Report to the European Commission on Pharmacovigilance audits carried out in the Bulgarian Drug Agency
period of time from April 2011 to June 2013

1. INTRODUCTION

This report provides an overview of the audits conducted at the Bulgarian Drug Agency (BDA) from April 2011 to June 2013, by the international certification organisation Intertek-Moody, by external auditors and internal auditors from the BDA.

2. BRIEF DESCRIPTION OF THE PHARMACOVIGILANCE SYSTEM

An integrated quality management and information security system developed in compliance with the requirements of the international standards ISO 9001:2008 and ISO/IEC 27001:2005 was implemented in the Bulgarian Drug Agency in March 2011. In July 2011 this integrated quality management and information security system was certified by the internationally accredited organisation Intertek-Moody. The Medicines Use Control Department has developed and maintains a pharmacovigilance system monitoring the safety of all medicinal products on the market. All pharmacovigilance activities are described in procedures which form an integral part of the integrated quality management and information security system. The pharmacovigilance system is recorded in the following policies and procedures:

MP 7000 Medicines Use Control

SOP 7011 Stages of handling adverse drug reaction /ADR/ reports during the post-marketing authorization period of medicinal products

SOP 7012 Stages of handling direct healthcare professional communication (DHPC) and/or training materials (TM)

SOP 7013 Stages of handling periodic safety update reports

SOP 7015 Preparation and performance of inspections of the pharmacovigilance system of marketing authorisation holders

SOP 0008-5 Control measures in response to signal of adverse reaction and/or suspected drug quality defects

SOP 0008-2 Publication of information on BDA's website

By order of the Executive Director of the BDA an employee from the directorate was appointed, who has the required quality management qualifications and is in charge of the requirements for the quality of the pharmacovigilance system which is a part of the integrated quality management and information security system.

Legislation

In the performance of the activities related to pharmacovigilance, the Bulgarian Drug Agency follows the prescriptions of the Law on Medicinal Products for Human Use (after implementing DIRECTIVE 2010/84/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 15 December 2010 amending, as regards pharmacovigilance, Directive

2001/83/EC.), the Statute of the BDA and the Good Pharmacovigilance Practices issued by the European Medicines Agency, the legislation valid in the territory of the European Union (REGULATION (EC) No 726/2004, REGULATION (EU) No 1235/2010, COMMISSION IMPLEMENTING REGULATION (EU) No 520/2012, REGULATION (EU) No 1027/2012), Implementing Regulation (EC) No. 198/2013 of 07 March 2013, the Public Officials Act, etc. In the pharmacovigilance of authorised vaccines in the Republic of Bulgaria, the Bulgarian Drug Agency complies with the requirements of REGULATION No. 15 of 12 May 2005 on the immunisations in the Republic of Bulgaria, issued by the Ministry of Health, and the methodical guidance for the monitoring of adverse drug reactions following vaccination.

All changes in the legislation are incorporated in the documents of the integrated system within the regulated timeframe, and are made known to all interested parties.

Organisation structure, responsibilities and resources

The BDA is a legal entity with an annual operating state budget. The Head of the BDA is a second-level budget credit administrator under the direction of the Minister of Health. The scope of the Agency's operations, structure, organization, and staff, the powers of the Head of the Agency, and the relations of the BDA with other governmental bodies, offices, non-governmental and other national and international organizations and institutions are governed by the Statute of the BDA. The structure of the BDA is organized in general and specialized administration departments according to the activities, which are conducted in them. Staff allocation among the various administrative units is presented in an organogram published on the website of the Agency and documented in the integrated management system manual.

The Head of the BDA is responsible for all taken regulatory and management decisions. The decision-making powers of the Head of the BDA are specified in the relevant legislation and the Statute of the BDA. The timeframes for decision-making follow the legal requirements. The responsibility of the participants in the decision-making process is recorded in their job descriptions, the integrated management system manual, various policies, standard operating procedures, information security procedures and orders.

The allocation of human resources is made in compliance with the activities defined for each department according to the Statute of the BDA, and according to the approved list of positions and names of staff members. To conduct the operations related to pharmacovigilance, the Bulgarian Drug Agency has hired 7 qualified and properly trained employees (experts/inspectors) who work at the Pharmacovigilance Division of the Medicines Use Control Department subordinated directly to the Head of the Devision and the Director of the Department.

Training

Training programmes are planned on an annual basis and they cover general aspects of the functions of the integrated quality management and information security system, as well as some more specific aspects of the operations conducted at the division/department. The main

goal of these training programmes is the accomplishment of measurable parameters (measurable targets) as a result of the training.

Once every year personal training plans are developed for each staff member as well as a summarized annual training plan for the whole staff of the Bulgarian Drug Agency whose purpose is to plan and organize training sessions directly related to the specific duties of the individual staff members and the functions of the unit, and also corresponding to the objectives set forth in the work plans and the plans for development and improvement of the staff. The entire process is focused on the needs of the BDA and on increasing the motivation of the staff.

All members of the staff undergo initial, further (if required) and periodic training.

The staff members of the BDA undergo an introductory quality management and information security training course. The purpose of this course is to acquaint them with the integrated quality management and information security system, and with their duties related to quality management and information security.

The employees working at the Pharmacovigilance Division undergo the following specialised training programmes related to pharmacovigilance and organised by EMA:

MedDRA- 2 employees (Head of department, Head of Pharmacovigilance Division)

EudraVigilance - electronic reporting of ICSRs training - 5 employees (Head of Pharmacovigilance Division**,** 2 experts, 2 inspectors)

EV Data Analysis System (EVDAS) Training for National Competent Authorities - 4 employees **(**Head of department**,** 2 experts, 1 inspector**)**

Internal training sessions are organised for the employees at the Pharmacovigilance Division, due to changes in the legislation.

Facilities and equipment

Working systems and facilities are in place and are maintained for the operations of the Agency and serve as tools for assessors and inspectors in their work.

These systems are monitored and their results analysed. Measures are taken for their continuous improvement and maintenance.

The Agency is housed in a building with a local network. There is an active directory and all computers are connected to it. There are servers that run the active directory, electronic mail and website; a file server; database control servers; an antivirus control server. There is a DMZ and a firewall. There are also external hard drives for backup copies.

An automated information system is integrated in the BDA to monitor document flow and circulation, which makes possible the traceability of documents and ensures that they cannot be modified after they are completed.

There is an information system which includes a database of the medicinal products, DRUMS. It also contains data modules from periodic safety update reports (PSUR) and information from adverse drug reaction reports. These modules are maintained and used by the employees of the Pharmacovigilance Division.

Appointed employees, who are in charge of pharmacovigilance, have access to EPITT – the European Pharmacovigilance Issues Tracking Tool, Eudravigilance Data Base Post-authorisation module (EVPM) and WHO database (VigiBase). Information is entered in EVPM by employees who hold EMA certificates, and is sent in compliance with the Note for Guidance and Regulation No. 520/2012 – EudraVigilance Human – Processing of safety messages and individual case safety reports (ICSRs) EMA/H/20665/04/Final Rev. 2, 15 October 2010, EudraVigilance Expert Working Group within the legal timeframes (15 days for ICSRs; 2 days for acknowledgement).

Compliance with the set deadlines for sending information to the Eudravigilance database may be traced by reports generated by the EVDAS (EudraVigilance Data Analysis System), which is used in the analyses of data from EVPM.

Every year a full assessment of the workload, capacity and functional qualification of the IT facilities is made within the integrated management system of the BDA.

Compliance management

There are regular internal audits to ensure compliance with the requirements of the implemented integrated quality management and information security system, and to identify opportunities for improvement. The requirements of the existing *Internal Audits* Procedure are followed.

The audits of the Pharmacovigilance Division are part of the regular audits of the integrated quality management and information security system. They are conducted annually and the results are documented in reports. Corrective and preventive measures are identified for the improvement of the processes related to pharmacovigilance. The audit reports and the corrective and preventive measures are approved by the senior management of the Agency and reported to the Council of management.

Record management

There is a record management procedure which defines the scope, order, responsibilities and operations involved in the creation, identification, storage, access, archiving and destruction of management records, technical records and electronic records. Compliance with this procedure ensures protection of the information in the Bulgarian Drug Agency and prevents the loss of data due to failures or to extraordinary circumstances. The timeframes for archiving the records related to pharmacovigilance follow the requirements of Regulation No. 520/2012.

This procedure is implemented by the employees of all structural units of the Bulgarian Drug Agency.

Documentation of the quality system

The documentation of the integrated quality management and information security system is developed in compliance with the requirements of the international standards ISO 9001:2008 and ISO/IEC 27001:2005 and the existing regulations. It includes an integrated system manual, management procedures, information security policies and procedures, standard operating procedures and work instructions describing the main operations of the Bulgarian Drug Agency.

The quality management and information security system manual is the master document for the management of the Bulgarian Drug Agency. It reflects the management policy and identifies the principles and major rules for the conduct of operations related to quality and information security.

The documents of the integrated system are available to all employees of the Agency. They are published as protected files in the general access directory of the server.

Business continuity arrangements

The Bulgarian Drug Agency has developed a Continuity plan and an Emergency plan for disasters and breakdowns. These plans are developed on the basis of risk assessment of the possible emergencies that may occur, and analysis of the impact on the work of the BDA. A training drill programme is implemented to test the effectiveness of the continuity plan. The programme includes drills on the various scenarios associated with the plan in order to assess the readiness for adequate reaction in crises. There are training sessions for the staff. Immediate reaction teams are appointed. Plans are reviewed and their adequacy assessed regularly. The results of the drills are analysed and corrective/preventive measures are recommended. Upon incident of a higher order plans are revised and, if necessary, updated.

There is an information security crisis management policy.

Monitoring of performance and effectiveness

Performance is evaluated on an annual basis and there are interim meetings to discuss the work of each staff member and to see if the work plans yield successful results. If necessary, corrections are made to the plans.

The results of the work of the various departments are presented in an annual report on the overall performance of the department. These reports are summarized in a final report on the work of the BDA which is approved by the Head of the BDA and submitted to the Ministry of Health; after that it is published on the website of the BDA.

Compliance with the statutory obligations and the effectiveness of the processes that take place in the agency are inspected with the internal quality and information security audits and

the annual management reviews. The requirements that apply are those of the integrated procedures.

The BDA undergoes external performance assessment by the competent authorities of the Ministry of Health and a financial audit by the National Audit Office.

The results of the work of the specialised department are summarised periodically and submitted to EMA, WHO and the European Commission.

Delegation of tasks

The management decision-making system is in line with the existing legislation. The Head of the Agency is responsible for all regulatory and management decisions. The decision-making powers of the Head of the agency are defined in the existing legislation and the Statute of the BDA. The decision-making deadlines are consistent with the statutory requirements. The responsibilities of the participants in the decision-making process at the different levels are defined in their job descriptions, in the integrated management system manual, the standard operating procedures, and the information security policies and procedures.

All staff members working at the agency are acquainted with the decision-making regulations and this is acknowledged with a signature in their job descriptions.

3. INTERNAL AUDIT ACTIVITY FOR THE PERIOD UNDER REVIEW

3.1 RISK ASSESSMENT

A risk assessment exercise was conducted in order to determine the pharmacovigilance system audit priorities for the period under review. The final audit strategy was prepared based on this risk assessment and was approved by Council of management on 17th of September 2013.

The main purpose of the internal audits is to assess the effectiveness of the integrated management system and the need for improvement or corrective measures.

There is an Internal Audits Procedure which describes the procedure and rules for planning, conducting and recording the internal audits of the Bulgarian Drug Agency, as well as the presentation and use of the results of such audits. The internal audits cover the different processes/operations/units of the organisation – elements of the integrated management system, as well as the integrated quality management and information security system as a whole.

Every year an annual programme for internal audits is approved, which covers all primary and secondary processes in the agency. In the development of the annual programme the management gives special consideration to those activities/units in which deficiencies/incidents were found during previous audits. The annual programme is based on the good practices of the standard EN ISO 19011:2011 and covers all structural units and processes. Audits on the various processes are planned and conducted. The annual

programme is agreed with all directors of departments, then approved by the Head of the BDA, and finally sent to all staff members. There are specific plans for on-site audits, of which the audited unit is notified in advance. The results of the audits are recorded in reports; recommendations are given of corrective and preventive measures for improvement of the processes. The staff members at the quality management department monitor the implementation of the recommended corrective and preventive measures and report the results to the management at the meetings of the Council of management and during management reviews. There is training for qualified internal auditors who participate actively in the internal audits. The BDA has 25 internal auditors trained on the international standards ISO 9001:2008, ISO/IEC 27001:2005 and ISO 19011:2011. If necessary, external auditors and experts are summoned.

The audits of the Pharmacovigilance Division are part of the regular audits of the integrated quality management and information security system. They are conducted on an annual basis and their results are documented in reports. Relevant corrective and preventive measures are identified for the improvement of the processes related to pharmacovigilance. The internal audit reports and the corrective and preventive measures are approved by the senior management of the BDA and reported to the Council of management.

The agency has a framework for risk-based regulation. It includes identification, evaluation and control of potential events or situations which may have a negative impact on the accomplishment of the set objectives and is designed to provide reasonable confidence that they will be accomplished. The Head of the Agency defines the acceptable risk level. Each structural unit of the Agency analyses and identifies the risks which may affect it and reports them to the Head of the BDA. The annual risk analysis and assessment report on the work of the agency is submitted to the Minister of Health.

The audits conducted from April 2011 to June 2013 comply with the existing legislation, the international standards ISO 9001:2008, ISO/IEC 27001:2005 and ISO 19011:2011, and the *Internal Audits* Management Procedure of the integrated quality management and information security system. A strategy is in place for the pharmacovigilance audits, which is approved by the Council of management of the Agency on 17.09.2013.

3.2 SUMMARY OF THE AUDITS FOR THE PERIOD UNDER REVIEW

The audits conducted in the period from April 2011 to June 2013 include one certification audit in two stages and two control audits of the implemented integrated quality management and information security system by the internationally accredited organisation Intertek-Moody, two information security audits aiming to verify compliance with the requirements of the standard BS EN ISO 27001: 2006 conducted by external auditors and 33 internal auditors, six of which were of the Medicines Use Control Department, where pharmacovigilance activities are carried out, aiming to verify compliance with the requirements of the standard BS EN ISO 9001:2008, the existing legislation and the integrated quality management and information security system. The internal audits showed that the organisation created the required conditions for compliance with the requirements of the integrated quality management and information security system, and that processes are in place for its further development and improvement.

In the beginning of October 2012, an audit was conducted at the Bulgarian Drug Agency by the WHO for the regular reassessment of the national regulatory authority responsible for the regulatory oversight of vaccines, manufactured on their territory. The WHO found that the regulatory oversight of vaccines by the Bulgarian Drug Agency complies with the international standards and that the national regulatory system continues to be functional as per the critical parameters listed by the WHO.

In late November 2012, a partner inspection was conducted at the Bulgarian Drug Agency, Benchmarking of European Medicines Agencies (BEMA), by a team of specially trained assessors from the German, Portuguese and UK drug agencies. In their report the assessors indicated as very good the levels of all parameters and pointed out the following best practices of the BDA:

1. The Bulgarian Drug Agency has implemented, maintains and continuously improves an integrated quality management and information security system. It holds a certificate issued by an internationally accredited organisation for compliance of the integrated systems with the requirements of the international standards EN ISO 9001:2008 and ISO/IEC-27001:2005. The implemented system ensures the proper application of all processes in the agency.

2. The BDA has implemented an information classification system and an information security policy which are based on the requirements of the standard ISO / IEC 27001:2005. These procedures make possible the effective and efficient storage and protection of information according to its confidentiality level.

3. The Agency has developed a human resource management procedure covering the stages of research, selection, recruitment, training and attestation of staff. The effectiveness of the human resource management is assessed, analysed and improved on the basis of the results of the audits.

3.2.1 AUDIT ASSIGNMENTS FOR THE PERIOD UNDER REVIEW

Regular internal audits are conducted at the Bulgarian Drug Agency to verify its compliance with the requirements of the integrated management system and for identification of the opportunities for improvement. The applied requirements are those of the implemented procedures and international standards ISO 9001:2008, ISO/IEC 27001:2005 and ISO 19011:2011. Registers of corrective and preventive measures are in place.

All listed audits are conducted in compliance with the international standards ISO 9001:2008, ISO/IEC 27001:2005 and ISO 19011:2011.

Audit No	Audit title	Date of audit report
1 / April 12-18, 2011	Compliance of the processes with the requirements of the standards BS EN ISO 9001:2008, BS ISO/IEC 27001:2006 and the	April 21, 2011

	implemented integrated quality management and information security system. /Medicines Use Control Department/	
2 / June 02 -03, 2011	Review of the corrective measures implemented in response to the findings of the internal audit conducted in April 2011 and assessment of their effectiveness and efficiency. / Medicines Use Control Department /	June 14, 2011
3 / June 16-17, 2011 July 06-08, 2011	Expert assessment and oversight of the quality, safety and efficacy of medicinal products; Expert assessment, registration and oversight of the market of the medical devices; Control of the blood transfusion system. Certification audit	July 08, 2011
4 / April 05-06, 2012	Compliance of processes with the requirements of the standard BS EN ISO 9001:2008, the implemented integrated quality management and information security system, and the existing regulations. /Medicines Use Control Department/	April 17, 2012
5 / April 09 – 26, 2012 May 02 – 03, 2012	Compliance of the processes with the requirements of the standards BS EN ISO 9001:2008 (clauses 5 and 8), BS ISO/IEC 27001:2006 and the implemented integrated quality management and information security system /Medicines Use Control Department/	May 17, 2012
6 / June 18-19, 2012	Expert assessment and oversight of the quality, safety and efficacy of medicinal products; Expert assessment, registration and oversight of the market of medical devices; Control of the blood transfusion system. Control audit	June 20, 2012
7 / June 27-28, 2012	Compliance of the process *Measuring Customer Satisfaction* with the requirements of BS EN ISO 9001:2008 /clause 8.2.1/ and the implemented integrated quality management and information security system. /Medicines Use Control Department/	June 29, 2012
8 / September 17-18, 2012	Compliance of the process *Inspection of the Pharmacovigilance System of Marketing Authorisation Holders* with the requirements of	September 18, 2012

	BS EN ISO 9001:2008 and the implemented integrated quality management and information security system / Medicines Use Control Department/	
9 / October 01-05, 2012 December 05, 2012	Assessment of the national regulatory system for regulatory oversight of vaccines – of the regulatory body BDA – by assessors of WHO /Medicines Use Control Department/	January 10, 2013
10/ November 27-29, 2012	Benchmarking of European Medicines Agencies (BEMA) Partner audit /Medicines Use Control Department/	December 05, 2012
11 / April 03-04, 2013	Compliance of the processes with the requirements of BS EN ISO 9001:2008 and the implemented integrated quality management and information security system. /Medicines Use Control Department/	April 04, 2013
12 / April 29-30, 2013	Compliance of the processes with the requirements of the standards BS EN ISO 9001:2008 (clauses 5 and 8), BS ISO/IEC 27001:2006 and the implemented integrated quality management and information security system. /Medicines Use Control Department/	May 08, 2013
13 / June 05-06, 2013	Expert assessment and oversight of the quality, safety and efficacy of medicinal products; Expert assessment, registration and oversight of the market of medical devices; Control of the blood transfusion system. Control audit	June 17, 2013

1 /April 12-18, 2011

3.2.2 AUDIT TITLE Compliance of the processes with the requirements of standards BS EN ISO 9001:2008, BS ISO/IEC 27001:2006 and the implemented integrated quality management and information security system.

/Medicines Use Control Department/

3.2.2.1 Objective and scope: To establish to what extent the processes taking place at the Bulgarian Drug Agency comply with the requirements of the international standards BS EN ISO 9001:2008 and BS ISO/IEC 27001:2006, and with the documents of the integrated quality management and information security system.

3.2.2.2 Audit body: External auditors and trainee auditors of the Bulgarian Drug Agency

Opinion: The Bulgarian Drug Agency has documented and implemented an integrated quality management and information security system in compliance with the standards BS EN ISO 9001:2008 and BS ISO/IEC 27001:2006. Two deficiencies were found during the audit of the Medicines Use Control Department:

Deficiency No. 5 (BS ISO/IEC 27001:2006, clause A7.1.3., ISP 07) – Some documents on paper classified in group 3 and documents containing personal data are stored in open cabinets.

Deficiency No. 6 (BS ISO/IEC 27001:2006, clause A.7.2.2., ISP 04) – Some documents on paper found at the work stations were not classified as required in ISP 04.

2 / June 02 -03, 2011

3.2.2 AUDIT TITLE Review of the corrective measures taken in response to the findings (deficiencies and areas for improvement) of the internal audit conducted in April 2011, and assessment of their effectiveness and efficacy.

/Medicines Use Control Department/

3.2.2.1 Objective and scope: Review of the corrective measures taken in response to the findings of the internal audit conducted in April 2011, and assessment of their effectiveness and efficiency according to the requirements of standards BS EN ISO 9001:2008 and BS ISO/IEC 27001:2006.

3.2.2.2 Audit body: External auditors and trainee auditors of the Bulgarian Drug Agency

3.2.2.3 Opinion: The deficiencies found in the Medicines Use Control Department during the previous audit are closed as follows:

- The documents classified in group 3 during the previous audit are now classified in a group of lower value. The documents are stored in a fashion appropriate to their classification group.

- The documents at the Medicines Use Control Department are classified in compliance with the requirements of ISP 04.

3 / June 16-17, 2011

July 06-08, 2011 – Certification audit

3.2.2 AUDIT TITLE Expert assessment and oversight of the quality, safety and efficacy of medicinal products; Expert assessment, registration and oversight of the market of medicinal products; Control of the blood transfusion system.

/Medicines Use Control Department/

3.2.2.1 Objective and scope: Inspection of the implemented system for compliance with the standards BS EN ISO 9001:2008 and BS ISO/IEC 27001:2006, and assessment of the preparedness of the system for certification.

3.2.2.2 Audit body: International certification organisation Intertek-Moody

3.2.2.3 Opinion: There is proof of compliance with the requirements of the standard ISO 9001:2008 and ISO 27001:2005. Activities have been introduced which lead to the improvement of the integrated quality management and information security system. The organisation has created the required conditions for compliance with the requirements of the implemented integrated quality management and information security system and its improvement. No deficiencies were found that require the implementation of corrective measures. On the basis of the conclusions from the audit, it is recommendable that the Bulgarian Drug Agency should get registered for compliance with the requirements of standards ISO 9001:2008 and ISO 27001:2005.

4 /April 05-06, 2012

3.2.2 AUDIT TITLE Compliance of the processes with the requirements of the standard BS EN ISO 9001:2008, the implemented integrated quality management and information security system and the existing regulations.

/Medicines Use Control Department /

3.2.2.1 Objective and scope: Compliance of the processes with the requirements of the standards BS EN ISO 9001:2008 and the implemented integrated quality management and information security system and the existing regulations.

3.2.2.2 Audit body: Internal auditors from the Bulgarian Drug Agency

3.2.2.3 Opinion: The required management procedures and standard operating procedures have been implemented in the Medicines Use Control Department and are strictly followed. It is necessary to undertake measures to deal with the two deficiencies and the two areas for improvement that were found.

Deficiency No. 1 /BS EN ISO 9001:2008 clause 4.2.4 MP-0002 paragraph 8.2/: There are records which are not kept properly – they are not dated and do not follow the established form; there is no information or clarification as required under paragraph 8.2.

Deficiency No. 2 /BS EN ISO 9000:2008 and SOP-7011/ No document was presented of the review and analysis carried out every six months in relation to the adverse drug reaction reports submitted to the Medicines Use Control Department.

Area for improvement No. 1 The annual plan for inspections of the pharmacovigilance system of marketing authorisation holders should be prepared by the end of the previous calendar year.

Area for improvement No. 2 /BS EN ISO 9000:2008/ There are documents outside the scope of the integrated management system. There is an electronic register of adverse drug reactions which does not exist as a form in the integrated quality management and information security system.

5 / April 09 – 26, 2012

May 02 – 03, 2012

3.2.2 AUDIT TITLE Compliance of the processes with the requirements of the standards BS EN ISO 9001:2008 (clauses 5 and 8), BS ISO/IEC 27001:2006 and the implemented integrated quality management and information security system

/Medicines Use Control Department/

3.2.2.1 Objective and scope: Compliance of the processes with the requirements of the standards BS EN ISO 9001:2008 (clauses 5 and 8), BS ISO/IEC 27001:2006 and the implemented integrated quality management and information security system, the existing regulations and contracts

3.2.2.2 Audit body: External auditors

3.2.2.3 Opinion: Two areas for improvement were found in the Medicines Use Control Department

Area for improvement No. 41 (BS ISO/IEC 27001:2006, clause A.7.2.2 ISP 04) – Portable flash memory drives are in use, but are not identified with the relevant reference numbers from the list of documents/register of confidential electronic media.

Area for improvement No. 42 (BS ISO/IEC 27001:2006, clause A.9.2.3, ISP 09) – There is unsafe electrical wiring on the floor.

6 / June 18-19, 2012 – Control Audit

3.2.2 AUDIT TITLE Expert assessment and oversight of the quality, safety and efficacy of medicinal products; Expert assessment, registration and oversight of the market of medical devices; Control of the blood transfusion system.

3.2.2.1 Objective and scope: To verify the sustainable effectiveness of the system, commitment and continuous improvement

3.2.2.2 Audit body: International certification organisation Intertek-Moody

3.2.2.3 Opinion: Activities have been introduced that lead to the improvement of the implemented integrated quality management and information security system. The organisation has created the required conditions for compliance with the requirements of the implemented integrated quality management and information security system and its improvement.

7 / June 27-28, 2012

3.2.2 AUDIT TITLE Compliance of the process *Measuring Customer Satisfaction* with the requirements of BS EN ISO 9001:2008 /clause 8.2.1/ and the implemented integrated quality management and information security system.

/Medicines Use Control Department/

3.2.2.1 Objective and scope: Compliance of the process *Measuring Customer Satisfaction* with the requirements of BS EN ISO 9001:2008 /clause 8.2.1/ and the implemented integrated quality management and information security system.

3.2.2.2 Audit body: Internal auditors from the Bulgarian Drug Agency

3.2.2.3 Opinion: All audited employees from the Medicines Use Control Department demonstrate a high level of competence and awareness of the process *Measuring Customer Satisfaction*. The process *Measuring Customer Satisfaction* of the Bulgarian Drug Agency was found to be compliant with the requirements of the standard BS EN ISO 9001:2008 /clause 8.2.1/ and the implemented integrated quality management and information security system.

The Medicines Use Control Department publishes on the website of the Bulgarian Drug Agency two bulletins, *Adverse Drug Reactions* and *Medicinal Bulletin*, which have a

feedback form. Telephone numbers and an e-mail address are made available to the customers for contacts with the employees of the department.

8 /September 17-18, 2012

3.2.2 AUDIT TITLE Compliance of the process *Inspection of the Pharmacovigilance System of Manufacturing Authorisation Holders* with the requirements of the standard BS EN ISO 9001:2008 and the implemented integrated quality management and information security system

/Medicines Use Control Department/

3.2.2.1 Objective and scope: Compliance of the process *Inspection of the Pharmacovigilance System of Manufacturing Authorisation Holders* with the requirements of standard EN ISO 9001:2008 and the implemented integrated quality management and information security system in the Medicines Use Control Department

3.2.2.2 Audit body: Internal auditors from the Bulgarian Drug Agency

3.2.2.3 Opinion: MP 7000 and SOP 7015 have been implemented and are currently used in the Medicines Use Control Department. Measures should be taken for the closure of the three deficiencies and two areas for improvement found during the audit.

Deficiency No. 1 ISO 9001: 2008 clause 4.2.3. There is an outdated internal document (instruction).

Deficiency No. 2 ISO 9001: 2008 clause 4.2.4. Form F 7015 /01 *Statement of Findings* is not completed correctly.

Deficiency No. 3 ISO 9001: 2008 clause 4.2.3 Internal documents which are not part of the quality management system (electronic table for conducted inspections) are used in the Medicines Use Control Department.

Area for improvement No. 1 ISO 9001:2008 clause 4.2.3 SOP 7015 does not contain a description of the procedure and manner of collaboration between the Medicines Use Control Department and the Administrative Services Department.

Area for improvement No. 2 ISO 9001:2008 clause 4.2.4 The reference numbers of the inspection reports do not give accurate information about the number of conducted inspections during the current year

9 /October 01-05, 2012

December 05, 2012

3.2.2 AUDIT TITLE Assessment of the national regulatory authority responsible for the regulatory oversight of vaccines – the Bulgarian Drug Agency – by WHO assessors

/Medicines Use Control Department/

3.2.2.1 Objective and scope: To update the requalification status of the vaccines manufactured in Bulgaria. To assess all regulatory functions for compliance with the parameters published by WHO in relation to vaccines

3.2.2.2 Audit body: – five WHO assessors and four assessors from France, Tunisia, and Romania

3.2.2.3 Opinion: The regulation of vaccines by BDA complies with the international standards and the national regulatory system continues to be functional as per the critical parameters listed by WHO. A certified quality system is in place, covering all processes which take place at BDA. With its Pharmacovigilance system, BDA participates in the electronic exchange of information on adverse drug reactions with EMA (Eudra Vigilance) and WHO (Uppsala Monitoring Center of ADR).

Area for improvement No. 1 ISO 9001:2008 clause 6.2.2 A training seminar should be organised with the technical support of WHO on vaccine pharmacovigilance.

10 /November 27-29, 2012

3.2.2 AUDIT TITLE Benchmarking of European Medicines Agencies (BEMA)

/Medicines Use Control Department/

3.2.2.1 Objective and scope: Provision of information to assist the management of the BDA by prioritising its need of resources and by decreasing the existing risks. This information is focused on the effectiveness of the system of the agency and gives guidance as to the opportunities for improvement.

Partner assessment aiming to define the maturity level of the management system of the BDA, by using the BEMA questionnaire for the various fields of work of the agency, connected to pre- and post- marketing authorisation activities, pharmacovigilance assessment, inspections and others.

3.2.2.2 Audit body: Assessors from the German, Portuguese, and UK medicines agencies.

3.2.2.3 Opinion: The report of the visit assesses as very good the levels of all parameters and points out the following best practices of the agency:

1. The Bulgarian Drug Agency has implemented, maintains and continuously improves an integrated quality management and information security system. It holds a certificate issued by an internationally accredited organisation for the compliance of the integrated systems with the requirements of the international standards EN ISO 9001:2008 and ISO/IEC-27001:2005. The implemented system ensures proper application of all processes in the agency.

2. The BDA has implemented an information classification system and an information security policy which are based on the requirements of the standard ISO / IEC 27001:2005. These procedures make possible the effective and efficient storage and protection of information according to its confidentiality level.

3. The BDA has developed a human resource management procedure covering the stages of research, selection, recruitment, training and attestation of staff. The effectiveness of the human resource management procedure is assessed, analysed and improved on the basis of the results of audits.

11 / April 03-04, 2013

3.2.2 AUDIT TITLE Compliance of the processes with the requirements of standards BS EN ISO 9001:2008 and the implemented integrated quality management and information security system.

/Medicines Use Control Department/

3.2.2.1 Objective and scope: Compliance of the processes with the requirements of standards BS EN ISO 9001:2008 and the implemented integrated quality management and information security system in the Medicines Use Control Department.

3.2.2.2 Audit body: Internal auditors of the Bulgarian Drug Agency

3.2.2.3 Opinion: The processes carried out at the Medicines Use Control Department comply with the standard BS EN ISO 9001:2008 and the implemented integrated quality management and information security system. Only one deficiency was found. Corrective measures have to be taken to eliminate this deficiency.

Deficiency 1 /ISO 9001:2008 /clause 7.5.1/ Production management – Non-compliance with the deadlines for preparation of inspection reports specified in paragraph 8.5.2 of SOP 7015.

12 /April 29-30, 2013

3.2.2 AUDIT TITLE Compliance of the processes with the requirements of standards BS EN ISO 9001:2008 (clauses 5 and 8), BS ISO/IEC 27001:2006 and the implemented integrated quality management and information security system.

/Medicines Use Control Department/

3.2.2.1 Objective and scope: Compliance of the processes with the requirements of standards BS EN ISO 9001:2008 (clauses 5 and 8), BS ISO/IEC 27001:2006, the implemented integrated quality management and information security system, the existing regulations and contracts

3.2.2.2 Audit body: External auditors and internal auditors from BDA

3.2.2.3 Opinion: The implemented integrated quality management and information security system of the Bulgarian Drug Agency is maintained and operated in compliance with the standards BS EN ISO 9001:2008 and BS ISO/IEC 27001:2006. The documentation of the implemented integrated quality management system is brought in line with all changes. The senior management of the Bulgarian Drug Agency provides management support and adequate organisational, financial and IT resources for the implementation of the processes and for the maintenance of the integrated quality management and information security system. The awareness levels of the staff of the Bulgarian Drug Agency on the requirements for compliance with the integrated management system are high.

13 /June 05-06, 2013 – Control Audit

3.2.2 AUDIT TITLE Expert assessment and oversight of the quality, safety and efficacy of medicinal products; Expert assessment, registration and oversight of the market of medicical devices; Control of the blood transfusion system.

3.2.2.1 Objective and scope: To verify the sustainable effectiveness of the system, commitment and continuous improvement

3.2.2.2 Audit body: International certification organisation Intertek-Moody

3.2.2.3 Opinion: It was found that the organisation maintains an integrated management system in compliance with the requirements of ISO 9001:2008 and ISO 27001:2005. There are clearly defined objectives of the control mechanisms. Most of these mechanisms operate in compliance with the regulations.

3.2.2.3 Audit outcomes and actions

Measures taken in response to 8 deficiencies and 7 areas for improvement reported and inspected for compliance with the international standards ISO 9001:2008, ISO/IEC 27001:2005 and ISO 19011:2011.

Complete table with headlines and summary of the results of each audit / action

Audit №	Find No	Audit outcomes description	Grading	Action short description	Action end date	Comments on status of actions	Type of follow-up required
1	1 / April 12-18 2011	Deficiency No. 5 (BS ISO/IEC 27001:2006, clause A7.1.3., ISP 07) - There are documents on paper classified in group 3 and documents containing personal data stored in open cabinets.	Deficiency	Organisational measures should be taken to store the documents in lockable cabinets.	June 03, 2011	Complete	Monitoring during next audit
		Deficiency No. 6 (BS ISO/IEC 27001:2006, clause A.7.2.2., ISP 04) - Some of the documents on paper were not classified as required in ISP 04.	Deficiency	Organisational measures should be taken to indicate the classification level of documents on paper as required in ISP 04	June 03, 2011	Complete	Monitoring during next audit
2	2 / June 2 – 3, 2011	No deficiencies were found	–	–	–	–	–
3	3 / June 16-17, 2011 July 06-08, 2011	No deficiencies were found	–	–	–	–	–
4	4 / April 05-06, 2012	Deficiency No. 1 /BS EN ISO 9001:2008 clause 4.2.4 MP-0002 paragraph 8.2/: There are records which are not kept properly – they are not dated and do not	Deficiency	Staff should undergo training on MP 0002 Record management	May 11, 2012	Complete	Monitoring during next audit

		follow the established form; there is no information or clarification as required under paragraph 8.2					
		Deficiency No. 2 /BS EN ISO 9000:2008 and SOP -7011/ No document was presented of the review and analysis carried out every six months in relation to the adverse drug reaction reports submitted to the Medicines Use Control Department.	Deficiency	Staff should undergo training on SOP 7011	May 11, 2012	Complete	Monitoring during next audit
		Area for improvement No. 1 The annual plan for inspections of the pharmacovigilance system of marketing authorisation holders should be prepared by the end of the previous calendar year.	Deficiency	The annual plan for inspections of the pharmacovigilance system of marketing authorisation holders should be prepared by the end of the previous calendar year.	April 4, 2013	Complete	Monitoring during next audit
		Area for improvement No. 2 /BS EN ISO 9000:2008/ There are documents outside the scope of the integrated management system. There is an electronic register of adverse drug reactions which does not exist as a form in the integrated quality management and information security system.	Area for improvement	To develop a form of the electronic register of adverse drug reactions and include it in the integrated management system.	April 4, 2013	Complete	Monitoring during next audit

5	5 / April 9 – 26, 2012 May 2 –3, 2012	Area for improvement No. 41 (BS ISO/IEC 27001:2006, clause A.7.2.2 ISP 04) – Portable flash memory drives are in use, but are not indentified with the relevant reference numbers from the list of documents/register of confidential electronic media.	Area for improvement	To identify all portable flash memory drives with reference numbers from the list of documents or the register of confidential electronic media.	June 10, 2012	Complete	Monitoring during next audit
		Area for improvement No. 42 (BS ISO/IEC 27001:2006, clause A.9.2.3, ISP 09) – There is unsafe electrical wiring on the floor.	Area for improvement	To secure the electrical wiring	May 31, 2012	Complete	Monitoring during next audit
6	6 / June 18-19, 2012	No deficiencies were found	–	–	–	–	–
7	7 / June 27-28, 2012	No deficiencies were found	–	–	–	–	–
8	8 / September 17-18, 2012	Deficiency No. 1 ISO 9001: 2008 clause 4.2.3. There is an outdated internal document (instruction)	Deficiency	To introduce and use the updated version of the instruction	September 24, 2012	Complete	Monitoring during next audit
		Deficiency No. 2 ISO 9001: 2008 clause 4.2.4. Form F 7015 /01 *Statement of Findings* is not completed correctly	Deficiency	Internal training of inspectors / inspecting staff on how to complete Form F 7015/01 *Statement of Findings*	October 10, 2012	Complete	Monitoring during next audit

		Deficiency No. 3. ISO 9001: 2008 clause 4.2.3 Internal documents which are not part of the quality management system (electronic table for conducted inspections) are used in the Medicines Use Control Department	Deficiency	Inclusion of the electronic table for conducted inspections as a form in SOP 7015.	December 17, 2012	Complete	Monitoring during next audit
		Area for improvement No. 1 ISO 9001:2008 clause 4.2.3 SOP 7015 does not contain a description of the procedure and manner of collaboration between the Medicines Use Control Department and the Administrative Services Department	Area for improvement	In SOP 7015 to be included a description of the procedure and manner of collaboration between the Medicines Use Control Department and the Administrative Services Department	–	In progress	Monitoring during next audit
		Area for improvement No. 2 ISO 9001:2008 clause 4.2.4 The reference numbers of the inspection reports do not give accurate information about the number of conducted inspections during the current year	Area for improvement	To give inspection reports reference numbers which correspond to the conducted inspections, so that they provide accurate information about the number of inspections conducted during the current year.	April 4, 2013	Complete	Monitoring during next audit
9	9/ October 1-5, 2012 December 5, 2012	Area for improvement No. 1 ISO 9001:2008 clause 6.2.2 A training seminar should be organised with the technical support of WHO on vaccine pharmacovigilance.	Area for improvement	To organise a training seminar for the staff of the Bulgarian Drug Agency with the technical support of WHO	–	In progress	Monitoring during next audit

10	10/ November 27-29, 2012	No deficiencies were found	–	–	–	–	–
11	11 / April 3-4, 2013	Deficiency No. 1 /ISO 9001:2008 /clause 7.5.1/ Production management – Non-compliance with the deadlines for preparation of inspection reports specified in paragraph 8.5.2 of SOP 7015.	Deficiency	The final inspection report should be based on the statement of findings report and should describe in detail only the deficiencies and the recommendations for their elimination. Training of staff.	July 18, 2013	Complete	Monitoring during next audit
12	12 / April 29-30, 2013 г.	No deficiencies were found	–	–	–	–	–
13	13 / June 5-6, 2013	No deficiencies were found	–	–	–	–	–

Notes: This classification complies with the requirements of the *Internal Audits* Procedure

Deficiency – non-compliance with a requirement;

Area for improvement – action for elimination of the reason for a potential deficiency or other potential undesirable circumstances

4. FOLLOW-UP

4.1 SUMMARY OF ACTION PLANS FROM PRIOR BIENNIAL REPORTS

The table below gives an overview of the results of audits conducted by the international certification organisation Intertek-Moody, external auditors and internal auditors from the Bulgarian Drug Agency, and their implementation by the Medicines Use Control Department in the period from April 2011 to June 2013.

For action from audit outcome graded as:	Total	Number implemented	Number not implemented	
			Not started	In progress
Deficiencies	8	8	–	–
Areas for improvement	7	5	–	2
Total	15	13	–	2

Notes: This classification complies with the requirements of the *Internal Audits* Procedure

Deficiency – non-compliance with a requirement;

Area for improvement – action for elimination of the reason for a potential deficiency or other potential undesirable circumstances

4.2 OUTSTANDING ISSUES FROM PRIOR BIENNIAL REPORTS

[This section should address outstanding issues identified in previous biennial report(s) that still require follow-up action(s).]

5. DECLARATION

The Quality management division confirm that this report contains a complete account of all pharmacovigilance system audit activity performed in the period under review to fulfil the obligations of this organisation under Directive 2001/83/EC /Regulation (EC) No.726/2004[1].

Iskra Peytcheva **20.09.2013**
Head of the Quality management division **Date**

1 Delete as necessary – National Competent Authorities are required to perform a regular audit of their Pharmacovigilance system and report the results to the Commission on 21 September 2013 at the latest and then every 2 years thereafter. (Directive 2001/83/EC Art.101(2), The European Medicines Agency is required regular independent audits of its pharmacovigilance tasks and report the results to its Management Board on a 2-yearly basis. (Regulation (EC) No.726/2004 Art 28f)