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

Part 1	General information
Manufacturers Details	
Company information	
Name of manufacturer	UAB Santonika
Corporate address of manufacturer	Veiveriu str. 134B, Kaunas, LT- 46353, Lithuania
Inspected site	
Address of inspected manufacturing site if different from that given above	S Veiveriu str. 134B, Kaunas, LT- 46353, Lithuania GPS Coordinates: 54 52 22W 23 53 19E
Inspection details	
Dates of inspection	4 – 6 June 2018
Type of inspection	Initial
Introduction	
Brief summary of the manufacturing activities	UAB Santonika manufactures aseptically filled and terminally sterilized liquids as well as capsules and tablets. The company also engages in the manufacture of food supplements
General information about the company and site	UAB Santonika was registered as a legal entity on 28 July 2015, following a transfer of the rights and assets of the company AB Sanitas to UAB Santonika. The site was located in Aleksotas, Kaunas and the manufacturing facilities were completed in 2008. Laboratories were located in a separate building which was established in 1993.
History	This was the first WHO inspection of this site. The site was inspected periodically by the Lithuanian NRA
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

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	• 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 • Staring 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
Restrictions	The inspection was restricted to the production of Oxytocin manufacturing line.
Out of scope	All other products and workshops were outside of the inspection scope and were not visited.
WHO product numbers covered by the inspection	Oxytocin 10 IU/ml solution for infusion 1 ml ampoule.

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Abbreviations	Meaning
AHU	air handling unit
ALCOA	attributable, legible, contemporaneous, original and accurate
API	active pharmaceutical ingredient
APQR	annual product quality review
BDL	below detection limit
BMR	batch manufacturing record
BPR	batch packaging record
CAPA	corrective actions and preventive actions
CC	change control
CFU	colony-forming unit
CoA	certificate of analysis
CpK	process capability index
DQ	design qualification
EM	environmental monitoring
FAT	factory acceptance test
FBD	fluid bed dryer
FMEA	failure modes and effects analysis
FPP	finished pharmaceutical product
FTA	fault tree analysis
FTIR	Fourier transform infrared spectrometer
GC	gas chromatograph
GMP	good manufacturing practice
HACCP	hazard analysis and critical control points
HPLC	high-performance liquid chromatograph
HVAC	heating, ventilation and air conditioning
IR	infrared spectrophotometer
IQ	installation qualification
KF	Karl Fisher
LAF	laminar air flow
LIMS	laboratory information management system
LoD	limit of detection
LOD	loss on drying
MB	Microbiology
MBL	microbiology laboratory
MF	master formulae
MR	management review
NMR	nuclear magnetic resonance spectroscopy
NRA	national regulatory agency
OQ	operational qualification
PHA	process hazard analysis
PM	preventive maintenance
PpK	process performance index
PQ	performance qualification
PQR	product quality review
PQS	pharmaceutical quality system
QA	quality assurance

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QC	quality control
QCL	quality control laboratory
QRM	quality risk management
RA	risk assessment
RCA	root cause analysis
SOP	standard operating procedure
TAMC	total aerobic microbial count
TFC	total fungi count
TLC	thin layer chromatography
URS	user requirements specifications
UV	ultraviolet-visible spectrophotometer

Part 2	**Brief summary of the findings and comments (where applicable)**

1. Pharmaceutical quality system

A pharmaceutical quality system (PQS) was established, with written procedures covering essential GMP principles for the site. Most of the main procedures were in Lithuanian and it was not always possible to translate in detail. Procedures that were reviewed and discussed during the inspection were generally presented promptly, however not all of these procedures were sufficiently detailed or satisfactorily implemented. The company applied appropriate corrective actions.

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. Oxytocin PQRs for 2016 was reviewed. PQRs were not complete since release, on-going stability studies, complaints and recalls were managed by Grindeks who was responsible for completing these parts of the PQR. Representatives of Grindeks provided copies of the PQR part conducted by Grindeks.

Quality Risk Management (QRM)

A QRM procedure was available. The QRM procedure applied on manufacturing operations including but not limited to change control and deviation management, production and complaints. However, it was observed that the application of QRM principles was not uniformly applied and it was recommended to improve this area.

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. Deviations were recorded and assessed. Root cause investigations were conducted in most of the cases and relevant CAPA were identified and implemented.

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.

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

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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.

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. 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 for Oxytocin the responsibility for handling complaints was assigned to Grindeks. UAB Santonika was responsible for assisting in the investigations as appropriate. Records indicated that no complaints were registered in 2017 and one complaint was registered in 2016.

6. Product recalls

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

7. Contract production, analysis and other activities

The company was engaging in contract manufacturing. A technical agreement between UAB Santonika and Grindeks was available. The original agreement was signed in November 2000 and it was renewed and updated in May 2013. A new Annex was added in May 2017.

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

Self-inspection was not reviewed in detail. A procedure for qualifying suppliers was presented. Suppliers were evaluated and approved based on a matrix with established criteria. All suppliers had to be audited every 3 years but the frequency could be relaxed based on the evaluation which classified suppliers in four categories, class 4 was considered as high risk. Qualification of ampoules supplier, was reviewed. Records were made available. The supplier was audited in February 2013

9. Personnel

A general organization chart was available reflecting administrative structure. This organigram was included in the Site Master File. Detailed organograms for Quality Control and Quality Assurance were included as Annexes to training procedures. Job descriptions of the production manager, a QC and Qualified Person were checked. The personnel met during the inspection had 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. Responsibilities for production and QC 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 records were presented. A training

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matrix was used to identify needs and plan training sessions. Major changes in procedures would trigger the organization of training sessions. These sessions were evaluated in writing. Minor changes in procedures would also trigger the organization of training sessions however no written test was foreseen.

11. Personal hygiene

Procedures on personal hygiene were available. System to ensure good personnel hygiene was provided. Procedure for health checks for newly recruited personnel and existing staff was provided. Training on basic GMP was organized and evaluated. Gowning procedures were posted at entry points, and mirrors provided for self-assessment. Hand washing steps were reflected on pictorials. Sanitizers were provided at changing areas. Where need be according to classification of the area double gowning was provided. Medical records were available and annual medical check-ups were scheduled and conducted.

12. Premises

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. Warehousing conditions were appropriate. Oxytocin was stored in a small refrigerator in the warehouse. Premises were designed to facilitate cleaning and sanitation. The procedure on Cleaning the Sampling room was reviewed. 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.

During the inspection the technical floor was visited. There was a central AHU which supplied air to smaller units. AHU CDZ-140 was supplying air to Grade B area. It was equipped with G4, F7, F9 filters and H14 terminal filters. A computerized system was in place to monitor the performance of AHUs and differential pressure between filters. AHU filters were checked weekly and logbooks were available. Flexible joints, ducting and heating actuator were also checked and records were maintained.

The water generation system was also installed on the technical floor. City water underwent filtration through a 50µm filter, then hypochlorite solution was used to remove iron salts and after this treatment water was processed by a softener column and filtered through 25µm before reaching reverse osmosis. Double distillation was used to produce WFI

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. Computerized systems were used in the warehouse for material management and logistic administration. The ampoule filling machine was installed in 2008 and IQ, OQ protocols and reports were available. A new qualification was initiated due to replacement of several parts but it had not been completed at the time of inspection

14. Materials

Incoming materials were purchased from approved suppliers, sampled and tested according to specifications and testing procedure. Oxytocin FPP was released by Grindeks. There was a procedure in place for receipt of raw and packaging material in the warehouse as well as procedure for handling temperature sensitive materials. Its application to Oxytocin was checked and it was observed that temperature excursions in data loggers were not checked and documented. The company applied appropriate CAPA

The company had a license to manufacture food supplements. APIs and raw materials for food supplements were stored in the same warehouse as pharmaceuticals. No risk assessment was presented addressing the issues of cross-contamination and mix-up. The company applied appropriate CAPA

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15. Documentation

Documentation exists in electronic as well as hard copy. Non-validated spreadsheets were used in the laboratory. Most of the procedures were in Lithuanian and the inspection process was delayed because of the translation. Raw data concerning completed analyses and reports with the test results were recorded manually. Approved, signed and dated analytical methods and specifications were available for starting and packaging materials and for finished products. 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 agent 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. Oxytocin was sampled in production area rather the sampling booth in the warehouse. A Grade A booth was used for sampling while the surrounding environment was Grade C

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. Oxytocin API was sampled in the production area. The microbiological laboratory was segregated from the analytical laboratory. Growth promotion testing was carried out on media. On-going stability studies were conducted by Grindeks and the results of stability testing were not discussed with UAB. Specifications and manufacturer's certificates for ampoules used in Oxytocin were presented.

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, ***UAB Santonika,*** located at ***Veiveriu str. 134B, Kaunas, LT- 46352, Lithuania*** 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**

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

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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. WHO guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 5
Short name: WHO TRS No. 961, Annex 5
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

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/

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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

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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 prosecution 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. WHO good manufacturing practices for biological products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3
Short name: WHO TRS No. 996, Annex 3
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf

22. 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

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