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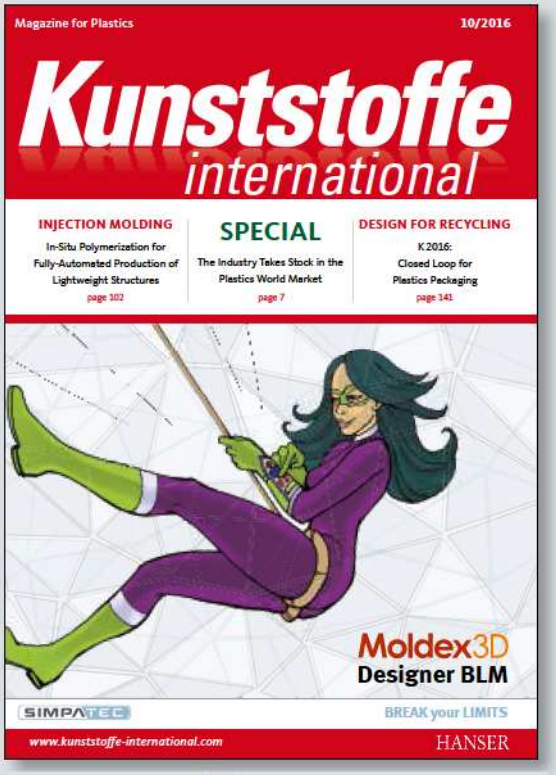
GMP and Cleanroom Packaging to Protect against Contamination



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Clean or Uncontaminated Packaging?

GMP and Cleanroom Packaging to Protect against Contamination

The quality standards and regulatory requirements for pharmaceutical and medical technology products keep getting stricter. While packaging is intended to protect them, it represents a risk to product quality if it is produced subject to lower quality standards than the product being packaged.

Cleanroom production [1, 2] has become standard when it comes to meeting strict cleanliness and hygiene requirements. This applies in particular to the pharmaceuticals, medical technology, life science, and health care industries but increasingly also to technology sectors such as optics, sensor systems, lasers, automotive, aerospace, and electronics.

Especially in the pharmaceutical/medical technology sector, these high quality standards for all structural and process elements are comprehensively described in the GMP (good manufacturing practices) guideline [3]. One can actually speak of a GMP mega-trend in these industries and here, packaging is an issue raised all along the line – often at the same level as raw and primary materials: "Just as much attention should be paid to the purchasing, handling, and inspection of primary and printed packaging materials as base materials" [3].

Against this background it is little wonder that packaging in these industries is often subject to the same quality standards as raw materials. Packaging materials usually have to be used directly in the GMP production environment. The packaging is brought into GMP departments where it is used and stored. Usually it also comes into direct contact with product surfaces as well as process surfaces such as work tables, fixtures, and tools. Last but not least, personnel is in direct contact with the materials. In summary, packaging thereby constitutes a relevant product quality factor. This means it is essential for packaging to be GMP-compliant and suitable for cleanrooms. That is why the VDI Directive 2083 [4] defines requirements for cleanroom compatible packaging materials. In addition to the GMP guidelines, there are numerous regulations for GMP-compliant process design such as DIN 15378 (primary packaging for pharmaceutical products), DIN 15593 (hygiene management in the production of food packaging), the ISO 14644 series of standards for cleanrooms and, with regards to product quality, the European Pharmacopoeia / U.S. Pharmacopeial Convention (USP) as well as volume 19, part 1 and 2 on technical cleanliness published by the VDA.

Plastic Packaging in the Cleanroom Process Chain

The products manufactured in these industries require end-to-end quality monitoring. This applies to pharmaceutical active ingredients and substances just as much as to plastic components like implants, instruments, pumps, hoses, and much more. Products need to be packaged before leaving the cleanroom to ensure they are not damaged or contaminated during handling and transportation. Plastic packaging (films, sleeves, bags) is used for this purpose (**Fig. 1**) [5, 6]. Film packaging is used in every stage along the cleanroom supply chain – from the active substance manufacturer to the component and assembly manufacturer

Fig. 1. Cleanroom packaging: Pharmaglas (left) or plastic bags (center), cleanroom film for implants (right) (© Strubl)

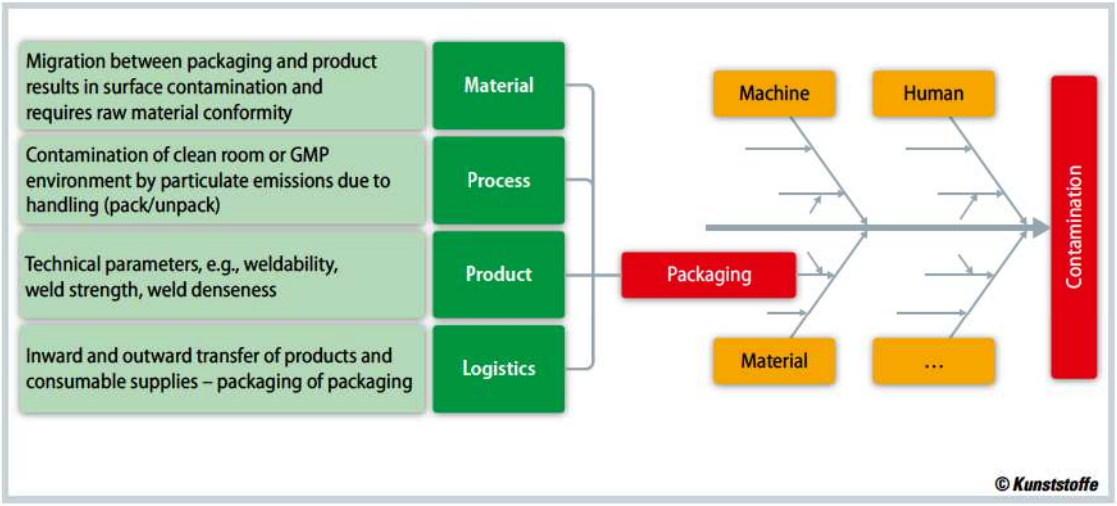

Fig. 2. Risk analysis: Contamination by packaging is possible through the raw material, handling process, technical product parameters, and logistics (source: Strubl)

to packaging partners and service providers. This means film packaging always has the status of "primary packaging" from the perspective of the respective product, and speaking of a "cleanroom process chain" across companies is more than justified [7]. Packaging serves the key purpose at all levels of protecting the product quality of all components and assemblies equally and preventing contamination.

Contamination Risks of Plastic Packaging

Risk management has become a basic element of responsible and foresighted management in many fields today. That is why risk management tools are gaining more and more attention in the aforementioned standards as well as DIN ISO 9001. At its core it is about the active and preventive avoidance of risks. This can be achieved through interdisciplinary teams that systematically investigate the respective root causes of risks and initiate preventive and corrective actions to eliminate them [8, 9].

A risk analysis of packaging materials is certain to identify the following problems (**Fig. 2**): Risks associated with packaging raw materials, the product quality of the packaging, but also process, handling, and logistics risks related to using packaging in a cleanroom or GMP environment. These risks must be assessed for the entire cleanroom supply chain. Here a crucial criterion is that the packaging materials used have to correspond to the same quality and hygiene standards as the packaged product. Therefore, packaging suitable for cleanrooms is essential in the pharmaceuticals/medical products' sector.

The Fraunhofer Institute for Manufacturing Engineering and Automation in Stuttgart, Germany, Cleanroom and Microproduction department, has developed a practical procedure for evaluating cleanroom compatibility that is now used for cleanroom materials and consumables in many segments [10]. The requirements for cleanroom compatible packaging materials according to VDI Directive 2083 Sheet 9.2 [3] were defined using this as a basis. Packaging manufacturers have to set up an adequate production system in a complex, organizational development process in order to meet the requirements.

Fig. 3. Cleanroom production for manufacturing cleanroom packaging (© Strubl)

GMP Culture as a Learning Process

A fundamental redesign of organizational processes in the entire product creation value stream modeled after the pharmaceutical industry, making all employees and processes the object of GMP design, is required here. Attempts to implement GMP only in production are bound to fail due to the GMP focus on processes, since interfaces as well as upstream and downstream processes always have to be considered equally. While the GMP guidelines define relevant requirements for the product and process, they do not specify one best way. A company-specific GMP system has to be developed instead, harmonizing product and process requirements with the quality and GMP/cleanroom requirements of the customers.

Good manufacturing practices begin in the minds of employees: Only when their daily work is GMP-compliant can the system consistently produce the required quality. Since well-rehearsed behaviors have to be discarded or changed, accomplishing this can sometimes be a protracted process. This process therefore

has the nature of company-wide learning [11] and requires extensive leadership, coaching, and communication [12]. Examples include transferring into the cleanroom area, hand hygiene, documentation and preparing quality-related records, production data capture (batch records), making handwritten corrections on production paperwork, and also the intensity of quality control and documentation, which goes far beyond the common ISO 9001 requirements. A selection of important methods and concepts can help support this development process:

- Installation of cleanroom production with zone and lock concepts as well as hygiene management according to the normative requirements of ISO 14644 (**Fig. 3**).
- Monitoring and audits: Audits, especially those conducted by customers, make a major contribution to process improvement. Audit reports generally contain qualified observations, often classified and/or assessed according to three levels (critical, major, and minor), indicating the urgency of improvement measures.
- The Capa concept (corrective and preventive actions) is intended for the permanent improvement of the system. Here all activities and decisions are documented and monitored (organizational learning [12]).
- Training programs for employees are essential for the life of a GMP system. Lasting changes in behaviors and attitudes can only be accomplished through training and instruction in practical processes.
- The validation and qualification of processes and systems leads to reproducible process security, especially where the verification of quality criteria is only possible through destructive testing.
- Coaching by external experts is often an expedient way to overcome resistance to change and barriers to implementation in particular (**Fig. 4**).

Conclusion

Packaging for pharmaceutical and medical technology products must meet the highest standards with regards to cleanliness, hygiene, GMP requirements, and cleanroom compatibility [5, 6], because the strict requirements for cleanroom production processes also apply to the packaging that is used. A product produced in the cleanroom must be packaged to protect it from contamination and so it can be processed through the logistics chain with no impairment of its high quality. Finally, the packaging being used must not contaminate the cleanroom process. Cleanroom packaging is the right solution here. The qualitative and regulatory requirements for the process to manufacture packaging suitable for cleanrooms are extremely strict. Cleanroom production according to ISO 14644 and consistent process design based on the GMP guidelines of the pharmaceutical industry are essential. ■

Fig. 4. Employees as a key factor: Qualification and a GMP culture are essential for high quality
(© Strubl)

Company Profile

Strubl GmbH & Co. KG Kunststoffverpackungen, Wendelstein, Germany, developed and steadily expanded its business area for "cleanroom packaging to protect against contamination". Today it supplies companies in the pharmaceuticals' industry and medical technology sector across Europe. The products (films and bags) are used both as primary and as secondary packaging.

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References & Digital Version

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