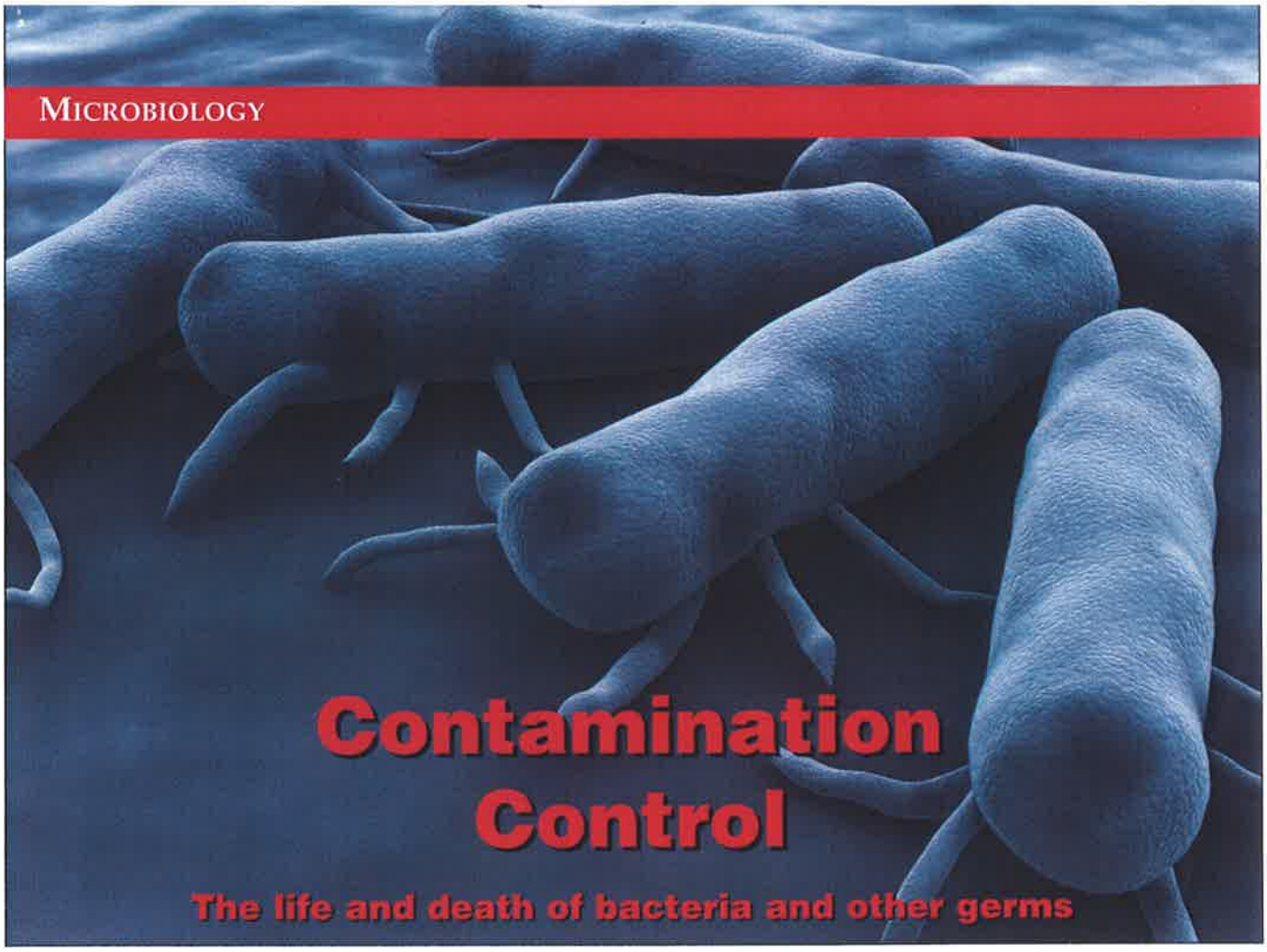

Contamination Control

The life and death of bacteria and other germs

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In February of 1965 Professor L.W. Kallings appeared before the Swedish National Board of Health in Stockholm and advised, "We have typhoid fever. We have deaths." He was asked to write a report, in which he concluded, "it is neither from food nor water, it's from a medicine."

We now know that Prof. Kallings had detected strains of *Salmonella* in a standard oral drug, a dry thyroid powder from domestic animals that was not much changed from the 1940 edition of USP VI .The drug was Thyroideum, U.S.P. In the same year, Prof. Kallings wrote a second report to the Swedish National Board of Health entitled, "Microbiological Contamination of Medical Preparations". In 1966 he expanded his investigation of contamination in the Pharma industry and reported that blindness and eye infections were due to ophthalmics contaminated with *Pseudomonas aeruginosa.* In 1967 the Swedish National Board published the first manufacturing guide on Contamination Control, "Production, Hygiene and Bacteriological Control in the Manufacture of Pharmaceuticals".

In these same years the FDA published surveys of *Pseudomonas, Serratia* and *Klebsiella* infections, all from aqueous eye makeups, creams, topical drugs, baby lotions, liquid soap, and skin antiseptics. Children died in a Texas hospital following application of a baby lotion to the umbilicus, and iodophor solutions in a Massachusetts hospital were found to be contaminated with *Pseudomonas cepacia* in instances too numerous to count. In a rapid turnaround, USP 18 (1970) switched its sole attention from sterility tests and antibiotic assays to non-sterile drugs and "Contamination Control," the subject of this article some 35 years later.

The historic fountainhead for the field of contamination control was the USP 18 Chapter, "Microbial Limits Test". The fields of "Contamination Control" and "Water Validation" were thus born. Shortly after publication of USP 18, a series of deaths occurred nationwide from a large volume parenteral, intravenous infections and endotoxin shock from a product that passed the USP sterility test. In court the FDA lost its case against the manufacturer because the manufacturer had performed the sterility test as promulgated in USP 18 (liquid contents) and did not test the screw cap because it "didn't have to." By using a swab and not a membrane filtration apparatus, the FDA found that when the bottle was turned upside down, the gram negative rods were transferred from liner to drug and no one, not even the nurses, noticed that they were infusing a cloudy suspension into the vein. It was not reported because "they didn't have to." Thus the field of "validation" was born. "Process Control" trumped "Final Product Testing" and the modern era of Contamination Control was on the march for all pharmaceutical dosage forms, sterile, non-sterile, prescription or over-the-counter. This is our subject.

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This article, which is based on historic as well as current knowledge, is intended to act as a basic primer for microbiologists and manufacturing personnel on the relationship between the microbial world and the quality, safety and efficacy of pharmaceutical articles. It contains some important information from USP publications. There is a lurking microbial cloud which can be transported silently from the outermost Class 100,000 portions to the innermost critical areas, putting product, consumer and company at risk. The physical, behavioral and chemical interventions that prevent this "invasion" will be discussed.

The subject of Contamination Control describes the methods for detecting, removing and destroying the microorganisms that might become resident in critical and non-critical areas of manufacture. We address how we can measure a population of microorganisms and how the application of trend analysis and adherence to standards can enhance the goal of quality.

We will deal heavily with experimental data, moving from theory to practice. In so doing we review some prior experimental data published from this laboratory and elsewhere, with references and attribution. The paper also contains certain unpublished data on the distribution, identification and control of bacteria, fungi and viruses, with special reference to the use of chemical germicides, a subject now receiving high priority from the expert committee of the current USP. The sections provided on growth, desiccation resistance and sensitivity or resistance to disinfectants, and choice of germicides, help to establish the subtitle of this article: "The Life and Death of Bacteria and Other Germs".

Organisms found in the Pharmaceutical Manufacturing Environment

A review of isolations obtained from Class 100,000 and 10,000 areas was conducted in a search for bacteria, yeasts and molds. That data are summarized in Table 1.

Table 1 An analysis of 315 environmental cultures from manufacturing sites, air and surfaces (Class 10,000; 100,000)

	Type of organisms	% of time recovered
Group 1	All bacteria (ubiquitous)	52%
	Diphtheroids (Skin)	1%
	Gram-negative rods (soil, dust, skin, etc)	10%
	Gram-positive bacillus (spore formers) (vegetation soil)	25%
	Gram positive cocci (many species of *staphylococci* and *micrococci*) (soil, human, skin, vegetation, etc.)	16%
Group 2	Yeast (vegetation, skin, soil)	1%
Group 3	Filamentous fungi (ubiquitous) (mostly class 100,000)	48%

It is noted that 42% of the isolates consisted of Gram-positive organisms, a finding consistent with our D¬10 desiccation resistance data table 3. The low number of Gram-negative rods isolates (10%) is also consistent with D10 desiccation resistance data. An analysis of speciation revealed that non-pathogens were the predominant flora.

Table 2 Surfaces to be decontaminated by disinfectants in non-sterile and sterile product manufacturing areas

Material	Application
Stainless steel	Filling equipment, tanks, etc.
Glass	Windows, vessels
Plastic, Vinyl	Curtains
Plastic, polycarbonate	Insulation coating
Plexiglass	Shields
Epoxy coated gypsum, Fiberglass plastic	Walls and ceilings
Tyvek	Equipment wraps
Terrazzo tiles	Floors
Various materials	Fixtures, shelving, cabinets, teflon surfaces, bench surfaces
Metals	Door knobs, equipment

The detection of organisms on environmental and equipment surfaces is Part I of a contamination control program. Part II is to determine how they can be eliminated and Part III speaks to the issue of propagation dissemination (in other words how did they get there?). When EPA-registered disinfectants are used it must be pointed out that they have been tested primarily against human or veterinary pathogens and not environmental isolates. They are approved only for non-porous hard surfaces. EPA-registered commercial disinfectants are not certified for any surface of a physical nature that departs even slightly from polished stainless steel. EPA-registered disinfectants are approved to kill at least 10,000 organisms in 10 minutes or less. Given the clean state of most pharmaceuticals surfaces, a lesser application is probably effective.

The Survival of Microorganisms on Surfaces in the Absence of Disinfectants

Table 3 presents current and previously reported data (Prince 1984) on the life and death of a variety of bacteria, yeasts, molds and viruses on the type of surfaces in Table 2.

Table 3 Approximate Scale of Resistance on Hard Surfaces

Organism	~D_{10} Value*	Susceptibility Group[a]
P. aeruginosa, E. coli, S. epidermidis	1 – 2 hours	A
P. acnes, S. choleraesuis, Enterobacter, S. pullorum, Influenza A virus,	4 – 5 hours	B
A. niger, Herpes simplex I, Vaccinia virus, Penicillium, Paecilomyces	7 – 9 hours	C
Poliovirus, coxsackie, HAV	13 hours	D
S. aureus, S. warneri, S. hermanii, C. albicans, S. hominis, S. simulans	6 – 20 hours	E
M. luteus, M. lylae	48 hours	F
B. pumilus, B. cereus, B. subtilis, B anthracis (spores)	~3 years	G

[a]Increasing resistance to ambient desiccation
*D = length of time for dried population to decrease 1-log (90%) calculated as $D = \frac{time}{\log N_0 - \log N_1}$

The data in Table 3 (showing a high degree of desiccation resistance for the Gram Positive bacteria) agree with the data in Table 1 in which it was shown that the majority of bacteria isolated from environmental surfaces are of the Gram Positive variety. Once deposited on any inanimate surface in the Pharma manufacturing area, growth is nearly impossible, with the exception of excessive relative humidity and incomplete removal of organic matter, which can trigger extensions in viability.

DISINFECTANTS

A USP informational chapter on disinfectants has been circulated for comments, indicating a tremendous interest in the use and effectiveness of chemical germicides in the drug industry. A general discussion seems warranted. Disinfectants generally used in pharmaceutical manufacturing fall into three categories:

a) Sporicides (chemosterilizers): consisting usually of oxidizing agents (e.g. bleach, peroxides, peracetic acid). These are rapidly active and kill most microorganisms they encounter. However, some spores are resistant. These products can be corrosive and irritating.

b) Alcohols (disinfectants): as either ethanol or isopropanol. Some are made sterile by membrane filtration or irradiation. They are fast acting but must be left in contact long enough to avoid evaporation. In the laboratory they can kill vegetative bacteria in seconds. They have no immediate effect on spores. Their action against filamentous molds is not as fast as against bacteria.

c) General disinfectants (quaternary ammonium compounds "quats" and phenolics): either type of product can consist of a single active compound or mixtures of different structures within the molecular species. The quaternary compounds can kill more rapidly than the phenolics, and are more soluble. They also provide detergency. The advantage of phenolics is that they kill TB and hydrophilic viruses (e.g., polio). But since these organisms are rarely found as contaminants in the pharmaceutical industry, the value of these traits is limited. As with antibiotics there are first, second and third generation quats and phenolics, with improvements centering around enhanced spectra, speed of action and resistance to hard water. In general, quats, halogens, alcohols and phenolics kill in seconds when in suspension, but kill slowly when exposed to organisms in the dry state. Many firms challenge commercial disinfectants with organism isolates from the manufacturing environment.

d) The rotation of disinfectants is unnecessary except in food establishments, as we have written in a previous publication, because selection of theoretical mutants is unlikely. (Prince, 1984)

e) Any credible use of disinfectants (an intervention as critical as air filtration in contamination control) requires knowl-

Table 4 Approximate Disinfection Scale for all Organisms in Order of Increasing Resistance (Response to Commercial Disinfectants) (after Prince and Prince, Block 2001)

Microbial susceptibility group	Microorganisms (dried on carriers)
A	Retroviruses (AIDS), ortho and paramyxoviruses, herpes viruses (enveloped lipophiles), vaccinia, corona, other enveloped viruses, gram-negative rods and some filamentous fungi; some gram-positive cocci, human hepatitis B and C viruses
B	Staphylococcus aureus, some diphasic and filamentous fungi, yeasts and algae, some gram-negative rods
C	Adenoviruses (capsomeric lipophiles)
D	Mycobacterium tuberculosis (BCG strain), rotaviruses, reoviruses, some mold ascospores
E	Picornaviruses (polio, rhino) Parvoviruses (SS DNA), hepatitis A
F	Bacterial endospores (Bacillus, Clostridium); viroids (Plant RNA)
G	Prions (TDE Agents or "Mad Cow")

edge of how sensitive or resistant the environmental bioburden is. We have studied this problem and a scale of disinfectant effectiveness was published earlier (part of this is summarized in table 4).

The data in Table 4 show the difference in susceptibility of the various microorganisms to standard EPA registered disinfectants. Again as shown in Table 3 (desiccation resistance) S. aureus was among the more resistant bacteria. Our studies were further analyzed using stainless steel AOAC/EPA use dilution method in terms of what percent were killed by commercial disinfectants (Table 5).

Table 5 Effectiveness of Commercial Quaternary and Phenolic Disinfectants against Plant Isolates

Type	# species isolated	% Fail AOAC/EPA Test
Bacteria (vegetative)	24	29%
Fungi	39	41%
Bacillus (spores)	9	100%

The results summarized in Table 5 with Bacteria and Fungi are not unexpected since commercial disinfectants are rarely tested against wild-type environmental organisms as part of EPA pre-market approval. The results with spores were predictable with these types of agents. When chemosterilizers were used (oxidizers) such as 10% (0.525% Sodium hypochlorite) bleach, all bacterial spores were killed.

Sources and Control of Microbial Contaminants

The reduction transit from class 100,000 to an ultimate aseptic area requires intervention in five areas as shown in Table 6:

Table 6 Sources and Control of Contaminants – A General Guide

Source	Control
Air	HEPA filtration, UV
Environmental Surfaces	Cleaning, Chemical Germicides
Raw Materials	Sub-lethal Sterilization, USP/CTFA Microbial Limits Screen/FDA Manual
Water and ion exchange beds*	Filtration, UV Light, Sanitization of Cationic and Anionic beds
Personnel	Hygiene, Training, Gowning, Motion Restriction

*Gram negative bacilli (Pseudomonas, Enterobacter, Aeromonas, Klebsiella, Serratia, etc.) predominate, the opposite of the gram positive surface persistence in table 1

Current Status of USP Microbiology In Contamination Control

The current edition of USP 27 contains articles on contamination control and a partial list is provided. All are available on the Internet.

1. Chapter 61. This chapter, entitled Microbial Limits Test is essentially unchanged since its inception 35 years ago. This landmark collection of methods is the ultimate arbiter of whether or not a non-sterile article is free of microbial adulteration. It has been copied worldwide The current chapter is being divided into two portions, one to cover the total bacterial and mold count (quantitative chapter) and a new section (chapter 62) that speaks to the detection of certain objectionable or indicator organisms, *Staphylococcus aureus, Escherichia coli, Salmonella* species, *Pseudomonas aeruginosa, Candida albicans* and *Clostridium* species (qualitative chapter). A valuable new statistical concept is proposed that will loosen the guidelines on counting bacteria. Thus, when counts are spoken of as in the order of 10 per gram, this can be as large as 20 CFU/gram, likewise 100 per gram and 1000 per gram (and so on) can be construed 200 and 2000, respectively.

2. Chapter 1111. "Microbiological Quality of Non-sterile Products". This informational chapter depends heavily upon chapters 61 and 62 and is not harmonized. It has some important additions: the term "objectionable" is removed and methods for yeast and mold count have been added for oromucosal, gingival, gingival cutaneous (mucocutaneous), nasal, auricular, vaginal, inhalation and transdermal dosage forms. Also, oral preparations have been separated into liquid/solid based on different acceptance criteria for anhydrous vs. aqueous products.

3. Chapter 1116. "Microbiological Evaluation of Clean Room and Other Controlled Environment." This important chapter covers the following subjects: aseptic processing of bulk substances, dosage forms, certain medical devices and microbial content of the manufacturing environment. Guidance is also provided on clean room classification, Federal Standard 209E, training of personnel, microbial environmental control programs, establishing sampling plans and sites, frequency of sampling in critical areas, alert and action levels, and a discussion of air samplers. Alert and action levels are defined. Certain important teaching is obtained from USP informational chapters. They can be listed as follows:

1. There is no scientific agreement on the relationship between non-viable particulates (as used in classification of air) and viable counts.
2. Microbial sampling should occur during normal operation and with personnel and materials within area.
3. Microbial monitoring of clean rooms and other controlled area should include air, compressed air, surfaces, equipment, sanitization containers, walls, floors, gowns and gloves.

Table 7, 8 and 9 are attributed to USP Chapter 1116

Table 7 Suggested Frequency of Sampling on the basis of Criticality of Controlled Environment (Based on USP Chapter 1116 Aseptic Fill Operations)

Area To Be Sampled	Schedule of Sampling*
Class 100 or Better	Each Operating Shift
Area Immediately Adjacent to	Each Operating Shift
Class 100 area (e.g. class 10,000) Other Support Areas	Twice per Week
Potential Product/Container Contact Areas	Twice per Week
Other Areas Supporting Aseptic Process Area	Once per Week

* = Air, surfaces, Personnel

Table 8 With respect to air sampling, air cleanliness guidelines have been suggested by USP in chapter 1116,

Class (S.I.)	U.S. Customary	cfu/cubic meter	cfu/cubic foot
M3.5	100	Less than 3	Less than 0.1
M5.5	10,000	Less then 20	Less than 0.5
M6.5	100,000	Less than 100	Less than 2.5

Table 9 Surface Cleanliness For Controlled Environments, USP 1116

cfu per contact plate

Class (U.S.)	Equipment & Facility	Personnel
100	3 includes floor	Gloves 3 Clothing/garb 5
10,000	5, but floor=10	Gloves 10 Clothing 20

Surface sampling should be conducted at the conclusion of operations. Swabs or contact plates may be used and incubated with culture conditions as specified in company SOP or with specific reference to the USP guidelines, which are informational only. With respect to microbial identification, an appropriate knowledge of genus and species is valuable in (a) determining trends and shifts, (b) evaluating the effectiveness of cleaning and sanitizing treatments, and (c) investigating sources of contamination. The pathogenicity of environmental isolates is left to medical authorities, but the term "adulteration" in the FDA sense is not limited to pathogens.

Viruses in Contamination Control

The question of contamination control arises on the presence of or inactivation of viruses in the manufacturing environment, or on the detection of these agents in the USP Sterility Test, especially for articles sterilized by membrane filtration. There is no virus that we know of today that can withstand the 10-6 SAL terminal process of steam, ethylene oxide or irradiation. Viruses are unlikely in the controlled environment, unless shed by personnel. The only likely human reservoir would be respiratory virions shed from the throat or nasal droplets, especially from talking, coughing and sneezing, and excessive body movement, from personnel unaware of barrier limitations for these very small organisms. Viruses most likely to be shed are:

A. Respiratory
   1. Lipophilic (enveloped)
   2. Influenza A, B, C
   3. Measles
   4. RSV
   5. MUMPS
   6. German Measles

B. Partially Lipid Adenoviruses

C. Hydrophilic (naked)
   1. Rhinoviruses (more than 100) common cold
   2. Coxsackie viruses
   3. ECHO viruses

D. Mucotaneous Dermal
   1. Herpes 1
   2. Herpes 2
   3. Vaccinia

(after Prince and Prince, Block, 2001)

The life cycle of viruses in human infections teaches that the greatest amount of aerosol shedding frequently occurs before signs and symptoms. If you are uncertain of the health status of a worker and the possibility of vectoring these agents to critical areas and surfaces, one can take either of two approaches: (1) do nothing and allow normal die-off as described in the desiccation kinetics in Table 3, or (2) quickly apply 3, 5, or 10% fresh hydrogen peroxide solution, depending if you wish complete inactivation in 10, 5 or 2 seconds for a lipid virus (influenza). If you suspect a partially lipophilic virus (adenovirus) or naked hydrophilic agent (Rhinovirus), choose fresh 5% hydrogen peroxide solution and apply for at least 30 seconds (Gibraltar Laboratories, unpublished data) The hydrogen peroxide will turn to sterile water and nascent oxygen, which can be wiped away. Do not use any other chemical germicide (quaternary, phenolic, aldehyde, iodophor, etc.) because this represents a needless contamination with extraneous organic matter. If you choose alcohol make sure it is sterile and a mixture of ethanol and isopropanol 50:50. All of the aforementioned is as much directed to regulatory and legal personnel within the firm as for scientific personnel, for consumer complaints about virus infections occur from time to time (herpes from lipstick or sterile catheters, AIDS virus from a vaccine, polio from water for injection and a scientific defense is possible). Viruses can neither survive nor replicate in or on inanimate materials.

Summary

In this article, we have presented some concepts and experimental data on the existence and persistence of certain bacteria, yeasts and molds and viruses and how they may be controlled

by disinfectants, HEPA filtration and training of personnel. We have presented pertinent USP documents, such as USP 6, USP 18 and USP 27.

It cannot be stressed more strongly that USP informational chapters are for guidance only and are not necessarily obligatory for any firm. Recognizing the fluidity and changes in methods and standards that is part of the biological process, USP administers a well-organized program of revision. USP actively solicits feedback from the "consumer" pharmaceutical scientist and publishes the highly-valued Pharmacoepial Forum publications. Special attention must be paid to these in-process documents. When a USP official states that it is the Pharma community as a whole that is responsible for the contents of the Official and Informational chapters of USP, he is correct. Further, it is to be stressed that microbial content values published in USP are not verified by any one standard of experimental data. We are not aware of any data from any firm that correlates action levels with product failure in terms of microbial content. The important thing is that surface, air and personnel counts are measurable and reproducible. What cannot be measured cannot be changed. What cannot be changed cannot be improved. When the constant search for improvement ends, quality becomes more difficult to maintain and complacency is inevitable. We dare not go back to the days of Prof. Kallings. ■

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