

Viability of microorganisms in cytotoxic and antiviral drug solutions



UNIVERSITÄTS**medizin.**

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MAINZ

Presentation outline

- Definition of microbiological stability
- Viability of microorganisms in compounded cytotoxic drug solutions
- Antimicrobial activity and assignment of expiration dates to cytotoxic drug solutions

Microbiological Stability

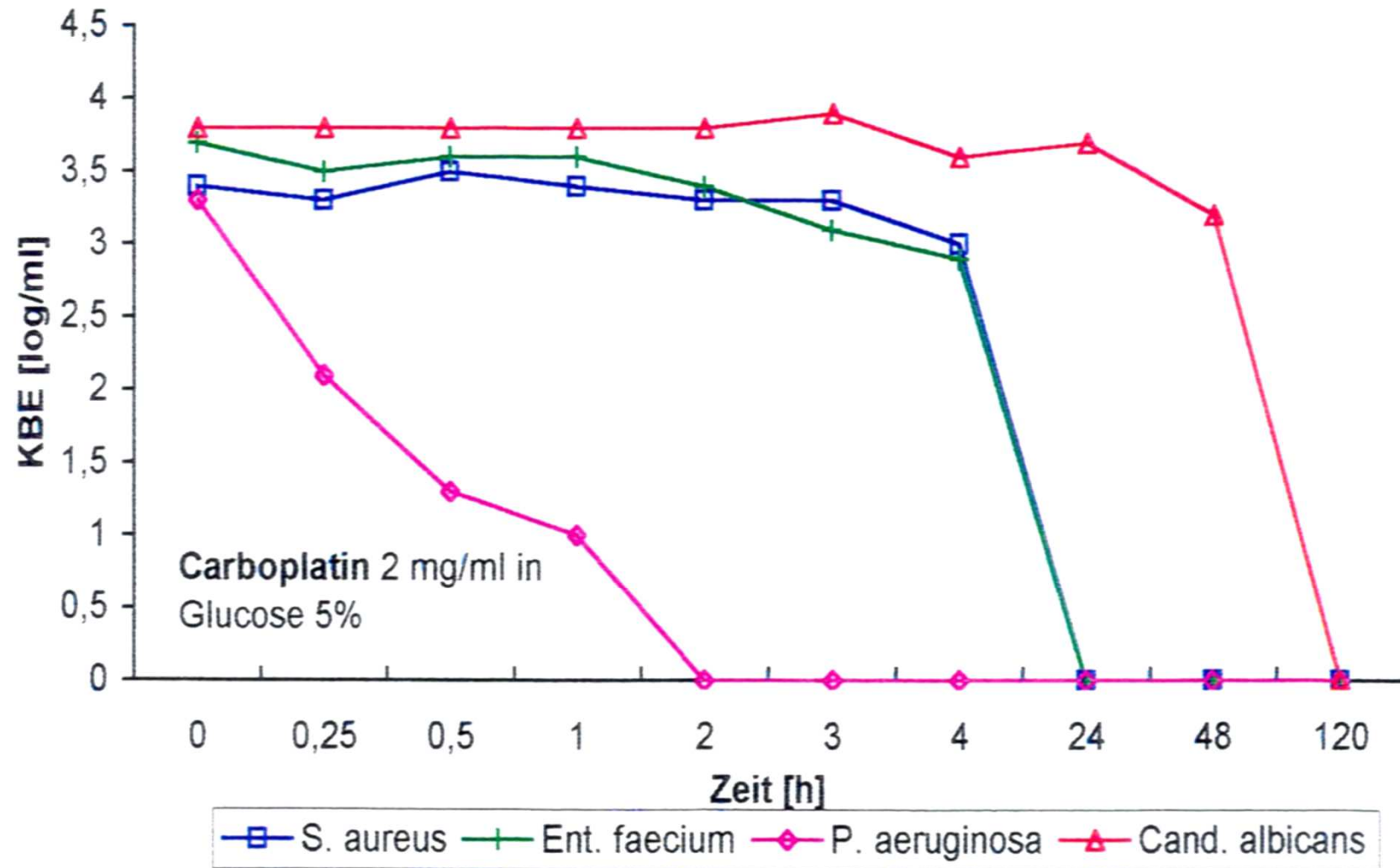
- Sterility or resistance to microbial growth
- Microbiological degradation =
contamination with microbes, microbial growth
risk to the patient's health and life
- Benchmark of contamination rate in aseptic
preparation: 0.1%

Viability of microbes in cytotoxic drug solutions

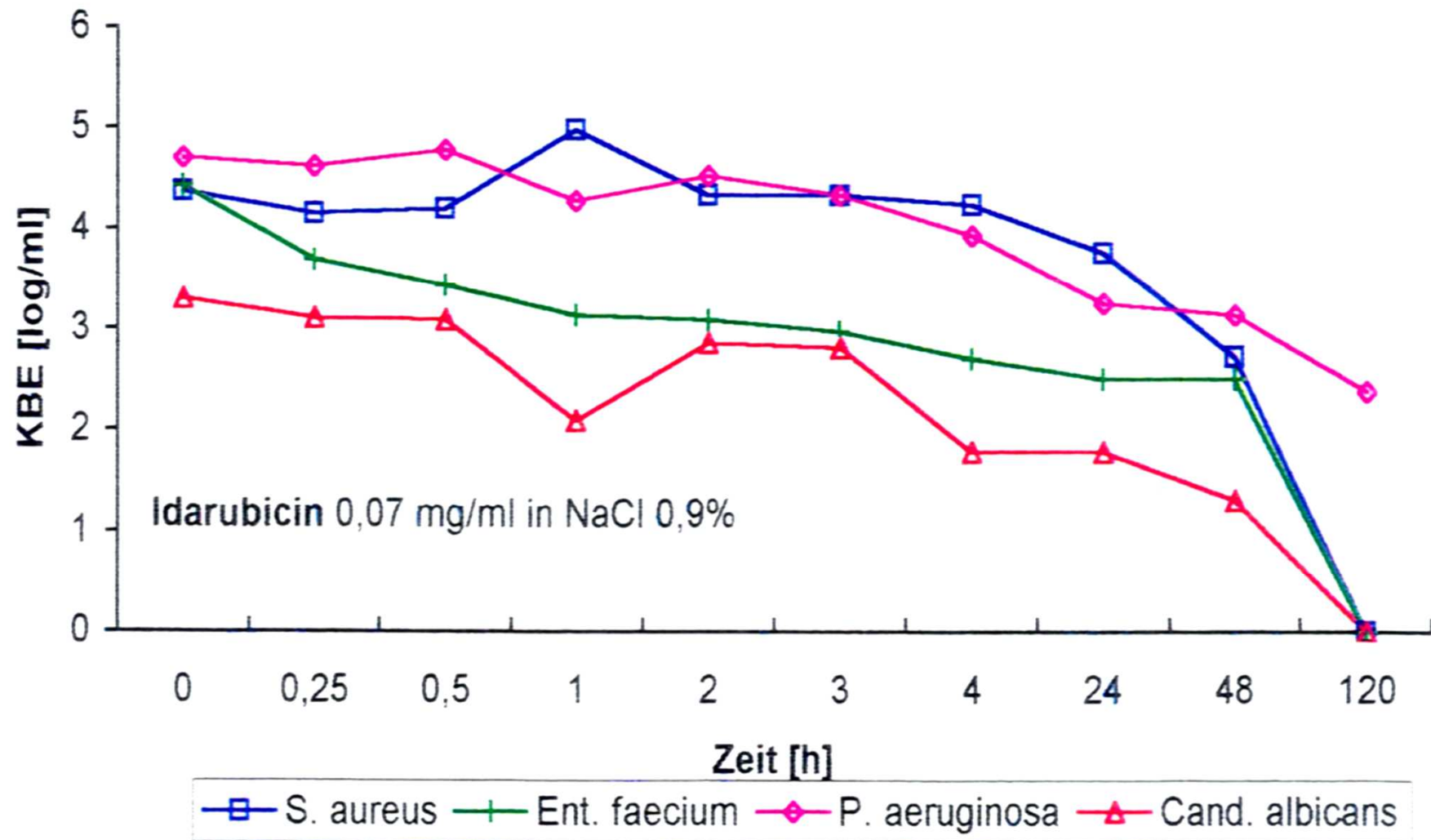
Test method

- Lowest concentrations of drug substances used in daily practice (0.9% NaCl, G5 solution)
- Selected microbes commonly associated with nosocomial infections: *S. aureus*, *E. faecium*, *P. aeruginosa*, *C. albicans*
- Low level contamination (10^4 microorganisms/mL)
- Storage at elevated temperatures (22 °C, 37 °C)

Viability of microorganisms in diluted Carboplatin Drug Solutions



Viability of microorganisms in diluted Idarubicin Drug Solutions



Viability of *C. albicans* in drug solutions (CFU log/mL)

	0 min	15 min	2 h	24 h	48 h	120 h
0.9 % NaCl solution	5.2	5.2	5.2	5.2	5.2	4.4
	5.2	5.2	5.2	5.2	5.2	4.3
5 % Dextrose solution	5.2	5.2	5.2	5.2	5.2	4.3
	5.2	5.2	5.2	5.2	5.2	4.2
Alemtuzumab	5.2	5.2	5.2	5.2	5.2	5.1
	5.2	5.2	5.2	5.2	5.2	5.1
Busulfan concentrate	5.2	3.1	0	0	0	0
Busulfan diluted	5.2	5.2	5.2	5.2	5.2	4.8
	5.2	5.2	5.2	5.2	5.2	4.8
Cetuximab	5.2	5.2	5.2	5.2	5.2	4.7
	5.2	5.2	5.2	5.2	5.2	4.8
Etoposide phosphate	5.2	5.2	5.2	5.2	5.1	2.8
	5.2	5.2	5.2	5.2	5.1	2.6
Irinotecan	5.2	5.2	5.2	5.2	5.2	4.8
	5.2	5.2	5.2	5.2	5.2	4.8
Liposomal Doxorubicin	5.2	5.2	5.2	5.2	5.2	5.2
	5.2	5.2	5.2	5.2	5.2	5.2
Sodium folinate	5.2	5.2	5.2	5.2	5.2	4.3
	5.2	5.2	5.2	5.2	5.2	4.5
Rituximab	5.2	5.2	5.2	5.2	5.2	4.7
	5.2	5.2	5.2	5.2	5.2	4.7
Streptozocin	5.2	5.2	5.2	0	0	0
	5.2	5.2	5.2	0	0	0
Trastuzumab	5.2	5.2	5.2	5.2	5.2	5.1
	5.2	5.2	5.2	5.2	5.2	5.0

Viability of *P. aeruginosa* in drug solutions (CFU log /mL)

	0 min	15 min	2 h	24 h	48 h	120 h
0.9 % NaCl solution	5.1	5.2	5.2	5.1	4.8	4.9
	5.1	5.1	5.1	5.1	4.8	4.9
5 % Dextrose solution	5.1	5.1	5.1	5.1	4.8	4.3
	5.2	5.2	5.1	5.1	4.8	4.3
Alemtuzumab	5.0	5.0	5.1	5.0	4.4	4.9
	5.0	5.0	5.1	5.1	4.8	4.8
Busulfan diluted	5.0	5.0	5.0	1.6	0	0
	5.1	5.1	5.0	0	0	0
Cetuximab	5.0	5.0	5.1	5.1	4.8	4.9
	5.1	5.1	5.1	5.1	4.8	4.9
Etoposide phosphate	5.2	5.2	5.1	5.1	4.8	4.5
	5.2	5.2	5.1	5.1	4.8	4.5
Irinotecan	5.2	5.2	5.1	5.1	4.8	4.7
	5.2	5.2	5.1	5.2	4.8	4.6
Liposomal Doxorubicin	5.2	5.2	5.1	5.1	4.9	5.0
	5.2	5.2	5.1	5.1	4.8	5.0
Sodium folinate	5.2	5.2	5.1	5.1	4.8	4.8
	5.2	5.2	5.1	5.1	4.8	4.9
Pemetrexed	5.2	5.2	5.1	5.1	4.8	4.9
	5.2	5.2	5.1	5.1	4.8	4.9
Rituximab	5.2	5.2	5.1	5.0	4.8	4.9
	5.3	5.2	5.1	5.1	4.8	4.9
Streptozocin	5.3	5.3	4.6	0	0	0
	5.2	5.2	4.6	0	0	0
Trastuzumab	5.2	5.2	5.1	5.0	4.8	4.9
	5.2	5.2	5.1	5.1	4.8	4.9

Viability of *S. aureus* in cytotoxic drug solutions (CFU log /mL)

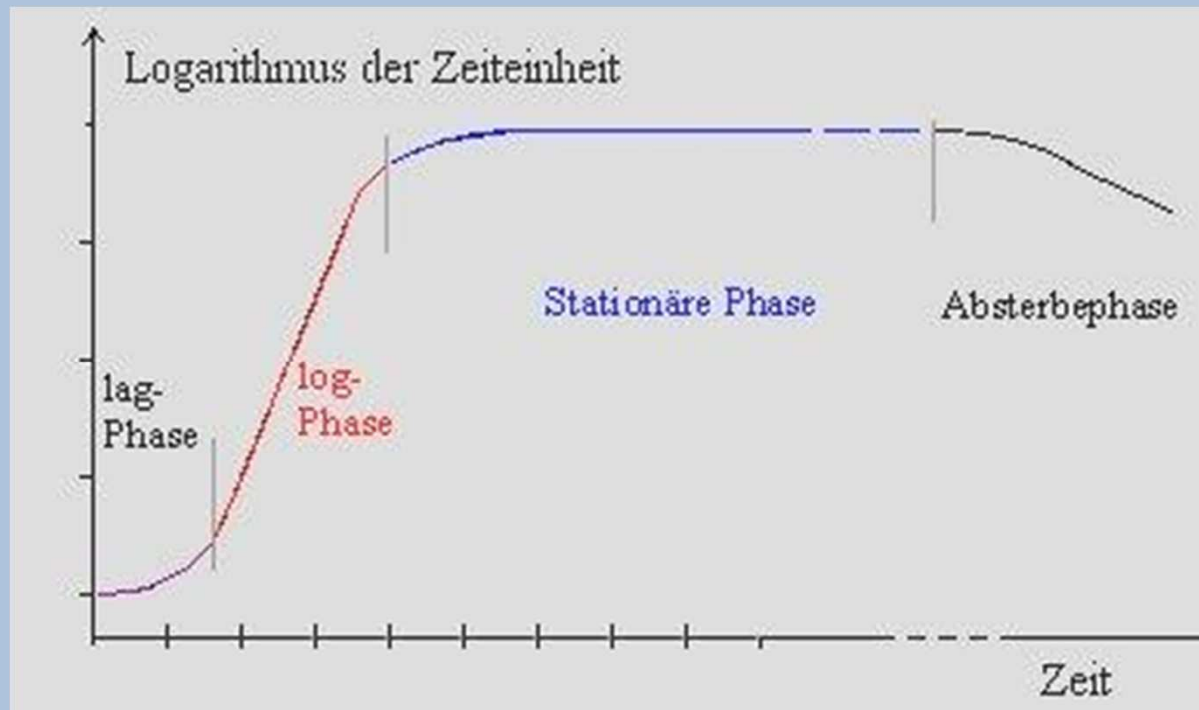
	0 min	15 min	2 h	24 h	48 h	120 h
0.9 % NaCl solution	4.7	4.8	4.8	4.7	4.6	2.4
	4.8	4.7	4.7	4.7	4.6	2.3
5 % Dextrose solution	4.8	4.8	4.7	4.7	4.6	1.8
	4.7	4.7	4.7	4.7	4.6	1.6
Alemtuzumab	4.7	4.7	4.7	4.7	4.6	2.8
	4.7	4.7	4.7	4.7	4.7	2.8
Bortezomib	4.7	4.7	4.7	4.3	4.7	1.9
Busulfan concentrate	4.7	4.4	0	0	0	0
Busulfan diluted	4.7	4.7	4.7	0	0	0
	4.7	4.7	4.7	0	0	0
Cetuximab	4.7	4.7	4.7	4.7	4.7	2.7
	4.7	4.7	4.7	4.7	4.7	2.7
Etoposide phosphate	4.7	4.7	4.7	4.7	4.7	1.3
	4.7	4.7	4.7	4.7	4.7	1.6
Irinotecan	4.8	4.7	4.7	4.7	4.7	2.6
	4.7	4.7	4.7	4.7	4.7	2.5
Liposomal Doxorubicin	4.7	4.7	4.7	4.7	4.7	2.2
	4.7	4.7	4.7	4.7	4.7	2.3
Sodium folinate	4.8	4.7	4.7	4.7	4.7	2.6
	4.8	4.8	4.7	4.7	4.7	2.5
Pemetrexed	4.7	4.8	4.7	4.7	4.6	0
	4.8	4.7	4.7	4.7	4.6	0
Rituximab	4.8	4.8	4.7	4.7	4.7	2.8
	4.7	4.7	4.7	4.7	4.7	2.6
Streptozocin	4.7	4.7	4.7	0	0	0
	4.7	4.7	4.7	0	0	0
Trastuzumab	4.7	4.7	4.7	4.7	4.6	2.6
	4.7	4.7	4.7	4.7	4.6	2.4

Antimicrobial activity of cytotoxic drug solutions

- Significant (species-specific) antibacterial activity
 - Busulfan, carboplatin, cisplatin, dacarbazine, 5-FU, oxaliplatin, streptozocin, treosulfan
- Significant antifungal activity
 - Amsacrine, Carmustine, Epirubicin, 5-FU, Mitoxantrone, Streptozocin
- **Lack of antimicrobial activity of most cytotoxic drug substances and their drug solutions**
- Missing link between antimicrobial activity and chemical structure or pharmacological principal
- Missing antimicrobial activity of solvents, surfactants, pH

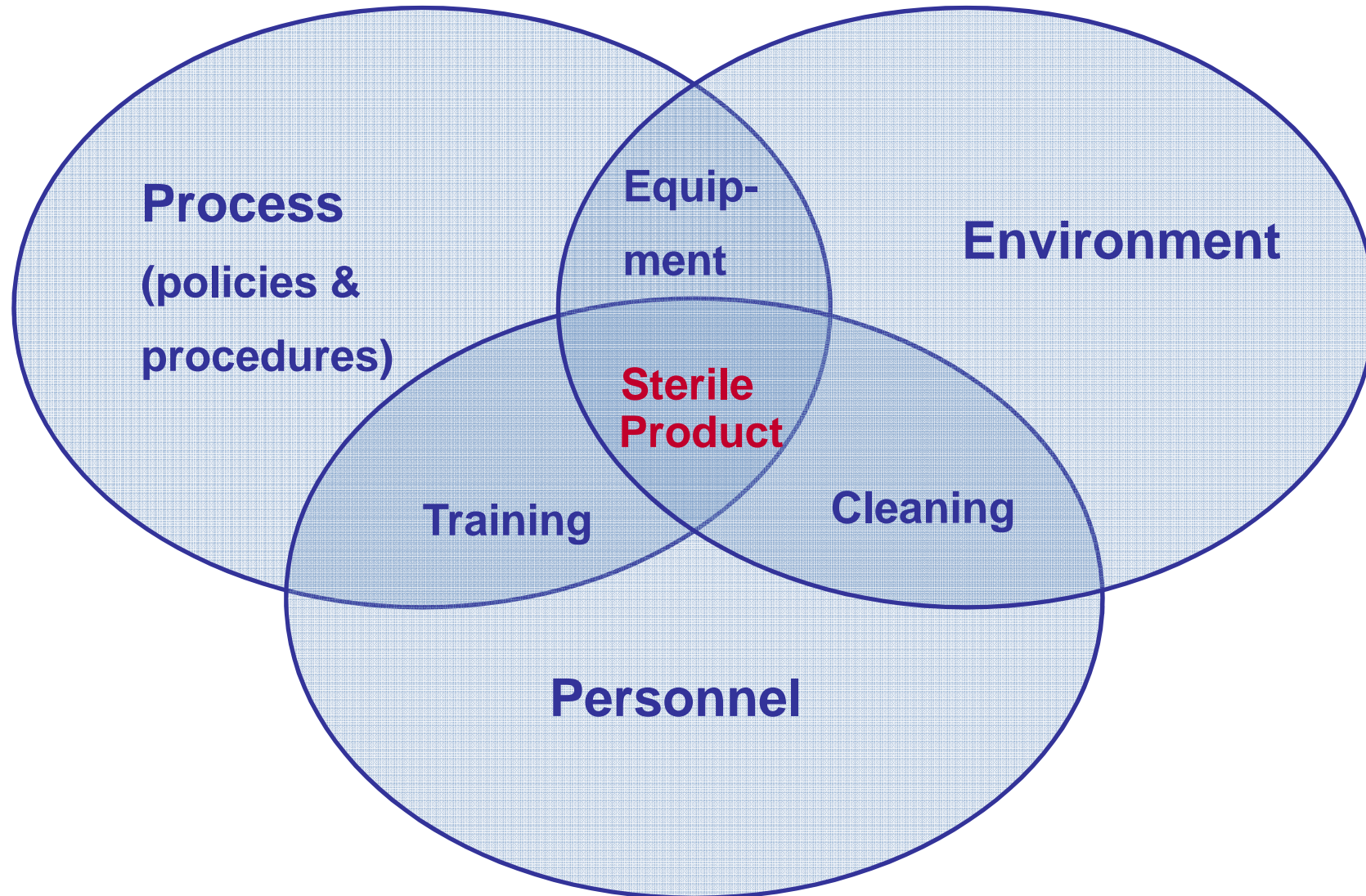
Antimicrobial activity of cytotoxic drug solutions

- Declining of CFU over time caused by exhaustion of nutritive substances
- No cytotoxic drug solutions with nutritive value



Consequences of lacking antimicrobial activity of cytotoxic drug solutions

- Endproduct sterility testing possible by direct transfer of a sample aliquot into sterile culture media (e.g. Bactec® blood culture system, Aerobic, Anaerobic vials)
- Storage of products under refrigeration whenever possible
- Immediate use of solutions prepared for intrathecal administration
- **Expiration date limited by microbiological stability**



Importance of QA program and documentation