edqm
European Directorate for the Quality of Medicines & HealthCare
Direction européenne de la qualité du médicament & soins de santé

COUNCIL OF EUROPE
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The Director

CARBOGEN AMCIS B.V.
Mrs Wilma VAN OEVELEN
Nieuweweg 2A
The Netherlands-3901 BE
Veenendaal

CEP_RZ_PH_2005-285-1283349 Strasbourg, 19 March 2020

TH / mr

Re: **DECISION TO SUSPEND A CERTIFICATE OF SUITABILITY**

Re: **DECISION TO REVISE A CERTIFICATE OF SUITABILITY (removal of a manufacturing site)**

Dear Mrs VAN OEVELEN,

Following the inspection of the manufacturing site:

DISHMAN CARBOGEN AMCIS LIMITED
Survey No. 47, Paiki Sub Plot No. 1
Taluka Sanand, District Ahmedabad
India-382 220 Village Lodariyal ,Gujarat

carried out from 26 February 2020 to 28 February 2020 as part of the EDQM Inspection Programme, the conclusion of the inspectors is that this manufacturing site is not compliant with EU GMP and is not performing manufacturing in accordance with the approved dossier. The company has, in addition, failed to fulfil their commitments as set out in their CEP applications.

This inspection identified one critical and several major deficiencies to EU GMP Part II and other relevant Annexes. It was concluded that the combination of the deficiencies identified constitutes a critical risk of producing products, which could be harmful to the patient:

1) [**Critical**] A lack of QA oversight and/or technical knowledge was observed as evidenced by a significant number of major and other deficiencies found during the inspection. In particular, the major observations related to preventing risk of contamination/cross-contamination (flaws identified when introducing new chemical entities/APIs into the facility and the shortcomings observed with regard to cleaning and cleaning validation) led to the conclusion that risks toward the human or veterinary patients cannot be excluded.
(EU GMP Part II, no. 2.11, 2.12 2.19, 2.20, 2.21; ICH Q9)

2) [**Major**] The firm's approach to materials management, including the labelling, traceability, storage conditions, dispensing, cleaning and pest control of raw materials, intermediates, solvents and recovered solvents was considered as not in compliance with EU GMP based on the following observations:
   a. With regard to labelling and traceability the following observations were made:
      i. Fresh and recovered solvents stored in tanks were not traceable because no individual batch number was assigned. Furthermore, no status label reflected the usage/non-usage of the solvents. For instance, it was not possible to verify the input of recovered solvents in the batch records of [redacted] as the analytical record numbers mentioned in the records could not be traced to the content of the tanks from which they were supposed to have been dispensed.
      ii. Drums with recovered Acetone/Petroleum ether from [redacted] stage I were seen in the tank yard area next to Unit 13. The labels were lacking the status and the fate of the material. The firm explained that the solvent mixture was to be sold; however this was not clear either from the identification of the area or the labelling of the material.
      iii. The materials kept in the recovery solvent storage facility next to Unit 7C were in very poor condition evidenced as follows: numerous drums and containers were substantially covered with dust, dirt and cobwebs indicating that the area was not subject to any cleaning. In addition, and similar to the aforementioned observations, the materials were not labelled according to GMP: origin of recovered solvents, batch numbers, status, etc. were found to be missing. In addition and in contradiction to the designated function of the area, released bags of sodium chloride were stored in this facility.
      iv. In the warehouse for hazardous material, drums containing dimethyl sulphate were seen bearing only the material name, quantities and a batch number, which was potentially that of the supplier. The supplier was not mentioned on the label and no status was assigned to the material.
   b. Haphazard storage of various materials, such as brooms, flexible hoses, packaging material, recovered solvents, approved raw materials ([redacted], batch no. 1100125820), advanced intermediates ([redacted] batch no. 119TAEC027) and APIs (e.g. [redacted] final stage III, batch no. 120BAEC016) was seen inside the so-called Drum Storage Area I next to Utility Block III. The area was not controlled in terms of storage conditions, not monitored in terms of temperature and not protected against the entry of insects, rodents and birds. The area was almost inaccessible due to the large amount of material kept there and was found to be in a very dirty state. Altogether, a negative impact on the quality of the materials stored and eventually on the APIs to be manufactured cannot be excluded. Furthermore, as seen at various locations, the labelling of the material was not in accordance to GMP as necessary information, such as origin of material, status of intermediates, etc. was missing.

c. The inspection team checked the reconciliation of recovered/spent catalysts. As for other materials, the labelling was insufficient in order to allow traceability of the catalysts used. For instance, the material codes were not part of any label and no status was assigned. Some of the drums containing the recovered catalysts were labelled as "to be re-used"; however no dispensing records were available. Furthermore, the quantities the firm recorded in the inventory provided upon request did not confirm the actual amount seen on containers: e.g. the recorded amount of recovered palladium dioxide in the inventory was 1.88 kg, whilst two drums with 3.35 kg and 3.7 kg were seen in the warehouse.
d. The firm's approach to pest control was considered as insufficient based on the following observations:
    i. A lizard was seen in the drum storage facility shed inside the packaging material area
    ii. Birds were observed inside the packaging material area. This observation was regarded as a repetition of deficiency 2a from the 2009 EDQM inspection.
e. The dispensing of fresh solvents into the movable 1500 L carts and drums posed a potential risk to the dispensed solvents as the dispensing took place outside protected only by a roof. In addition, the filling nozzles were not protected against accumulation of dust and dirt. NB: This did not apply to the dispensing of solvents coming from underground storages tanks into drums.

(EU GMP part II, 2.4-5, 2.4-7, 2.44.10, 5.10, 7.40, 7.41, 7.42, 7.43, 10.10, 12.74, 14.40, 14.41, 14.42, 14.43)

3) [**Major**] The following risks associated with the introduction of new chemical entities/products/APIs were identified:
    a. No procedure/guidance was in place describing how to evaluate, address and eventually mitigate the risks associated with the introduction of new chemical entities into commercial production facilities, i.e. intermediates and active pharmaceutical ingredients. This led to the situation where the firm failed to evaluate the impact of pharmacological and toxicological characteristics of the substances to be produced, including the raw/starting materials used.
    b. Some years ago, the firm had introduced the manufacture of [redacted] a key starting material used for the manufacture of [redacted]. The raw material used to produce [redacted] was [redacted], a highly active sex hormone. The firm addressed only process-related risks, and not the risks associated with contamination/cross contamination of storage and production facilities, personnel flow and protection and impact on the other products. Furthermore, the product was temporarily manufactured in the Pilot Plant PP-RG-05 in November 2017 (scale-up batches) without any change control that might have addressed the risks associated.
    c. At the time of the inspection, the firm was manufacturing validation batches of [redacted] a substance with psychotropic activities and in many countries regulated as a controlled substance. No risk assessment was performed with regard to pharmacological and toxicological characteristics of the API. Moreover, the risk evaluation performed was lacking in the following aspects:
        i. The Risk Assessment did not address risks associated with the flow of personnel and material.
        ii. No. 6 of the risk evaluation recommended as a risk mitigation measure a "systematic procedure of cleaning validation". However, the related "CAPA assessment form" (i.e. proof of risk mitigation measure implementation) showed that no cleaning validation had been performed

iii. The documentation was found incomplete and ambiguous as neither the risk assessment nor the assessment report actually mentioned the substance [redacted] to be introduced into the facility.

(EU GMP part II, 2.20, 2.21, 4.42, 5.15, 5.25, 7.40, 8.50)

4) [**Major**] The following observation was made with regard to the recovery of solvents in solvent recovery facility Unit 5: according to the company, at the time of the inspection on 27 February 2020, the recovery of Acetonitrile batch no. 20EAAB1007 took place. However, the related batch record, issued on 22 February 2020 was not filled in. This was considered as particularly severe since the recovery process had finished and the batch had already been analysed by the firm (according to the QC logbook on the 26 February 2020).
(EU GMP part II, 6.14, 14.40, 14.41, 14.43)

5) [**Major**] An overall and serious lack of maintenance was observed by the inspectors, mainly with regard to Unit 5 (solvent recovery plant) and to Units 3A and 3B (intermediate manufacturing plants) evidenced as follows:
   a. Units 3A and 3B, used to perform the second stage of the dihydrotachysterol manufacture, had been under shutdown since December 2019. The area was to be refurbished and therefore some of the equipment was found dismantled. However, the area and the remaining equipment was seen to be in an unacceptable state of maintenance. Therefore, batches of Dihydrotachysterol manufactured to date had been produced under conditions which could affect the quality of the intermediate manufactured.
   b. The Unit 5 facility was found rusty and dirty with broken equipment and roofs, and in addition was used as a storage facility for waste material. Furthermore, the temperature sensor on top of the column used to recover Acetonitrile was not identifiable.
   c. SOP BDEG-604 Rev 05 effective 02.10.2018 on "good engineering practices" addressed the maintenance of buildings; however solvent recovery plant unit 5 was not included in the scope of the procedure or in the maintenance schedule.
   d. The checklist for "monitoring & control of civil activities for general area" of buildings 3A and 3B for 2018 and 2019 was verified. It stated that maintenance activities were carried out as scheduled. However, based on the observations made, it became apparent that either the maintenance was not carried out appropriately or that the maintenance approach of the firm was insufficient to keep the facilities in a GMP compliant state.
   e. The following observations were made with regard to maintenance/identification of equipment other than that located in Units 5, 3A and 3B:
      i. The charging pipes leading to storage tank 13-ST-04 were not identified with regard to their content.
      ii. According to the schedule, the air vent filter of tank 13-ST-04 was supposed to have been cleaned/replaced in November 2019. However, according to the status label, no such cleaning/replacement had been conducted. Furthermore, one flange of the filter was leaking and, based on the large amount of spilled residues on the tank's surface, had been doing so for a long time without repair.
      iii. Some of the mobile tanks with a capacity of about 1500 L were seen to be not identifiable by their content (e.g. in front of Unit 7H).

(EU GMP part II, 4.23, 4.42, 4.70, 4.71, 5.10, 5.13, 5.22, 5.24, 7.24, 7.40, 16.10)

6) [**Major**] The following observations were made with regard to the process validation activities related to Dihydrotachysterol: the last validation performed in 2011 used 1.6 kg Ergocalciferol acetate (stage I) as input material for stage II. However, according to the current approved batch manufacturing record (BMR), the input of stage I material was 5.0 kg. In 2019 the input of Ergocalciferol acetate varied from 4.0 to 6.2 kg. The increase in batch size was not covered by any process validation. This was considered as particularly severe as the increase in batch size also resulted in a necessary change of the manufacturing area, i.e. the manufacture of stage II was transferred from the pilot plant where the validation activities took place to Unit 3A/B. Moreover, this incident was also considered as a failure to comply with section 6.21.1 of the Process Validation SOP which states that revalidation has to be performed in case of major process changes. According to the change control SOP Annexure 1 section 2, the increase of batch size is considered as a major change. Furthermore, the validation conclusion did not address whether or not all critical process parameters were met.
(EU GMP part II 2.32-10, 2.4-8, 12.10, 12.11, 12.12, 12.20, 12.21, 12.50)

7) [**Major**] The cleaning of sampling and dispensing rooms in warehouse 1 where open material was handled were considered as not in compliance to GMP and therefore posing a risk for contamination/cross-contamination evidenced as follows:
   a) The firm's cleaning of this area was not scientifically justified; therefore, the existing cleaning procedure cannot be considered as sound and eventual contamination of the area and subsequently other material cannot be excluded. This was particularly considered as severe as the facilities were also used to sample and dispense the sex hormone [redacted]. In addition no instructions were available addressing the handling of this highly active material in order to avoid contamination of personnel, facilities and equipment in, for instance, SOPs on "Handling and Cleaning of sampling devices and room" (BDQC-388) or SOP on "Dispensing, issuing & transporting of raw material" (BDWH-154).
   b) The dispensing rooms were segregated by a lamellar plastic curtain, which was considered as difficult to clean once contaminated by the materials handled in this facility. A similar situation was noted with regard to the sampling cabins. Furthermore, in SOP BDWH-163 on "Cleaning of dispensing rooms and utensils" Rev 07 effective 15.02.2020 and SOP BDQC-388 on "Handling and cleaning of sampling devices and room" Rev 08 effective 25.09.2018, the cleaning of the lamellar plastic curtains was not addressed at all.

   (EU GMP part II 2.4-5, 7.40, 12.70, 12.71, 12.72, 12.73, 12.74, 16.10)

8) [**Major**] No cleaning validation was performed in Unit 3C where manufacturing of intermediates took place, despite SOP BDQA-298 on "Cleaning Validation" stating in section 6.12.1 "cleaning matrix approach" that if multiple products are manufactured in a facility the related equipment shall be subject of cleaning validation." The execution of cleaning validation of this manufacturing unit was considered particularly important - although if it referred to the production of a(n) intermediate(s) - as highly active material [redacted] was handled in this facility.
   (EU GMP part II 12.7ff)

Therefore, the EDQM Ad Hoc Committee has taken the following decisions:

- **To suspend the certificate of suitability**
  - **CEP 2005-285 / Dihydrotachysterol**

- **To revise the certificate of suitability (removal of inspected site)**
  - **CEP 2001-199 / Cholesterol HP**

This decision to suspend the certificates of suitability is valid for **two years** and the CEP can only be restored when the following conditions are met:

- You have proposed appropriate corrective actions and a new inspection has verified their implementation and demonstrated compliance with EU GMP requirements when the workshops are in operation.

You should inform the EDQM as soon as appropriate corrective actions have been fully implemented and the site is ready to be re-inspected, and before the end of this 2-year period. An extension of the suspension may be exceptionally possible upon justified request. Such a request should be made at least 6 months before the end of the 2-year period.

Failure to request a re-inspection in time would lead to the withdrawal of the CEPs concerned.

No other CEP for a substance manufactured by the concerned manufacturing site can be granted unless the above-mentioned issues are resolved. Should you wish to include the site in a CEP application in the future via a revision of a new application, a pre-approval inspection would be required.

You are reminded that it is your responsibility to inform all your customers about this decision. Please note that the Licensing Authorities of the member states of the Convention on the Elaboration of a European Pharmacopoeia and EDQM international partners, will be informed of this decision. The decision in relation to the CEPs will be published on the EDQM website.

.../...

According to Resolution AP-CSP (07) 1 of the Council of Europe, you are given the possibility to request a hearing in order to ask the EDQM Ad Hoc Committee to review its decision(s). **Please note that the hearing is a written procedure.** Any request for such a hearing should address any discrepancy/error that might have occurred and should be supported by appropriate justifications for the issue(s) you may have identified. **This request has to be submitted in writing via email to cep@edqm.eu within 14 days following receipt of this letter.**

Yours sincerely,

pp Dr Susanne KEITEL

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