efficiency to minimize the potential for cross-contamination.

The following activities performed during sterile manufacturing must be conducted in area classified in accordance with the tables below.

5.2.1.1 Terminally Sterilized Products

For those products that are sterilized in their final container/closure system the following apply:

Grade	Examples of operations for terminally sterilized products
A	Filling of products, when unusually at risk *.
C	Preparation of solutions, when unusually at risk. Filling of products.
D	Preparation of solutions and components for subsequent filling.

(*) When the product is at risk of contamination from the environment, for example because the filling operation is slow or the containers are wide-necked or are necessarily exposed for more than a few seconds before sealing.

5.2.1.2 Aseptic Preparations

For those products that cannot be sterilized in their final container/closure system the following apply:

Grade	Examples of operations for aseptic preparations
A	Aseptic preparation and filling.
C	Preparation of solutions to be filtered, crimping of vials and stoppered vials to be crimped after freeze-drying.
D	Handling of components after washing.

5.2.1.3 Isolator Technology

The use of isolator technology to minimize human interventions in processing areas may result in a significant decrease in the risk of contamination of aseptically manufactured products from the environment.

Grade	Examples of operations for isolator technology
At least D	The background environment for aseptic processing. *

(*) The air classification required for the background environment depends on the design of the isolator and its application.

5.2.1.4 Blow/fill/seal Technology

The use of blow/fill/seal technology offers a number of aseptic advantages Including minimizing the time between the sterilization of the pack (in situ, on formation) and filling and sealing. Human interventions in processing areas are

6 Appendices

Appendix A - Comparison table particles, EU GMP Annex 1, FDA Guidance for Industry "Sterile Drug Products Produced by Aseptic Processing" and ISO 14644-1.

EU GMP Annex 1					FDA		ISO 14644-1	
Grade	At rest		In operation		Description	In operation	In operation	
	Maximum permitted number of **particles/m^3** equal to or above		Maximum permitted number of **particles/m^3** equal to or above			Maximum permitted number of **particles/ m^3** equal to or above	Maximum permitted number of **particles/m^3** equal to or above	
	0,5 µm	5 µm	0,5 µm	5 µm		0,5 µm	ISO Class	0,5 µm
A	3.500	1	3.500	1	Critical	3.520	5	3.520
B	3.500	1	350.000	2.000	Supporting Clean Area	352.000	7	352.000
C	350.000	2.000	3.500.000	20.000	Supporting Clean Area	3.520.000	8	3.520.000
D	3.500.000	20.000	-	-	-	-	9	35.200.000

* - = not defined

