

## The importance of microbiological quality control in the pharmaceutical industry



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### **Microbiologics, Inc.**

In recent years, the number of major drug recalls within the Pharmaceutical industry has skyrocketed from 426 in 2008 to 1,742 in 2009 according to CNNMoney.<sup>1</sup> Even more alarming is the increase in drug recalls due to microbial contamination, which are among the most dangerous as they can result in serious illness or death.

A recent example is the January 2011 recall of Alcohol Prep Pads, Alcohol Swabs and Alcohol Swabsticks, manufactured by the Triad Group.<sup>2</sup> This recall was initiated due to potential contamination of *Bacillus cereus*. Another pharmaceutical product that was recently recalled due to microbial contamination included two brands of antiseptic-antiplaque mouthwash that were contaminated with *Burkholderia cepacia*. This recall took place in November 2010, and was issued by the Health Sciences Authority in Singapore.<sup>3</sup>

Undoubtedly, a company suffers enormous damage when a drug product is recalled. The direct hit will include loss of product sales, decreased customer confidence, damage to the brand and company name, and in many cases, legal proceedings. The overall costs associated with a major drug recall are almost immeasurable.

Quality Control is an essential function of the Pharmaceutical industry. Drug manufacturers must thoroughly test materials, processes, equipment, techniques,

environments and personnel in order to ensure their final products are consistent, safe, effective and predictable.

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### **Pharmacopeias**

In addition to their local government authorities, many pharmaceutical manufacturers look to a Pharmacopeia for guidance on ensuring the quality, safety and benefit of the medicines they produce. A Pharmacopeia is an organization that develops and publishes standards for manufacturing prescription and over-the-counter medicines as well as other healthcare products.

Three major Pharmacopeias throughout the world include: the United States Pharmacopeia (USP), the European Pharmacopoeia (Ph. Eur.) and the Japanese Pharmacopoeia (JP). Each of these organizations has their own set of standards; however the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is working to facilitate international harmonization in the interpretation and application of technical guidelines and requirements for the pharmaceutical industry.

### **The growth promotion test**

The Growth Promotion Test is a very important Quality Control function in the Pharmaceutical industry. It is imperative for establishing the nutritive properties of the microbiological culture medium that will be used in a pharmacopeial procedure, such as a test for specified microorganisms. Culture medium (or media) refers to a liquid or gel substance that is used to support the growth of microorganism or cell.

The Growth Promotion Test is necessary to ensure that the culture medium is able to support the growth of small numbers of microorganisms, and that selective medium will

grow specified microorganisms. If the new batch of media is not able to properly support growth, the pharmacopeial tests for which it is used will fail.

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There are three key tests in the pharmacopeias that outline growth promotion testing. These chapters have been harmonized in the United States Pharmacopeia (USP), the European Pharmacopoeia (Ph. Eur.) and the Japanese Pharmacopoeia (JP).

#### *Microbial enumeration tests*

This test establishes the ability of the new lots of medium to support growth when the inoculum contains a small number of microorganisms. This test is used for both solid and liquid media.

#### *Tests for specified microorganisms*

This test establishes the ability of the selective medium to meet three criteria:

- Growth promoting properties – the growth of selected microorganism is supported
- Indicative properties – the colonies have specific morphological characteristics (see figure1)
- Inhibitory properties – organisms that should be inhibited on the medium should not grow



*Figure 1: This image illustrates the specific morphological characteristics of three different organisms grown on MacConkey Agar. Top: Escherichia coli, Bottom left: Proteus vulgaris, Bottom right: Pseudomonas aeruginosa.*

### *Sterility tests*

This test establishes the ability of new lots of medium to support growth when the inoculum contains a small number of microorganisms. This test is used for liquid medium only.

### **Requirements of the growth promotion test**

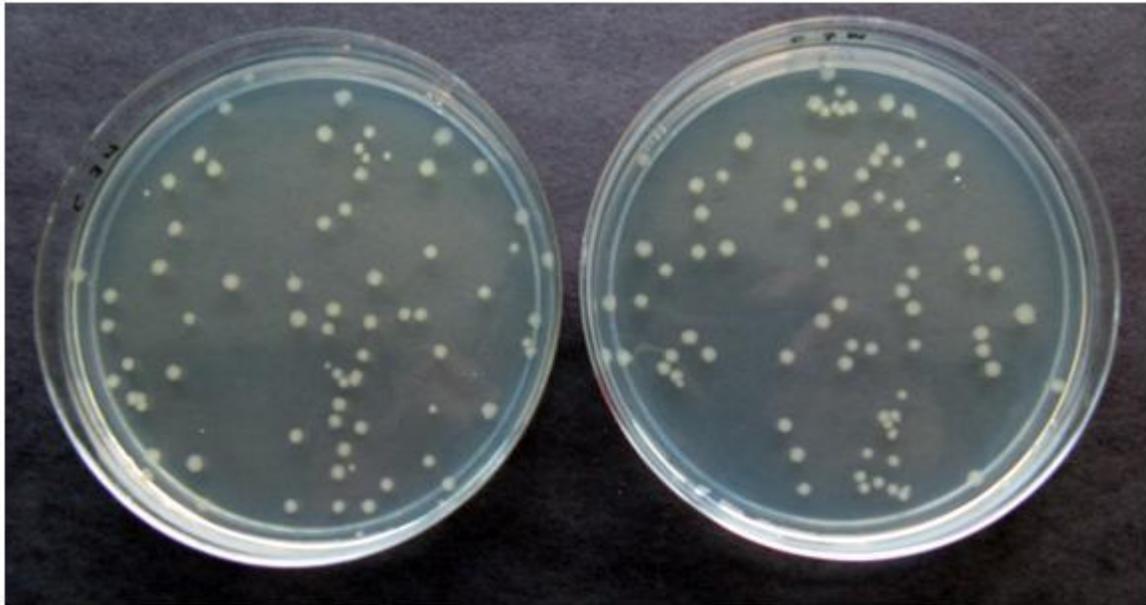
Growth promotion testing must be done for each and every new batch of culture medium, both solid and liquid, that will be used in a Pharmacopeial procedure. This includes purchased pre-prepared or dehydrated medium, or medium that was prepared in house. At a minimum, the testing must be done with the list of organisms specified in the pharmacopeia. Additional organisms may be needed depending on the requirements and SOPs for each individual laboratory or situation.

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The basic requirements for the GPT are as follows:

1. The new batch of medium must be inoculated with a small number of microorganisms (less than 100 Colony Forming Units).
2. The laboratory should test the medium with the microorganisms required by the pharmacopoeias.
3. The microorganisms must not be more than five passages removed from Reference Culture (also called the original master seed lot).

In order for the new batch of medium to be approved for use, growth on the new batch of medium must be comparable to growth obtained on a batch of medium previously approved by the laboratory (see figure 2).



*Figure 2: For best results use parallel testing. This is when the new medium and the previously approved medium are inoculated with the same inoculum, by the same technician, and are subjected to identical incubation conditions. This way the only variable is the medium.*

### **Microorganisms for growth promotion testing**

The challenge microorganisms for use in Growth Promotion Testing can be purchased from a culture collection, or from a licensed commercial manufacturer.

The use of strains directly from a culture collection requires the construction of a calibration curve for each organism, because each organism will have a different curve. This can be done using McFarland standards to visually approximate and interpret turbidity of a cell suspension, or by using a spectrophotometer to directly measure turbidity of the cell suspension.

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These methods are very time consuming, and must be done over a number of days because incubation is required for the growth of the organism. The use of McFarland standards also introduces significant variability because this is a subjective measurement.

Ready-to-use certified strains are available as quantitative preparations. These samples can be used with only a few quick and simple steps. Using these preparations will save time because no growth time is required, and hands -on work time is reduced by eliminating the need for any measurement or interpretation of cell density. An additional benefit is the reduced risk of contamination of the sample and in the environment because the use of the prepared strains is short term.

### **Conclusion**

Quality control is an essential part of the laboratory routine. It is not only important for compliance with standards, but also reduces risk to the end user, and, consequently, to the manufacturer.

### **References:**

1. Kavilanz, Parija. Drug recalls surge. CNNMoney. [Online] August 16, 2010. [Cited: May 27, 2011.]  
[http://money.cnn.com/2010/08/16/news/companies/drug\\_recall\\_surge/index.htm](http://money.cnn.com/2010/08/16/news/companies/drug_recall_surge/index.htm).
2. Triad Group Issues a Voluntary Nationwide Recall of All Lots of Alcohol Prep Pads, Alcohol Swabs, and Alcohol Swabsticks Due to Potential Microbial Contamination. U.S. Food and Drug Administration. [Online] January 5, 2011.

[Cited: May 27, 2011.]

<http://www.fda.gov/Safety/Recalls/ucm239219.htm>.

3. Voluntary Recall of “Oral Guard Antiseptic-Antiplaque Mouthwash”. Health Sciences Authority. [Online] November 16, 2010. [Cited: May 27, 2011.]

[https://www.hsa.gov.sg/publish/hsaportal/en/health\\_products\\_regulation/safety\\_information/product\\_safety\\_alerts/safety\\_alerts\\_2010/voluntary\\_recall\\_of.html](https://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/safety_information/product_safety_alerts/safety_alerts_2010/voluntary_recall_of.html).

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