Englisch translation of the German original publication

"Joint Assessment of Occupational Safety and GMP Aspects"

A new chapter for the current ISPE D/A/CH Containment Manual – Part 1[1)]

Richard Denk[1], Martin Pernau[2], Dr. Reinhold Maeck[3], Dr. Hartmut F. Zimmermann[3], Dr. Gabriele Schönberger[4], Dr. Andreas Flückiger[5], Markus Rückert[6], Daniela Kovats[7], Jessica Redmer[8]

[1]SKAN AG, Allschwil, Switzerland, [2]Bayer AG, Leverkusen, Germany, [3]Boehringer Ingelheim GmbH, Ingelheim am Rhein, Germany, [4]ZS.CTIS Consulting GmbH, Harxheim, Germany, [5]F. Hoffmann-La Roche AG, Basel, Switzerland, [6]Pharma Containment Solutions, Edingen-Neckarhausen, Germany, [7]Excella GmbH & Co. KG, Feucht, Germany, [8]Greenpower, Kerkrade, Netherlands

The ISPE DACH Community of Practice (CoP) Containment was founded in 2008 during the ISPE DACH Containment Workshop. It currently comprises 19 members from a range of fields including pharmaceutical and API manufacturing, service providers and process equipment manufacturers. In addition to planning an annual technical discussion on a given topic, the CoP has also spent the last few years producing a document on the subject of containment. The resulting Containment Manual was published in November 2015, and almost 500 copies have been sold to date. Based on the high level of demand from non-German-speaking countries, the document has also been translated into English.

The Containment Manual

The concept of containment is understood in different ways by different people. The original idea of creating a glossary of key terms evolved into a Containment Manual in which all aspects of the manufacture of highly active hazardous substances could be examined.

The Containment Manual has 10 chapters and describes the fundamental considerations, the critical points in the various manufacturing processes and equipment, primary and secondary containment and the issues of occupational hygiene/industrial hygiene validation, cleaning/waste treatment and personnel. The focus of the manual is on occupational safety.

Following the introduction, the chapter entitled "Fundamental Considerations" explains both the general concept of containment and the specific terms of primary and secondary containment. This chapter also contains details of how the ADE (Acceptable Daily Exposure) and OEL (Occupational Exposure Limit) are derived and used to define the threshold values in the system design process. Regulatory and legal requirements are also mentioned, and basic concepts introduced. Subsequent chapters deal with the subjects of "Risk Assessment" and the "Life-Cycle of Containment Solutions", which stretches from commissioning through maintenance and repair and ends with decommissioning. This is followed by the "Process Requirements" chapter, which is divided into pharmaceutical and API manufacturing, and "Technical Systems". Both chapters describe the possible process systems and their functions. These chapters also refer to the critical points in the process systems where containment concerns can arise, as well as possible technical containment systems as flexible compensation. The first part of the "Technical Systems" chapter describes the currently most popular primary containment systems and their possible applications, while the second part deals with secondary containment systems such as rooms and airlocks, and the third focuses on dust removal/filter technology.

The manual is concluded with the "Occupational Hygiene/Industrial Hygiene Validation", "Cleaning/Waste Treatment" and "Personnel" chapters.

A New Chapter for the Containment Manual

The decision to add a new chapter was triggered by a variety of factors. Containment influences GMP with regard to additional areas and interfaces to be cleaned, for example, and GMP, for its part, has an impact on containment through the pressure level in the working area, for example. Risk assessments that consider the aspects of GMP and occupational safety must be carried out: can (or even must) these assessments be carried out jointly? A further factor is the EMA's new "Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities". Based on the current relevance of this guideline, the authors have decided to publish the

1) ISPE D/A/CH Community of Practice Containment; *https://ispe-dach.org/die-ispe-dach-arbeitsgruppen-2/regional-cop-containment/*

additional final chapter to the current ISPE Containment Manual in advance, with a view to making it accessible to a wider audience.

Correspondence:
Richard Denk
SKAN AG
Head Sales Containment
Binningerstr. 116
4123 Allschwil (Switzerland)
e-mail: richard.denk@skan.ch

Appendix 1: The new chapter of the current ISPE D/A/CH Containment Manual, entitled "Joint Assessment of Occupational Safety and GMP Aspects".

Joint Assessment of Occupational Safety and GMP Aspects

Authors:
Richard Denk SKAN AG
Martin Pernau Bayer AG
Dr. Reinhold Maeck Boehringer Ingelheim GmbH
Dr. Hartmut Zimmermann Boehringer Ingelheim GmbH
Dr. Gabriele Schönberger ZS CTIS Consulting GmbH
Dr. Andreas Flueckiger F. Hoffmann-La Roche AG
Markus Rueckert Pharma Containment Solutions
Daniela Kovats Excella GmbH & Co. KG
Jessica Redmer Greenpower

Product protection (GMP) and occupational safety (containment) are both extremely important in the field of pharmaceutical manufacture, and the two "opposing" perspectives must be reconciled. Risk analyses are essential on both sides.

In work involving highly active substances, toxicological data also serve as a basis for cleaning and exposure threshold values. Exposure measurements can be used to estimate cross-contamination (*EU Guidelines to Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use, Part I, Chapter 5: Production*) [3].

The following chapter takes a joint look at the shared and varying regulatory and organizational aspects of GMP and occupational safety.

1. What are the regulatory requirements / issues to be considered with regard to GMP, and in comparison with occupational safety?

The necessity, scope and quality of containment in the manufacture of APIs and pharmaceuticals is an important issue that is not determined by occupational safety aspects alone. Aspects of good manufacturing practice (GMP) must also be considered, and the focus here is on patient safety, which must be ensured by means of product quality. This is in turn ensured by aspects such as contamination control, i.e. minimizing the risk of contamination of any kind (particulate, microbiological, chemical) by means of structural, system/process-based and operational measures.

Regardless of the product, the focus here is on preventing particles from being carried in or occurring as a result of the process, and on reducing cross-contamination, i.e. contamination of one product by another. The primary focus in the manufacture of sterile products is on avoiding microbiological contamination, while at the same time bearing in mind the issues of cross-contamination and occupational safety.

The aspect of microbiological contamination often plays an essential role in the containment decision for a manufacturing process, particularly as the use of containment is implied from a regulatory perspective for sterile production in Annex 1 (Chapter Containment Technology 21) [2]. The discussion of regulatory requirements with regard to GMP and the comparison with occupational safety therefore focus on the issue of cross-contamination when it comes to containment, as the technological measures demanded of the pharmaceutical manufacture in this context are not directly defined.

Against this backdrop and in view of the need to take into account all aspects, from occupational safety to protection against microbiological contamination, containment is now often the preferred solution. The major advantage in the use of containment is that the surrounding room itself is not contaminated. This not only reduces the risk of airborne cross-contamination, but also the mechanical contamination risk, e.g. via staff or mechanical equipment (see Chapter 5.21 EMA GMP guidelines) [3]. It is important to point out, however, that this does not automatically resolve the issue of cross-contamination. In addition to human error, the greatest risk continues to be contamination due to unclean surfaces with direct product contact. The additional barrier of containment can also make cleaning, during product change for example, significantly more difficult. Modern CIP systems take this aspect into account, however.

The significant advantages of containment lie in the restriction of intake air volumes, separation of people

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and product, and in the possibility of separating exhaust air systems from the product.

The varying aspects of occupational safety on the one hand and GMP (cross-contamination) on the other are presented in Table 1.

When it comes to discussing regulatory requirements in concrete terms: it is appropriate to refer first to internationally recognized regulations.

The ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) has approved a series of "Harmonised Tripartite Guidelines" [4] that are equally valid in the European Union, the USA and Japan following implementation in national law. Q7, the "Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients" [5] issued in 2000, stipulates that *"appropriate measures should be established and implemented to prevent cross-contamination from personnel, materials."* The Containment section, however, also calls for dedicated production areas for *"highly sensitising materials." "Dedicated production areas ... should be considered for ... high pharmacological activity or [if] toxicity is involved ... unless validated inactivation and/or cleaning procedures are established and maintained ..."*

Quality risk management is described in general in ICH Q9 "Quality Risk Management" [6]. The two ICH guidelines are included in Part II and as an annex to the EU GMP guidelines.

From an international perspective, the requirements placed on cleanrooms and room classes are described extensively in the ISO 14644 [7] standards. It is important to note that these ISO standards are even mentioned explicitly at several points in Annex 1 of the EU GMP guidelines (Sterile Production) [2], thereby providing them with direct regulatory relevance. This annex, however, also refers in general to ISO EN standards involving the identification of microbiological and cleanroom contamination with particles, etc., which should also be taken into account.

This also applies to other key standards and regulations. The ISPE, as a professional association, is an important stakeholder in this area. The ISPE Baseline Guides should therefore be used as a reference in the planning of GMP facilities, as they generally reflect the state of the art in terms of technology.

For production facilities used to manufacture more than one product, the ISPE Baseline Guide "Risk-Based Manufacture of Pharmaceutical Products" (Risk-MaPP) [8] provides a scientific risk-based approach. This approach is based on ICH Q9 "Quality Risk Management" [6], to managing the risk of cross-contami-

■ **Table 1**

A comparison of the aspects of occupational safety and GMP.

	Occupational safety/hygiene	**Good manufacturing practice (GMP) Focus on contamination control**
Target group	Production staff	Patients*
Primary protection goal	Protection of the environment against substances released	Protection of the product against contamination from the environment
Type of exposure or dosage form of the product	for the worker: • inhaled • dermal • (oral**)	for the patient* depending on the dosage form • oral • parenteral • inhaled
Timing of exposure to substance/ contamination	during work/production	during administration/treatment
Assumptions regarding duration of exposure/intake of product	Entire working life, every working day, 8-hour shifts	Daily dose/lifelong treatment with the product
Threshold value for substance/ contamination	Concentration in room air (OEL, proportionate to PDE (inhaled))	Level of contamination in the daily dose of a medicinal product (PDE (oral, parenteral***))

*This refers to the ultimate protection goal – the primary protection goal is to protect the pharmaceutical product against contamination (microbial, another API, etc.).
**In the event of poor hygiene and hand-to-mouth contact
***The relevant factor is the route of administration of the contaminated product.

nation in order to achieve and maintain an appropriate balance between product quality and operator safety.

The ISPE Baseline Guide Volume 3, "Sterile Product Manufacturing Facilities", Second Edition Sept 2011 [9], is extremely important in the context of sterile products. This applies not only to products exported to the USA, but also in general as a reference document for the FDA guideline for sterile products (FDA Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing) [10].

Regulatory requirements concerning GMP and cross-contamination in Europe are defined for the most part in EU GMP Part 1 for medicinal products and Part 2 for active substances [3]. Significant changes have been made since 2014 with regard to the requirements for preventing cross-contamination (see Table 2). Particularly important in the containment discussion are Part 1, Chapter 3 (premises and equipment and their potential for reducing cross-contamination) and 5 (production), as well as Annex 15 [11], for medicinal products, and additionally Annex 1 for aseptic production. Part 2 is relevant for API manufacture. Assessment of premises and equipment and their potential for reducing cross-contamination is specified in Chapter 3. Chapter 5 deals in turn with the subject of production, with section 5.21 illustrating various technical and organizational measures for reducing the risk of cross-contamination. With the new revised version of Annex 15, it is now compulsory to carry out a toxicological assessment based on *"... setting health based limits"* (see Annex 15). This step leads to "carry-over" assessments, which are to be carried

Table 2

Relevant regulations.

	Manufacture of active ingredients			**Manufacture of pharmaceutical products**
	ICH Harmonized Tripartite Guideline	Commission Delegated Regulation (EU) No. 1252/2014 of 28 May 2014 supplementing Directive 2001/83/EC of the European Parliament and of the Council with regard to principles and guidelines of good manufacturing practice for active substances for medicinal products for human use	Volume 4 of "The rules governing medicinal products in the European Union" contains guidance for the interpretation of the principles and guidelines of good manufacturing practices for medicinal products for human and veterinary use laid down in Commission Directives 91/356/EEC, as amended by Directive 2003/94/EC, and 91/412/EEC respectively.	
Contamination control (including respective risk assessments)	ICH Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients (November 2000)	• Article 5 Buildings and facilities • Article 9 Production and in-process control	• Part II – Basic Requirements for Active Substances used as Starting Materials (August 2014)	• Part I, Chapter 3 Premise and Equipment (revised, August 2014) • **Part I, Chapter 5 Production** (revised, August 2014) • **Annex 1 Manufacture of Sterile Medicinal Products** (November 2008, currently under revision)
Cleaning validation				• **Annex 15 Qualification and Validation** (revised, March 2015)
	EMA, Committees			
Definition of PDE values	Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities (20 November 2014) EMA/CHMP/CVMP/SWP/169430/2012			
	ICH Harmonized Tripartite Guideline			
Quality risk management (in general)	ICH Q9 Quality Risk Management (November 2005)			

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out by means of a concrete derivation from a PDE value. Please refer to the *"Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities",* which explains how PDE values are defined.

All of the regulations quoted require that the corresponding risk analyses be carried out. This also applies to API manufacture (see "Commission Delegated Regulation (EU) No 1252/2014" [12]). A risk assessment is compulsory here, as is its documentation in written form.

The special requirements placed on aseptic production are summarized in Annex 1, which contains a definition of the requirements of cleanroom classes A to D.

Table 2 contains a summary of the EU GMP regulations mentioned.

Documented risk assessments must be carried out by the manufacturer in accordance with these regulatory requirements, and must be based on scientific and toxicological data. These assessments make it possible to carry out, evaluate and carefully weigh up GMP and occupational safety assessments.

Containment offers the advantage of limiting, in a highly effective manner, the contamination within a small defined space (i.e. the interior of the process equipment that comes into contact with the product) and separating people from the product in this way. This often enables both GMP and occupational safety targets to be achieved directly.

Two examples of the results of this weighing up in terms of the direction of positive pressure on an isolator are shown in Table 3. In the one example it is the aspect of occupational safety that has priority, while in the other it is the aspect of product safety. The level of protection offered by an isolator is already extremely high, and enables it to cover both aspects safely in these cases.

While the case is not always quite so clear-cut, however, it is nevertheless legally required to take all aspects into account as appropriate, in order to ensure the protection of both the employee and the patient. In such complex cases it can be necessary, for example, to use a sterile isolator with an additional level of protection. For such cases there are additional filter technologies available before the return air ducts, various pressure cascades with a sink to the critical area, as well as active mouseholes at open interfaces. With sterile production in particular, product safety is often the dominating aspect. These additional protective measures and regular occupational hygiene monitoring can also enable work on highly active substances to be carried out in the isolator in positive pressure, without staff having to wear personal protective equipment.

When it comes to the toxicological assessment, absorption via the lungs is generally the key aspect with regard to occupational safety. The route of administration of the potentially cross-contaminated product is the determining factor. In the manufacture of active ingredients, an orally administered drug can be followed by one intended for parenteral administration. In such a situation, a parenteral PDE must be available or derived for the oral product. It is key to take the critical route of exposure and the daily dose into account.

The starting point for threshold value calculation is very similar as for the occupational exposure limits (OELs) with regard to occupational safety. The EMA Guideline [1] mentioned includes an explanation of how a "health based exposure limit" can be determined.

As these "health based exposure limits" in the manufacture of medicinal products for human use must be limits for humans, data gathered directly from humans, i.e. clinical data, are particularly relevant.

When animal testing data are used for calculation, the no observed effect level (NOEL) of the most relevant study is found. This is generally expressed in mg/kg bodyweight, making it important to adjust in line with the bodyweight of a human. In accordance with the EMA, a standard weight of 50 kg is used, and the result is then corrected using the corresponding "adjustment factors" F1 to F5.

Table 3

Sample isolator assessment.

	Occupational safety has priority	Product safety has priority
Examples of the results of a joint risk assessment (in one case the aspects of occupational safety have priority, in the other GMP)	Work with a non-sterile highly active substance in an isolator.	Work with a sterile but non-hazardous substance in an isolator.
	In order to protect the environment, this substance should ideally be handled in an isolator in negative pressure.	The isolator should be operated in positive pressure in order to ensure sterility.

PDE = NO(A)EL * weight adjustment (50 kg) / F1*F2*F3*F4*F5

By way of explanation:

- F1: Factor for differences between animals and humans (inter-species variation)
- F2: Factor for differences between humans (intra-species variation)
- F3: Factor to correct data from an insufficiently long period of application (short study duration)
- F4: Factor for the severity of the effect (e.g. deformities, severe organ damage, cancer)
- F5: Correction factor when the starting point for the calculation is not a NO(A)EL

This formula is mentioned in exactly this form in the EMA Guideline [1], and is also identical to the formula typically used in occupational safety. If the same studies with different routes of administration (e.g. oral and intravenous) are available, the NOELs may vary. The adjustment factors are determined by the quality of the starting point of the calculation. The closer this starting point is to the definition of the PDE (i.e. threshold value for humans, lifelong exposure, protective for the most sensitive), the lower the cumulative adjustment factor *(Note: The terms "safety factors" and "adjustment factors" are often used interchangeably here, as is the case with PDE and ADE. The EMA Guideline [1] refers to PDE values and adjustment factors).*

As a rule, the PDE is first calculated for the route of absorption for which the best data are available, and the PDEs for the other routes are subsequently derived from this best-documented value.

The PDE value plays an important role both in cleaning validation and when it comes to determining the threshold value for transfer from one product to the next. The adjustment factors applied in the calculation must be determined by a toxicologist and an appropriate team of experts. The PDE relevant for the route of absorption of the subsequent product must be used in cleaning validation. If this route is not (yet) known, the most conservative PDE should be used (generally the parenteral PDE).

Maximal permissible contamination of the product:

$$MK_F\ [\mu g/g] \approx \frac{\text{PDE } [\mu g]}{\text{Dose}_{\text{Following Product [g]}}}$$

With regard to occupational safety, on the other hand, the focus is on possible airborne exposure while working. In this case, therefore, the PDE value concerns the employee and the inhalation route of exposure. This PDE (inhalation route and focusing on the employee) must then be converted into an OEL, and a working day of 8 hours with a respiratory volume of 10 m^3 is generally used as a basis.

Occupational exposure limit:

$OEL\ [\mu g/m^3] = PDE_{(inhalation)}\ [\mu g/d] / 10\ [m^3/d]$

A direct comparison of the two formulae underlines how close occupational safety and patient safety actually are, despite all of the differences mentioned.

2. Does a joint risk assessment for GMP and occupational safety make sense?

Documented risk assessments must be carried out by the manufacturer in accordance with the regulatory requirements quoted in the first section, and must be based on scientific and toxicological data.

With a view to answering the question as to whether a joint or separate risk assessment should be carried out for occupational safety and GMP, the first step is to clarify what is required, and various different constellations are possible:

– GMP and occupational safety (e.g. toxic product in a single or multi-product facility)
– No GMP, but occupational safety (e.g. treatment of toxic waste)
– GMP, but low occupational safety requirements (e.g. manufacture of substances with high OELs)

Ultimately, every risk assessment involves evaluating manufacturing equipment and processes, including interfaces, with regard to function and protective mechanisms, and then deciding how much containment needs be built around the actual manufacturing equipment. The answers to be found as part of this process can be divided into the following categories:

– Process-specific
– Product-specific
– Quality-specific
– Occupational safety-specific

During the risk identification process – with the aid of a fishbone diagram, for example – the risks to be taken into account can be highlighted in order to determine whether they should be attributed to occupational safety and/or GMP.

A risk assessment must always be carried out in a team-based approach, and suggestions for the composition of risk assessment teams can be found in Table 4.

In view of the fact that the composition of the two teams is almost identical, it makes sense when both GMP and occupational safety aspects are to be considered to carry out the risk assessment with a combined team. The benefits of this approach are that the flow of information is improved, more information can be taken into account, and different perspectives and experience can be exploited. The increased effort may be seen as a disadvantage, however.

The decision as to whether the risk assessment report is to be produced as a single document or two

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■ **Table 4**

Occupational safety and GMP team composition.

Occupational safety	GMP
Project manager	Project manager
Production/manufacturing area	Production/manufacturing area
Toxicologist	Quality assurance
Additional experts, e.g. engineering, safety	Additional experts, e.g. engineering, safety

separate ones can depend on the requirements of the relevant regional authorities and operational structures within the company. One effective approach is to label the identified risks as relevant to either GMP or occupational safety.

The recommendation, therefore, is to carry out a joint risk assessment when both occupational safety and GMP aspects are to be considered, or alternatively to document the two separately if appropriate.

"Joint Assessment of Occupational Safety and GMP Aspects"

A new chapter for the current ISPE D/A/CH Containment Manual[1)] – Part 2*)

Richard Denk[1], Martin Pernau[2], Dr. Reinhold Maeck[3], Dr. Hartmut F. Zimmermann[3], Dr. Gabriele Schönberger[4], Dr. Andreas Flückiger[5], Markus Rückert[6], Daniela Kovats[7], Jessica Redmer[8]

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3. Technical Measures for Compliance with GMP and Containment Requirements

Containment systems are used to provide active protection for personnel during the manufacture of a pharmaceutical product. Depending on their design and application, they can have an influence on the manufacturing process. From a GMP perspective, such influences can include additional intervention in the process, extra cleaning due to additional integrated containment systems and an increased risk of cross-contamination due to the use of these systems. Especially when it comes to a PDE (permitted daily exposure) in the low microgram or nanogram range, it is advisable to carry out a joint analysis of containment and GMP requirements with a view to excluding possible GMP risks.

In the case of a very low PDE, connectors, seals, fastening systems, filter connections and the various containment systems with product transfer are considered critical as they all have areas where the smallest product particles can adhere or be deposited.

With isolators, the barrier (housing, excluding gloves) has only indirect contact with the product. Isolators serve to contain dust pollution within a small defined space, and are usually easier to clean than it is to clean the whole room in the case of open handling.

However, mechanical influences or airflows can also lead to product deposits on surfaces without direct product contact and result in cross-contamination. Please refer to Chapter 5 of the EU-GMP guideline [1] in this context.

Possible GMP risks:

- Additional surfaces, gloves and seals on isolators or containment transfer systems, rapid transfer ports or split butterfly valves can lead to contact contamination of the product on surfaces, and should therefore be subject to cleaning validation or replacement on product change.
- Filter change and resulting possible re-contamination of product
- Foreign particles in the product due to damaged surfaces or seals
- Difficulty in accessing the manufacturing process and cleaning surfaces
- Changes to external conditions such as temperature, humidity, air flows
- Changes to cleaning method

Containment systems are commonly made up of various components and procedures that combine to provide effective personal protection. Three examples of containment systems and the possible associated GMP influences are described below.

a) Isolators operated in negative pressure to protect personnel and the environment against contamination (Table 5)

Example of a possible technical solution for preventing contamination of gloves and glass panel seals:

- Glove shoulder rings are secured by means of an additional mechanical seal on the glove sleeve, thereby preventing product dust from being deposited at the point where the glove is attached to the isolator. The glass panel is connected to the isolator housing using a pneumatic seal with a hygienic design.

1)ISPE D/A/CH Community of Practice Containment; *https://ispe-dach.org/die-ispe-dach-arbeitsgruppen-2/regional-cop-containment/*

*)See Pharm. Ind. 2017;79(4):492–498 for Part 1.

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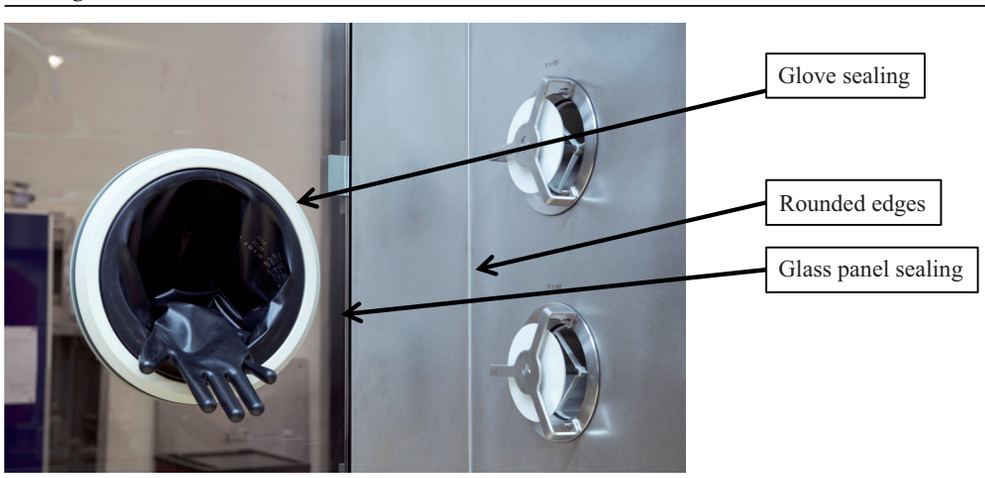
■ **Table 5**

Isolators operated in negative pressure to protect personnel and the environment against contamination.

Component/method for personal protection	Possible GMP influence	Possible solutions
Negative pressure in the isolator	• Absorption of contaminated external air and contamination of the product in the isolator	• Filtration of inlet air according to the relevant specifications • Absorption of inlet air from an environment with the required air quality • Positioning of the isolator in an environment with the required air quality • Leak test before processing the product in the isolator
Isolator housing as a barrier between the highly active product and the environment	• Additional surfaces and more complex cleaning processes • Cross-contamination with previous product and microbiological contamination	• WIP/CIP of the interior surfaces of the isolator (Fig. 1) • Automated cleaning process and cleaning validation (Fig. 1) • Decontamination of the isolator interior using hydrogen peroxide (H_2O_2) • High surface quality with no damage (e.g. scratches) • Optimal design of surfaces for cleaning, e.g. rounded corners and good accessibility (Fig. 1)
Gloves	• Absorption of contaminated external air and contamination of the product in the isolator in the event of a leak • An inadequate seal between the glove and the shoulder ring can result in concealed product deposits • Product migration into glove material	• Leak test of gloves and glove seats before processing the product in the isolator • GMP-compliant glove seal at shoulder rings in order to prevent product deposits on the glove seals • Dedicated gloves, or change of gloves on product change
Glass panel seals	• Absorption in of contaminated external air and contamination of the product in the isolator in the event of a leak • Inadequate glass panel seals resulting in product deposits in difficult-to-access areas that may release quantities of highly active product when the glass panels are opened	• Use of low-dead-space pneumatic seals • Continuous monitoring of seals for possible loss of pressure
Endless liner	• Absorption in of contaminated external air and contamination of the product in the isolator in the event of a leak	• Leak test before processing the product in the isolator • Exchange of liner on product change • Visual inspection of endless liner film for damage • Use of tight film sealing systems
RTP	• Absorption in of contaminated external air and contamination of the product in the isolator in the event of a leaking connection	• Leak test before processing the product in the isolator • Maintenance or regular exchange of seals
Dust removal filter systems	• Possible re-contamination on filter change due to transfer of particles from the contaminated filter to the new one	• Testing of function and tight seal • Do not insert the new filter until the contaminated one has been removed and the filter seat has been cleaned (Fig. 3–8)

■ **Figure 1**



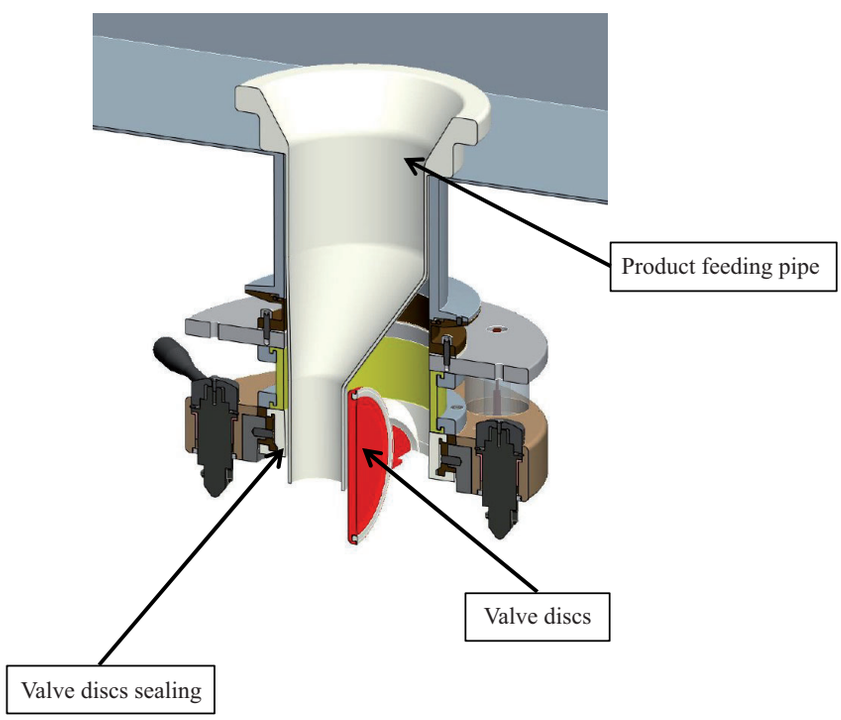
Isolator.

Table 6

Split butterfly valve systems.

Component/method for personal protection	Possible GMP influence	Possible solutions
Seals	• Incorrect fitting of seals • Surface tears on seals due to repeated opening and closing of the valve disc	• Avoidance of possible contact with the product, e.g. via a product feeding pipe inserted between the seal and the valve disc (Fig. 2) • Regular maintenance and definition of exchange intervals
Valve surface	• Wear and tear on surface due to mechanical influences as a result of use and cleaning	• Avoidance of possible contact by the product being processed, e.g. via a product feeding pipe inserted around the open valve discs (Fig. 2) • Regular maintenance and definition of exchange intervals

Figure 2



Product feeding pipe to protect the seal and discs from product deposits.

b) Split butterfly valve systems (Table 6)
Example of a possible technical solution for preventing contamination of the seal and the disc:

- The product feeding pipe is inserted once the disc has been opened, thereby preventing the highly active substance from coming into contact with the valve seal and disc. This measure also increases the level of containment.

c) Exhaust air/return air filter systems (Table 7)
Example of a possible technical solution (FIPA system) for preventing contamination of a new exhaust air filter:

- The filter system is connected to the isolator wall (barrier) with a dust-proof bayonet mount, with the individual filter elements directed into the exhaust air/return air duct (Fig. 4) in order to concentrate the exhaust air/return air flow.
- Once the manufacturing process in the isolator is complete, the filter air inlet (contaminated area) (Fig. 5) can be sealed from the exterior (non-contaminated area) in a dust-tight manner (Fig. 6).
- The isolator is wetted and cleaned from the inside until it can be opened with no risk.

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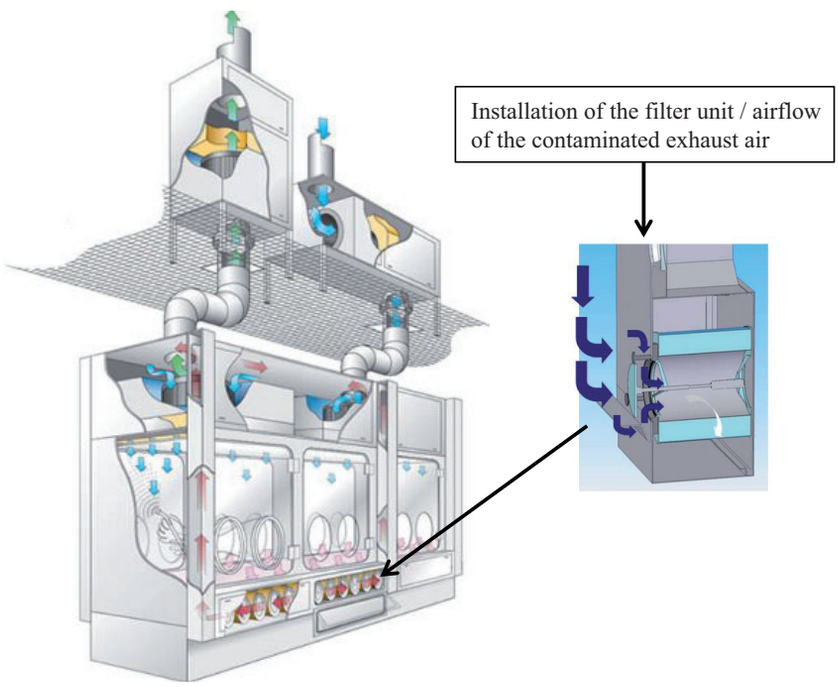
Table 7

Exhaust air/return air filter systems#

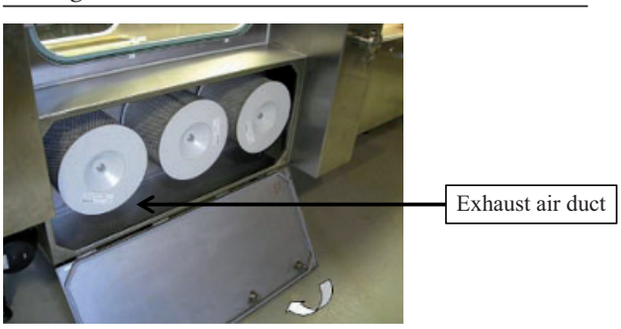
Component/method for personal protection	Possible GMP influence	Possible solutions
Filter seat seal	• Tight fit of filter not properly tested, and product deposits on critical surfaces that are difficult to clean on product change	• Filter technologies with containment docking adapter for preventing product deposits in critical areas (Fig. 3–8)
Filter change	• Product particles may become detached from the contaminated filter and contaminate the new one when the filter is changed	• Avoiding a filter change in which the new filter can come into contact with the contaminated one (Fig. 3–8)

Figure 3



Isolator with FIPA filter elements.

Figure 4



Exhaust air duct with filter elements.

Figure 5

Filter cover plate from the inside (contaminated).

Figure 6

Sealing mechanism from the outside (non-contaminated).

Figure 7

Disconnecting the filter element.

Figure 8

Removing the filter element.

- The closed filters remain dry within the interior, and can be opened and used again in the case of campaign manufacturing, for example.
- The closed filters can be disconnected with a twist, removed with no risk of contamination and sealed in a plastic bag for added safety.
- Depending on the intended use, filter elements can be stored and used again for a specific product or discarded.

4. Using Occupational Hygiene Threshold Values for Evaluating Possible Cross-Contamination (Mechanical and Airborne Transfer)

Using Containment Data in a GMP Context

Preventing cross-contamination is an important concern in GMP. Contamination of products with foreign APIs or excipients, for example, can create risks for any patient taking or being administered a drug contaminated in this way.

The key causes of cross-contamination are:

- mix-up of materials,
- excessive quantities of the previous product remaining within an item of equipment subsequently used to manufacture another product and
- airborne contamination by another product (e.g. via ventilation systems) or contamination by mechanical transfer, e.g. due to contaminated clothing or contaminated objects that come into contact with the product.

The risk of such cross-contamination must be evaluated via the appropriate risk analysis processes, e.g. as per ICH Q9, in order to determine the necessary risk management measures, such as:

- organizational measures for avoiding human error,
- cleaning validation in multi-product facilities to minimize carryover due to contaminated shared product contact surfaces and
- segregation of facilities and rooms by means of structural or organizational measures (e.g. doors, airlocks, separate and/or filter-equipped room ventilation systems, pressure gradients between rooms, compulsory change of clothing).

Organizational measures aimed at preventing human error and cleaning validation are both well established, whereas segregation measures are more controversial. In the past, the segregation discussion has focused primarily on secondary containment measures, i.e. how it is possible to prevent material released in the production room from spreading.

Only recently have GMP guidelines begun explicitly taking into account the fact that the risk of airborne contamination or contamination by mechanical transfer is not only influenced by secondary containment but also, or even much more so, by the quality of the primary containment. If the product remains within the equipment, it cannot escape and cannot be spread in the air or via mechanical transfer. When it comes to preventing airborne contamination or contamination by mechanical transfer, therefore, primary and secondary containment must both be taken into account. If a facility offers compliant primary containment, it may be possible for secondary containment measures to be less stringent. If processes are "much too open", however, even very good secondary containment may be insufficient to reliably prevent carryover.

This observation is included in Chapter 5.21 of the EU GMP guidelines published in 2014, which contains a total of 23 technical and organizational measures

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that a company can invoke as evidence for having cross-contamination risks under control.

Organizational measure (iv) reads as follows:

"Depending on the contamination risk, verification of cleaning of non product contact surfaces and monitoring of air within the manufacturing area and/or adjoining areas in order to demonstrate effectiveness of control measures against airborne contamination or contamination by mechanical transfer [.]"

This is in essence a suggestion to review primary containment, and it reflects the observation that protection of the workers from overexposure by technical means is also beneficial in terms of GMP.

Many companies have carried out air measurements in manufacturing areas and adjoining areas as part of their evaluations of workplace exposure. Several of them also carried out swab tests during the same measurement campaigns (ISPE Good Practice Guide "Assessing the Particulate Containment Performance of Pharmaceutical Equipment" (Second Edition)).

In principle, it should also be possible to use these data collected for occupational hygiene purposes in a GMP context. However, in this new context, interpreting the measurement results is very challenging.

- What does it mean for the risk of cross-contamination of Product A, which is manufactured in Room A, when an air concentration of Product B of for example 10 $\mu g/m^3$ is measured in the neighbouring Room B?
- What does it mean, expressed in terms of the cross-contamination risk for the next product to be manufactured in the same room, when for example 1 $\mu g/cm^2$ of the previous product is still present on the walls and floor?
- What does it mean when for example 0.5 $\mu g/m^3$ of a product is measured in the air of a "clean corridor", where it has drifted from an adjoining production room?

The contamination measured must be seen in the context of the corresponding PDEs, i.e. the more critical the substance, the lower its PDE, and hence the tolerable contamination of air and non-product contact surfaces.

Furthermore, a product is increasingly at risk the longer it is exposed to a potentially contaminated environment during the manufacturing process. The risk of airborne contamination or contamination by mechanical transfer is lower when the product is contained within a closed facility and nothing can penetrate from the environment.

Various factors therefore need to be taken into account during risk analysis, and when interpreting the measurement results, e.g.:

- Potency of the contaminant (expressed as a PDE)
- Maximum therapeutic dose of the recipient of the cross-contamination
- Length of time the recipient of the cross-contamination is exposed to the atmosphere of the production room
- Existing filter systems and pressure gradients when evaluating airborne cross-contamination
- In the event of accidental contamination, the question as to whether the contamination would be distributed throughout the entire batch and therefore be diluted, or whether everything would be found in one or a small number of individual doses of the recipient product.
- The extent to which contaminants could become detached from non-product contact surfaces and contaminate the next product

The valid GMP regulations stipulate that APIs and medicinal products must be manufactured with consistent quality and under consistent conditions – batch for batch, dose for dose. Deviations are accepted only within narrow limits.

Occupational hygiene is a different matter. Upset conditions can occur, and there are measures in place for dealing with them. A plastic bag can tear, a vacuum transfer line can become blocked and may need to be opened up, or intervention in an otherwise closed manufacturing process may be required. Were exposure values to be measured during such situations, they would be significantly higher than under routine conditions. Air measurements cannot be made in the event of an accident, as they need to be prepared carefully and cannot be organized from one minute to the next; swab tests are possible, but not necessarily conclusive.

Not only are accidents associated with unusually high exposure levels, therefore, but these levels are also extremely difficult to quantify.

What does GMP do with such "outlier data"?

- Was the entire production now "out of specification" because the exposure data could not be complied with?
- Do products manufactured in the adjoining room as the incident occurred have to be destroyed because the previously measured normal conditions were not respected?
- Which sampling cassettes should be used for air measurements? The sampling cassettes commonly used in occupational hygiene are particle-size-selective, i.e. they measure particulate matter as it is inhaled by humans. However, this particle-size-selectivity is not relevant in a GMP context.
- Where exactly are measurements to be carried out?
- Should dry or wet swab tests be performed?
- How must the measuring methods have been validated, and how sensitive do they have to be?

- What are the requirements for the analytical laboratory?

These are examples of questions that need to be answered when swab samples are taken from non-product contact parts, or air measurements are carried out in manufacturing areas and adjoining areas, in order to then use the results as GMP data.

Extensive evaluation of scenarios involving air contamination and contamination of non-product-contact surfaces show that the risks for the patient that may arise as a result of airborne transfer or contamination by mechanical transfer are generally extremely low. The hypothetical worst-case scenario – that the entire substance content of many m^3 of room air can penetrate a batch or even an individual dose of another substance – can almost always be excluded. It is equally unlikely that the entire substance still remaining in many m^2 of visually clean surfaces can find its way into a batch of another product. This is, however, the only form of cross-contamination that would exceed the PDE of the contaminant in a daily dose of the product concerned.

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Correspondence:
Richard Denk
SKAN AG
Head Sales Containment
Binningerstr. 116
4123 Allschwil (Switzerland)
e-mail: richard.denk@skan.ch

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