

Bioserv Corporation CMO: A Guide to Fill and Finish Services and Clinical Trials

Marianna Tcherpakov, PhD, is the Business Development Manager of Bioserv Corporation, a U.S. boutique cGMP contract manufacturing organization (CMO) specialized in aseptic, non-aseptic, and high-potency fill and finish services for the pharmaceutical, biotechnology, and life science industries.

In this discussion, she and Patricio Ledesma, Head Of Clinical Operations at Sofpromed, will address the topic of drug product manufacturing in the context of early phase clinical trials, with particular focus on aseptic and high-potency fill and finish processes.

PATRICIO LEDESMA (PL): Hi, Marianna. Thank you very much for this opportunity to talk about fill and finish services for drug products to be used in clinical trials.

Let's start by learning a bit more about your company's background. What is your expertise in the field of drug product manufacturing?

MARIANNA TCHERPAKOV (MT): My name is Marianna Tcherpakov. I have worked as a business development manager at Bioserv for five years. I have an MSc in biotechnology from Tel-Aviv University, a PhD in molecular neurobiology from Weizmann Institute, and an MSc in science management from Polytechnic University in New York City. After an academic career, I worked in variety of biotech companies on assay development, antibody manufacturing, and gene editing/cell therapies.

Currently, at Bioserv, my role is not only to find potential clients, but also to work closely with them to understand their specific needs for drug product manufacturing.

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In addition, Bioserv offers a broad range of manufacturing suites to meet clients' production needs. Bioserv's manufacturing facilities include certified Class 100 (Class 5 or Class A), Class 10,000 (Class 7 or Class C), Class 100,000 (Class 8 or Class D) areas, and clean, unclassified laboratory rooms.

We have filled a significant number of cGMP finished drug product lots for our clients to support their Phase I and Phase II clinical trial needs. We have a broad level of highly skilled production experts



Marianna Tcherpakov, PhD
Business Development Manager
Bioserv Corporation



Patricio Ledesma
Head Of Clinical Operations
Sofpromed

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that have worked with very complex formulations, including liposomes, emulsions, nanoparticles, small molecules, conjugates, and adjuvants.

Overall, Bioserv is well established in the fill/finish industry, and most of our clients come back to work with us again on drug product manufacturing.

PL: For readers that may not be so familiar with aseptic, non-aseptic, and high-potency fill and finish services, could you explain these manufacturing techniques?

MT: Aseptic fill is defined as a process in which the drug product, container, and closure are first subjected to sterilization methods separately, and then brought together under aseptic/sterile conditions. Overall, aseptic manufacturing requires specially designed cleanroom that prevent contamination of the drug product from harmful living microorganisms such as bacteria, viruses, and others.

Based on this definition, pharma manufacturing industry classifies cleanroom in different categories. Aseptic fill requires Class 100/Class A/ISO5 cleanroom/aseptic core. The aseptic core is the area where the sterile drug is transferred from the filling needles to the sterile container. Typically, the stoppering or closing of the container occurs immediately after, with the exception of when the drug requires sterile lyophilization.

Non-aseptic filling is a non-aseptic process that requires the coordination and interaction between personnel, product, the manual fill/finish equipment system, laboratory space, and support facilities. In this case, lower classification cleanroom (Class 100,000/Class B/ISO7) or Clean, Unclassified Lab Areas can be used. The non-aseptic lab space is where many reagents or products that can be further terminally sterilized can be filled.

In addition, when working with cytotoxic compounds such as oncology drugs, additional

isolation is required to protect manufacturing personnel from toxic exposure. For that reason, isolators are built to fill cytotoxic drug products under protected conditions.

Bioserv's facilities are spread out on more than 36,000 square feet. We can offer a wide range of classified cleanrooms (Class 100, Class 10,000, Class 100,000, and non-cleanroom lab space) that can be used and adjusted to aseptic and non-aseptic manufacturing.

Moreover, we have lyophilization equipment that can be used in aseptic and non-aseptic settings.

Overall, Bioserv is equipped to provide different types of fill/finish services.

PL: What specific types of drugs require fill and finish processes? With what kind of drugs do you have more experience?

MT: In general, every drug product that goes into clinical trials will require fill/finish. It can be done by aseptic processes as well as non-aseptic manufacturing depending on route of administration. Injectable/parenteral drug products must be sterile, either through terminal sterilization or via aseptic processing.

Bioserv makes, on average, 30 different products per year. And we can proudly say that we worked with almost every possible type of drug and a variety of indications: oncology, ophthalmology, vaccines, dermatology, and more.

Moreover, we expanded into fill/finish of live cells last year. This is an emerging trend in the manufacturing industry since more companies are working on cell-based therapy and require unique capabilities in the preparation of live cells drug products for clinical trials.

Importantly, many clients require specialized formulations, processes, and custom pharmaceutical reagent manufacturing. Bioserv provides custom contract manufacturing services such as lyophilization, microfluidization, nanoemulsions preparations, high-shear mixing, and much more.

PL: Biotech startups may experience difficulties when finding a suitable CMO to manufacture small batches of drug product for early-phase clinical trials. How does Bioserv help clients in this situation?

MT: Bioserv is especially equipped to help small clients like biotech startups. The company does

manual fill, which means we are limited to relatively small batch sizes in comparison to big providers. However, this is also our strength: We can manufacture one vial if needed.

Our approach is personalized by design. When you call/contact Bioserv, you get to speak directly to me or our COO about the project.

We customized our manufacturing based on clients' needs and work closely with each customer. In many cases we help and advise in process development or formulation activities and provide overall consultation for drug product manufacturing strategy.

PL: With regard to sterile fill and finish processes, what are the main challenges of this type of filling and how does Bioserv ensure top quality manufacturing for sterile filling?

MT: It is very important for Bioserv to understand the details of specific drug manufacturing. For example, how long is the formulation? Is the solution viscous? Can we keep it room temperature during the fill? All these questions and answers are very crucial for successful fill/finish outcome.

In many cases, especially when start-up companies are involved, there is no clear or finalized manufacturing process.

Bioserv works closely with each client and can make suggestions based on company's more than 30 years' experience.

Moreover, we always suggest that our clients do engineering run/pilot small scale fill in order to practice and eliminate potential challenges during the actual drug product fill. This approach was shown to be very helpful, especially when unique equipment operation is needed during formulation.

PL: Could you explain in more detail your high-potency fill and finish capabilities?

MT: In the last decade, there are more companies working on cytotoxic drugs, especially in oncology sector. Indeed, a growing number of antibody-drug conjugates (ADC) were approved by FDA in the last couple of years.

These drug products can't be filled under "normal" aseptic conditions, however, because they are dangerous for a manufacturing team.

Bioserv invested in custom-made isolators when cytotoxic drugs including ADC can be manually

filled. Overall, our manufacturing team can fill as many as 2,000 vials per shift.

Although we don't have a lyophilizer for high-potency drugs, we work closely with each client to offer them solution for high-potency compounds fill.

PL: What key strategic recommendations would you provide to biotech companies immersed in early-phase clinical trials as far as drug product manufacturing is concerned?

MT: The main objective is to address process development challenges and plan ahead your manufacturing schedule in context of clinical trials.

Many times, our client are not aware that just batch record writing and overall set up can take at least two months. Moreover, some clients need to perform engineering run/pilot run to address specific technical issues during manufacturing process.

Release testing may also take a while.

Clients must also remember that as successful manufacturing facilities, Bioserv may not be available right away. Overall, we suggest that our clients should be diligent about their process, address potential pitfalls, and have timeline and schedule ahead of their manufacturing and testing activities. We recommend planning manufacturing for Phase 1/2 clinical trials 8-10 months in advance.

PL: Biotech companies must document manufacturing quality aspects of their drug substances and products in the CMC sections of the IND (United States) and IMPD (Europe). What is your advice to build solid CMC documentation? Are there any differences in terms of demands and strictness between US and EU regulators when assessing the manufacturing quality of a compound?

MT: Bioserv is currently registered with the United States Food and Drug Administration (U.S. FDA)

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for both Pharmaceutical and Medical Device manufacturing. The FDA Drug Center has inspected our facility for routine inspections. The FDA Device Centers have performed inspections of the facility for routine inspections and for pre- and post-market approval. Bioserv is currently licensed by the State of California for Pharmaceutical and Medical Device manufacturing, and for interstate commerce.

Bioserv is also ISO 13485:2016 Certified (FM 77429). Although the scope of Bioserv's ISO Certification is limited to Medical Devices at this time, Bioserv's one (1) Quality System is suitable for both Medical Devices and Pharmaceutical production. The Company also produces sterile products compliant for use in the EU.

Overall, Bioserv has a strong quality assurance group that is familiar with difference between Europe and US regulatory requirements.

We work closely with our customers to address their specific needs. For example, our contracts include free auditing of our facilities. We also welcome and performed QP audits for European customers.

As I mentioned, Bioserv is EU compliant and qualified to manufacture drug products for clinical trials in Europe. Previously, we implemented needed changes to our facilities and follow regulatory guidelines needed for European clinical trials.

In general, Bioserv can provide all the requirement documents and certifications needed for proper CMC documentation.

PL: What current trends are you observing in the drug product manufacturing industry? What drug manufacturing innovations will be gaining popularity in the years ahead?

MT: Obviously, Covid-19 pandemic has a strong impact on pharmaceutical industry. Many of

our customers focus on treatment and vaccine development for coronavirus.

Nevertheless, we still see many drug products with indications in oncology, ophthalmology and other medical conditions.

We believe that biologics such as mAbs will continue to grow in popularity, especially due to approval of cancer immuno-therapies Keytruda and Opdivo. With more personalized approach in medical treatment, different antibodies/biologics can tackle a variety of cancers.

Overall, there are more niche therapies coming to market that require smaller quantities of individual biotherapeutics.

In addition, the cost of production of such biologics is significantly lower due to single-use technologies, which will also continue to be used more in the marketplace. Therefore, with more mAbs/biologics in development, more fill/finish services will be required.

In addition, cell and gene therapy sector is also expanding. With more regulatory approvals, we believe that more customers may need live cell fill/finish and Bioserv has already experience in this niche.

In general, with more technological advancement, we will see unique formulations and manufacturing processes that require customized approach. Bioserv is definitely the right choice for future drug product manufacturing.

PL: Marianna Tcherpakov, thanks a lot for this great conversation. I appreciate your time and valuable thoughts.

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For further information about drug product manufacturing and fill/finish services, please contact us at: info@sofpromed.com