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Prequalification Unit Inspection services
WHO INSPECTION REPORT

Desk Assessment of Finished Product Manufacturer

Part 1	**General information**
Company information	
Name of Manufacturer	Laboratoires Pharmaceutiques Rodael
Corporate address of manufacturer	N/A
Contact person	Marine Cochez marine.cochez@rodael.fr Quality Assurance Manager Mr Laurent Equipart laurent.equipart@rodael.fr
Inspected site	
Name & address of manufacturing site	Laboratoires Pharmaceutiques Rodael 1 route de SOCX, Bierne, 59380, France GPS coordinates: Latitude: (decimal) 50.95830646507623 (sexagésimal) N 50"57'29.9016" (+50° 57' 29.9016") Longitude: (decimal) 2.4148826296386687 (sexagesimal) E 2° 24' 53.5788" (+2° 24' 53.5788") GLN: 3701334800010
Production Block/Unit	N/A
Manufacturing license number	M 15/79
Desk assessment details	
Start and end dates of review	01 – 23 September 2020
Inspection record number	INSP-2014-0314
Inspector	Iveta STREIPA
Products covered by this desk assessment	DI002 Zinc (sulfate) Tablet, Dispersible 20mg
List of documents submitted	1. Cover letter 2. List of regulatory inspections in past 5 years 3. ANSM Direction of inspection Pharmaceuticals Inspection and Anti-fraud Division preliminary inspection report, dates of inspection 3 – 6 September 2018 4. ANSM Direction of inspection Pharmaceuticals Inspection and Anti-fraud

	Devision final inspection report, dates of inspection 3 – 6 September 2018 5. CAPAs implementation ANSM, dates of inspection 3 – 6 September 2018 6. Manufacturing authorization M 15/79, dated 25 March 2015 7. GMP certificate 2019/HPF/FR7077, dated 2019-03-05 8. Status report (authorization) for Starting materials for pharmaceutical use manufacture, distribution and import activities, dated 27 July 2017 9. SMF, year 2019 – annul update 10. List of products manufactured at site 11. PQR 1 May – 30 April 2020 12. BMR/BPR, batch No R10 13. Analytical raw data, batch No R10 14. Master batch record 15. Declaration: recalls 16. Declaration: self-inspection 17. Declaration: out-of-stock situation 18. ANSM Decision to suspend the marketing authorization, dated 19 February 2016 19. ANSM Injunction on the pharmaceutical establishment 20. Parts of the manufacturing process covered by ANSM inspection	
Any documents missing?	N/A	
Part 2	**Summary of SRA/NRA inspection evidence considered (from most recent to last) and comments**	
ANSM Direction of inspection Pharmaceuticals Inspection and Anti-fraud Decision, France	Dates of inspection:	3 – 6 September 2018
	Type of inspection:	The inspection verified the degree of compliance of the establishment with the current reference regulatory documents
	Block/Unit:	N/A
	Type of products/Dosage forms covered:	Tablets, granules and capsules WHO product under PQ were not covered
	Physical areas/systems/documents inspected:	All manufacturing areas • Pharmaceutical Quality system o PQR o Deviations anomaly • Personnel o Staff training / training of temporary workers o Staff hygiene • Materials • Equipment • Air treatment • Computer systems • Documentation • Production o Storage o Prevention of cross-contamination during manufacturing o Validation, VMP, re-qualification, cleaning

		validation o Raw materials o Packaging operations o Finished products • Quality control o Sampling o Physical-chemical control • Complaints • Recall or withdrawal from the drug market • Outsourced activities • Self-inspections • Transport
	Any sections of GMP not covered?	N/A
	Summary of major deficiencies observed:	No critical deficiencies reported Two (2) major deficiencies reported: 1. Complaint management procedure is not satisfactory for the following reasons: a. It does not plan an assessment of the initial criticality of the complaint, which does not allow for the prioritization of its treatment b. The final assessment of criticality at the end of the investigation is not always appropriate, especially in the case of complaints for microbiological contamination c. It does not plan the determination of the recurrence of the quality defect 2. Investigations following a complaint are not complete: a. In the event of microbiological contamination, it is not planned to verify the impact on products that have been manufactured on the same equipment train and in the same premises b. The actions put in place as a result of the investigations are not systematically recorded in the CAPA board. Some are included either in the final report (the case of the FER 18-002 complaint) or in internal emails, which does not ensure its follow-up or traceability c. Investigations are sometimes incomplete, for example for the FER 18-004 complaint, it was indicated d. by the Head Pharmacist during the

		inspection, that Aspergillus had been detected on the equipment, and that an alcohol disinfection had been performed. However, the effectiveness of alcohol on this strain has not been demonstrated. In addition, there could not be presented a chronological summary of the events Thirty-one (31) other deficiencies reported
	Description of CAPA:	According to the ANSM final report all responses to the deficiencies were evaluated and find satisfactory. Some responses to deviations or remarks in the initial report may be subject to specific monitoring.
	Final conclusion of the inspection report:	GMP certificate issued
	Comments/observations on the scope and comprehensiveness of the inspection report and on the appropriateness of the CAPAs in lieu of an onsite inspection by WHO:	Although WHO FPP was not specifically inspected, the conclusions that were made can be extended to the entire site as they are under a common quality management system, therefore inspection report is appropriate in lieu of and onsite inspection by WHO for DI002 Zinc (sulfate) Tablet, Dispersible 20mg
Part 3	**Summary of the last WHO inspection**	
Date and conclusion of most recent WHO inspection	The site was inspected by the WHO 5 – 7 October 2010 – initial inspection. Initial conclusion: 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, a decision on the compliance of Laboratoires Pharmaceutiques Rodael S.A.S, 1 route de SOCX, 59380 BIERNE, France, with WHO GMP guidelines will be made after the manufacturers response to the observations has been assessed. Inspection was closed: 22 February 2011 as GMP compliant	
Summary of manufacturing activities as of October 2010	Manufacturing, packaging, quality control and batch release of dispersible tablets	
General information about the company and manufacturing site as of October	Rodael was established by Mr. Jacques Equipart in 1962 under the name Equipart. The name was changed to Laboratoires Pharmaceutiques Rodael in 1987. In 1993, the company was purchased by Mr. Paul Equipart, the current owner and son of the founder. The factory at the current site, Bierne, was established in 2000 and was significantly expanded in 2008. It manufactures mainly tablets, hard gelatine capsules granules and powders for pharmaceutical use and as nutritional supplements. Rodael is purely a contract acceptor manufacturing company, manufacturing products for	

2010	other licence holders without holding any marketing authorization of its own. It also specializes in manufacturing on pilot scale and placebos for clinical trials; taste masking including client tailored manufacturing.
Focus of the last WHO inspection	The inspection focused on the production and control of D002: Zinc Sulphate 20mg Dispersible Tablets. The inspection covered selected sections of the WHO GMP text, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities
Areas inspected	Quality assurance GMP for pharmaceutical products Sanitation and hygiene Qualification and validation Complaints Product recalls Contract production and analysis Self-inspection and quality audit Personnel Training Personnel hygiene Premises a) Ancillary areas b) Storage areas c) Production areas d) Packaging area e) Packaging area Equipment Materials a) Starting materials b) Packaging materials c) Intermediate and bulk products d) Finished products Documentation Good practices in production Good practices in quality control
Out of scope and restrictions (last WHO inspection)	Products not submitted to WHO for Prequalification
WHO products covered by the last WHO inspection	D002: Zinc Sulfate 20mg Dispersible Tablets
Additional products to be covered by this desk assessment:	N/A

Abbreviations	Meaning
BMR	Batch manufacturing record
BPR	Batch production record
CAPA	Corrective and preventive action
CC	Change control
HVAC	Heating ventilation and air conditioning system
FPP	Finished pharmaceutical product
GMP	Good manufacturing practices
OOS	Out of specification
OOT	Out of trend
PQR	Product quality review
SMF	Site master file

Part 4	Summary of the assessment of supporting documentation

a) List of all regulatory inspections performed in the last 5 years and their outcomes:

Date	Authority	Outcome
03-06/09/2018	ANSM Direction of inspection Pharmaceuticals Inspection and Anti-fraud Division	Renewal of GMP certificate, dated 5th of March 2019.
13-15/09/2016	ANSM Direction of inspection Pharmaceuticals Inspection and Anti-fraud Division	Renewal of GMP certificate, dated 4th of November 2016
30/11/2015	ANSM Direction of inspection Pharmaceuticals Inspection and Anti-fraud Division	Suspension S16/041 of manufacturing authorisation, dated February 19, 2016 with deferred effect to October 31, 2016

b) Manufacturing authorization granted by national authorities:
Manufacturing authorization M 15/79, dated 25 March 2015
GMP certificate 2019/HPF/FR7077, dated 2019-03-05

c) Site master file:
SMF submitted and reviewed. SMF written according to the WHO TRS No. 961, Annex 14

d) List of all the products and dosage forms manufactured on-site:
See Annex I to the DA report LPR - List of all products manufactured on site

e) Most recent product quality review (PQR) of the concerned WHO product:
PQR Zinc (sulfate) Tablet, Dispersible 20mg, 1 May – 30 April 2020 submitted and reviewed:

- 11 batches manufactured and released
- 2 OOS:
- 3 deviations
- No CC, complaints, recalls and returns

f) Batch manufacturing and packaging records, including the analytical part, for the most recently released batch of relevant product:
BMR/BPR and analytical raw data of Zinc (sulfate) Tablet, Dispersible 20mg, batch R10 submitted and reviewed

g) Master batch manufacturing and packaging record of the product of interest:
Master BMR/BPR submitted and reviewed

h) If any of the products are sterile, the completed batch records for the most recent media fill validation that is relevant to the product of interest and report on its outcome:
N/A

i) Recalls in the past three years related to products with quality defects:
Declaration submitted: no recalls is past 3 years

j) Confirmation by the senior quality assurance representative that a full self-inspection or external audit dedicated to the product has been performed and all matters dealt with:
Declaration submitted: that a full self-inspection or external audit dedicated to the product has been performed and all matters dealt with.

k) Copy of any warning letter, or equivalent regulatory action, issued by any authority to which the site provides or has applied to provide the product:
Copy of ANSM Decision to suspend the marketing authorization, dated 19 February 2016 submitted

l) Out-of-stock situations:
Declaration submitted: no out-of-stock situations

m) Additional documents submitted:
N/A

Part 5	**Conclusion – Desk assessment outcome**

Based on the previous WHO inspections and on the GMP evidence received and reviewed, it is considered that a desk assessment is acceptable in lieu of a WHO onsite inspection. The site ***Laboratoires Pharmaceutiques Rodael***, located at ***1 route de SOCX, Bierne, 59380, France*** is considered to be operating at an acceptable level of compliance with WHO GMP guidelines.

This compliance status shall be valid until 6 September 2021 (3 years after ANSM inspection) or when another inspection is conducted by WHO or by a stringent regulatory authority. It remains the prerogative of WHO to carry out an inspection any time prior to that.

Name	Iveta Streipa
Signature	
Date of signature	23 September 2020

Part 6	List of guidelines referenced in this 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 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 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. 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 guidance or **WHO TRS No. 996, Annex 5**
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

21. 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 Multisource guidance or **WHO TRS No. 996, Annex 10**
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf

22. 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

23. Production of water for injection by means other than distillation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 3.
Short name: WHO TRS No. 1025, Annex 3
https://www.who.int/publications-detail/978-92-4-000182-4

24. Good chromatography practice. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 4.
Short name: WHO TRS No. 1025, Annex 4
https://www.who.int/publications-detail/978-92-4-000182-4

25. Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 6.
Short name: WHO TRS No. 1025, Annex 6
https://www.who.int/publications-detail/978-92-4-000182-4

26. WHO guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report. Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 9.
Short name: WHO TRS 1010, Annex 9
https://www.who.int/medicines/areas/quality_safety/quality_assurance/TRS1010annex9.pdf?ua=1