Anforderungen an Luft-Filtersysteme für Reinräume in der pharmazeutischen und biotechnologischen Industrie

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Übersicht

- Dohm Pharmaceutical Engineering - DPhE -
- derzeitige Anforderungen
  - Partikuläre Kontamination
  - Mikrobiologische Kontamination
- zukünftige Anforderungen ?
  - Molekulare Kontamination

DPhE

- Engineering & Consulting for the Pharmaceutical and Biotech Industry
- Founded 1993 by Christopher Dohm
- Headquarters in Berlin / GER and Branch Offices in Mannheim, Ludwigshafen and Munich (all GER)
- 30 highly qualified Consultants (Chemical and Mechanical Engineers, Construction Manager, Biotech Engineers, Microbiologists)
- Accreditation by DAkkS (Cleanroom Certification)
- International Projects in USA, France, Belgium, Singapore

Leads Resume Summaries

- Christopher Dohm, Dipl.-Ing. (17 years exp.)
  - Project Management
  - Clean Utility Systems
  - Fast-track projects

- Alexander Gierse, Ph.D. (6 years exp.)
  - Water Systems
  - Aseptic processing
  - Qualification and Validation

- Martin Wilhelm, Dipl.-Ing. (13 years exp.)
  - Design of pharmaceutical cleanrooms
  - Clean Utility systems and HVAC
  - Validation

Leads Resume Summaries

Matthias Nieber, Ph.D. (6 years exp.)

- Isolators
- Qualification, Validation
- Calibration, Cleanroom certification

Kirstin Hebenbrock, Prof. Ph. D. (15 years exp.)

- QA
- GMP-Consulting
- Drug Delivery Technologies

Derzeitige Anforderungen

- Qualität der Arzneimittel wird sichergestellt durch:
  - Gesetzliche Bestimmungen
    - Arzneimittel-Gesetzbuch
      - GMP-Richtlinien (EU)
    - Code of Federal Regulations (US)
      - FDA-Guidlines
  - Freiwillige Kontrolle

FDA -Guidelines

- Guidance for Industry
  - Sterile Drug Products produced by Aseptic Processing – Current Good Manufacturing Practice

21 CFR 211.42(c) states, in part, that "Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas or such other control systems for the firm's operations as are necessary to prevent contamination or mixups during the course of the following procedures: * * * (10) Aseptic processing, which includes as appropriate: (i) Floors, walls, and ceilings of smooth, hard surfaces that are easily cleanable; (ii) Temperature and humidity controls; (iii) An air supply filtered through high-efficiency particulate air filters under positive pressure, regardless of whether flow is laminar or nonlaminar; (iv) A system for monitoring environmental conditions; (v) A system for cleaning and disinfecting the room and equipment to produce aseptic conditions; (vi) A system for maintaining any equipment used to control the aseptic conditions."

21 CFR 211.46(b) states that "Equipment for adequate control over air pressure, micro-organisms, dust, humidity, and temperature shall be provided when appropriate for the manufacture, processing, packing, or holding of a drug product."

21 CFR 211.46(c) states, in part, that "Air filtration systems, including prefilters and particulate matter air filters, shall be used when appropriate on air supplies to production areas * * *."

FDA -Guidelines

- Guidance for Industry
  - Sterile Drug Products produced by Aseptic Processing – Current Good Manufacturing Practice
    - HEPA-filtered
      - Geforderte Mindest-Abscheideeffizienz (0,3 µm Partikel): 99.97%

There is a major difference between *filter leak testing* and *efficiency testing*. An efficiency test is a general test used to determine the rating of the filter.[8] An intact HEPA filter should be capable of retaining at least 99.97 percent of particulates greater than 0.3 µm in diameter.

GMP-Richtlinien

- Eudralex: The Rules Governing Medicinal Products in the European Union
  - Volume 4: EU Guidelines to Good manufacturing Practice Medicinal Products for Human and Veterinary Use
    - Annex 1: Manufacture of Sterile Medicinal Products

GMP-Richtlinien

- Annex 1: Manufacture of Sterile Medicinal Products

	Maximum permitted number of particles per m^3 equal to or greater than the tabulated size			
	At rest		In operation	
Grade	**0.5 µm**	**5.0µm**	**0.5 µm**	**5.0µm**
A	3 520	20	3 520	20
B	3 520	29	352 000	2 900
C	352 000	2 900	3 520 000	29 000
D	3 520 000	29 000	Not defined	Not defined

	Recommended limits for microbial contamination (a)			
Grade	air sample cfu/m^3	settle plates (diameter 90 mm) cfu/4 hours (b)	contact plates (diameter 55 mm) cfu/plate	glove print 5 fingers cfu/glove
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

ISO-Richtlinien

- ISO 14644:
  - Reinräume und zugehörige Reinraumbereiche

Tabelle 1: Ausgewählte Partikelreinheitsklassen der Luft für Reinräume und Reine Bereiche

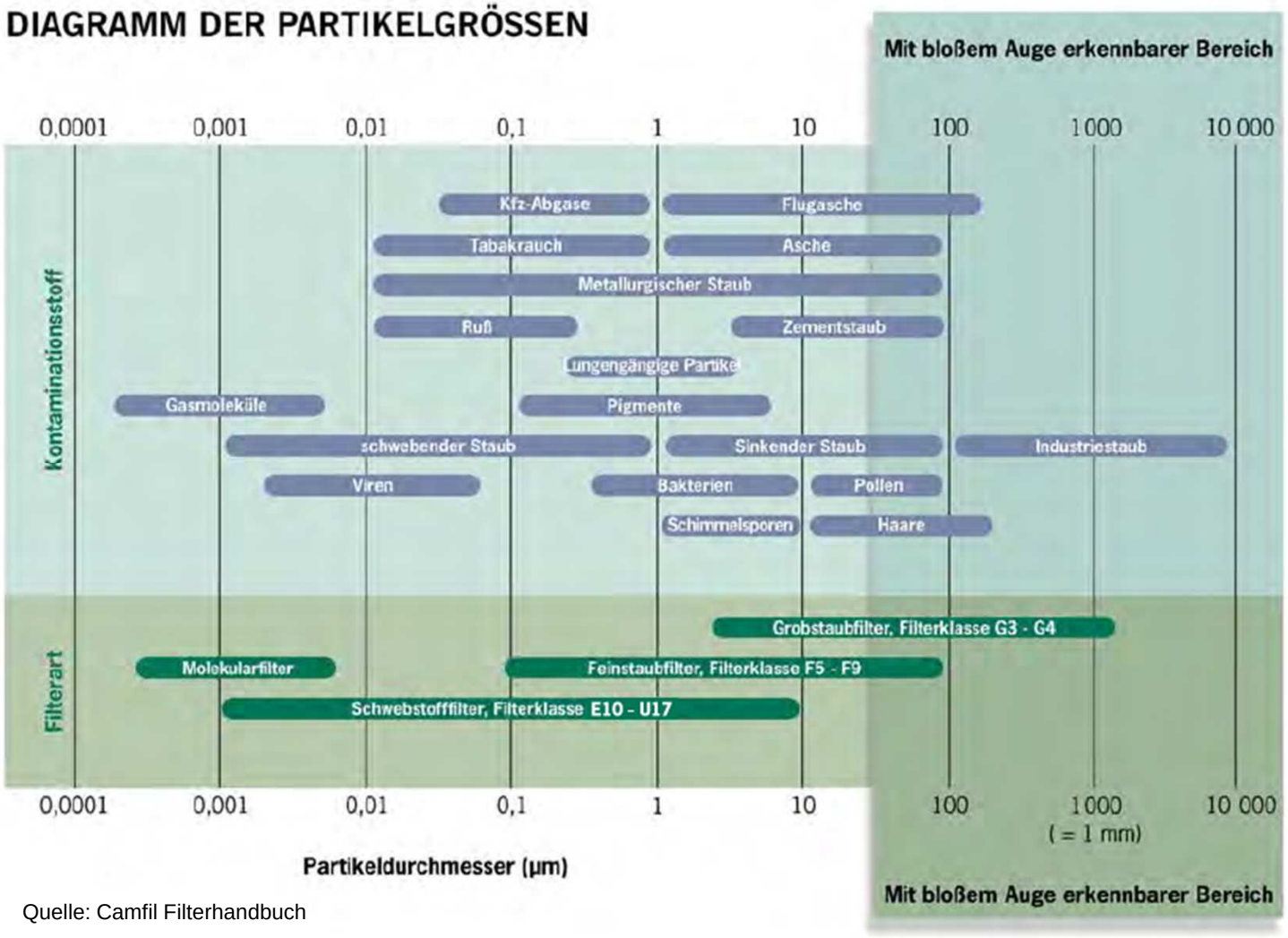
ISO-Klassifizierungszahl (N)	Höchstwert der Partikelkonzentrationen (Partikel je Kubikmeter Luft) gleich oder größer als die betrachteten Größen, welche nachfolgend abgebildet sind (Die Konzentrationsgrenzen sind nach Gleichung (1) in 3.2 berechnet.)					
	0,1 µm	0,2 µm	0,3 µm	0,5 µm	1 µm	5 µm
ISO-Klasse 1	10	2	—	—	—	—
ISO-Klasse 2	100	24	10	4	—	—
ISO-Klasse 3	1 000	237	102	35	8	—
ISO-Klasse 4	10 000	2 370	1 020	352	83	—
ISO-Klasse 5	100 000	23 700	10 200	3 520	832	29
ISO-Klasse 6	1 000 000	237 000	102 000	35 200	8 320	293
ISO-Klasse 7	—	—	—	352 000	83 200	2 930
ISO-Klasse 8	—	—	—	3 520 000	832 000	29 300
ISO-Klasse 9	—	—	—	35 200 000	8 320 000	293 000

ANMERKUNG: Unsicherheiten bei dem Meßvorgang verlangen, daß Konzentrationsdaten aus nicht mehr als drei geltenden Zahlen zur Bestimmung des Klassifizierungsgrads verwendet werden.

Derzeitige Anforderungen

- Kontaminations-Quellen
  - Außenluft
    - Luft-Filtration
  - Operator
    - Reinraumkleidung
  - Fertigungs-Prozess

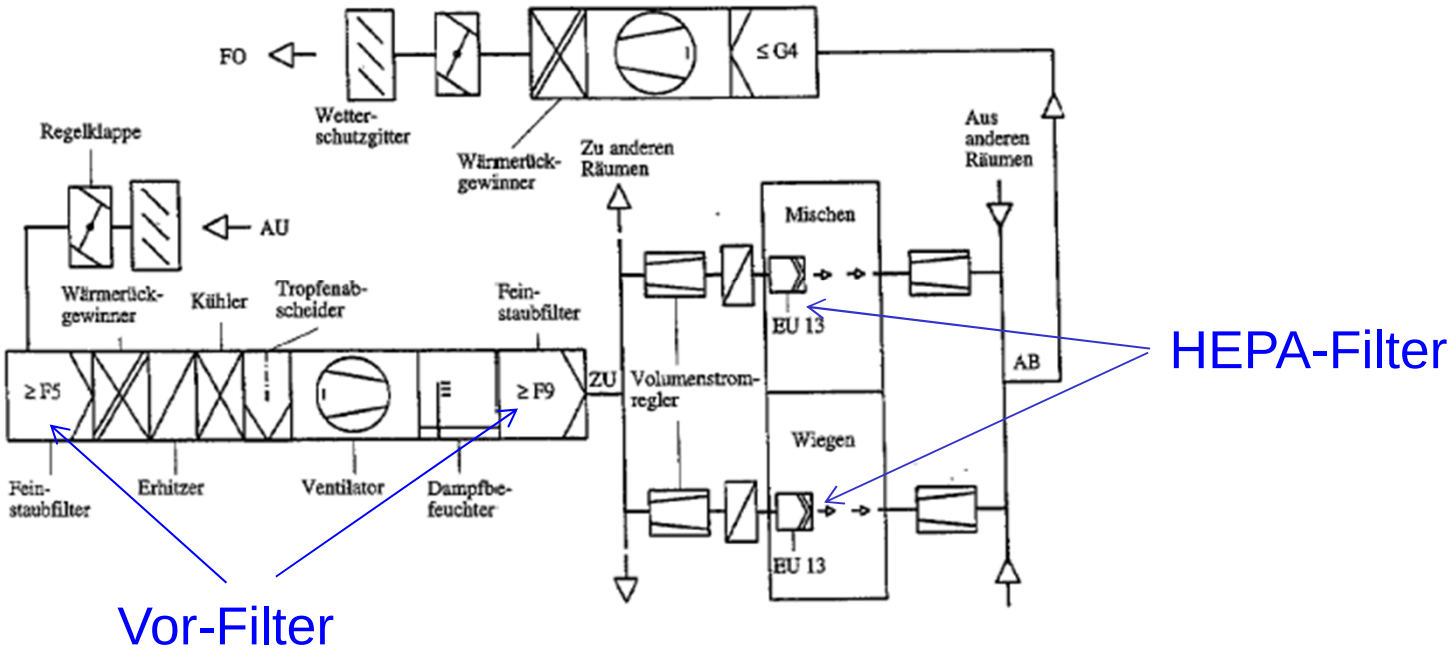
Kontaminations-Quellen



Quelle: Camfil Filterhandbuch

Derzeitige Anforderungen

- Aufbau eines Lüftungssystems (Pharma)



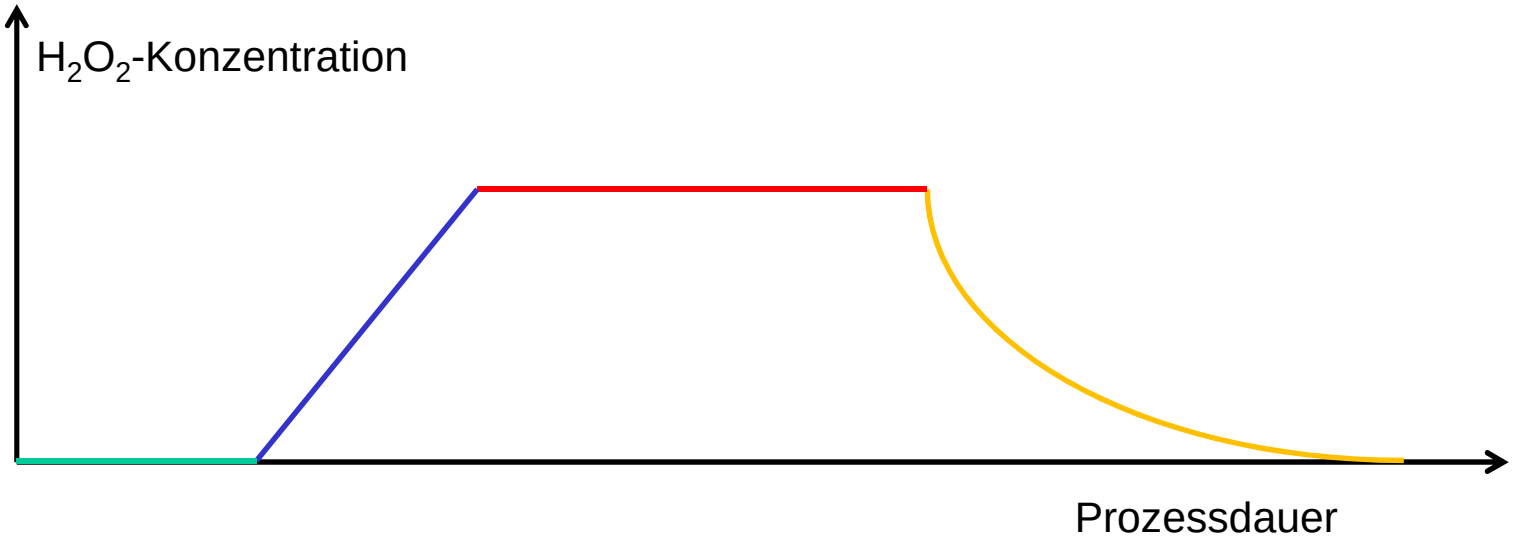
Quelle: W. Ziemer, Reinraumtechnik für die pharmazeutische Industrie

Derzeitige Anforderungen

- Dekontamination der Reinräume
  - Begasung mit
    - Ozon
    - Chlordioxid
    - Ethylenoxid
    - Peressigsäure
    - Formalin
    - Wasserstoff-Peroxid (H_2O_2)

H_2O_2-Begasung

- Begasungs-Zyklus
  - Pre-Konditionieren
  - Konditionieren
  - Gasphase
  - Belüften



H_2O_2-Begasung

- Dekontaminationsmittel
  - verweilt im Raum
  - kann ins Produkt gelangen und Wirkstoff oxidieren
    - Lange Belüftungszeiten

Zukünftige Anforderungen ?

- Nachweis der Konzentration vor Abfüllung
  - Dekontaminationsmittel
  - weitere, den Wirkstoff oxidierende Substanzen
- Filtrationsmöglichkeiten
  - AMC-Filter (Halbleiter-Industrie)
    - Aktivkohle
    - Strömungsführung
  - Plasma-Filtration
    - Dynamisch anpassbar
    - Konstruktiv anpassbar?
    - Partikel-Generierung?
    - …

DOHM
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