Report

Webinar 30 September 2021

Challenges in biologicals manufacturing in contract manufacturing Facilities

In the EBPMN webinar Dr. Carlos Melo, Senior expert for pharmaceutical and bio industries highlighted the challenges in "Biologicals manufacturing in Contract Manufacturing Facilities". The Webinar was moderated by Mireille Gerrits.
During the Webinar Dr Melo presented challenges in production in up-scaling, technology transfer, and regulatory submission and biotechnology business challenges. He provided examples of mistakes which should be avoided, and emphasis the importance of go / no-go decisions during development.
A summary of the webinar is presented below.

1. Production challenges – Technology Transfer

Items that are important for technology transfer are:

a) Use the same equipment: same brand, same volume, same particularities;
b) Staff needs to have adequate experience;
c) Make sure the donor provides all the necessary information;
d) Each technology transfer step must be done and checked by both parties;
e) Define "similar quality";
f) Prepare a good estimation of the costs of production.

All these issues should be addressed before starting the technology transfer

2. Production challenges – Development by company itself

Items that are important for development of biosimilar by the company are:

a) Chose the right target: The target should be profitable, which can be a problem for instance for rare diseases;
b) Staff must have adequate experience and skills;
c) Chose the right expression system, preferably the same as the originator;
d) Have the right tests and documentation done on time. The documentation needs to be available for each step at the time this step is performed. Not at the end;
e) Define quality for the product and the limits of acceptation. A common mistake is that the quality is defined early on in the development, on the first production batches when the characteristics of the product and variability are not yet well-know;
f) Costs need to be known in advance to set a competitive price.

3. Biotechnology business - Challenges

Once the product is available, there are other challenges to bring the product to the market.

a) Challenges in developing a product in a technical and economical feasible way.
Mistakes to avoid:

- Not understand the difference between spending and investing: do not develop in the cheapest way, but invest in a good product;
- Not perform a realistic marketing study: look at the pricing each region, not only in the high-priced countries;
- Not realize the economic impact of "time to market": if development time is long, the market may be changed;
- Not understand -not foresee, costs nor productive systems available: look at different technologies and select the system that is most cost-effective;
- Hire scientists and professors for achieving technical developments. Academia are very good in basic research, but the knowledge on the specific needs for industrial development is often lacking;
- Employ vectors, hosts, and processes under IP protection without knowing it. Often when IP protection is researched, this is done in the US, while each country has its own specific regulation, which different issues.

b) Challenges in having all the right regulatory documentation and generated on time.
Mistakes to avoid:

- Not understand the difference in between spending and investing: If you do not have the right documentation, you will lose time in getting approval;
- Do not know the local requirements. Countries may have different requirements for the tests, clinical studies, and documentations. For example you need to perform studies with different races, applicable for each country;
- Do the comparative studies with too few batches of each product. You need to have as many batches as necessary for robustness and statistical significance testing;
- Prepare the CTD without a sole responsible for it with the power for deciding. The CTD should be controlled by one person of groups of persons to maintain consistency and avoid discrepancies between the different sections;
- The responsible person(s) for the CTD does not understand the whole picture of the technology and the regulatory issues. Note that it is very difficult to have a person that knows everything;
- Translate the CTD with the cheaper -and not the best, translator;
- Defend the CTD with collaborators that do not understand the technology at all. The collaborator should have experience with biotechnology;
- At first develop production, then perform pre-clinical and clinical trials with the resulting product, and afterwards decide to change the production system to improve costs, productivity, or quality. You should have a solid production process, before starting the pre-clinical and clinical development. After each change in the production process the (pre-) clinical studies need to be redone to prove safety;
- Do not perform the right studies comparing the new system product against the old one and against the innovator´s. You need to redo the comparisons with the innovators if the system is changed;

- Not prepare different CTDs adapted for each country that has different requirements. CTD should be consistent with local regulations and needs to be specific for each country.

c) Challenges in understanding how to sell the product in regions where we have no knowledge, not experience.
Mistakes to avoid:
- Not understand the difference in between spending and investing. For local production you need experienced local persons even if they are more expensive;
- Our negotiators do not know the region. For example negotiations in China and Brazil are very different. You need to know how products need to be sold in each country;
- Our local CEO has his own interest. The local CEO may work also for competitors;
- The corporate -as well as the local representative, have no idea of the opposition they will suffer once the product is approved by the local authorities. The approval is just the beginning of the process. You will need to defend against competitors and the innovator;
- Do not understand the particular mechanism for selling a given product in a given country;
- Try to get all the profit for us instead of sharing the business with the local licensee. Both the company and the local licensees need to have a good share of the profits.

d) Forecast the very intense opposition in:
- Regulatory issues: all weaknesses in outcomes of clinical studies, even it was sufficient for regulatory approval, will be used by the opposition;
- Safety: the opposition will study the CTD to find safety issues, which they will use to block approval or inform physicians;
- Lack of experience: If you have less experience compared to the competitors it is difficult to get place on the market;
- Patents: competitors may go to layers challenging your patent;
- Difference against the innovator: the innovator may perform additional bio comparison studies and if they find differences, they may start a lawsuit;
- Exchangeability: you need to prove that your product can be exchanged with the innovator, which is difficult to do;
- Physicians are loyal to the innovator. There may be (economic) reasons for the investigators to remain prescribing the innovative product;
- Fear of patients to change from brand.

4. Rational go/to go

- Do not start a project if you have not identified, understood in deep and solved all the factors mentioned.
- For commercialization of a product produced by a third party, first analyze in deep their CTD and inspect the production plant before signing a contract and starting the registration process.

5. Suggestions

- Consider, know, and solve **all** the factors here presented. If not, then approval is never going to arrive. Or if it arrives, you will not sell anything.

- Spending years/decades solving problems without arriving to the market results in huge loss of profits. Which costs more then making the right investments and decisions.
- The loss of profit is much higher than the assumed saved investments.

6. Facts

- The market is full of examples of companies that made the mistakes presented here and failed completely.
- The bad examples convinced many investors and companies that this activity is not profitable.
- Most of the companies that follow this way, continue to make the same mistakes.

Questions:

- Question: Does the WHO pre-qualification process play a role in this process
- Answer: The right qualifications of the equipment, processes and facilities is always very important. The WHO pre-qualification process is now important with the COVID vaccine approval. Carlos Melo has no experience with this WHO process for other products.

- Question: What are main mistakes in selecting CMOs
- Answer: The CMO needs to have experience in the kind of process that you using for your product and must produce preferably according to FDA/EU GMP rules. A CMO is an investment, do not hire the cheapest one.

- Question: What is the key issue.
- Not to have the documentation at the right time, do not cut corners.