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Prequalification Unit Inspection services
WHO PUBLIC INSPECTION REPORT

Desk Assessment of Active Pharmaceutical Ingredient (API) Manufacturer

Part 1	**General information**
Company information	
Name of Manufacturer	Química Sintética SA
Corporate address of manufacturer	Chemo C/ Dulcinea s/n, 28805 Alcalá de Henares (Madrid), Spain
Inspected site	
Name & address of manufacturing site	Química Sintética SA C/ Dulcinea s/n, 28805 Alcalá de Henares (Madrid), Spain GPS coordinates: Longitude: -3,356935 Latitude: 40,491911
Synthetic Unit/Block/Work shop	• Levofloxacin: Workshop 11, Workshop 5 • Ivermectin: Workshop 26, Workshop 5
Manufacturing license number	No M00742, issued by Spanish Agency of Medicines and Medical Devices
Desk assessment details	
Start and end dates of review	17 – 21 June 2021
APIs covered by this desk assessment	**Active Pharmaceutical Ingredient** / **Prequalification status** Levofloxacin (hemihydrate) / Accepted Ivermectin / Accepted
List of documents submitted	1. Spanish Agency of Medicines and Medical Devices inspection report, dates of inspection 20 – 22 March 2019 and CAPAs 2. Spanish Agency of Medicines and Medical Devices final report, dated 28 May 2019 3. Spanish Agency of Medicines and Medical Devices GMP certificate No ES/072/19, dated 13 June 2019 4. Química Sintética registration – EudraGMDP 5. List of regulatory inspection in the last 5 years 6. SMF and Annexes: 7. PQRs: 7.1. Ivermectin 7.2. Levofloxacin 8. Batch records/analytical data 8.1. Ivermectin 8.2. Levofloxacin 9. Master batch records 9.1. Ivermectin 9.2. Levofloxacin 10. Risk assessments: 10.1. Potential presence of Nitrosamines in Levofloxacin (Active Substance) 10.2. Potential presence of Nitrosamines in Ivermectin (Active Substance)

	10.3. Potential presence of Nitrosamines in Active Substances manufactured at Química Sintética due to contamination with Sartan group of APIs 11. Cover letter 12. List of documents submitted 13. Declaration: recalls 14. Declaration: self-inspection 15. Declaration: out-of-stock situation 16. Declaration: warning letters	
Any documents missing?	N/A	
Part 2	**Summary of SRA/NRA inspection evidence considered**	
Spanish Agency for Medical Products and Medical Devices (AEMPS)	Dates of inspection:	20 – 22 March 2019
	Type of inspection:	A periodical inspection included in the Annual Programme of GMP Inspections for verification of compliance with Good Manufacturing Practices (GMP)
	Buildings:	• Building 33 • Building 11 • Building 12 • Building 26 - pilot plant • Building 38 - centrifuge room • Building 5 – finished APIs
	APIs covered:	APIs manufactured on site
Part 3	**Summary of the last WHO inspection**	
Date and conclusion of most recent WHO inspection	The site was never inspected by the WHO PQT	
Brief summary of manufacturing activities according to the SMF	Manufacture of active pharmaceutical ingredients	
General information about the company and manufacturing site according to the SMF	Química Sintética SA is a company dedicated to the manufacture of active pharmaceutical ingredients both human and veterinary use. All APIs are produced by chemical synthesis. The site is registered in EudraGMDP database	
Abbreviations		
BMR	Batch manufacturing record	
BPR	Batch production record	
CAPA	Corrective and preventive action	
CC	Change control	
GMP	Good manufacturing practices	
NC	Non conformity	

NRA	National regulatory agency
PQR	Product quality review
PQS	Pharmaceutical quality system
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
SOP	Standard operating procedure

Part 4	**Summary of the assessment of supporting documentation**

a) Manufacturing authorization and GMP certificate granted by the local authority:
Manufacturing authorization No M00742, issued by Spanish Agency of Medicines and Medical Devices

Spanish Agency of Medicines Medical Devices GMP certificate No ES/072/19, dated 13 June 2019

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

c) List of all the APIs manufactured on-site:
Total number of APIs manufactured on-site – 61
Therapeutic groups:

- Endocrine therapy
- Antibiotics and chemotherapeutics for dermatological use
- Antivirals for systemic use
- Ophthalmologicals
- Immunosuppressants
- Antibacterials for systemic use
- Calcium channel blockers
- Antiprotozoals
- Psycholeptics
- Agents acting on the renin-angiotensin system
- Anti-inflammatory and antirheumatic products
- Corticosteroids, dermatological preparations
- Otologicals
- Antithrombotic agents
- Sex hormones and modulators of the genital system
- Cardiac therapy
- Other nervous system drugs
- Antifungals for dermatological use
- Antihemorrhagics
- Drugs for acid-related disorders
- Antigout preparations
- Psychoanaleptics
- Antihypersensives

- Antiprotozoals
- Diuretics
- Analgesics
- Antimycotics for systemic use
- Other dermatological preparation
- Anthelmintics
- Antifungals for dermatological use
- Gynecological anti-infectives and antiseptics
- Nasal preparations
- Antihistamines for systemic use
- Urologicals

d) List of all regulatory inspections performed in the last 3 years and their outcomes:

Authority	Date of inspection	Outcome
AEMPS, Spain	17-20 July 2017	Approved
Ministry of Industry and Trade of the Russian Federation. State Institute of Drugs and Good Practices, Russia	13-16 March 2018	Approved
AEMPS, Spain	20-22 March2019	Approved

e) Most recent product quality reviews (PQRs) of the concerned WHO APIs:
Submitted and reviewed:
- Ivermectin
- Levofloxacin, review period 1 October 2019 – 30 September 2020

f) Batch manufacturing and packaging records, including the analytical part, for the most recently released batch of relevant APIs:
Submitted and reviewed:
- Ivermectin
- Levofloxacin

g) Master batch manufacturing and packaging records of the APIs of interest:
- Ivermectin
- Levofloxacin

h) Recalls in the past three years related to APIs with quality defects:
Declaration submitted

i) Confirmation by the senior quality assurance representative that a full self-inspection or external audit dedicated to the API(s) has been performed and all matters dealt with:
Declaration submitted: that a full self-inspection or external audit dedicated to the APIs has been performed and all matters dealt with

j) Copy of any warning letter, or equivalent regulatory action, issued by any authority for their market, to which the site provides or has applied to provide the API(s):
Declaration submitted: no warning letter, or equivalent regulatory action, issued by any authority

k) Out-of-stock situations:

Declaration submitted: no out-of-stock situations

l) Additional documents submitted:

Risk assessments:

- Potential presence of Nitrosamines in Levofloxacin (Active Substance)
- Potential presence of Nitrosamines in Ivermectin (Active Substance
- Potential presence of Nitrosamines in Active Substances manufactured at Química Sintética due to contamination with Sartan group of APIs

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 **Química Sintética SA, Workshops No 5, 11 and 26**, located at **C/ Dulcinea s/n, 28805 Alcalá de Henares (Madrid), Spain** is considered to be operating at an acceptable level of compliance with WHO GMP guidelines for APIs.

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

Part 6	List of guidelines referenced in this inspection report

1. 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/

2. 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/

3. 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

4. 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

5. 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

6. 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/

7. 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 3.
   Short name: WHO TRS No. 957, Annex 3
   http://www.who.int/medicines/publications/44threport/en/

8. 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

9. 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

10. 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

11. 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

12. 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

13. 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/

14. 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/

15. 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

16. 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

17. 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

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

19. 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/

20. 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

21. 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

22. Production of water for injection by means other than distillation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Forth 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

23. Good chromatography practice. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Forth 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

24. 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-Forth 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

25. Points to consider when including Health-Based Exposure Limits (HBELs) in cleaning validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 2. ***Short name: WHO TRS 1033, Annex 2***
https://www.who.int/publications/i/item/55th-report-of-the-who-expert-committee-on-specifications-for-pharmaceutical-preparations¨

26. WHO good manufacturing practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 3. ***Short name: WHO TRS 1033, Annex 3***
https://www.who.int/publications/i/item/55th-report-of-the-who-expert-committee-on-specifications-for-pharmaceutical-preparations

27. Guideline on data integrity. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 4. ***Short name: WHO TRS 1033, Annex 4***
https://www.who.int/publications/i/item/55th-report-of-the-who-expert-committee-on-specifications-for-pharmaceutical-preparations