Medicines and Healthcare products Regulatory Agency

CERTIFICATE NUMBER : UK API 1108 Insp GMP/GDP 1108/1893-0018

CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER*(1),(2)*

Part 1

Issued following an inspection in accordance with :
Regulation 331A of The Human Medicines Regulations 2012 (SI 2012/1916)

The competent authority of United Kingdom confirms the following :

The Manufacturer : MACFARLAN SMITH LIMITED

Site address : MACFARLAN SMITH LIMITED, 10 WHEATFIELD ROAD, EDINBURGH, EH11 2QA, UNITED KINGDOM

Is an active substance manufacturer that has been inspected in accordance with Regulation 327 of The Human Medicines Regulations 2012 (SI 2012/1916).

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on 29/11/2021 , it is considered that it complies with

- The principles of GMP for active substances referred to in Regulation B17 and C17 of the Human Medicines Regulations 2012 (SI 2012/1916)

This certificate reflects the status of the manufacturing site at the time of the inspection noted above and should not be relied upon to reflect the compliance status if more than three years have elapsed since the date of that inspection. However, this period of validity may be reduced or extended using regulatory risk management principles by an entry in the Restrictions or Clarifying remarks field. This certificate is valid only when presented with all pages and both Parts 1 and 2. The authenticity of this certificate may be verified in MHRA-GMDP. If it does not appear, please contact the issuing authority.

- *(1) Guidance on the interpretation of this template can be found in the Help menu of MHRA-GMDP database.*
- *(2) These requirements fulfil the GMP recommendations of WHO.*

Part 2

Human Medicinal Products

Manufacture of active substance. Names of substances subject to inspection :

- [2000007584] FENTANYL CITRATE
- [2000008277] BUPRENORPHINE HYDROCHLORIDE
- [4000006163] MORPHINE SULFATE
- [2000007776] DIAMORPHINE HYDROCHLORIDE
- [2000015376] CODEINE SULFATE
- [1000010779] MORPHINE
- [1000002290] FENTANYL

- [2000008305] METHYLPHENIDATE HYDROCHLORIDE
- [1000003221] DIAMORPHINE
- [2000008051] APOMORPHINE HYDROCHLORIDE
- [2000008540] ALFENTANIL HYDROCHLORIDE
- [2000006818] SUFENTANIL CITRATE
- [1000007438] OXYCODONE
- [2000006722] OXYCODONE HYDROCHLORIDE
- [1000009886] PHOLCODINE
- [1000003943] COCAINE
- [2000008247] MORPHINE HYDROCHLORIDE
- [1000007171] BUPRENORPHINE
- [4000006570] CODEINE PHOSPHATE HEMIHYDRATE
- [2000007868] HYDROMORPHONE HYDROCHLORIDE
- [2000008245] MORPHINE TARTRATE
- [4000008052] DIHYDROCODEINE HYDROGEN TARTRATE
- [1000003912] CODEINE
- [2000007435] REMIFENTANIL HYDROCHLORIDE
- [2000007943] COCAINE HYDROCHLORIDE
- [2000008238] NALOXONE HYDROCHLORIDE

3. MANUFACTURING OPERATIONS - ACTIVE SUBSTANCES

FENTANYL CITRATE

3.1	Manufacture of Active Substance by Chemical Synthesis
	3.1.1 Manufacture Of Active Substance Intermediates
	3.1.2 Manufacture Of Crude Active Substance
	3.1.3 Salt Formation/Purification steps (eg. Crystallisation) Salt formation
3.5	General Finishing Steps
	3.5.1 Physical Processing Steps Drying, Milling
	3.5.2 Primary Packaging
	3.5.3 Secondary Packaging
3.6	Quality Control Testing
	3.6.1 Physical / Chemical testing
	3.6.2 Microbiological testing (excluding sterility testing)

BUPRENORPHINE HYDROCHLORIDE

3.1	Manufacture of Active Substance by Chemical Synthesis
	3.1.1 Manufacture Of Active Substance Intermediates
	3.1.2 Manufacture Of Crude Active Substance

	3.1.3 Salt Formation/Purification steps (eg. Crystallisation) Salt Formation, Crystallisation
3.5	General Finishing Steps
	3.5.1 Physical Processing Steps Drying, Milling
	3.5.2 Primary Packaging
	3.5.3 Secondary Packaging
3.6	Quality Control Testing
	3.6.1 Physical / Chemical testing
	3.6.2 Microbiological testing (excluding sterility testing)

MORPHINE SULFATE

3.1	Manufacture of Active Substance by Chemical Synthesis
	3.1.1 Manufacture Of Active Substance Intermediates
	3.1.2 Manufacture Of Crude Active Substance
	3.1.3 Salt Formation/Purification steps (eg. Crystallisation) Salt formation, Crystallisation
3.5	General Finishing Steps
	3.5.1 Physical Processing Steps Drying, Milling
	3.5.2 Primary Packaging
	3.5.3 Secondary Packaging
3.6	Quality Control Testing
	3.6.1 Physical / Chemical testing
	3.6.2 Microbiological testing (excluding sterility testing)

DIAMORPHINE HYDROCHLORIDE

3.1	Manufacture of Active Substance by Chemical Synthesis
	3.1.1 Manufacture Of Active Substance Intermediates
	3.1.2 Manufacture Of Crude Active Substance
	3.1.3 Salt Formation/Purification steps (eg. Crystallisation) Salt Formation
3.5	General Finishing Steps

	3.5.1 Physical Processing Steps Drying, Milling
	3.5.2 Primary Packaging
	3.5.3 Secondary Packaging
3.6	Quality Control Testing
	3.6.1 Physical / Chemical testing
	3.6.2 Microbiological testing (excluding sterility testing)

CODEINE SULFATE

3.1	Manufacture of Active Substance by Chemical Synthesis
	3.1.1 Manufacture Of Active Substance Intermediates
	3.1.2 Manufacture Of Crude Active Substance
	3.1.3 Salt Formation/Purification steps (eg. Crystallisation) Salt formation, Crystallisation
3.5	General Finishing Steps
	3.5.1 Physical Processing Steps Drying, Milling
	3.5.2 Primary Packaging
	3.5.3 Secondary Packaging
3.6	Quality Control Testing
	3.6.1 Physical / Chemical testing

MORPHINE

3.1	Manufacture of Active Substance by Chemical Synthesis
	3.1.1 Manufacture Of Active Substance Intermediates
	3.1.2 Manufacture Of Crude Active Substance
	3.1.3 Salt Formation/Purification steps (eg. Crystallisation) Crystallisation
3.5	General Finishing Steps
	3.5.1 Physical Processing Steps Drying, Milling
	3.5.2 Primary Packaging
	3.5.3 Secondary Packaging

3.6	Quality Control Testing
	3.6.1 Physical / Chemical testing

FENTANYL

3.1	Manufacture of Active Substance by Chemical Synthesis
	3.1.1 Manufacture Of Active Substance Intermediates
	3.1.2 Manufacture Of Crude Active Substance
	3.1.3 Salt Formation/Purification steps (eg. Crystallisation) Recrystallisation
3.5	General Finishing Steps
	3.5.1 Physical Processing Steps Drying, Milling
	3.5.2 Primary Packaging
	3.5.3 Secondary Packaging
3.6	Quality Control Testing
	3.6.1 Physical / Chemical testing

METHYLPHENIDATE HYDROCHLORIDE

3.1	Manufacture of Active Substance by Chemical Synthesis
	3.1.1 Manufacture Of Active Substance Intermediates
	3.1.2 Manufacture Of Crude Active Substance
	3.1.3 Salt Formation/Purification steps (eg. Crystallisation) Salt formation, Crystallisation
3.5	General Finishing Steps
	3.5.1 Physical Processing Steps Drying, Milling
	3.5.2 Primary Packaging
	3.5.3 Secondary Packaging
3.6	Quality Control Testing
	3.6.1 Physical / Chemical testing

DIAMORPHINE

3.1	Manufacture of Active Substance by Chemical Synthesis
	3.1.1 Manufacture Of Active Substance Intermediates

	3.1.2 Manufacture Of Crude Active Substance
	3.1.3 Salt Formation/Purification steps (eg. Crystallisation) Recrystallisation
3.5	General Finishing Steps
	3.5.1 Physical Processing Steps Drying, Milling
	3.5.2 Primary Packaging
	3.5.3 Secondary Packaging
3.6	Quality Control Testing
	3.6.1 Physical / Chemical testing

APOMORPHINE HYDROCHLORIDE

3.1	Manufacture of Active Substance by Chemical Synthesis
	3.1.1 Manufacture Of Active Substance Intermediates
	3.1.2 Manufacture Of Crude Active Substance
	3.1.3 Salt Formation/Purification steps (eg. Crystallisation) Salt Formation, Filtration, Recrystallisation
3.5	General Finishing Steps
	3.5.1 Physical Processing Steps Drying, Milling
	3.5.2 Primary Packaging
	3.5.3 Secondary Packaging
3.6	Quality Control Testing
	3.6.1 Physical / Chemical testing
	3.6.2 Microbiological testing (excluding sterility testing)

ALFENTANIL HYDROCHLORIDE

3.1	Manufacture of Active Substance by Chemical Synthesis
	3.1.1 Manufacture Of Active Substance Intermediates
	3.1.2 Manufacture Of Crude Active Substance
	3.1.3 Salt Formation/Purification steps (eg. Crystallisation) Salt Formation, Filtration, Recrystallisation
3.5	General Finishing Steps

	3.5.1 Physical Processing Steps Drying, Sieving
	3.5.2 Primary Packaging
	3.5.3 Secondary Packaging
3.6	Quality Control Testing
	3.6.1 Physical / Chemical testing
	3.6.2 Microbiological testing (excluding sterility testing)

SUFENTANIL CITRATE

3.1	Manufacture of Active Substance by Chemical Synthesis
	3.1.1 Manufacture Of Active Substance Intermediates
	3.1.2 Manufacture Of Crude Active Substance
	3.1.3 Salt Formation/Purification steps (eg. Crystallisation) Salt formation, Recrystallisation
3.5	General Finishing Steps
	3.5.1 Physical Processing Steps Drying, Sieving
	3.5.2 Primary Packaging
	3.5.3 Secondary Packaging
3.6	Quality Control Testing
	3.6.1 Physical / Chemical testing
	3.6.2 Microbiological testing (excluding sterility testing)

OXYCODONE

3.1	Manufacture of Active Substance by Chemical Synthesis
	3.1.1 Manufacture Of Active Substance Intermediates
	3.1.2 Manufacture Of Crude Active Substance
	3.1.3 Salt Formation/Purification steps (eg. Crystallisation) Crytsallisation
3.5	General Finishing Steps
	3.5.1 Physical Processing Steps Drying and milling
	3.5.2 Primary Packaging

3.5.3 Secondary Packaging

3.6 Quality Control Testing

3.6.1 Physical / Chemical testing

OXYCODONE HYDROCHLORIDE

3.1 Manufacture of Active Substance by Chemical Synthesis

3.1.1 Manufacture Of Active Substance Intermediates

3.1.2 Manufacture Of Crude Active Substance

3.1.3 Salt Formation/Purification steps (eg. Crystallisation)
Salt formation, Crystallisation

3.5 General Finishing Steps

3.5.1 Physical Processing Steps
Drying, Milling

3.5.2 Primary Packaging

3.5.3 Secondary Packaging

3.6 Quality Control Testing

3.6.1 Physical / Chemical testing

3.6.2 Microbiological testing (excluding sterility testing)

PHOLCODINE

3.1 Manufacture of Active Substance by Chemical Synthesis

3.1.1 Manufacture Of Active Substance Intermediates

3.1.2 Manufacture Of Crude Active Substance

3.1.3 Salt Formation/Purification steps (eg. Crystallisation)
Crystallisation

3.5 General Finishing Steps

3.5.1 Physical Processing Steps
Drying, Milling

3.5.2 Primary Packaging

3.5.3 Secondary Packaging

3.6 Quality Control Testing

3.6.1 Physical / Chemical testing

COCAINE

3.1	Manufacture of Active Substance by Chemical Synthesis
	3.1.1 Manufacture Of Active Substance Intermediates
	3.1.2 Manufacture Of Crude Active Substance
	3.1.3 Salt Formation/Purification steps (eg. Crystallisation) Recrystallisation
3.5	General Finishing Steps
	3.5.1 Physical Processing Steps Drying, Milling
	3.5.2 Primary Packaging
	3.5.3 Secondary Packaging
3.6	Quality Control Testing
	3.6.1 Physical / Chemical testing

MORPHINE HYDROCHLORIDE

3.1	Manufacture of Active Substance by Chemical Synthesis
	3.1.1 Manufacture Of Active Substance Intermediates
	3.1.2 Manufacture Of Crude Active Substance
	3.1.3 Salt Formation/Purification steps (eg. Crystallisation) Crystallisation
3.5	General Finishing Steps
	3.5.1 Physical Processing Steps Drying, Milling
	3.5.2 Primary Packaging
	3.5.3 Secondary Packaging
3.6	Quality Control Testing
	3.6.1 Physical / Chemical testing
	3.6.2 Microbiological testing (excluding sterility testing)

BUPRENORPHINE

3.1	Manufacture of Active Substance by Chemical Synthesis
	3.1.1 Manufacture Of Active Substance Intermediates
	3.1.2 Manufacture Of Crude Active Substance

	3.1.3 Salt Formation/Purification steps (eg. Crystallisation) Crystallisation
3.5	General Finishing Steps
	3.5.1 Physical Processing Steps Drying, Milling
	3.5.2 Primary Packaging
	3.5.3 Secondary Packaging
3.6	Quality Control Testing
	3.6.1 Physical / Chemical testing

CODEINE PHOSPHATE HEMIHYDRATE

3.1	Manufacture of Active Substance by Chemical Synthesis
	3.1.1 Manufacture Of Active Substance Intermediates
	3.1.2 Manufacture Of Crude Active Substance
	3.1.3 Salt Formation/Purification steps (eg. Crystallisation) Salt formation, Crystallisation
3.5	General Finishing Steps
	3.5.1 Physical Processing Steps Drying, Milling
	3.5.2 Primary Packaging
	3.5.3 Secondary Packaging
3.6	Quality Control Testing
	3.6.1 Physical / Chemical testing

HYDROMORPHONE HYDROCHLORIDE

3.1	Manufacture of Active Substance by Chemical Synthesis
	3.1.1 Manufacture Of Active Substance Intermediates
	3.1.2 Manufacture Of Crude Active Substance
	3.1.3 Salt Formation/Purification steps (eg. Crystallisation) Salt formation, Recrystallisation
3.5	General Finishing Steps
	3.5.1 Physical Processing Steps Drying, Milling
	3.5.2 Primary Packaging

	3.5.3 Secondary Packaging
3.6	Quality Control Testing
	3.6.1 Physical / Chemical testing
	3.6.2 Microbiological testing (excluding sterility testing)

MORPHINE TARTRATE

3.1	Manufacture of Active Substance by Chemical Synthesis
	3.1.1 Manufacture Of Active Substance Intermediates
	3.1.2 Manufacture Of Crude Active Substance
	3.1.3 Salt Formation/Purification steps (eg. Crystallisation) Salt formation
3.5	General Finishing Steps
	3.5.1 Physical Processing Steps Drying, Milling
	3.5.2 Primary Packaging
	3.5.3 Secondary Packaging
3.6	Quality Control Testing
	3.6.1 Physical / Chemical testing

DIHYDROCODEINE HYDROGEN TARTRATE

3.1	Manufacture of Active Substance by Chemical Synthesis
	3.1.1 Manufacture Of Active Substance Intermediates
	3.1.2 Manufacture Of Crude Active Substance
	3.1.3 Salt Formation/Purification steps (eg. Crystallisation) Salt formation, Crystallisation
3.5	General Finishing Steps
	3.5.1 Physical Processing Steps Drying, Milling
	3.5.2 Primary Packaging
	3.5.3 Secondary Packaging
3.6	Quality Control Testing
	3.6.1 Physical / Chemical testing

CODEINE

3.1	Manufacture of Active Substance by Chemical Synthesis
	3.1.1 Manufacture Of Active Substance Intermediates
	3.1.2 Manufacture Of Crude Active Substance
	3.1.3 Salt Formation/Purification steps (eg. Crystallisation) Crystallisation
3.5	General Finishing Steps
	3.5.1 Physical Processing Steps Drying and milling
	3.5.2 Primary Packaging
	3.5.3 Secondary Packaging
3.6	Quality Control Testing
	3.6.1 Physical / Chemical testing

REMIFENTANIL HYDROCHLORIDE

3.1	Manufacture of Active Substance by Chemical Synthesis
	3.1.1 Manufacture Of Active Substance Intermediates
	3.1.2 Manufacture Of Crude Active Substance
	3.1.3 Salt Formation/Purification steps (eg. Crystallisation) Salt Formation, Recrystallisation
3.5	General Finishing Steps
	3.5.1 Physical Processing Steps Drying, Sieving
	3.5.2 Primary Packaging
	3.5.3 Secondary Packaging
3.6	Quality Control Testing
	3.6.1 Physical / Chemical testing
	3.6.2 Microbiological testing (excluding sterility testing)

COCAINE HYDROCHLORIDE

3.1	Manufacture of Active Substance by Chemical Synthesis
	3.1.1 Manufacture Of Active Substance Intermediates
	3.1.2 Manufacture Of Crude Active Substance

	3.1.3 Salt Formation/Purification steps (eg. Crystallisation) Salt formation, Crystallisation
3.5	General Finishing Steps
	3.5.1 Physical Processing Steps Drying, Milling
	3.5.2 Primary Packaging
	3.5.3 Secondary Packaging
3.6	Quality Control Testing
	3.6.1 Physical / Chemical testing

NALOXONE HYDROCHLORIDE

3.1	Manufacture of Active Substance by Chemical Synthesis
	3.1.1 Manufacture Of Active Substance Intermediates
	3.1.2 Manufacture Of Crude Active Substance
	3.1.3 Salt Formation/Purification steps (eg. Crystallisation) Salt formation, Recrystallisation
3.5	General Finishing Steps
	3.5.1 Physical Processing Steps Drying, Milling
	3.5.2 Primary Packaging
	3.5.3 Secondary Packaging
3.6	Quality Control Testing
	3.6.1 Physical / Chemical testing
	3.6.2 Microbiological testing (excluding sterility testing)

12/09/2022	Name and signature of the authorised person of the Competent Authority of United Kingdom Confidential Medicines and Healthcare products Regulatory Agency Tel : Confidential