National Agency For The Safety Of Medicine And Health Products

Report No: ***22MPP058NCR***

STATEMENT OF NON-COMPLIANCE WITH GMP

Exchange of information between National Competent Authorities (NCAs) of the EEA following the discovery of serious GMP non-compliance at a manufacturer[1]

Part 1

Issued following an inspection in accordance with :
Art. 111(7) of Directive 2001/83/EC as amended

The competent authority of France confirms the following:
The manufacturer: ***Mac-Chem Products (India) Private Limited***
Site address: ***Plot No N 211/2/10 ThaneTarapur Midc, Boisar, 401506, India***
OMS Organisation Id. / OMS Location Id.: ***ORG-100023737*** / ***LOC-100032907***
DUNS Number: ***86-379-2703***

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2022-09-07***, it is considered that **it does not comply with the Good Manufacturing Practice** requirements referred to in

- The principles of GMP for active substances referred to in Article 47 of Directive 2001/83/EC.

[1] *The statement of non-compliance referred to in paragraph 111(7) of Directive 2001/83/EC and 80(7) of Directive 2001/82/EC, as amended, shall also be required for imports coming from third countries into a Member State.*

Part 2

1 NON-COMPLIANT MANUFACTURING OPERATIONS	
Include total and partial manufacturing (including various processes of dividing up, packaging or presentation), batch release and certification, storage and distribution of specified dosage forms unless informed to the contrary;	
1.2	**Non-sterile products**
	1.2.1 Non-sterile products (processing operations for the following dosage forms) 1.2.1.17 Other: Active substances(en)

Manufacture of active substance. Names of substances subject to non-compliant:
SUXAMETHONIUM CHLORIDE(en)

Clarifying remarks (for public users)

Signatory : Mr Guillaume Renaud, Director of inspection division --- The ANSM does not issue hard copies

Part 3

1.Nature of non-compliance:

During this joint ANSM/EDQM inspection, around 24 deficiencies were observed, out of which two were classified as critical and three as major // Critical 1 : A number of severe violations of EU GMP Part II, potentially posing a risk to the quality of manufactured products and therefore to the patient, demonstrated a lack of Quality Assurance oversight and understanding of core requirements. Significant shortcomings were observed across the GMP spectrum, including significant deficiencies documented as part of this inspection such as cross contamination control in shared facilities, maintenance of facilities and equipment, management of cleaning validation, and management of suppliers of intermediates and APIs // Critical 2 : Line 2 of the oncological products manufacturing section (Room P-111) was inspected. The line is used to manufacture highly active APIs (production of advanced intermediates and crude APIs), some of which destined to be used in sterile medicinal products for parenteral application. The small area (approximately 10.5 m2) and its equipment were found in an unacceptable state of maintenance and cleaning and of inappropriate design. Therefore, the contamination/cross contamination of advanced intermediates/APIs cannot be excluded // Major 1 : Deficiencies concerning vendor qualification practices, out of which the absence of mandatory requirement to follow EU GMP Part II for advanced intermediates and crude APIs suppliers, as for the vast majority of APIs produced on site, the manufacturing operations starts with advanced intermediates or crude APIs // Major 2 : Deficiencies concerning the management of cleaning validation // Major 3 : Deficiencies on risk assessments concerning vendors

Action taken/proposed by the NCA

Recall of batches already released
A recall of products should be considered using QRM principles.

Prohibition of supply
After issuance of the non-compliance report and as long as it remains active, prohibition of supply of APIs is recommended, unless there are no alternative suppliers and there is a risk of shortage.

Suspension or voiding of CEP (action to be taken by EDQM)
EDQM to consider : - the suspension of several CEPs : CEP 2012-025 / Suxamethonium Chloride CEP 2012-251 / Cytarabine CEP 2012-350 / Letrozole CEP 2012-147 / Carboplatin CEP 2012-066 / Dacarbazine CEP 2017-164 /

Gefitinib CEP 2017-246 / Ropivacaine hydrochloride monohydrate CEP 2015-141 / Pemetrexed disodium heptahydrate CEP 2019-024 / Neostigmine methylsulfate CEP 2018-063 / Irinotecan hydrochloride trihydrate CEP 2019-329 / Bicalutamide CEP 2020-012 / Cisplatin CEP 2020-074 / Etoposide - the closure of assessment of current CEP applications CEP 2019-174 / Gemcitabine hydrochloride CEP 2020-361 / Imatinib mesilate CEP 2021-426 / Anastrozole
Additional comments Hungary NCA to consider the withdrawal of GMP certificate OGYÉI/29225-8/2021 // The existence of MAs or MA variations referencing an active substance manufactured by this site has to be verified. ln these circumstances, the removal of the site from the MA should be considered using QRM principles // This inspection was performed in the framework of the CEP dossier for the manufacture of Suxamethonium chloride. The deficiencies found could affect the other APIs manufactured at the site as listed below (list communicated by the company): General APIs: Anidulafungin, Aprepitant, Atracurium Br, Azathioprine, Colistimethate Na, Chlorthalidone, Deferasirox, Dexmedetomidine HCl, Epalrestat, Erdosteine, Febuxostat, Fosaprepitant dimeglumine, Gliclazide, Micafungin Na, Mycophenolate Na, Mycophenolate Mofetil, Neostigmine Br, Neostigmine Methylsulfate, Polymyxin G Sulphate, Posaconazole, Ropivacaine HCl monohydrate, S-Bupivacaine HCl, Sugammadex Na, Suxamethonium Chloride, Tigecycline, Tofacitinib Citrate, Vecuronium Br // Oncological APIs: Abiraterone acetate (Line 1), Anastrozole (Line 1), Azacitidine (Line 1), Bendamustine HCl (Line 1), Bicalutamide (Line 1), Bortezomib (Line 2), Capecitabine (Line 1), Carboplatin (Line 1), Cisplatin (Line 2), Cladribine (Line 2), Cytarabine (Line 1), Cytarabine HCl (Line 1), Dacarbazine (Line 1), Dasatinib (Line 2), Docetaxel 3H2O (Lines 1 & 2), Enzalutamide (Line 2), Erlotinib HCl (Line 1), Etoposide (Lines 1 & 2), Exemestane (Line 1), Fludarabine Phosphate (Line 2), Gefitinib (Line 1), Gemcitabine HCl (Line 1), Imatinib mesilate (Line 1), Irinotecan HCl (Lines 1&2), Irinotecan HCl Trihydrate (Lines 1&2), Lapatinib ditosylate (Line 1), Lenalidomide (Line 1), Letrozole (Lines 1&2), Methotrexate (Line 1), Nilotinib HCl, Oxaliplatin (Lines 1&2), Paclitaxel (Lines 1&2), Permetrexed disodium heptahydrate (Line 1), Procarbazine HCl (Line 1), Pomalidomide (Line 2), Sorafenib Tosylate (Line 2), Sunitinib Malate (Line 2), Temozolomide (Line 1), Topotecan HCl (Line 2), Zoledronic acid (Line 2)

2022-11-16

Name and signature of the authorised person of the Competent Authority of France

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