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

Part 1	**General information**
Manufacturers details	
Name of manufacturer	Grindeks JSC
Corporate address of manufacturer	53 Krustpils Street, Riga, 1057, Latvia
Inspected site	
Name & address of inspected manufacturing site if different from that given above	Krustpils iela 53, Rīga (I vieta), LV-1057, Latvia (main campus) Krustpils iela 71A, Rīga (II vieta), LV-1057, Latvia (FPP warehouse)
Inspection details	
Dates of inspection	13 – 14 December 2018
Type of inspection	Initial inspection
Introduction	
Brief description of the manufacturing activities	Grindeks manufactures Oxytocin API. Production and quality control of the corresponding FPP is outsourced to two companies, namely HBM Pharma Sro and UAB Santonika. Similarly manufacture of Magnesium sulfate ampoules (applicant Kalceks belonging to Grindeks group of companies) is outsourced to HBM Pharma Sro. Grindeks performs QC and stability testing, release, storage and distribution of the FPP. Retained samples are also maintained by Grindeks.
General information about the company and site	The Grindeks campus is located approximately 20 Km from Riga International Airport. Grindeks was established in 1946 as an experimental vitamin site under the umbrella of the Latvian Academy of Sciences. In 1997 the company was privatized and within the following decade several mergers and acquisitions took place while the corporate structure became Grindeks Group of Companies. In 2007 the FPP site was established followed by the semisolid unit in 2012 and renovation of QC laboratories in 2014. The FPP warehouse was located about one kilometer away from Grindeks campus, on the same street.

History	This was the first WHO inspection of Grindeks for finished product manufacturing.
Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	**Document reviewed including but not limited** • Contracts with HBM and UAB • Quality Management System- Quality Manual • Deviations- CAPA • Change Control • PQR • Complaints-Recalls • Finished Pharmaceutical Product inventory management • Retained Samples • Batch release • Laboratories • OOS and OOT • Stability **Site visited:** • FPP warehouse • QC laboratories • Stability chambers and retained samples area.
Restrictions	N/A
Out of scope	Products and operations not related to WHO Prequalification
WHO products covered by the inspection	RH079 - Oxytocin 10 IU/ml solution for infusion 1 ml ampoule. RH063 - Magnesium sulfate Solution for injection 500mg/ml (2ml) RH064 - Magnesium sulfate Solution for injection 500mg/ml (10ml)
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
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	Summary of the findings and comments (where applicable)

1. Pharmaceutical quality system

A pharmaceutical quality system (PQS) was established, with Quality Manual (QM), policies and written procedures. According to the company the principles, the PQS were described in QM and in SMF. The SMF was provided before the inspection and the QM was presented and was briefly reviewed during the inspection. It was noted that the QM was based on ISO principles and did not fully cover all GMP related activities. Management review meetings were held annually. The agenda and the minutes of the February 2018 meeting were presented. Identified observations were adequately addressed by the company's CAPA plan.

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. PQRs for Oxytocin and Magnesium sulfate were performed by contract manufacturers and reviewed by Grindeks. The company was also responsible for adding information and data related to stability studies where appropriate. Statistical analysis was not harmonized among contract manufacturers and Grindeks had not defined the level of analysis expected from contract manufacturers. Identified observations were adequately addressed by the company's CAPA plan.

Quality Risk Management (QRM)

A QRM procedure was available but it did not fully apply to all GMP activities and operations. Identified observations were adequately addressed by the company's CAPA plan.

Change and deviation management

The company had in place procedures for change and deviation management. Criticality of changes was assigned based on marketing authorization impact using as reference the EU variation of marketing authorization system. Change requests were registered in the Electronic Documentation Management System by the initiator and all relevant departments had to provide feedback including the Authorized Person/Qualified Person. QA was responsible for approving or rejecting a change request and for assigning implementation of the change to relevant department and person. 2018 change requests were spot-checked

The procedure on deviations was reviewed. A paragraph dedicated to handling of contract manufacturers' deviations described how Grindek's Qualified Person had to review the relevant documentation including CAPA. If further measures had to be taken these were recorded in EDMS as CAPA and the Qualified Person was responsible for following up the actions. Records relating to Oxytocin manufacturing deviations were reviewed

CAPA management

A CAPA management procedure sufficiently described a system for conducting and documenting activities for remedial actions. CAPA of reported deviations were registered in EDMS.

Investigation of Out of Specification
During the QC laboratory visit, the procedure and approach of handling OOS results was reviewed and discussed. The company had in place appropriate reporting means and investigation methods.

2. Good manufacturing practices for pharmaceutical products
Basic principles of good manufacturing practices were generally described and implemented. Required resources were available, including adequate storage areas, chemical and microbiological laboratories as well as appropriate QC equipment. Qualified personnel were employed

3. Sanitation and hygiene
Warehouse and laboratories were generally maintained at an acceptable level of cleanliness

4. Qualification and validation
The key principles of laboratory equipment qualification and calibration program were defined and documented.

5. Complaints
The company had in place a procedure on registering, investigating and monitoring complaints. Any employee in the company could be the recipient of complaints. Complaints were classified in five categories according to criticality and nature of the complaint. Identified observations were adequately addressed by the company's CAPA plan.

6. Product recalls
The company had in place a procedure describing measures for recalling products from the market. A mock recall was carried out annually covering on a rotational basis all dosage forms and APIs. The 2018 mock recall was reviewed.

7. Contract production, analysis and other activities
Grindeks was contracting out manufacture and quality control of Oxytocin ampoules to HBM Pharma Sro and UAB Santonika. The latter companies were inspected by WHO in Q2 2018 and several issues in relation to defining responsibilities for contract giver and contract acceptor were identified. Grindeks committed to review the contract and establish new ones. At the time of inspection Grindeks was still performing a review of responsibilities and the contracts were in draft. Grindeks committed to establish new contracts early in 2019 and submit the relevant variations to Oxytocin PQ dossier.

8. Self-inspection, quality audits and suppliers' audits and approval
Self-inspections were not reviewed in detail. Grindeks was the manufacturer of Oxytocin API. Key excipients' suppliers and packaging material suppliers were audited by contract manufacturers and the approach of supplier qualification was reviewed during the inspections of the contract manufacturers which took place in Q2 2018.

9. Personnel
Organization charts were available reflecting administrative structure. Job descriptions were prepared according to a procedure and taking into account EU legislation and GMP.

10. Training

Personnel training was not checked in detail due to time constraints.

11. Personal hygiene

Initial medical examinations and annual medical checkups were performed. Gowning procedures for entering the microbiological laboratory were established.

12. Premises

Laboratories were located on different floors of K18 building. HPLC laboratories were located on the second floor while wet chemistry laboratories were located on 3rd and 4th floor. Microbiological laboratories were located on the 1st floor. These laboratories were performing testing both on APIs and FPPs. The microbiological laboratories were revamped in 2014 and were divided in three major areas (method development, sterility room, general area). Each area was supplied with clean air by separate AHUs. Appropriate airlocks and personnel change rooms were established. The background area of the sterility room was classified as Grade D as well as the personnel airlock before entry to the sterility room. Sterility testing was carried out in a two-compartment isolator/glovebox which was classified as Grade A. Stability chambers and Oxytocin retained samples chambers were installed in a separate room which was kept under lock and key.

FPP warehouse was located approximately one kilometre away from the main campus. Oxytocin was stored in a cold room. Temperature mapping was performed during the summer and 12 loggers were used. The protocol identified and justified the number and location of loggers. Worst case scenarios were covered by placing loggers near the cooling system, near the doors and the ceiling. Hottest and coldest points were identified.

13. Equipment

HPLC equipment was appropriately labelled and qualified. Instructions for use of HPLC equipment and storage of chromatographic columns were established. Sterility testing was carried out in a two-compartment isolator/glovebox. The glovebox was classified as Grade A and the initial qualification was carried out in 2014. Leak test on isolator gloves was performed in June 2018 and was reviewed in detail as well as filter integrity and air velocity qualification.

14. Materials

There were procedures in place describing storage and distribution of FPPs. The company had performed extensive testing and qualification of cold boxes and cooling elements used in the distribution of Oxytocin FPP. Initial selection of candidate cold boxes was based on average quantity handled per order. Studies were performed using 6 button thermocouples and cold boxes and cooling elements were tested for up to three days including stress tests exposing the cold boxes to external temperature of 35°C.

15. Documentation

A documentation system was in place. Procedures defined and supported quality control and distribution operations. In general documents were approved, signed and dated by appropriate responsible persons, reviewed and kept up to date. An EDMS system was in place. Stock management of the FPP warehouse was handled by using a Warehouse Management System.

16. Good practices in production

Not applicable for this inspection.

17. Good practices in quality control

Quality control laboratories were separated from production areas. Chemical laboratories were visited as well as the separate areas where stability chambers were installed. The QC lab was well organized and equipped. Analytical equipment was installed in separate rooms and logbooks for use and maintenance of equipment were presented.

The microbiological laboratory was also visited. Three autoclaves were used to sterilize media. Autoclave No. 2 was out of order and it was appropriately labeled. Autoclaves were qualified annually. Bowie-Dick test was performed every week and leak test every day. Media and cultures were destroyed in an autoclave which was located in a separate room. It was noted that this room was not tidy. The loading patterns and relevant qualification of one of the autoclaves were checked. Certificates for microorganisms and media were presented. Identified observations were adequately addressed by the company's CAPA plan.

Part 3	**Conclusion – Inspection outcome**

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, of ***Grindeks JSC,*** located at ***53 Krustpils Street, Riga, 1057, Latvia*** 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 WHO Guidelines referenced in the inspection report**

1. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Eighth 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 GMP for APIs*** or ***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-Sixth 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 GPPQCL Guidelines or ***TRS No. 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. Fiftieth Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5
Short name: WHO GDRMP or ***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. Fiftieth 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

23. Stability testing of active pharmaceutical ingredients and finished 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 10.
Short name: WHO TRS No. 1010, Annex 10
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf