Article

Steriles

Matching manufacturing controls to the needs of early injectable development

Balancing microbiological quality with process flexibility

The early development of injectable drug products presents a practical challenge. Teams need material for non-clinical studies while formulations and manufacturing processes may still be evolving. At the same time, the material must meet predefined quality requirements without restricting the flexibility to adjust formulations, optimize processes and produce additional batches as the program progresses.

For injectable products used exclusively in non-clinical toxicology studies, this does not necessarily require the full pharmaceutical quality system applied to clinical Good Manufacturing Practice (GMP) batches. It does, however, require a clear understanding of the product- and process-specific risks at this stage and the controls needed during early development.

Microbiological quality is a key consideration in this context. Maintaining it depends on controls that address potential sources of contamination throughout the manufacturing process, while preserving the adaptability needed during early development.

Start with intended use and risk

The appropriate level of control should reflect how the material will be used. GMP manufacturing provides the comprehensive quality system required for drug products intended for clinical use. For batches dedicated exclusively to non-clinical toxicology studies, however, controls can be tailored to the specific risks associated with the product, manufacturing process, and study requirements.

A GMP pharmaceutical quality system encompasses far more than the manufacturing operation itself, including formal quality oversight, documentation, change control, deviation management, personnel qualification and batch disposition. Those requirements are essential when GMP applies.

For non-clinical toxicology batches, the emphasis can instead be placed on identifying the risks specific to the material and process and determining how best to manage them. Once these risks have been assessed, appropriate controls can be applied throughout the manufacturing process. Microbiological quality does not depend on finished-product testing alone. It is influenced throughout the manufacturing process by equipment and process design, material preparation, product pathways, filtration, the manufacturing environment and operator interaction.

The practical question, then, is: *Which controls are necessary to manage those risks effectively for the material being produced?*

At the Thermo Fisher Scientific Formulation and Analytical Development Laboratory in Monza, Italy, that question is addressed through a non-GMP manufacturing approach for injectable toxicology batches. The approach combines science- and risk-based contamination controls, minimized operator intervention, automated filling technology, and microbiological testing appropriate to the product and its purpose.

Build microbiological quality into the process

The key priority is to understand where contamination risk can arise and to incorporate appropriate controls throughout the manufacturing process. That means looking beyond the filling operation itself.

Potential sources of contamination can be assessed across the manufacturing workflow, from material and equipment preparation through product transfer, filtration, filling, stoppering and finished-product handling. Appropriate controls can then be selected based on the product and process characteristics, as well as the potential for contamination at each step.

At the Monza laboratory, these measures include closed product pathways, sterile single-use assemblies, controlled preparation of materials and equipment, and sterilizing-grade filtration immediately before filling. Critical fill-finish operations are also conducted under unidirectional laminar airflow to further minimize the potential for contamination.

Operator interaction is another important consideration. Because personnel can be a significant source of contamination during injectable manufacturing, process design plays an important role alongside environmental controls in minimizing contamination risk.

Where possible, operator-dependent activities can be concentrated in equipment preparation, system setup and verification before processing begins. Once the product pathway is assembled, automated filling and stoppering can minimize manual intervention during critical operations while improving process consistency.

The effectiveness of these preventive controls then needs to be demonstrated. Appropriate environmental monitoring and finished-product microbiological testing, including bioburden, bacterial endotoxins and, when appropriate, sterility testing, provide evidence that predefined requirements have been met.

Microbiological control, however, is only one consideration. Early development can involve products with widely differing characteristics and processing requirements, making flexibility an important part of the manufacturing approach.

Planning a toxicology batch

A fit-for-purpose manufacturing strategy starts with the specific needs and risks of the program. Key considerations include:

Product characteristics

Which formulation properties could affect manufacturing or product quality?

Contamination risk

Where could microbial contamination arise across the manufacturing process?

Operator intervention

Where can manual interaction be minimized during critical operations?

Process relevance

Can the setup reflect the planned GMP process where this would support later development?

Testing and verification

What process and microbiological testing is appropriate to demonstrate that predefined requirements have been met?

Adapt the approach to the product

At the Monza laboratory, a common manufacturing framework has been adapted across multiple vial-filling campaigns involving monoclonal antibodies, small interfering RNA and lipid nanoparticles, including solutions, suspensions, freeze-dried products and colloidal dispersions.

One project illustrates the importance of this flexibility particularly well.

The product was a high-concentration monoclonal antibody suspension consisting of protein nanoparticles dispersed in a lipid-based vehicle. With a protein concentration of 500 mg/mL and a viscosity above 100 cP, the formulation presented processing considerations that extended beyond microbiological control. Its heterogeneous particle distribution and tendency to segregate made maintaining suspension homogeneity throughout transfer and filling critical to dose consistency.

The laboratory-scale process was also designed to reflect the planned GMP manufacturing configuration.

The bulk product was supplied in a stirred stainless-steel tank and transferred through a sterile single-use line to an intermediate filling vessel. The transfer configuration was designed to replicate the planned GMP setup, including a 122-cm transfer tube routed through a peristaltic pump. Continuous mixing in both vessels helped limit sedimentation and preserve suspension homogeneity throughout filling.

Once the filling system was prepared and assembled, filling and stoppering proceeded automatically with minimal operator intervention under unidirectional airflow protection. Process parameters were optimized to promote consistent and reproducible filling performance.

The next step was to determine whether this approach could achieve the required process performance while maintaining microbiological quality.

Assessing process and microbiological performance

The campaign produced 1,000 finished units. Filling weight was assessed at the beginning, middle and end of the filling process, with all measurements remaining within the predefined alert limits of target weight ±2%.

Finished-product testing showed a bioburden of 0 CFU/10 mL and bacterial endotoxin levels below 0.01 EU/mg, meeting the predefined acceptance criteria for the toxicology batch.

Together, these results demonstrate that the approach could accommodate a technically challenging formulation while meeting predefined process and microbiological requirements. They also illustrate how controls tailored to product- and process-specific risks can support the manufacture of non-GMP toxicology batches with defined quality requirements

The broader implication is that rigor in early development does not require applying the same manufacturing framework at every stage. Rather, it comes from aligning the level of control with the purpose of the material and the specific risks that need to be managed.

Match the manufacturing approach to the development need

For injectable toxicology batches, the objective should not be to reproduce GMP manufacturing before it is required. At the same time, a non-GMP approach should not mean accepting unnecessary risks to product quality. The objective is to understand the intended use of the material, identify the risks that matter and establish controls appropriate to those risks.

Applied effectively, this approach gives development teams the flexibility to work with evolving formulations and processes while generating material that meets predefined requirements for non-clinical use. When appropriate, the manufacturing setup can also reflect the future GMP process, allowing knowledge gained during early development to inform subsequent stages.

The key question, then, is not simply whether a batch is manufactured under a GMP or non-GMP environment, but whether the manufacturing approach and controls are appropriate for the product, the process, and the requirements of that stage of development.

Making that distinction early helps focus controls where they are most relevant while building the process knowledge needed to support later development and the eventual transition to GMP manufacturing.

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