Aseptic transfer of RTU containers in light of the new Annex 1

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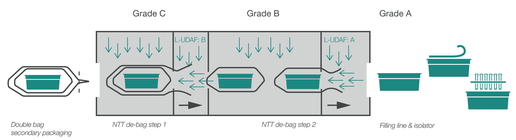
No-Touch-Transfer (NTT)



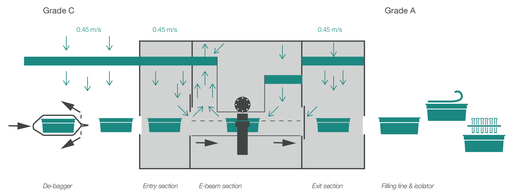
Operating principle:
Removal of wrapping (bag) between different cleanroom zones. A pressure cascade between the cleanroom zones ensures an overflow of clean air.
Prerequisite is that the cleaner part (1st bag and 2nd tub) is not exposed to the lower grade environment. Therefore, the handover between zones happens at the mouse-hole. The transfer goes from C to B to A.

Sterility principle:
The RTU containers are supplied pre-sterilised with ethylene oxide (ETO) or steam by the packaging material supplier in a double bag configuration. Prerequisite is the assumption that sterility is maintained inside the bags throughout the complete supply chain.

Validation principle:
The validation is based on the environmental monitoring (total particles and viables) that classifies the different cleanroom zones that the tub passes through. In addition to the environmental monitoring, a pressure cascade needs to be maintained at the mouseholes to ensure an overflow of grade A air from the higher, i.e. cleaner, cleanroom grade. The pressure cascade needs to be validated by smoke studies showing that there is no ingress or reversal of the airflow as the tub approaches the mousehole.

Pros	Cons
Fewer utilities required	Waste material management at the point of component introduction
No residuals from a decontamination cycle	Inspection required of primary packaging suppliers of to ensure sterility and quality of secondary and tertiary packaging of components
High-speed processing is possible	Possibly higher costs for additional containment and second de-bagger

E-Beam sterilisation



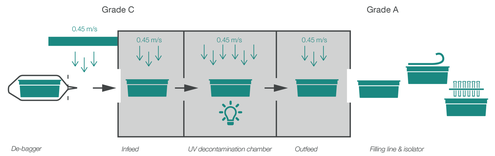
Operating principle:
Removal of wrapping (bag) prior to introduction of the tub into the infeed section under laminar air flow. Sterilisation of the tub in the closed e-beam section by β-electron beams applied by, for example, three electron emitters arranged in a triangular shape. A HEPA-filtered airflow is maintained in the sterilisation chamber to extract any residuals such as ozone that are generated during sterilisation. After the process is finished, the tub enters the out-feed and finally the grade A zone.

Sterility principle:
The RTU containers are supplied pre-sterilised with ethylene oxide (ETO) or steam by the packaging material supplier in a single bag design. By using ionised radiation, the cell DNA is damaged, which leads to the destruction of the cell. The energetic electrons destroy all types of pathogens like viruses, fungi, bacteria, parasites and spores with the ability to emit energy onto complex surfaces and around minor contours.

Validation principle:
The validation is based on the ISO 11137 “Sterilisation of health care products – Radiation”, method 2, which sets the required sterilisation dose at 25 kGy. This value needs to be applied and verified. Verification is done using calibrated film dosimeters to confirm that the correct dose has been applied. Another way to define the sterilisation dose is to determine the average bioburden. This can be done by using a D-value determination with H2O2 (ISO 11137 “Sterilisation of health care products – Radiation”, method 1).

Pros	Cons
Easy-to-validate process, ability to demonstrate a clear 6-log reduction in resistant micro-organisms	Risk of free radicals and/or ozone residuals
Simplified contamination control strategy through in-line decontamination management	In-line decontamination process increases line complexity and may impact building construction
Grade transfer from C to A	Radiation protection required to ensure personnel are protected from radiation
High-speed processing is possible	Requires personal protection and health and safety officers for the process

UV-light surface decontamination



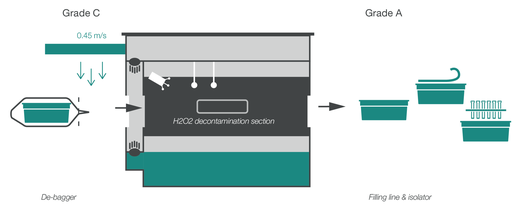
Operating principle:
Removal of wrapping (bag) prior to introduction of the tub into the infeed section under laminar air flow. Decontamination of the tub in the closed pulsed light section by short duration emissions (300 micro-seconds per flash) of intense, broad-spectrum white light (between 200 and 1100 nm, with 15% UV-C, 50% visible and 35% near IR) from a xenon lamp to sterilise surfaces. After the process is finished, the tub enters the outfeed and finally the grade A zone.

Sterility principle:
The RTU containers are supplied pre-sterilised with ethylene oxide (ETO) or steam by the packaging material supplier in a single bag design. By using UV light flashes, especially in the UV-C range (100 - 280 nm) of the spectrum, the microorganisms change their molecular configuration and the covalent bonds break. The reason for this is absorption spectrum of DNA and proteins, which lies between 200 and 300 nm. There are two ways of destroying microorganisms 1) photothermal effect (temperature increase until explosion) and 2) photochemical effect (alteration of DNA and proteins).

Validation principle:
The validation process is based on biological indicators (BI). The BIs have a known bioburden, which is prepared with a special spray inoculation of spores. Important is that the BIs have only a monolayer of spores due to the shadowing effect of the pulsed light. The number of flashes needed for a 6-log reduction is determined by removing the BIs consecutively until the desired reduction rate is achieved.

Pros	Cons
No residuals	4-log reduction with conventional BIs (new way of validation with spray inoculation to achieve 6-log)
Simple technology compared to other decontamination processes	High-speed processing is not yet possible
Small footprint, especially suitable for small batch application	Shadowing effect has to be considered
Grade transfer from C to A	

H2O2 surface decontamination



Operating principle:
Removal of wrapping (bag) prior to introduction of the tub into the infeed section under laminar air flow. Transfer of the tub into the H2O2 chamber. Conditioning of the chamber to required temperature and humidity. Introduction of VPHP or H2O2 fog into the chamber. After defined dwell time the chamber is aerated to a certain level of residual H2O2 (e.g., 1 ppm). After aeration, transfer of the tub into the grade A zone.

Sterility principle:
The RTU containers are supplied pre-sterilised with ethylene oxide (ETO) or steam by the packaging material supplier in a double bag design. The biocidal effect of hydrogen peroxide results from its high oxidising capacity and leads to rapid effectiveness against most microorganisms due to the formation of free radicals. The denaturation leads to inhibition of metabolism and ultimately to the death of the microorganism.

Validation principle:
The validation process is based on biological indicators (BI). The BIs have a known bioburden that needs to be reduced to at least 6-log by H2O2. To determine the amount of H2O2 and the holding time, the D value calculation is used. To determine the D value, the BIs (3 BIs at each position) are placed inside the transfer chamber and extracted in specific sequence to find the correct process parameters.

Pros	Cons
Easy-to-validate process, ability to demonstrate a clear 6-log reduction in resistant micro-organisms	Risk of H2O2 residuals and outgassing of polymer components
Simplified contamination control strategy through in-line decontamination management	High-speed processing is not yet possible
Grade transfer from C to A	Protection of operators from H2O2 (limit is 1 ppm exposure)
Ideal for small batch applications	

Regulatory view (EudraLex - Volume 4 - Annex 1)

4.10 The transfer of equipment and materials into and out of the cleanrooms and critical zones is one of the greatest potential sources of contamination. […]

4.11 The transfer of materials, equipment, and components into the grade A or B areas should be carried out via a unidirectional process. Where possible, items should be sterilised […]. Where sterilisation* upon transfer of the items is not possible, a procedure which achieves the same objective of not introducing contamination should be validated and implemented, (e.g. using an effective transfer disinfection process, rapid transfer systems for isolators […]).

8.47 Where materials, equipment, components and ancillary items are sterilised in sealed packaging and then transferred into grade A, this should be done using appropriate validated methods (for example, airlocks or pass-through hatches) with accompanying disinfection of the exterior of the sealed packaging. […] the disinfection procedure should be demonstrated to be effective in reducing any contamination on the packaging to acceptable levels for entry of the item into the grade B and grade A areas.

8.48 Where materials, equipment, components and ancillary items are sterilised in sealed packaging or containers, the packaging should be qualified for minimising the risk of particulate, microbial, endotoxin/pyrogen or chemical contamination, and for compatibility with the selected sterilisation method. The packaging sealing process should be validated. […] The integrity of the sterile protective barrier system for each of the sterilised items should be checked prior to use.

*Sterilisation: Reduction of the number of viable microorganisms to 6-log (≤ 10-6) in a product

Conclusion

There are various methods for the introduction of RTU primary packaging materials into the aseptic process zone (grade A), which include but are not limited to those mentioned above. With the new Annex 1 becoming effective, there are new respectively expanded requirements for this process step. It gives a precise description on how to introduce packaging material into the grade A environment, especially focusing on the reduction of the risk of contamination. This is reflected in various points within the Annex 1, which are also summarised on this poster.

All the methods mentioned above are valid methods for transferring material into grade A if they have been considered within the quality risk analysis and reflected within the contamination control strategy (CCS). Since the Annex 1 requires a sterilisation on transfer to grade A (or an equivalent procedure to achieve the same objective) and sterilisation is defined by a 6-log reduction, a particular focus must be given on the procedure of NTT and UV pulsed light decontamination.

The NTT requires an integrity by design approach of the packaging material in an end-to-end process to maintain the sterility inside the last/inner bag prior to the transfer to grade A. Annex 1 states that this sterility needs to be validated (e.g., supplier and shipping validation, GMP-compliant storage) and that the integrity should be checked prior to use. The last sentence of section 8.48 makes the NTT concept challenging and the validation needs to be justified with a strong rationale within the QRM.

Having a look at pulsed light decontamination, the challenge is the validation of the 6-log reduction which is needed to achieve the sterility at grade A transfer. Current methods based on standard BIs cannot validate a 6-log reduction of bioburden. Therefore, either a new validation method (e.g., spray inoculation) needs to be implemented and established, or the transfer needs be to justified with a strong rationale within the QRM.

Both the e-beam technology and the H2O2 decontamination provide real sterilisation of the packaging material before the transfer into grade A and can therefore be validated using current methods such as e.g. BIs.

Nevertheless, the e-beam technology and the NTT process are the most commonly used principles in the industry. Both have their advantages, as well as disadvantages, especially in respect to small batch processing.

In conclusion, the suitability of the transfer method needs to be evaluated with respect to the whole process and the low bioburden RTU packaging components.