

**Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Finished Product Manufacturer**

Part 1	General information
Manufacturers details	
Name of manufacturer	HBM Pharma Sro.
Corporate address of manufacturer	Sklabinska 30, Martin, 036 80, Slovak Republic.
Inspected site	
Name & Address of inspected manufacturing site if different from that given above	Same as above
Inspection details	
Dates of inspection	27 – 29 June 2018
Type of inspection	Initial
Introduction	
Brief summary of the manufacturing activities	HBM manufactures aseptically filled and terminally sterilized liquids in ampoules as well as tablets.
General information about the company and site	The site was originally established as a joint-venture of Hoechst-Biotika, spol. s.r.o. In 2005 SANITAS, AB Kaunas Lithuania became a shareholder and in 2010 the company changed name HBM Pharma s.r.o. The same year LIPLATS, Latvia became the main shareholder. HBM is a contract manufacturer that provides analytical and development services as well as acting as a wholesaler. The company also holds integrated ISO certification system. HBM is contracted by Grindeks for the manufacture of two WHO prequalified products. The responsibilities of HBM are batch processing (formulation), ampoule filling, sealing, labelling, packing and QC testing. Filling Line 1 was of interest to WHO. Responsibilities of Grindeks is stability testing & batch release.
History	This was the first WHO inspection of this site. The site was inspected by various authorities for terminally sterilized and aseptically filled injections: • The Ukrainian Authorities in 2012 & 2013 • SIDC (SUKL) in 2013, 2014, 2015 & 2017 • Iranian authorities in 2016 • Russian authority in 2016 & 2017 • Belarus authority in 2017.

Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	Production and QC labs including: • Organization chart • Job description for key personnel: QA, QC, Production • SOP PQR and records. • Risk assessment SOP and list of carried out Risk assessments • Change control: SOP and summary list of changes (2017 and 2018) • Deviation management: SOP and summary list of deviations (2017 and 2018) • SOP CAPA and CAPA register (2017 and 2018) • Complaints: SOP and summary list of complaints of (2017 and 2018) • Recalls: SOP and summary list of recalls if any, mock recall (2017 and 2018) • SOP OOS and summary list of OOS (2017 and 2018) • SOP OOT and summary list of OOT (2017 and 2018) • SOP Vendors qualification, list of approved vendors • SOP Training, training plan and training modules if available • SOP Personnel Hygiene – Operator Qualification • Contracts (Technical agreements) • SOP Batch Number allocation • SOP Batch release • Validation Master Plan • Cleaning validation protocol/report + raw data • Process validation (Media fills) protocol/report + raw data • SOP Preventive Maintenance and schedule (2017-2018) • SOP calibration of equipment and schedule (2017-2018) • SOP for material management including starting materials, packaging materials and components (receiving, quarantine, sampling and storage) Site inspection: • Schematic drawing/ layout of production areas • Receiving area and stores • Storing materials • Sampling, dispensing and issuing • Production following material flow (Aseptic Filling included) • Pharmaceutical Water system schematic drawings, qualification and validation • HVAC system schematic drawings, qualification and validation • HVAC system inspection • PW / WFI system inspection • Compressed air system + Nitrogen (if applicable) QCL Inspection:

	• Wet chemistry laboratory • Instrumentation laboratory • Microbiology laboratory • SOP Stability testing and stability schedule • Retention samples storage
Out of scope	Products and workshops where that were not of relevance to WHO prequalification.
WHO products covered by the inspection	Terminally sterilized and aseptically filled ampoules. This included: Oxytocin 10 IU/mL solution for injection Magnesium sulfate 500 mg/mL (2 mL) solution for injection Magnesium sulfate 500 mg/mL (10 mL) solution for injection
Abbreviations	Meaning
AHU	Air handling unit
ALCOA	Attributable, legible, contemporaneous, original and accurate
API	Active pharmaceutical ingredient
APR	Annual product review
APS	Aseptic process simulation
BMR	Batch manufacturing record
BPR	Batch production record
CC	Change control
CFU	Colony-forming unit
CIP	Cleaning in place
CoA	Certificate of analysis
CpK	Process capability
DQ	Design qualification
EDI	Electronic deionization
EM	Environmental monitoring
FMEA	Failure modes and effects analysis
FPP	Finished pharmaceutical product
FTA	Fault tree analysis
GMP	Good manufacturing practices
GPT	Growth promotion test
HEPA	High efficiency particulate air
HPLC	High performance liquid chromatography (or high performance liquid chromatography equipment)
HVAC	Heating, ventilation and air conditioning
IQ	Installation qualification
LAF	Laminar air flow
LIMS	Laboratory information management system
MB	Microbiology
MBL	Microbiology laboratory
MF	Master formulae
MFT	Media fill Test
MR	Management review

NC	Non conformity
NCA	National control authority
NCL	National control laboratory
NRA	National regulatory agency
OQ	Operational qualification
PHA	Process hazard analysis
PLC	Programmable logic controller
PM	Preventive maintenance
PQ	Performance qualification
PQR	Product quality review
PQS	Pharmaceutical quality system
PW	Purified water
QA	Quality assurance
QC	Quality control
QCL	Quality control laboratory
QMS	Quality management system
QRM	Quality risk management
RA	Risk assessment
RCA	Root cause analysis
RO	Reverse osmosis
SIP	Sterilization in place
SMF	Site master file
SOP	Standard operating procedure
URS	User requirements specifications
UV	Ultraviolet-visible spectrophotometer
WFI	Water for injection

Part 2	Brief summary of the findings and comments (where applicable)
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1. Pharmaceutical quality system

A pharmaceutical quality system (PQS) was established, with Quality Manual, Policies and written procedures covering essential GMP principles for the site. Procedures that were reviewed and discussed during the inspection were generally presented promptly, however not a few of these procedures were not sufficiently detailed or satisfactorily implemented, and both procedure content and level of implementation had to be improved.

Product quality review (PQR)

A PQR procedure was in place describing the steps to verify consistency of existing processes, appropriateness of established specifications for starting materials, in process and finished products as well as monitoring trends. PQRs of WHO prequalified products for 2016 and 2017 were reviewed. PQRs were not complete since release, on-going stability studies, complaints and recalls are managed by Grindeks who is responsible for drafting these sections of the PQR.

Quality Risk Management (QRM)

A QRM procedure was available. QRM was applied on manufacturing operations including but not limited to change control and deviation management, production and complaints.

Change and deviation management

The company had procedures in place for change and deviation management. The procedure on handling of changes adequately described the stages of initiation, evaluation, approval, implementation and review. The proposed changes had to be justified by the head of the relevant department and a unique number was assigned by the QA department. Deviations were recorded and assessed. Root cause investigations were conducted and relevant CAPA were identified and implemented. Extensions were documented and could be granted upon justification.

2. Good manufacturing practices for pharmaceutical products

Basic principles of good manufacturing practices were generally described and implemented. Manufacturing processes were adequately defined and documented in BMRs and BPRs. Required resources were available, including adequate premises, equipment and utilities. Appropriately qualified personnel were employed.

There were three filling lines on the ground floor of production building. Line 1 (RAB 1) was used on campaign basis.

All the critical equipment were programmed and controlled by the use of PLCs. Aseptic filling was performed in Grade A area under LAF. The solution was prepared on the first floor and it was filtered through 0.2µm filter during transfer from mixing tank to holding tank. Then it was transferred to the ampoule filling lines through closed pipeline. A second filtration with 0.2µm filter, was performed before ampoule filling.

Visual inspection was carried by operators and by automatic visual inspection equipment followed by labelling and packaging operations.

Manufacturing processes were generally adequately defined in approved documents. Manufacturing steps were recorded in batch manufacturing and packaging records. Product was released by the authorized Qualified Persons.

3. Sanitation and hygiene

Premises and equipment were generally maintained at an acceptable level of cleanliness and they were appropriately labelled. The company had an SOP as the basis for its approach to hygiene and sanitation in its production facilities. Microbial monitoring of clean room personnel was performed as part of routine batch control. Sanitization agents used in the facility were rotated every two months. The frequency was not justified.

4. Qualification and validation

The key principles of qualification and validation program were defined and documented in the Validation Master Plan. The most recent Media fill study was reviewed, summary report of aseptic process simulation for vial line, and batch manufacturing record were discussed. Mapping and qualification of the cold room were also reviewed. Validation of transport of temperature sensitive products was also performed and the protocol and report were presented. Process validation of two

available batch sizes were reviewed. Some issues regarding OOS results observed during the initial phase of aseptic filling were outlined. Qualification of the depyrogenation tunnel as well as filling area were checked.

5. Complaints

The company had in place a procedure on registering, investigating and monitoring complaints. However since the company acted as a contract manufacturer the responsibility for handling complaints was assigned to Grindeks. HBM was responsible for assisting in the investigations as appropriate.

6. Product recalls

According to the contract Grindeks was responsible for taking a recall decision and for performing a recall. HBM was responsible for assisting Grindeks in the recall process.

7. Contract production, analysis and other activities

A technical agreement between HBM and Grindeks was available. The agreement was amended several times and annexes were included as part of the contract which was applicable to the manufacture of several injectable products. Several of the responsibilities described in the contract did not reflect the information in the dossier submitted to WHO.

8. Self-inspection, quality audits and suppliers' audits and approval

Self-inspection was not reviewed in detail. A procedure for qualifying suppliers was presented. The supplier qualification was presented and it covered API, excipients and packaging material suppliers.

9. Personnel

Organization charts were available reflecting administrative structure. In general personnel met during the inspection appeared aware of the basic principles of GMP. Job descriptions of the production manager, a QC and Qualified Person were checked. The personnel met during the inspection have awareness of the principles of GMP and showed that they received initial and continuing training, including hygiene training, relevant to their responsibilities in the production process. HBM employed about 365 people in the company including production. Steps taken to prevent unauthorized people from entering production and QC areas appeared to be effective. Responsibilities for production and QC/QA were well separated.

10. Training

A procedure on training was available and it provided adequate details about induction training and continual training. Log books for training and training plans were in place. Training was evaluated by written test, oral examination and by issuance of training certificate. The training log book for personnel was maintained as per company procedures.

11. Personal hygiene

Procedures on personal hygiene were available. Gowning procedures and different types of gowning were presented. Personnel were appropriately qualified. Medical records were available and annual medical check-ups were scheduled and conducted.

12. Premises

In the same lot another pharmaceutical manufacturer was also located but the facilities of the two companies were separated. The total area of HBM facilities was approximately 32,000 sqm. The premises were located, designed, constructed and maintained to suit the operations that were carried out. The design was such as to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid contamination. Premises were designed and constructed to facilitate good sanitation. Personnel access to different grade areas was achieved through a series of increasing cleanliness airlocks while material airlocks and pass-boxes were also available. Production premises were designed to allow production in a unidirectional flow.

13. Equipment

Production equipment was of good standard and records indicated that it was adequately maintained. Equipment location indicated a logical sequence as per process flow. There were three ampoule filling lines equipped. Filling line 1 was designed using RABS. Computerized systems were used in the warehouse for material management and logistic administration, as well as in the QC laboratory for management of testing results of the material and product testing and data management.

14. Materials

Incoming materials were purchased from approved suppliers, sampled and tested according to specifications and testing procedure. However, during material receipt at incoming materials were not verified that they are purchased from approved vendors and temperature excursion in data logger was not checked at warehouse level. The company applied appropriate CAPA following the inspection. Bar code was used on the material label for the material status and identification.

Product release was performed according to a written procedure and a check list was used. Finished products were held in quarantine until their final release, and stored under appropriate and monitored conditions. The finished product was released by Grindeks.

15. Documentation

Documentation exists in electronic as well as hard copy and some parts of the documentation system such as product specifications are provided in electronic form. Raw data concerning completed analyses and reports with the test results were recorded manually and/or electronically. Electronic files were saved and archived on the basis of a defined procedure. Approved, signed and dated analytical methods and specifications were available for starting and packaging materials and for finished products. 8-digit batch number was assigned as per batch numbering SOP and technical agreement with Grindeks. BMRs were retained for each batch processed.

16. Good practices in production

Clean areas for the manufacture of sterile products were classified according to the expected required characteristics of the environment. Appropriate disinfectants including a sporicidal were used on rotation in the clean rooms. Grade B gowning was sterilized and worn in grade B change room. For Grade A areas, particle monitoring was undertaken for the complete duration of critical processing including assembly of equipment. Microbiological and non-viable particles monitoring of Grades A–D was carried out. Appropriate action limits were set for the results of particulate and microbiological monitoring.

17. Good practices in quality control

The Quality Control laboratory was located on the second floor of the manufacturing building and it was independent of other departments. QC laboratories including microbiological laboratory were separated from production areas. The microbiological laboratory was segregated from the analytical laboratory. According to the company single use sampling tools were used for sampling. Sample receiving and distribution procedure were available, inspected and discussed. Ready to use media was used for EMP. Growth promotion testing was carried out on media but the rational of sampling was not justified. On-going stability studies were conducted at Grindeks premises the result of stability testing were not discussed with HBM and no review of stability data was available.

Part 3	Conclusion – Inspection outcome
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Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report, **HBM Pharma Sro**, located at **Sklabinska 30, Martin, 036 80, Slovak Republic** was considered to be operating at an acceptable level of compliance with WHO GMP Guidelines.

All the non-compliances observed during the inspection that were listed in the full report as well as those reflected in the WHOPIR, were addressed by the manufacturer, to a satisfactory level, prior to the publication of the WHOPIR.

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.

Part 4	List of GMP Guidelines referenced in the inspection report
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1. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eight Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2. **Short name: WHO TRS No. 986, Annex 2**
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/

2. WHO good manufacturing practices for active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2. **Short name: WHO TRS No. 957, Annex 2**
<http://www.who.int/medicines/publications/44threport/en/>
3. WHO good manufacturing practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-six Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 2
Short name: WHO TRS No. 970, Annex 2
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/
4. WHO guidelines for sampling of pharmaceutical products and related materials. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth Report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 4
Short name: WHO TRS No. 929, Annex 4
http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1
5. Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty Second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 8. **Short name: WHO TRS No. 1010, Annex 8**
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_1010/en/
6. Supplementary guidelines on good manufacturing practices: validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 4
Short name: WHO TRS No. 937, Annex 4
http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1
7. WHO Good Practices for Pharmaceutical Quality Control Laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957, Annex 1
Short name: WHO TRS No. 961, 957), Annex 1
<http://www.who.int/medicines/publications/44threport/en/>
8. WHO Good Practices for Pharmaceutical Products Containing Hazardous Substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2
Short name: WHO TRS No. 957, Annex 2
<http://www.who.int/medicines/publications/44threport/en/>

9. WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 6
Short name: WHO TRS No. 961, Annex 6
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
10. WHO guidelines on transfer of technology in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 7
Short name: WHO TRS No. 961, Annex 7
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
11. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9. **Short name: WHO TRS No. 961, Annex 9**
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
12. General guidelines for the establishment maintenance and distribution of chemical reference substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-First Report Geneva, World Health Organization 2007 (WHO Technical Report Series, No.943) Annex 3
Short name: WHO TRS No. 943, Annex 3
http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1
13. WHO good practices for pharmaceutical microbiology laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 2
Short name: WHO TRS No. 961, Annex 2
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
14. WHO guidelines on quality risk management. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 2. **Short name: WHO TRS No. 981, Annex 2**
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/
15. WHO guidelines on variation to a prequalified product. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 3. **Short name: WHO TRS No. 981, Annex 3**
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/
16. WHO guidelines for drafting a site master file. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 14. **Short name: WHO TRS No. 961, Annex 14**
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

17. WHO Guidelines on good manufacturing practices: validation, Appendix 7: non-sterile process validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 3. **Short name: WHO TRS No. 992, Annex 3**
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf
18. WHO General guidance on hold-time studies WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 4. **Short name: WHO TRS No. 992, Annex 4**
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf
19. WHO Technical supplements to Model Guidance for storage and transport of time – and temperature – sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 5. **Short name: WHO TRS No. 992, Annex 5**
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf
20. WHO Recommendations for quality requirements when plant – derived artemisin is used as a starting material in the production of antimalarial active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 6
Short name: WHO TRS No. 992, Annex 6
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf
21. Guidance on good data and record management practices. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5
Short name: WHO TRS No. 996, Annex 5
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf
22. WHO general guidance on variations to multisource pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 10
Short name: WHO TRS No. 996, Annex 10
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf