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Prequalification Unit Inspection Services
WHO INSPECTION REPORT
(WHOPIR)
Desk Assessment of Finished Product Manufacturer

Part 1	**General information**	
Company information		
Name of Manufacturer	Bayer de México S.A. de C.V.	
Corporate address of manufacturer	Av. Reforma No. 46, Colonia Potrerillo Ixtaczoquitlán, Veracruz de Ignacio de la Llave, C.P. 94450, México Phone: +52 272-742-5600	
Contact person	Mr Hector Quintero, Qualified person / Quality Assurance Manager Email: hector.quintero@bayer.com	
Inspected site		
Name & address of manufacturing site	Bayer de México S.A. de C.V. Av. Reforma No. 46, Colonia Potrerillo Ixtaczoquitlán, Veracruz de Ignacio de la Llave, C.P. 94450, México	
Production Block/Unit	*Sterile - hormonal*: solution for injection in ampoule, solution for injection in pre-filled syringe.	
Manufacturing license number	Manufacturing authorization issued by the national medicine's regulatory authority: COFEPRIS, México Certification number: 233300129X0165 valid until 24 July 2026. License Number 30 085 02 0001 Authorized manufacturing lines: • *Semisolids*: ovules, creams, • *Sterile - hormonal*: solution for injection in ampoule, solution for injection in pre-filled syringe.	
Desk assessment details		
Start and end dates of review	19 – 20 December 2023	
Inspection record number	INSP-FPP-2019-0060	
Products covered by this desk assessment	RH087 *Estradiol valerate/Norethisterone enantate* Solution for injection 5mg/ml-50mg/ml (Mesigyna – glass syringes). RH054 *Estradiol valerate/Norethisterone enantat*e Solution for injection 5mg/ml-50mg/ml (Norigynon – amber glass ampoules).	
Any documents missing?	Not Applicable	
Part 2	**Summary of SRA/NRA inspection evidence considered (from most recent to last) and comments**	
LAGeSo, Berlin, Germany	Dates of inspection:	22 March 2023
	Type of inspection:	Routine GMP inspection
	Block/Unit:	Manufacturing areas of aseptically prepared sterile products.
	Type of products/Dosage forms covered:	Aseptically prepared sterile products equivalent to the WHO prequalified products.
	Physical areas inspected:	All areas related to:

		• Sterile manufacturing • Microbiology laboratory • Chemical/physical laboratory
INFARMED, Portugal	Dates of inspection:	23 – 27 November 2020
	Type of inspection:	Distant / remote inspection
	Block/Unit:	Routine GMP with emphasis on manufacturing areas of ovules.
	Type of products/Dosage forms covered:	Ovules
Part 3	**Summary of the last WHO inspection**	
Date and conclusion of most recent WHO inspection	The inspection of Bayer de Mexico was last performed by WHO PQT from 9 to 12 October 2018. This was the 3rd inspection of this site. This inspection concluded that the site was considered to be compliant with WHO GMP guidelines after the submission and implementation of CAPAs in response to the identified deficiencies.	
Summary of manufacturing activities	The site is authorized to manufacture semi-solids (ovules, and creams) and aseptically filled syringes and ampoules (hormonal solutions) for human use. Production of aseptically filled ampoules and syringes took place on the second floor of the production building.	
General information about the company and manufacturing site	The Ixtaczoquitlan Bayer de Mexico site is located on the outskirts of Orizaba, approximately 270 km east of Mexico City and 130 km west of Veracruz International Airport. The manufacturing building became operational in 1967, changed ownership and now belongs to Productos Químicos Naturales, S.A. de C.V. (PROQUINA), an API manufacturer and a subsidiary of the Bayer de México group. The PROQUINA manufacturing facilities are located on the same campus but are physically and administratively separated from the Bayer de Mexico site. The Bayer building has been extended and remodelled several times. The sterile facilities were last renovated in 2011 which included the installation of a new HVAC system. Information on the site can be accessed through the SMF, reference number, REGS-MX01-LP-000002 version 19, effective date 27 November 2023.	
Focus of the last WHO inspection	Aseptic areas where solution for injection in ampoules and solution for injection in pre-filled syringes were manufactured.	
Areas inspected	**Documents reviewed included but not limited to** • Organization Chart. • Job descriptions for key personnel. • Personnel training and hygiene. • Product Quality Review. • Quality Risk Management. • Responsibilities of the quality units and production. • Complaints and Recalls. • Deviation control and change control. • CAPA procedure. • OOS and investigations. • Material release. • Vendor qualification. • Validation and qualification. • Equipment calibration. • Data integrity. • Sampling and testing of materials.	

	• Batch processing records. • Materials management system. • HVAC system. **Areas visited:** • Starting material warehouse, • Aseptic operations, • QC laboratories including chemical and microbiological, • Stability chambers and retained samples area.
Out of scope and restrictions (last WHO inspection)	Products not submitted to WHO for Prequalification
WHO products covered by the last WHO inspection	RH087 *Estradiol valerate/Norethisterone enantate* Solution for injection 5mg/ml-50mg/ml (Mesigyna – glass syringes). RH054 *Estradiol valerate/Norethisterone enantat*e Solution for injection 5mg/ml-50mg/ml (Norigynon – amber glass ampoules).
Additional products to be covered by this desk assessment:	Not Applicable

Abbreviations	**Meaning**
AHU	Air handling unit
API	Active pharmaceutical ingredient
BMR	Batch manufacturing record
BPR	Batch production record
CAPA	Corrective and preventive action
CC	Change control
FPP	Finished pharmaceutical product
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
SMF	Site master file
SOP	Standard operating procedure

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

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

Inspected by	Country	Year	Scope	Outcome

Landesamt für Gesundheit und Soziales (LAGeSo)	Germany	2023	Manufacture of oily parenteral solutions (prefilled syringe)	GMP compliance
Instituto Nacional de Vigilancia de Medicamentos y Alimentos (INVIMA)	Colombia	2022	Manufacture of Oily parenteral solutions and creams	GMP compliance
Turkish Medicines and Medical Devices Agency (Titck)	Turkiye	2022	Manufacture of Ovules and Oily parenteral solutions (prefilled syringes)	GMP compliance
Comisión Federal para la Protección Contra Riesgos Sanitarios (COFEPRIS)	Mexico	2021	Verification of all manufacturing lines included in the Manufacturing Authorization	GMP compliance
Autoridade Nacional do Medicamento e Produtos de Saúde IP (Infarmed I.P.)	Portugal	2020	Manufacture of ovules	GMP compliance
Agência Nacional de Vigilância Sanitária (ANVISA)	Brazil	2020	Manufacture of Ovules and Oily parenteral solutions	GMP compliance
World Health Organization (WHO) PQT INS	NA	2018	Prequalification Process: Oily parenteral solutions	GMP compliance

b) Manufacturing authorization granted by national authorities:
GMP certification issued by:

- INFARMED, Portugal, certificate issued in terms of EU Directive 2001/83/EC for the manufacturing of semi-solids, certification no: FT 084/MH/001/2021 issued: 04/12/2020, validity: 04/12/2022
- COFEPRIS, Mexico certificate number: 233300129X0165 valid until 24 July 2026.
- LAGeSo, Berlin, Germany certificate issued in terms of EU Directive 2001/83/EC for the manufacturing of aseptically prepared sterile products, certification no: DE-BE-01-GMP-2023-0033 issued 29 June 2023, validity: 22 March 2026

c) Site master file (SMF):
The SMF was submitted and found acceptable.

d) List of all the products and dosage forms manufactured on-site:
The list has been provided and reviewed as part of this desk assessment.

e) Most recent product quality review(s) (PQR)(s) of the concerned WHO product(s):
PQR: Mesigyna, RH 087
The PQR for Mesigyna, RH087, manufactured in the sterile production block, for domestic and ROW market produced 1 January 2022 – 31 December 2022 was submitted. During this period as per the PQR, a total of 46 batches were manufactured with 46 released. There were 10 complaints and no returned batches in the period. No batches were rejected. 10 Major Deviations were reported and addressed through CAPAs. Stability studies in support of a 60-month shelf life at 30°C/65% RH; 30°C/ 75%RH; 40°C/75RH were at various stages of accelerated conditions, long term and annual program. Qualification of equipment were reviewed. Upper and lower control limits were identified and recorded.

In general, the PQR was found to be comprehensive with no objectionable observations.

PQR for Norigynon, RH054

The PQR for Norigynon, RH054, manufactured in the sterile production block, for domestic and ROW market produced 1 January 2022 – 31 December 2022 was submitted. During this period as per the PQR, a total of 44 batches were manufactured with 38 released. Total number of 56 deviations were addressed during the period which, following evaluation determined to not have any impact on product quality. There were no returns / recalls during the period. The quality status of all equipment and utilities were addressed including all quality assurance and quality agreements with contractors. 6 change controls were addressed which did not have any impact on the quality of the product. Stability studies in support of a 60-month shelf life at 30°C/65% RH; 30°C/ 75%RH; 40°C/75RH were at various stages of accelerated conditions, long term and annual program. Qualification of equipment were reviewed. Upper and lower control limits were identified and recorded.

In general, the PQR was found to be comprehensive with no objectionable observations.

f) Batch manufacturing and packaging record(s), including the analytical part, for the most recently released batch of relevant product(s):

The manufacturing and packaging records), including the analytical part, of the last commercial batch of Mesigyna, RH 087 prefilled syringe manufactured in 2023 was submitted. These were generally found acceptable.

The manufacturing and packaging records), including the analytical part, of the last commercial batch of Norigynon, RH 054 ampoules manufactured in 2022 was submitted. These were generally found acceptable.

g) Master batch manufacturing and packaging record(s) of the product(s) of interest:

The master batch production, control records and batch packaging records for Norigynon/Mesigyna, oily solution 1ml, IM injection, syringe, were provided. These were generally found acceptable.

The master batch production, control records and batch packaging records for Norigynon/Mesigyna, 1ml ampoule injection, were provided. These were generally found acceptable.

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(s) of interest and report on its outcome:

The last batch manufacturing and packaging records including media fill data and outcome of Mesigyna, RH 087 prefilled syringe manufactured in 2023 was submitted. These were generally found acceptable.

The last batch manufacturing and packaging records including media fill data and outcome of Norigynon, RH 054 ampoules manufactured in 2023 was submitted. These were generally found acceptable.

i) Recalls in the past three years related to products with quality defects:

The company submitted a declaration on 14/12/2023 that:

- No recalls have been performed for any product manufactured at the site in the last three years nor since the last WHO PQT inspection (dated 2018).

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

The company submitted a declaration indicating that they had procedures and processes in place for self-inspection and audits.

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:

The company submitted a declaration on 14/12/2023 that:

- No warning letters or regulatory actions provided by Health Authorities have been received for the products manufactured at the site.

l) Out-of-stock situations:

A confirmation from the company that there has been no recent or foreseen out-of-stock situations for the following products manufactured at Bayer de Mexico site:

- RH087 Estradiol valerate/Norethisterone enantate Solution for injection 5mg/ml-50mg/ml (Mesigyna – glass syringes)
- RH054 Estradiol valerate/Norethisterone enantate Solution for injection 5mg/ml-50mg/ml (Norigynon – amber glass ampoules)

m) Additional documents submitted:

Not applicable

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 ***Bayer de México, S.A. de C.V.*** located at ***Av. Reforma No. 46, Colonia Potrerillo, Ixtaczoquitlán, Veracruz de Ignacio de la Llave, México, C.P. 94450*** is considered to be operating at an acceptable level of compliance with WHO GMP guidelines.

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

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-eight Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2.
   Short name: WHO TRS No. 986, Annex 2
   https://www.who.int/publications/m/item/trs986-annex2

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
   https://www.who.int/publications/m/item/annex-2-trs-957

3. 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/publications/m/item/trs1010-annex9

4. 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 No. 1033, Annex 3
   https://www.who.int/publications/m/item/annex-3-trs-1033

5. 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
   https://www.who.int/publications/m/item/annex-4-trs-929

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
   https://www.who.int/publications/m/item/trs957-annex1

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
   https://www.who.int/publications/m/item/trs957-annex3

8. 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
   https://www.who.int/publications/m/item/Annex-8-trs-1010

9. Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. Part 2: Interpretation of Guidelines on heating, ventilation and air-conditionning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Third Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1019), Annex 2.
   Short name: WHO TRS No. 1019, Annex 2
   https://www.who.int/publications/m/item/trs1019-annex2

10. WHO guidelines on transfer of technology in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fifth Report Geneva, World Health Organization, 2022 (WHO Technical Report Series, No. 1044), Annex 4.
    Short name: WHO TRS No. 1044, Annex 4
    https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/guidelines/production/trs1044-annex4-technology-transfer-in-pharmaceutical-manufacturing.pdf

11. WHO good manufacturing practices for sterile pharmaceutical products. Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fifth Report Geneva, World Health Organization, 2022 (WHO Technical Report Series, No. 1044), Annex 4.
    Short name: WHO TRS No. 1044, Annex 2
    https://www.who.int/publications/m/item/trs1044-annex2

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***
https://www.who.int/publications/m/item/trs943-annex3

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
https://www.who.int/publications/m/item/trs961-annex2

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
https://www.who.int/publications/m/item/trs981-annex2

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
https://www.who.int/publications/m/item/annex-3-trs-981

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
https://www.who.int/publications/m/item/tr961-annex14

17. Good Manufacturing Practices: Guidelines on validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Third Report Geneva, World Health Organization, 2019 (WHO Technical Report Series, No. 1019), Annex 3.
Short name: WHO TRS No. 1019, Annex 3
https://www.who.int/publications/m/item/trs1019-annex3

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
https://www.who.int/publications/m/item/trs992-annex4

19. 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
https://www.who.int/publications/m/item/trs961-annex9-modelguidanceforstoragetransport

20. 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
https://www.who.int/publications/m/item/trs992-annex5

21. WHO Recommendations for quality requirements when plant – derived artemisinin 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
https://www.who.int/publications/m/item/trs-992-annex-6

22. 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 No. 1033, Annex 4
https://www.who.int/publications/m/item/annex-4-trs-1033

23. 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
https://www.who.int/publications/m/item/trs966-annex10

24. 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***
https://www.who.int/publications/m/item/trs1010-annex10

25. Points to consider when including Health-Based Exposure Limits 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 No. 1033, Annex 2
https://www.who.int/publications/m/item/annex-2-trs-1033

26. 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/m/item/trs-1025-annex-6

27. 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/m/item/trs-1025-annex-3-water-for-injection

28. 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/m/item/trs1025-annex4