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Editorial

Contents

Mini review section – The microbiology department of a manufacturing facility for non-sterile products can be extremely busy carrying out extensive tests on incoming materials, intermediates, water systems, production equipment, and environmental monitoring. Approaches to microbiological control of non-sterile products should be essentially the same as to all other products and strategies in the industry. It should be based upon an objective evaluation of risk.

Current Trends section – The use of disinfectants will always be part of a pharmaceutical facility cleaning programme. Verifying that the routine disinfectant procedures are able to achieve control over the range of possible pathogens must always form a key part of the facility process qualification. Disinfectant efficacy testing is concerned with demonstrating that a product possesses antimicrobial activity under defined laboratory test conditions. It is the process that is used to compare the antimicrobial activity of a product against other products or known standards.

In Profile Scientist – Homi Jehangir Bhabha was an Indian born nuclear physicist who made important contributions to quantum theory and cosmic radiation. He is known as the "father of Indian nuclear program."

Bug of the month – *Brucella abortus* is a gram-negative bacterium that is found in cattle populations. This intracellular parasite is a blood borne pathogen that causes premature abortion of a cattle fetus. What makes this bacterium so dangerous is that it is zoonotic, meaning it can be transferred from an animal to a human host and still remain pathogenic.

Did You Know? – Researchers are now getting closer to this goal with a type of bacteria called *Pseudomonas aeruginosa*, which is notorious for infecting patients with the lung disease cystic fibrosis. In a new study, researchers found that the bacteria send out warning signals to their conspecifics when attacked by antibiotics or the viruses called bacteriophages which kill bacteria. It is a smart survival mechanism for the bacteria. If it turns out that the bacteria use the same evasive manoeuvre when infecting humans, it may help explain why some bacterial infections cannot be effectively treated with antibiotics.

Best Practices – It is intuitive to think that the less a potentially contaminated surface is touched, the better, so the advent of automated sink fixtures as well as soap and towel dispensers has been heralded as an important way to reduce the opportunities for cross contamination and hand carriage of pathogenic microorganisms. Hand hygiene has grown to be regarded as the major weapon against HAI.

Have a light humour with some jokes in our **Relaxed Mood section**. Feedback & suggestions are always welcomed.

Microbial control of non-sterile medical products

Not so long ago, a microbiologist working for a producer of non-sterile medicines had a relatively easy life, a few total viable counts on some incoming materials here, an occasional test on the water system there, all very relaxed and low key. How life has changed! Now in some manufacturing establishments for non-sterile products, the microbiology department is as highly staffed and as busy as its counterpart in sterile manufacture, carrying extensive tests on incoming materials, intermediates, water systems, production equipment, production staff and extensive environmental monitoring.

Introduction

Ten years ago, seeing a settle plate in a tablet packing area would have been a cause for consternation, now it is relatively commonplace. All this leads a microbiologist, to ask the questions "is all this really necessary?" and "how is it benefiting the patient?" Our approach to microbiological control of nonsterile products should be essentially the same as to all other policies and strategies in our industry, it should be based upon an objective evaluation of **RISK**. Unfortunately, it is believed that, in terms of microbiology, much of what we currently do, and what we are encouraged to do by the regulators, is not based on risk and does not represent good science.

For example, European Council Directive 2003/94/EC on GMP states in Section 5.10

"At every stage of processing, products and materials should be protected from microbial and other contamination."

To what extent should they be protected from microbial contamination? Completely? If so, then all products should be produced sterile; if not, then how much contamination is acceptable. Such "blanket" statements are unhelpful! Most of the microbiologists would agree that, for the vast majority of non-sterile medicines, cross contamination represents a far greater threat to patient safety than does microbial contamination.

As for FDA, 21CFR211.113 states a requirement for…
"Written procedures describing the systems designed to prevent objectionable microorganisms."

Which begs the question "what is an objectionable microorganism?" This is not clearly defined, but it doesn't stop FDA from taking regulatory action; microbial contamination is a frequently cited reason for recalls in FDA-regulated markets, but it is by no means clear whether all these recalled products actually represented a health threat to patients.

In truth, we often over-estimate the risk to patient safety in our industry. Lets be clear; the majority of non-sterile medicines are administered to patients who are, by many criteria, fit and well. If patients were seriously ill, they would not be prescribed tablets, capsules, patches, etc. Thus, people suffering with headaches, muscle or joint pain, raised blood pressure, raised cholesterol, nicotine addiction and similar conditions are not especially at risk of microbiological infection. The microbiological content of their food intake is not monitored, so why should we make such a big deal out of the few grams of medicines they take each day?

Of course, many of you will counter this argument by quoting examples of non-sterile products which are administered to patients with heightened susceptibility to infection, and in these cases I fully agree that some measures need to be taken – this is the essence of RISK MANAGEMENT! However, adopting a "one size fits all" policy is unscientific, inefficient, costly and potentially dangerous in that it may dilute the effort put in to controlling those products and processes which really need it.

As part of a coherent, risk-based approach to the microbiological control of non-sterile products, we need to consider, in addition to the health status of the recipient, the potential sources of contamination as well as risk mitigating factors. Thus, we need to understand the risks from…

> Formulation
> Starting Materials
> Water
> Equipment
> People
> Process Environment

FORMULATION

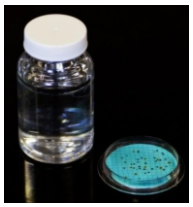
All microorganisms require water, and lots of it to grow. Many non-sterile formulations have very low levels of available water, either because they are dry or solid (tablets, capsules, powders, etc), they are water free (ointments), or they have formulation components which reduce the amount of water available to microorganisms (so-called humectants). It is only those products which contain substantial amounts of water (or intermediates and additives which do) which constitute a significant microbiological threat. Thus, oral liquids, topical liquids, creams, semi-solids, etc. constitute a potential microbiological risk, which is why so many of these products are formulated to contain a chemical preservative agent, the efficacy of which is established during development and confirmed periodically on commercial lots.

Thus, the nature of the formulation should be considered as part of the overall microbiological risk assessment.

STARTING MATERIALS

As dosage form manufacture consists in the main of mixing and packaging of actives and excipients, it follows that the microbiological content of medicines is derived largely from those starting materials. Thus, it makes sense that microbiological control of starting materials should be the foundation of any control strategy for non-sterile medicines. But, here again, we should apply risk principles and take into account the type of raw materials. Synthetic excipients or actives produced by an aggressive synthetic pathway are unlikely to be contaminated with significant levels of microorganisms as the temperatures, pressures, extremes of pH, etc. will have destroyed any contaminants. Only the final stages of preparation, such as crystallization from water, represent a potential threat. Thus, microbiological monitoring of such materials lot by lot would be excessive and unnecessary. On the other hand, materials of organic or natural origin (starches, sugars, gelatin, gums, etc.) are much more likely to carry a high bioburden and pose a much greater risk. Here, increased monitoring and control is warranted, and Pharmacopoeial requirements reflect this.

WATER



Water is potentially a major source of microbiological contamination, as a poorly designed and controlled water system can contain high numbers of microorganisms, especially Gram negative organisms which may be less susceptible to the killing effect of chemical preservatives. Thus, where water is a key formulation constituent or process component, its control is of crucial importance.

EQUIPMENT

If kept clean and dry, process equipment is unlikely to represent a significant source of microbiological contamination to medicines. However, poor design of equipment can result in the presence of "reservoirs" of potential contamination. Thus, the extent of microbiological monitoring of process equipment may range from none to a lot, depending upon the risk factors that exist. Please understand, though, that the best way to control contamination is to remove the potential source (i.e. re-design the equipment).

PEOPLE

Personnel: Sterile gowning

People are often cited as a major potential source of contamination to medicinal products. However, if we exclude sterile products from this discussion,When certain sensible prevention measures are taken, microbiological risks from people are actually small. An operator would have to bathe in a liquid product to contribute a significant microbiological challenge to it! This is not to trivialize the risk from people, rather it is intended to put it into perspective. Accepted practices of good gowning, good personal hygiene and adoption of clear hygiene practices, allied with instructions to minimize direct contact with product and product contact surfaces, should be sufficient. Actual microbiological monitoring of staff should be regarded, except in exceptional circumstances, as unnecessary and potentially misleading.

To assess the effectiveness of the gowning program personnel may be monitored on a regular basis for viable counts. Personnelmonitoring employs contact plates to assess microbial contamination of clean room personnel.

How Personnel are monitored in a Clean Room

Personnel in critical areas may be monitored for microbialcontamination utilizing the contact plates. The contact plates monitor areas of the body that may interact with the sterile field or product exposure areas. These may include gloved hands, forearms, or other areas. Personnel monitoring is a good indication of how well personnel are gowning when they enter the clean room. Many companies utilize this testing for proficiency based training programs for clean room personnel.

PROCESS ENVIRONMENT

If the contribution of people to microbiological contamination of non-sterile products can be considered relatively minor, the contribution from the air is, in the most part, negligible. True, there is a GMP requirement for some liquids and inhaled products to be processed in a controlled environment so as to minimize microbiological contamination, and this is entirely justified on a risk basis, but for the vast majority of non-sterile products, the environment contributes little risk to the product and so microbiological environmental monitoring constitutes at best a luxury and at worst a waste of valuable resource.

Before instituting a microbiological environmental monitoring program into a non-steriles facility, ask yourself a few questions…

- > What am I looking for?
- > Where will I monitor, how and how often?
- > What is the relationship, if any, between environmental monitoring data and patient risk?
- > How much is unacceptable and why?
- > What is acceptable and why?
- > What action will I take if results are high?
- > How will I assess the effectiveness of that action?

If you cannot answer most or all of these questions, why would you wish to go ahead?

IN SUMMARY

1. Effective microbiological control of non-sterile products is essential if we are to assure their fitness for use BUTthe extent of that control must be based upon an objective assessment of RISK
2. Know your…
   - > Products
   - > Processes
   - > Sources of contamination
   - > Mitigating factors
3. Remember that microbiological monitoring is not the same asmicrobiological control
4. Microbiological control strategies should be targeted to providing the following benefits…
   - > Better knowledge and control of risk areas
   - > Consistently good hygiene practices
   - > Elimination of microbiological "hot spots" in processing
   - > Reduced risks to patients and not just perceived regulatory compliance
5. Ensure you are adding VALUE, and not just cost

Disinfectant Efficacy Test

The design, validation and implementation of a documented and approved disinfectant programme must form a key part of any pharmaceutical production area qualification. There is significant regulatory interest in this area as it forms a fundamental part of any production facility maintenance schedule.

European pharmaceutical companies are required to implement the necessary measures in order to comply with the requirements set out in EudraLex Volume 14 of the "Rules Governing Medicinal Products in the European Union". These guidelines are more commonly known as the EU Guide on GMP (EU-GMP). Pharmaceutical companies who supply to the United States are also required to comply with the GMP requirements of 21 CFR 211.56 "Sanitation" and 21 CFR 211.67 "Equipment cleaning and maintenance".

This article will discuss the key industry standards and guidelines and highlight their significance within the pharmaceutical industry. The tasks that should be considered in order to validate your disinfectant products and cleaning programme will be outlined.

Within the European Union (EU) and also the United States (US), there are a number of definitions and terms that are used to describe public health antimicrobial products that are used on inanimate objects and surfaces. In the US, they are collectively known by the Environmental Protection Agency (EPA) as Antimicrobial Pesticide Products. In general, they are all substances or mixtures (blends) of substances that are used to destroy or suppress the growth of certain types of microorganism.

The following definitions are used in both the EU and the US:
Disinfectant
A chemical (or physical) agent that is used on hard inanimate surfaces such as walls, floors and other surfaces to destroy or inactivate bacteria and fungi, but not necessarily their spores. They are often referred to as low or medium level disinfectants, depending on their level of activity.

Sporicides
Often referred to as high level disinfectants, they are used to destroy all forms of microbial life including viruses, fungi, bacteria and also low levels of their spores. A high-level disinfectant can only be classed as a sterilant if it is capable of destroying all microorganisms present including high levels of spores.

Registration of antimicrobial products
In Europe, the registration of disinfectants is regulated by the 98/8/EC Directive known as the Biocidal Products Directive (BPD). The legislation which came into force in September 2000 outlined a plan lasting up to 10 years that was designed to harmonise the manufacture and supply of biocidal products within the European Union.

The principle aim is to ensure that all biocidal products marketed within the European Union are safe, effective and non-hazardous to the environment. Within the scheme, biocidal products are divided into 4 main groups. Disinfectants will fall into Main Group 1 "Disinfectants and General Biocidal Products".

The product dossiers for the active ingredients that were notified under the scheme are now under evaluation. Each product that is authorised for use within the EU will be added to the approved list known as "Annex 1". Ultimately, only those actives contained in Annex 1 will be approved for use in individual product formulations, which will be assessed in the next phase of the scheme.

Some active ingredient manufacturers opted not to include their products in the BPD scheme because the cost of the registration process was deemed to be too high for the potential financial gains. As a result of this, some disinfectant formulators were then forced to remove products containing these actives from the market or to reformulate the products. Products containing actives that were not deemed to be safe or were damaging to environment also had to be removed.

Manufacturers of chemical substances who produce or import more than one tonne per year of the chemical may also be required to register the chemical under the EC1907/2006 Regulation. This new European Community law is known as REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) and came into force on 1 June 2007. It was designed to improve the protection of health and also the impact on the environment of chemical substances. The scheme is currently only in the early registration phase and it will therefore be some time before the benefits are fully realised.

In the US, the manufacture and sale of disinfectants (known as antimicrobial pesticide products) is regulated by the EPA under the statutory authority of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) amended in 1996.

In order to market a disinfectant in the US, the active ingredient must be registered with the US EPA under Title 7 of the FIFRA and 40 CFR Parts 152 and 156. Disinfectants that are used on medical devices are regulated by the US Food and Drug Administration (FDA) under 21 CFR 880.6890, general purpose disinfectants and 21 CFR 880.6885, liquid chemical sterilants/ high-level disinfectants.

The test requirements for the product will be determined by the types of micro-organisms that it will be required to destroy. The manufacturer must submit efficacy test data to support the label claim for the activity of the product.

Companies wanting to market their products within the EU and the US are required to submit dossiers to support their products under both the BPD and EPA schemes.

Table 1: CEN-TC 216 Working Groups

Group Number	Areas of application
Working Group 1	Human Medicine Product Test Standards
Working Group 2	Veterinary Product Test Standards
Working Group 3	Food Hygiene, Domestic and Institutional applications
Working Group	Horizontal Working Group (harmonise standards across groups)

Efficacy testing of disinfectants

Although we often use the terms disinfectant efficacy testing and disinfectant validation in the same context, it is very important to make a distinction between these two terms. Disinfectant efficacy testing is concerned with demonstrating that a product possesses antimicrobial activity under defined laboratory test conditions. It is the process that is used to compare the antimicrobial activity of a product against other products or known standards.

Disinfectant validation should be viewed as a form of process validation and is a much more in depth and extended process. It is often site or facility specific. In summary:"Disinfectant validation is the documented verification and implementation of procedures that have been shown to consistently control the range and levels of micro-organisms that may be encountered on the surfaces in a facility".

We will discuss the steps that should be considered during a disinfectant validation programme in more detail later. We will first consider the efficacy tests that must be performed by the suppliers of the disinfectants to gain approval for their products. Under both the BPD and EPA schemes, manufacturers of disinfectants are required to submit efficacy data to support the antimicrobial claims for their product.

Within the EU, there have been a number of test methods published over the years by individual competent bodies. The French AFNOR method and German DGHM method are just a couple of examples. The European Committee for Standardisation (CEN-ComitéEuropeén de Normalisation) set up a group known as Technical Committee (TC) 216 in 1989. The aim of this group was to harmonise the approach used for the efficacy testing of disinfectants. There were four working groups (Table 1) set up to focus on different areas and applications.

The test procedures published by Working Group 3 (WG 3) are applicable to the pharmaceutical industry and have now been adopted by the British Standards Institution and published as BS EN standards. They consist of a phased test programme of suspension and surface tests using a range of standard test micro-organisms, they provide a useful framework of methods that can be used to verify the efficacy of the disinfectants under specific conditions.

Table 2: CEN-TC 216 Working Group 3 Test Standards

CEN TC 216 Test Phase	Outline of the tests	Examples of relevant test standards
Phase 1- Basic Suspension Tests	These tests are used as an initial screen to determine if the disinfectant possesses basic bactericidal or fungicidal activity under the defined conditions	BS EN 1040- Basic Bactericidal Activity BS EN 1275- Basic Fungicidal Activity
Phase 2, Step 1- Quantitative Suspension Tests	These tests are designed to demonstrate whether the disinfectant possesses activity under conditions that are more representative of actual use. Additional challenge organisms, product test concentrations and validation test controls are included. Interfering substances are also employed to simulate organic soiling or hard water	BS EN 1276- Quantitative Bacterial Suspension Test BS EN 1650- Quantitative Fungal Suspension Test BS EN 13704- Quantitative Sporicidal Suspension Test
Phase 2, Step 2 - Surface Tests	This test uses the same cultures as the Phase 2, Step 1 tests. It is designed to demonstrate that the disinfectant is able to destroy the challenge organisms when they are attached to a surface. Although the standard only specifies the use of stainless steel coupons, other materials, challenge organisms, contact times may be employed. The test criteria for both bacteria and fungi are included in the standard.	BS EN 13697- Quantitative Non Porous Surface Tests
Phase 3- Field Trials	The standards are expected to take into account other environmental factors and stresses. The scope of the standards has yet to be agreed.	Standards yet to be published

Table 3: Disinfectant Validation Key Steps

Key Step	Suggested factors to be considered and activities to be performed
Step 1	Perform a documented review of the materials used in the construction of the facilities. Highlight any materials or surfaces that may be hard to clean.
Step 2	Perform a review of the facility environmental monitoring data to establish the range of microorganisms that may be encountered in the facility. Establish the types of micro-organisms that would present a particular risk to the facility.
Step 3	Determine the level and spectrum of activity that the disinfectant would be required to provide i.e. bacteria, fungi, bacterial spore activity
Step 4	Perform a review of the available approved disinfectant products. Consult the manufacturers and use supplier efficacy tests and health and safety data to determine the most suitable product(s)
Step 5	Consider whether rotation of disinfectants or the periodic use of high level disinfectants is required. Verify the chemical compatibility of the disinfectant with other products.
Step 6	Perform efficacy tests using representative environmental isolates and surface materials. Determine the required contact (microbial kill) time for the disinfectants on the materials.
Step 7	Develop cleaning procedures that can be used to apply the disinfectant to the facility routinely. The procedures must reflect the efficacy test studies in order to ensure that the required exposure to the disinfectant is achieved. This may require multiple application.
Step 8	Perform field trials using the disinfectants. Establish environmental monitoring trends both before and after the use of the disinfectant. Determine whether the disinfectant has any unforeseen adverse affect on microbial trend, building materials or fabrics or personnel
Step 9	Implement the disinfectant for routine use and train staff in the procedures to be used. Continue to monitor the performance of the disinfectant

The following standards (Table 2) are examples of the tests used within the EU to verify the effectiveness of the disinfectants under the specified conditions. In the US, it is stipulated by the EPA under subdivision G of the Pesticide Assessment Guidelines that effectiveness testing must be performed using methods that are accepted by the Association of Official Analytical Chemists (AOAC).

A limited efficacy claim for a "Germicide" or "Disinfectant" may be obtained by satisfying the criteria of the AOAC Use-Dilution Method (955.14, 955.15 and 964.02) (water soluble powders or liquid products) or the AOAC Germicidal Spray Product Test (961.02) (spray products). To obtain a claim for effectiveness against Gram-negative bacteria, this must be performed against *Salmonella choleraesuis*. To obtain a claim for activity against Gram-positive bacteria, this must be performed against *Staphylococcus aureus*.

A general purpose or broad-spectrum efficacy claim would be required if the disinfectant must exhibit activity against a range of both Gram-positive and Gram-negative bacteria. This label claim may be obtained by satisfying the criteria of the AOAC Use-Dilution Method or the AOAC Germicidal Spray Product Test against both *Salmonella choleraesuis* and *Staphylococcus aureus*. A hospital or medical disinfectant claim may be obtained by satisfying the criteria of the AOAC Use-Dilution Method or the AOAC Germicidal Spray Product Test against *Salmonella choleraesuis*, *Staphylococcus aureus* and also *Pseudomonas aeruginosa*.

There are individual AOAC tests for fungicidal activity (955.17), tuberculocidal activity (965.12) and sporicidal activity (966.04). The specific criteria in each test must be satisfied in order to obtain the relevant label claim. The efficacy of disinfectants can be affected by a number of factors including pH, temperature, water hardness, organic soiling and dilution. Many of these variables are taken into account in the BS EN and AOAC standards and specific test conditions are stipulated.

Disinfectant validation

We have already discussed the tests that may be used to verify the efficacy of the disinfectants under specific conditions. These tests are very important because they determine the limitations of the disinfectant. Most importantly they help to establish the nominal

microbial kill times that will be required during routine use. Useful information will be available from the suppliers because they will have generated this data as part of their product registration and development process. Although the purchasers of disinfectants are under no obligation to use the BS EN (CEN 216) or AOAC tests, they do however provide a framework that can be used to devise efficacy tests that are representative of the end users' requirements.

Some companies fail to obtain satisfactory disinfectant data through lack of awareness of the test standards and how to interpret the often variable data. Contract testing companies who perform these tests on a regular basis will be much more aware of the key requirements of the tests and how to interpret the data. They will be able to advise companies on the tests that would be required and more importantly, the tests or requirements that may not apply. Examples include the omission of the use of interfering substances or hard water if these conditions do not reflect the way the disinfectant would be used.

The United States Pharmacopoeia (USP) General Chapter 1072 "Disinfectants and Antiseptics", outlines the key tests that should be performed to verify the efficacy of the disinfectant against representative organism types and surfaces. It also highlights the physical and chemical factors that may influence the test results and challenge levels that should be employed.

The chapter stipulates that a 3 log reduction in the viable microbial count should be demonstrated for bacteria. It is worth noting that a 3 log reduction may have a very different meaning depending on the starting point. A 3 log reduction from 107 cells to 104 viable cells would constitute a relatively large reduction in the microbial cell count. However, a 3 log reduction from 104 cells to 101 cells would constitute a much smaller reduction in the cell count. An analysis of the cell count reduction can therefore be very important.

Efficacy testing will be one of the key steps in the disinfectant validation process. However, you must also demonstrate that the procedures that are used to apply the disinfectants are able to routinely control the potential range of pathogens in the facility.

Table 3 provides an overview of the key steps that should be considered during a disinfectant validation programme:
The above list is not exhaustive. This is the type of process that should be followed to ensure that disinfectants are validated and implemented in a controlled and documented manner. There has been very little formal pharmacopoeial or industry guidance over the years regarding disinfectant process validation and how it should be conducted. The regulatory agencies themselves have also been reluctant to enforce specific guidelines onto the industry due to the wide array of practices that are employed. However, numerous citations have been issued to companies for failing to provide adequate documented evidence or procedures to support their disinfectant programme.

Like other forms of process validation, disinfectant validation data must also be reviewed periodically to determine whether the original work is still representative of the current process. Factors that may drive revalidation include regulatory requests, changes in the microbial trend data or changes to the materials used in the manufacture of the facility if they were deemed to be significant. It would be at the discretion of the company to decide whether this was deemed appropriate or necessary.

Conclusions

The use of disinfectants will always be part of a pharmaceutical facility cleaning programme. Verifying that the routine disinfectant procedures are able to achieve control over the range of possible pathogens must always form a key part of the facility process qualification.

We have discussed the tasks that should be considered during a disinfectant validation programme. The responsibilities placed on the manufacturers to provide supporting data and the importance of ensuring that the overall validation reflects the way the products are used has also been highlighted. Validation does not have to be done in isolation and support and advice is widely available to ensure that it is performed to a satisfactory standard.

The risk associated with not performing these studies far outweighs the cost of performing them. Pharmaceutical facilities must be kept clean and under microbial control in order to protect the integrity of the products and ultimately the safety of the patients.

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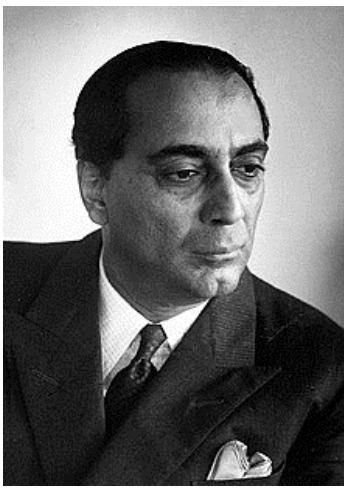
Homi Jehangir Bhabha



Homi Jehangir Bhabha was an Indian born nuclear physicist who made important contributions to quantum theory and cosmic radiation. He is known as the "father of Indian nuclear program."

He was the first Chairman of The Atomic Energy Commission of India.

Early Life:

Homi Jehangir Bhabha was born on 30 October, 1909 to a wealthy Parisi family in Mumbai that was very influential in the west of India. His father was Jehangir Hormusji Bhabha, a lawyer.

Initially Bhabha attended Cathedral School and he then enrolled for studies at Elphinstone College at the age of fifteen. This was followed by further studies at the Royal Institute of Science in Bombay.

Bhabha's father and uncle, Sir Dorab Tata, wanted him to study engineering at university so that Bhabha could take up a senior position at the Tata Iron and Steel Company on completion of his degree.

In 1927, Bhabha began his studies at Cambridge University, studying mechanical engineering according to his family's wishes. Soon, however, Bhabha became more interested in theoretical physics, being influenced by physicist Paul Dirac.

After passing the Mechanical Engineering Tripos with first class Bhabha remained at Cambridge and with his family's approval began studying theoretical physics.

In 1932 he passed the Mathematics Tripos, again with first class and he received his doctorate degree in nuclear physics from the University of Cambridge in 1934.

Contributions and Achievements:

Bhabha's first paper "The Absorption of Cosmic radiation" in 1933 earned him a three year Isaac Newton Studentship in 1934.

He worked alongside Neil Bohr in Copenhagen in addition to his research work at Cambridge. Bhabha published a paper in 1935, performing the first calculation to determine the cross section of electron-positron scattering.

Bhabha conducted research with Walter Heitler and in 1936 they made a breakthrough in the cosmic radiation's understanding by working on the cascade theory of electron showers. Their theory described how primary cosmic rays from outer space interact with the upper atmosphere producing observable particles at the ground level, making estimations of the number of electrons in the cascade process at different altitudes for different electron initiation energies.

In 1937, Bhabha was awarded the Senior Studentship of the 1851 exhibition.

With the outbreak of the Second World War in 1939, Bhabha returned to India accepting a position of reader of physics and establishing the Cosmic Ray Research Institute at the Indian Institute of Science in Bangalore.

In 1941, Bhabha was elected Fellow of the Royal Society. He also established the Tata Institute of Fundamental Research in Mumbai, becoming their director in 1945. He was a skillful manager and it was due to his prominence, devotion, wealth and comradeship with Jawaharlal Nehru, Prime Minister of India that he gained a leading position for allocating the scientific resources of India.

Bhabha become the first chairperson of India's Atomic Energy Commission in 1948. It was under his direction that the scientists of India made their way into making an atomic bomb ant the first atomic reactant was operated in Mumbai in 1956. Bhabha also led the first UN Conference held for the purpose of Peaceful Uses of Atomic Energy in Geneva, 1955.

It was then predicted by him that a limitless power of industries would be found through nuclear fusion's control. He promoted nuclear energy control and also prohibition of atomic bombs worldwide. He was absolutely against India manufacturing atomic bombs even if the country had enough resources to do so. Instead he suggested that the production of an atomic reactor should be used to lessen India's misery and poverty. A post in Indian Cabinet was rejected by him but he served as a scientific advisor to Prime Ministers Nehru and Lal Bahadur Shastri.

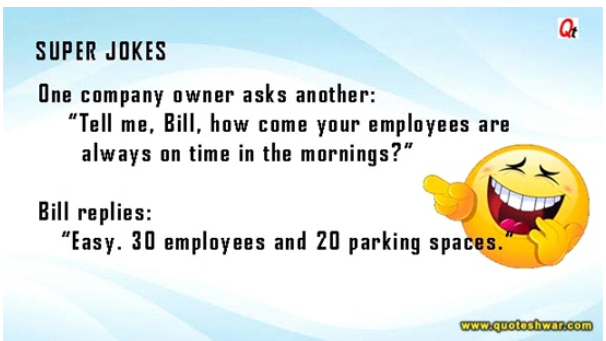
He realized the potential of India's large thorium reserves in addition to the country's small uranium deposits.

The total reserves of thorium in India amount to over 500,000 tons in the readily extractable form, while the known reserves of uranium are less than a tenth of this. The aim of long range atomic power program in India must therefore be to base the nuclear power generation as soon as possible on thorium rather than uranium.

Bhabha received many rewards and award from Indian as well as foreign universities and he was an associate of various societies of science including the American National Academy of Sciences. He was awarded Padma Bhushan in 1954, the third-highest civilian award in India.

Bhabha remained a bachelor during his life. His hobbies included painting, classical music and opera, and botany. He was killed in mysterious circumstances, aged 56, when Air India Flight 101 crashed on January 24, 1966 near Mont Blanc in Switzerland. In quantum physics, the cross section of electron-positron scattering was renamed "Bhabha scattering" in his honor.

Jokes



The Perfect Son.

A: I have the perfect son.
B: Does he smoke?
A: No, he doesn't.
B: Does he drink whiskey?
A: No, he doesn't.
B: Does he ever come home late?
A: No, he doesn't.
B: I guess you really do have the perfect son. How old is he?
A: He will be six months old next Wednesday.

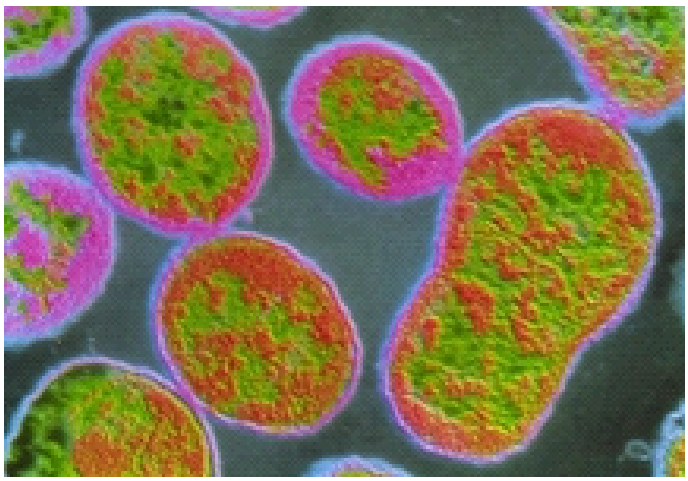
Three engineering students were gathered together discussing the possible designers of the human body.

One said, *"It was a mechanical engineer. Just look at all the joints."*

Another said, *"No, it was an electrical engineer. The nervous system has many thousands of electrical connections."*

The last one said, *"No, actually it had to have been a civil engineer. Who else would run a toxic waste pipeline through a recreational area?"*

Brucella abortus



Description and significance

Brucella abortus is a gram-negative bacterium that is found in cattle populations. This intracellular parasite is a blood borne pathogen that causes premature abortion of a cattle fetus. What makes this bacterium so dangerous is that it is zoonotic, meaning it can be transferred from an animal to a human host and still remain pathogenic. In humans this disease cause both acute and chronic symptoms, but can be treated with antibiotics. Because of this economic effect on the cattle business and the disease potential in humans, the US has spent close to $3.5 billion trying to vaccinate the cattle herds in the US. It is possible for *B. abortus* to be spread from wild populations of elk and bison into domestic cattle herds and this is why the US government continues to be vigilant in tracking potential cases within herds.

Genome structure

The *B. abortus* genome contains 2 circular DNA chromosomes. The first chromosome is 2,124,241 nucleotides long and codes for 2200 genes. The second chromosome is 1,162,204 nucleotides long and codes for 1156 genes. The genome has a GC content of 57%, and 81% of the genome is a coding region. This pathogen is different from many in that it does not contain any plasmids or genomic islands that relate to pathogenicity within its genome. In addition to lacking these two features, the genome also lacks many other genes that code for common virulence factors including "capsules, fimbriae, exotoxins, cytolysins, resistance forms, antigenic variation, plasmids, or lysogenic phages". The genes that do encode for virulence in *B. abortus* are being examined but they are not well enough understood to say for sure what the mode of virulence is for this intracellular pathogen.

Cell structure and metabolism

Brucella abortus are Gram-negative rod shaped bacteria that do not have flagella or pili, nor do they create capsule slime. They do produce endospores, which enable survival under long-term starvation and dessication. This heterotrophic bacterium carries out either aerobic or anaerobic respiration because it is a facultative bacterium . Thus, the bacteria can grow with or without oxygen present. In order to culture *Brucella abortus*, a complex medium is required, because the bacterium is a fastidious, requiring most essential nutrients to be imported into the cell from the host (4). Although it is a fastidious bacterium, *Brucella abortus* does have major biosynthetic pathways (5) available to it. In its primary host, cattle, the metabolic pathway for the breakdown of erythritol is one that is most desirable, it is even used "preferentially to glucose". This is a possible factor in the bacteria's virulence because erythritol is found in bovine placenta.

Ecology

Brucella abortus is an intracellular bacteria, which means that it does not replicate outside the host organism. This bacterium, as an intracellular pathogen, enters phagocytes, such as macrophages, in humans and in cows. It attaches to the endoplasmic reticulum of these cells (5). These smooth bacteria enter macrophages and then live in compartments of vacuolar space along the ER. The few cells that make it to these vacuolar spaces down regulate apoptosis genes within the macrophage and therefore cause the cell to resist self-death and these pathogens become resistant within these cells of the immune system. These resistant bacterium are what go on to cause chronic disease in human hosts.

In bovine species the bacteria also infects the trophoblast epithelial cells, which are the cells that provide nutrition to the embryo. After a number of rounds of cellular replication in the trophoblast the cells lyse, causing more bacteria cells to enter the blood stream of the developing embryo. These cells in the blood stream go on to colonize the placenta and fetus in pregnant female cows, and will go on to induce abortion of the fetus.

Though *Brucella abortus* is an intracellular bacterium it can remain alive outside the host without replicating. This bacterium can remain in the excrement of cattle and the aborted fetuses of the cattle for quite some time depending on the exact conditions; thought the average time is around 30 days. Outside the host the bacteria cells are affected by direct sunlight; the pathogen can be eliminated by pasteurization, and can be killed by disinfectants.

Pathology

Brucella abortus causes a disease called brucellosis, which used to be referred to as Malta Fever because it was first discovered in soldiers who were living on the island of Malta by Dr. David Bruce, for whom the pathogen gets its name. *B. abortus* is originally found in cattle and causes problems with fetus development and viability, but this pathogen can be passed to humans. It is uncommon in the US; most cases emerge from slaughterhouse workers, meat packers, or large animal veterinarians, but in the developing world the disease is much more common because their cattle herds are not vaccinated. In these cases the most common mode of transmission is through unpasteurized milk and cheese products because the bacteria is present it the milk glands of a female cow.

In humans the disease has both an acute and a chronic phase. The chronic phase will last as long as the host is alive without treatment. Acute symptoms include fever, chills, headache, backache, weakness, and weight loss. The chronic symptoms are usually recurring joint pain, fatigue, and headaches.

There is an antibiotic regiment for humans who come in contact with the disease that includes the antibiotics rifampin and doxycycline together.

Application to Biotechnology

Until 1969 the US ran a number of experiments with biological weapons. One of the bacteria used in this research was *Brucella suis*, that is almost identical to *Brucella abortus*, except that its preferential host is pigs instead of cows. One of the reasons that the *Brucella bacteria* were targeted for development into a biological weapon was because of the length of time that it causes disease and the fact that if affects both humans and livestock. Although it does not kill human hosts, this pathogen can cause a long and lingering chronic illness that will cause a great loss in productivity of a nation's workforce. Another reason this bacterium was targeted as a biological weapon is because humans consume many of the animals that it affects as food, such as pigs, cows, and goats. The final reason that this posed a great biological threat was that it can be spread through aerosols and therefore is easily dispersed, especially in an urban environment.

Current Research

Due to the new heightened threat of bioterrorism in last few years there is current research being done by the Armed Forces Institute of Pathology in a screening mechanism for such threats as *Brucella abortus*. The new research is being conducted on an optical detection system for such threats that combines spectroscopy and digital imaging that form a library, which can be screened. One positive to this screening mechanism is that the pathogens can be detected in complex environments and do not require amplification. The results of the preliminary test show that this screening method does have a high level of specificity and does accurately detect pathogens and correctly identify them.

As stated earlier, there is not much known about the exact pathway that enables the *Brucella abortus* pathogen to evade the immune system and become lodged in the ER of host macrophages. This process does enable the bacterium to remain virulent while evading the immune system. There has been research done to try and determine the virulence factors that allow the bacteria to reside in macrophages without the common virulence factors associated with pathogenic bacteria. One study found that PrpA is a gene encoded for on the bacterial genome, which cause IL-10 secretion in macrophages, is required to establish a chronic infection in mouse macrophages.

Although the US domestic cattle herds have all been vaccinated for *Brucella abortus*, there is now fear that *B. abortus* from wild bison and elk can infect domestic herds. Because of this possibility, researchers are looking to test the vaccine administered to cows in elk and see if the same immune response is seen. If the same response was seen it was hypothesized that the vaccine could be given to wild populations to further stop transmission and further protect the cattle. In this study the elk did seem to mount an immune response initially because the level of antibody production was higher in those elk that received the vaccine. The problem was that this response did not proliferate, so though there seemed to be an initial immune reaction it did not last. This means that the vaccine for cattle would offer little protect for the elk against *Brucella abortus*.

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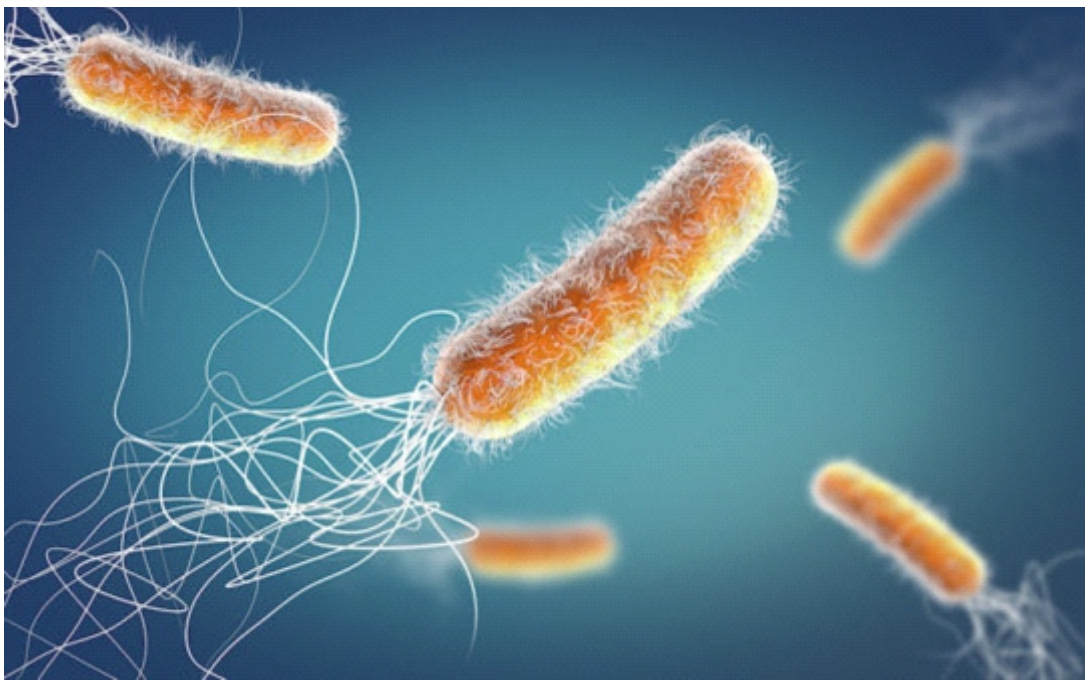
Dangerous bacteria communicate to avoid antibiotics



Researchers are now getting closer to this goal with a type of bacteria called *Pseudomonas aeruginosa*, which is notorious for infecting patients with the lung disease cystic fibrosis. In a new study, researchers found that the bacteria send out warning signals to their conspecifics when attacked by antibiotics or the viruses called bacteriophages which kill bacteria.

"We can see in the laboratory that the bacteria simply swim around the 'dangerous area' with antibiotics or bacteriophages. When they receive the warning signal from their conspecifics, you can see in the microscope that they are moving in a neat circle around. It is a smart survival mechanism for the bacteria. If it turns out that the bacteria use the same evasive manoeuvre when infecting humans, it may help explain why some bacterial infections cannot be effectively treated with antibiotics," says researcher Nina Molin Høyland-Kroghsbo, Assistant Professor at the Department of Veterinary and Animal Sciences and part of the research talent programme UCPH-Forward.

One United Organism

In the study, which is a collaboration between the University of Copenhagen and the University of California Irvine, researchers have studied the growth and distribution of bacteria in petri dishes. Here, they have created environments that resemble the surface of the mucous membranes where an infection can occur -- as is the case with the lungs of a person with cystic fibrosis.

In this environment, researchers can see both how bacteria usually behave and how they behave when they are affected by antibiotics and bacteriophages.

"It is quite fascinating for us to see how the bacteria communicate and change behaviour in order for the entire bacterial population to survive. You can almost say that they act as one united organism," says Nina Molin Høyland-Kroghsbo.

Possibility of Blocking

The *Pseudomonas aeruginosa* bacteria are such a big problem that they are found in the top category 'critical' in the World Health Organization's list of bacteria, where new types of antibiotics are most urgently needed. Therefore, the researchers are excited to make new discoveries about the ways in which this type of bacteria behaves and survives.

"Infections with this type of bacteria are a major problem worldwide with many hospitalisations and deaths. That is why we are really pleased to be able to contribute new knowledge that can potentially be used to fight these bacteria," says Nina Molin Høyland-Kroghsbo.

However, she emphasises that it will still take a long time for the new knowledge to result in better treatment. The next step is to research how to affect the bacteria's communication and warning signals.

"This clears the way for the use of drugs in an attempt to prevent that the warning signal is sent out in the first place. Alternatively, you could design substances that may block the signal from being received by the other bacteria, and this could potentially make treatment with antibiotics or bacteriophage viruses more effective," concludes Nina Molin Høyland-Kroghsbo.

Importance of Automated Liquid / Gel Dispenser for Hands in Hospitals, Pharmaceuticals and Food Industries

The relations among between the environment, hygiene, and hospital-acquired infections (HAIs) were first detailed in Ignaz Semmelweis's landmark 1846 study regarding infection in a Vienna maternity hospital. Semmelweis observed that the significantly higher postpartum maternal infection and mortality rate in one obstetrics ward was likely related to the poor hand hygiene practices of its healthcare workers (HCWs), who often came directly from the morgue after performing autopsies. He believed that the HCWs were transmitting "cadaverous particles" from the autopsy suite to the obstetrics ward via hand contact, resulting in puerperal sepsis. A subsequent change to more rigorous and mandatory hand hygiene greatly decreased the infection and mortality rates. Hand hygiene has since grown to be regarded as the major weapon against HAI.

Today, HAI continues to be a substantial problem, accounting for an estimated 1.7 million infections and 99,000 deaths each year in the United States. Such infections can be spread by direct person-to-person contact, as well as via contaminated inanimate objects in the environment, known as fomites. Fomites act as reservoirs for pathogens that can then be passed to the hands of HCWs, who, in turn, act as vectors in the spread of organisms to patients.

Fomites can be found throughout the hospital. Better-known fomites are the bed linens, bed rails, furniture, countertops, and floors of patient rooms. Door handles andcurtains have been found to harbour pathogens. Mobile fomites that may themselves act as vectors include stethoscopes, blood pressure cuffs, phlebotomy tourniquets, pens, staff identification badges, and cellular telephones.

Pathogens can survive on their inanimate hosts for long periods of time and may be difficult to eradicate despite conventional cleaning. The most common nosocomial pathogens may survive for months on dry, inanimate surfaces, with longer persistence associated with humid cool conditions, higher inoculum, and certain surface characteristics. Efficient transfer of pathogens from fomites to the hands of HCWs has been demonstrated. Finally, the subsequent transfer to patients resulting in HAI has been shown.

“Touchless technology is a good idea, because hard surfaces are significant transfer points for bacteria and viruses,” says Charles Gerba, PhD, a microbiologist at the University of Arizona, Tucson. “Much of what people put down on a surface can be picked up by the next person who comes along, and in an age where people share more spaces and surfaces than ever before, touchless technology can help prevent cross-contamination.”

It is intuitive to think that the less a potentially contaminated surface is touched, the better, so the advent of automated sink fixtures as well as soap and towel dispensers has been heralded as an important way to reduce the opportunities for cross contamination and hand carriage of pathogenic microorganisms. But how many clinicians consider the role that handwashing stations play in opportunities for cross-contamination?

As experts debate the role inanimate objects play in the transmission of infectious agents, few would doubt that the contamination of environmental surfaces such as handwashing sinks is a major issue. “Clearly inanimate surfaces play a role, particularly with organisms such as *vancomycin-resistant Enterococcus* (VRE) and *Clostridium difficile*,” says Columbia University's Elaine Larson, RN, PhD, FAAN, CIC. “But it seems pretty clear that direct contact (i.e., person-to-person touching) remains the most important mode of cross transmission. Nevertheless, housekeeping and environmental cleaning seem to have taken too much of a back seat and we need to re-emphasize the great importance of keeping the healthcare setting (as well as the people) free of a large microbial bioload.”

Supporters of touchless technology frequently point to a study by Larson et al. that compared the frequency of use of manually operated and touch-free dispensers of alcohol sanitizer installed in the emergency department and an intensive care unit of a large paediatric hospital for two, two-month periods for each type of dispenser. Counting devices installed in each dispenser and direct observations were used to determine actual frequency of and indications for hand hygiene. Larson et al. found that the touch-free dispensers were used significantly more often than were the manual dispensers. The means for the number of episodes of hand hygiene per hour were 4.42 for the touch-free dispensers and 3.33 for the manual dispensers (P = .04); the means for the number of episodes per patient per hour were 2.22 and 1.79, respectively (P = .004); and the means for the number of uses of the dispenser per day were 41.2 and 25.6, respectively (P = .02). However, the overall compliance rate was 38.4 percent (2,136 episodes of hand hygiene per 5,568 indications for hand hygiene).

The researchers concluded that while the type of dispensing system influenced hand hygiene behaviour, overall compliance remained low and that in order for interventions to have a major effect on hand hygiene, multiple factors must be considered.

Kampf,Girard, Bischoffand Pittet concur that hand hygiene compliance is boosted when convenient, readily accessible dispensers are installed, although Muto et al. found that compliance did not improve when alcohol dispensers were placed by every patient's door in two units. While every hospital's experience with touchless dispensers will undoubtedly be different, the hope of decreased cross-contamination and improved hand hygiene compliance is usually the biggest reason why healthcare facilities embrace this technology.

Larson et al write, “Although no evidence indicates that devices that must be manually pressed to dispense cleanser increase the risk of transferring microbes, healthcare staff may express concern about the safety of touching dispensers and may prefer dispensers that are more accessible and easier to use than the manual ones are. Such concerns may be a deterrent to using manual dispensers.” Larson et al. write further, “Our finding that the number of hand hygiene episodes overall was higher for the touch-free dispenser than for the manual dispenser is consistent with the hypothesis that the delivery system has an effect on behaviour and that a touch-free dispenser may be preferred by healthcare professionals, food and pharmaceutical industries.”

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Highlights of the coming issue

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