Six steps to handle high-potent molecules in a shared facility

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In recent years, the development of highly potent molecules has become more frequent, and around 25% of the components that are being developed are classified as potent. [1] As older products reach patent expiry, generic-drug companies are also moving into this space, increasing the demand for capability and capacity to manufacture highly potent Active Pharmaceutical Ingredients (APIs) [2]. High potent APIs are defined as a pharmacologically API or intermediate with biological activity at approximately 150 µg/kg of body weight or below in humans (therapeutic daily dose at or below 10 mg), with an occupational exposure limit (OEL) at or below 10 µg/m^3 of air as an 8 hour time-weighted average. Also, it is defined as a pharmacologically active ingredient or intermediate with high selectivity with the potential to cause cancer, mutations, developmental effects, or reproductive toxicity at low doses. [3]

Ivermectin, a highly potent compound, is a broad spectrum avermectin class antiparasitic agent and has antiviral activity against a wide range of viruses in vitro [4]. Recent studies have shown that this active principle ingredient (API) can inhibit the replication of SARS-CoV-2 [5], the virus that caused the COVID-19 pandemic. Several laboratories around the world have developed new products with Ivermectin API to help counteract the effects of this disease, however, the handling of this substance constitutes a real challenge because it is categorized as a toxic and potent API and both the safety and quality of the product must be guaranteed, ensuring that the risk of cross-contamination is mitigated as well as the safety of the operators who are exposed to it.

For this reason, a new methodology was developed in order to evaluate the inclusion of highly potent APIs and to its laboratories and the shared manufacturing plants which will be used during the development and commercialization of the product Ivermectin 3 mg Soft Gelatin Capsules (SGC) which we have summarized in the next six key steps. It is important to mention that this evaluation is applied at Procaps for each new API that is being introduced in our shared facility.

1. Consider toxicological classification as a decision factor for project assessment

The assessment of a development project considers the toxicological classification of the API, (in this case Ivermectin) in addition to considering the economic, market, patent; among other factors, in order to evaluate the viability and the total cost of the project.

This step is essential to carry out a good assessment of the project because according to the toxicological category of the components, it is determined if it is necessary to make additional investments for its execution. Perform a robust bibliographic review, including the categorization of the molecule, information related to the OEL value, NOEL value, regulatory requirements, indicators of health hazards for potent molecules, among others, must be considered in order to have an indication for a preliminary toxicological category.

2. Classify the API according to its toxicological category

Different classification systems exist around the world as ISPE, Merck, Lonza, Safebridge, among others [6,7]. From the Safebridge toxicological categories were determined in the classification system implemented for active principles in the organization. They are classified, after a rigorous technical-scientific bibliographic review of the API performed by a Toxicologic expert. Then the API is classified as:

- Category 1: APIs with low toxicity for active principles that can produce local effects and very few reversible effects at the systemic level.
- Category 2: APIs that have medium toxicity and can cause reversible effects at the systemic level, but without or very few permanent effects.
- Category 3: the toxic and potent components that can produce effects at the target organ level at low doses and that can cause permanent and potentially severe damage.
- Category 4: Toxic and very potent that can produce permanent and potentially severe effects to extremely low doses.

Ivermectin was categorized as toxicological category 4 due to its toxicological characteristics.

3. Define the toxicological risks associated with the handling of the API in the facilities

The inherent toxicological risks must be determined before starting activities within the areas where a potent active ingredient will be handled, during the development and commercialization stage, performing a risk analysis for each stage in the manufacturing process.

The methodology for risk analysis, developed and implemented by Procaps, was called Critical Risk Analysis Prioritization (CRAP). CRAP simplifies, reduces the time, and decreases the complexity of the toxicological risk assessment. It was obtained from a well-known risk assessment tool: Risk Analysis and Mitigation Matrix (RAMM) [8]. Finally, CRAP results can identify the risks to be evaluated using FMEA. CRAP analysis should be performed following these critical steps: a) Draw a process map with all the stages of the manufacture; b) Identify areas and equipment used in each stages; c) List all the steps for each stage of the manufacturing process; d) Prepare the matrix of evaluation to assess each step against the exposure routes of the API; for cross-contamination risks: mixture, mechanical transfer, air transfer and retention, and for occupational exposure risks: inhalation, dermal absorption, exposure to mucous membranes and ingestion. In this matrix, the steps are located on the rows and the exposure routes on the columns; e) Each step in the matrix, should be scored according to the effect of the molecule in patients or personnel depending on the exposure route evaluated. These scores are defined according to the probability that the evaluated risk occurs once the manufacturing step was executed.

4. Validate existing controls to mitigate toxicological risks

To ensure that the handling of potent active ingredients is carried out under controlled and effective processes that prevent the risk of cross-contamination and exposure of workers within the permissible limits, the controls implemented must be validated and documented to facilitate the availability of the information. The Ivermectin product is manufactured in a soft gelatin capsule multiproduct plant whose engineering controls, work practices and the use of personal protection elements are validated, standardized in procedures, and documented within the risk prevention plan.

5. Verify if additional controls are needed to mitigate residual risks.

If after the analysis of toxicological risks with the FMEA tool the residual risk is high, additional controls must be implemented to reduce the risk. These additional controls must be in place before to

start any activity using the API evaluated, therefore it is important that the implementation is followed by the establishment of responsible parties and execution dates. In the evaluation of toxicological risks of the product Ivermectin, it was found that all the scores of the toxicological risks were low, it is because Procaps implemented this program of toxicological classification of the APIs before to be introduced in the multiproduct facilities from 2017 and had been implemented exhaustive controls to handle all types of APIs.

6. Standardization of work procedures for the management of High-Potent APIs.

The success of the implemented methodology is associated with the generation of communication and training strategies for all the personnel involved in the manipulation of these components. This strategy may include but is not limited to, training in procedures for the containment of toxicological risks, the handling of personal protection elements, the communication of the risks associated with each API that must be handled within the facilities and the definition of roles and responsibilities within risk management. The personnel involved in the handling and manipulation of the Ivermectin product were trained and qualified to comply with the established work procedures to handle highly potent APIs.

If these six key steps for the inclusion and handling of high-potent APIs are correctly followed, the organization can demonstrate that the strategies implemented for risk mitigation in the areas where the API will be manipulated are effective. In this case, the implantation of these 6 steps for the product Ivermectin 3 mg can be handled within the laboratory areas and manufacturing plants for its development and production, ensuring the safety of the patients and the personnel.

Procaps offers high potent handling capability in multiple technologies and services. We have deep expertise handling all types of compounds from development to commercial supply, using a toxicologic classification system for high potent, hormonal and controlled compounds; among others.

Through our extensive capabilities and deep expertise in product development and softgel manufacturing, we help different companies bring innovative products to their markets faster, offering their patients and consumers an exceptional experience, high preference and superior adherence to different therapies. Our advanced delivery technologies, including Softgel and related technologies, our proven formulation, manufacturing and regulatory expertise, has enabled us to become an integrated CDMO (iCDMO), giving customers full-service, turnkey solutions in prescription drugs, OTC and dietary supplements across both development and delivery.

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