, A. Dimova, J. Kolev, P. Salchev. Analysis of the process and the provision of experts for the working commissions for evaluation of health technologies in Bulgaria, Social Medicine, 2017 (27), No.4, p.30-33.
2. Salchev, P., S. Dzhambazov, A. Nikolova, E. Mekov "Survey on Awareness of Health Technology Assessment Processes", Bulgarian Journal of Public Health, 2018, 2018 (10), No.2, p.10 -19. (Indexed in Web of Science)
3. Nikolova, A., E. Grigorov, I. Getov, P. Salchev. Research and analysis of awareness regarding the process of health technology assessment in Bulgaria, Bulgarian Journal of Public Health, 2019 (11), No.2, p.37-50. (Indexed in Web of Science)
4. Nikolova, A., E. Grigorov. Study of the terms for performing procedures under the HTA of a medicinal product in Bulgaria for the period 04.2016 - 12.2018, Social Medicine, 2019 (27), No.4, p.31-34.
5. Nikolova, A., E. Grigorov, I. Getov, P. Salchev. "Study and analysis of awareness of the HTA process among experts, members of WEG", Seventh Congress of Pharmacy with international participation, November 21-24, 2019, Hotel "Rila", Borovets