Growth promotion testing

SmartNote: Growth Promotion Testing for pharmaceutical microbiology

Dr. Tarun Chugh, CEO, SIMco Pharma Consultancy

Abstract

The Growth Promotion Test (GPT) is a critical component of quality assurance in pharmaceutical microbiology. It serves to validate the growth-supporting properties of culture media used for microbial testing, ensuring the reliable detection and enumeration of microorganisms. This report explores the fundamental principles, regulatory requirements, methods, and best practices associated with the Growth Promotion Test within the context of pharmaceutical microbiology. The report also discusses key considerations for conducting and interpreting GPT results, emphasizing the importance of this test in maintaining the quality and safety of pharmaceutical products.

1. Introduction

In the pharmaceutical industry, microbiological testing is essential to ensure the safety and efficacy of pharmaceutical products. The reliability of these tests heavily depends on the quality of culture media used for microbial growth. GPT plays a vital role in verifying the ability of these culture media to support the growth of specific microorganisms under defined conditions. The objective is to provide an in-depth analysis of the GPT, its significance, methods, and regulatory implications in pharmaceutical microbiology.

2. Purpose and significance of the Growth Promotion Test

The GPT is conducted to assess the ability of culture media to support the growth of specific microorganisms. It ensures that the culture media used in microbial testing are capable of promoting the growth of target organisms, thereby enabling accurate detection and enumeration. The test is crucial for maintaining the reliability and reproducibility of microbiological assays performed in pharmaceutical quality control and assurance processes.

Prior to performing the listed routine tests below, the Pharmaceutical Industry requires GPT to be conducted.

- Microbial limit test
- Environmental monitoring
- Sterility testing
- Microbiology assay
- Validation

3. Regulatory requirements

The Growth Promotion Test is governed by various regulatory guidelines and pharmacopoeia standards to ensure consistency and reliability in pharmaceutical microbiology. Regulatory bodies such as the United States Pharmacopeia (USP), European Pharmacopoeia (Ph. Eur.), and others provide specific requirements and methodologies for conducting the GPT using specified microbial cultures procured from the standard institutes e.g., ATCC/MTCC/NCIMB/CIP and kept on recommended temperature conditions as specified on the culture certificate during storage and incubation. Compliance with these standards is mandatory for pharmaceutical manufacturers to demonstrate the quality and suitability of their culture media for microbiological testing.

4. Principles of the Growth Promotion Test

The GPT is based on the principle of challenging culture media with specific microorganisms to verify their ability to support growth. Key principles include selecting appropriate test organisms, inoculation techniques, incubation conditions, and interpretation of results. The choice of test organisms should represent those commonly encountered in pharmaceutical manufacturing environments and include both bacteria and fungi.

5. Methods for conducting the Growth Promotion Test

The Growth Promotion Test involves several methodological steps, starting with the preparation of culture media and inoculum.

The following steps outline a typical GPT procedure:

a. Selection of test organisms: Identify relevant bacterial and fungal strains.

b. Preparation of inoculum: Cultivate organisms to a suitable growth phase.

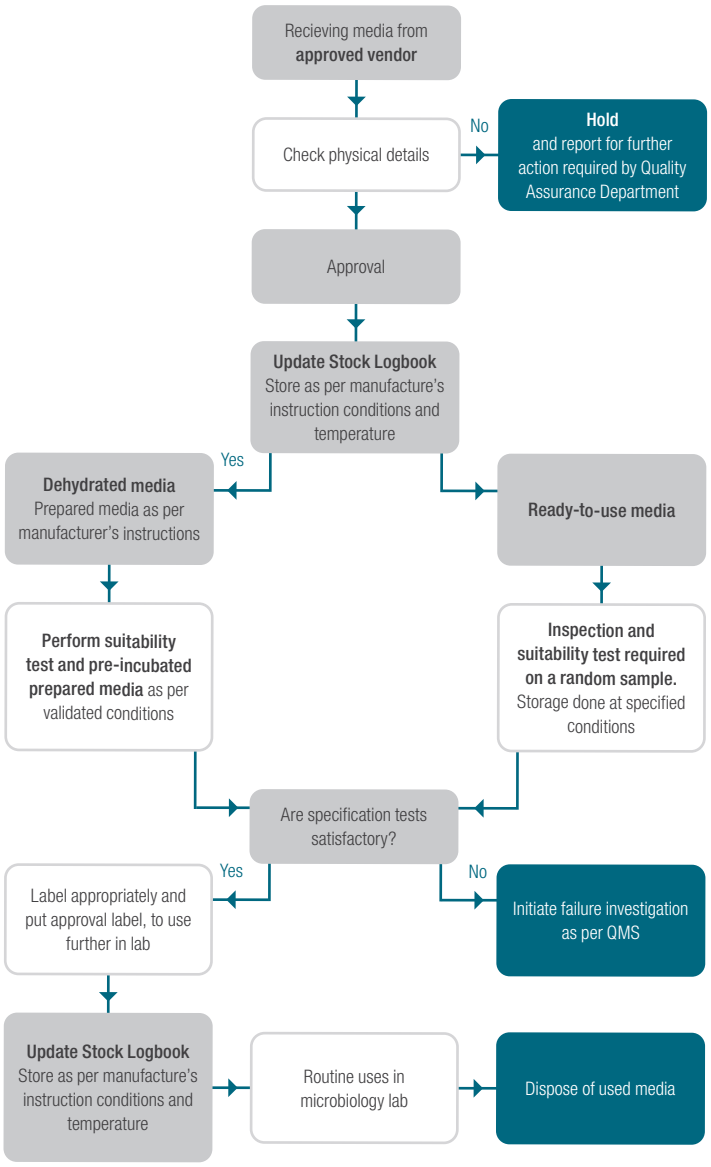
c. Incubation conditions: Determine optimal temperature and duration for growth.

d. Inoculation of media: Inoculate culture media with test organisms.

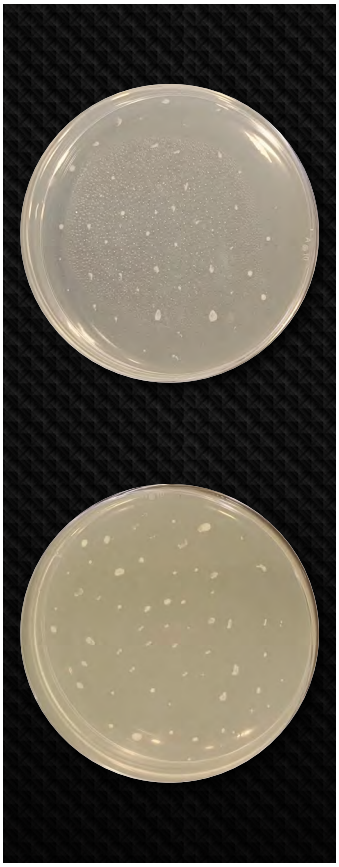
e. Monitoring and interpretation: Observe growth after incubation and interpret results according to defined criteria.

The serial dilution suspension method has been found challenging for achieving accurate results. Moreover, this approach is susceptible to flaws, especially since the inoculum lacks a Certificate of Analysis (CoA), and a gradual decrease in viability may not be easily identified. A CoA provides detailed information on the quality and specifications of the inoculum, including its concentration and viability. Without this certification, the inoculum's quality is uncertain, and any decline in its viability over time might go unnoticed. This lack of information can lead to inaccuracies in the initial microbial concentration, making it difficult to achieve reliable and reproducible results.

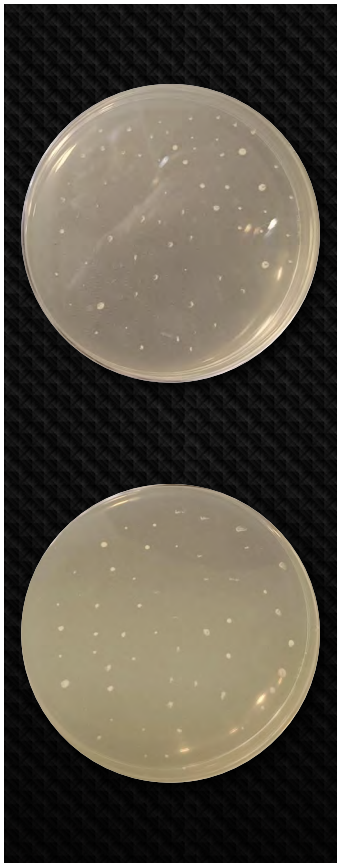
Testing with a reference material offers an alternative, providing an independent and precise external calibration point. Each batch of ready-to-use reference material should be sourced from an ISO 17034:2016 accredited manufacturer and include qualitative data specific to the batch on the CoA.



Flow diagram: Media suitability test and Growth Promotion Test



Previously approved medium



New medium

6. Interpreting GPT results

The interpretation of GPT results is based on predefined acceptance criteria established by pharmacopoeia standards or internal specifications. Media are considered suitable for use if growth occurs within specified timeframes and demonstrates the expected characteristics of the test organism. Failure to achieve growth or abnormal growth patterns may indicate issues with the culture media or testing conditions.

To assess, compare number of colonies on previously approved medium to the number on new medium

The number must be within a factor of 2. Examples:

- Previously approved medium = 40
- New batch of medium must = 20 to 80

USP reference:

“For solid media, growth obtained must not differ by a factor greater than 2 from the calculated value for a standardized inoculum. For a freshly prepared inoculum, growth of the microorganisms comparable to that previously obtained with a previously tested and approved batch of medium occurs. Liquid media are suitable if clearly visible growth of the microorganisms comparable to that previously obtained with a previously tested and approved batch of medium occurs.”

7. Quality control and assurance

The Growth Promotion Test is an integral part of quality control and assurance programs in pharmaceutical microbiology. It ensures the consistency and reliability of culture media used in microbial testing, contributing to the overall quality and safety of pharmaceutical products. Regular performance of the GPT is essential to detect any deviations that may affect the accuracy of microbiological test results.

8. Best practices and challenges

Adhering to best practices is essential for the successful implementation of the Growth Promotion Test. Key considerations include:

- Proper selection and handling of test organisms
- Validation of culture media batches
- Adequate documentation and record-keeping
- Routine monitoring of environmental conditions

Challenges associated with the GPT include variability in test organism behavior, environmental factors, and interpretation of ambiguous results. Overcoming these challenges requires a systematic approach and continuous improvement of testing methodologies.

Previously approved broth

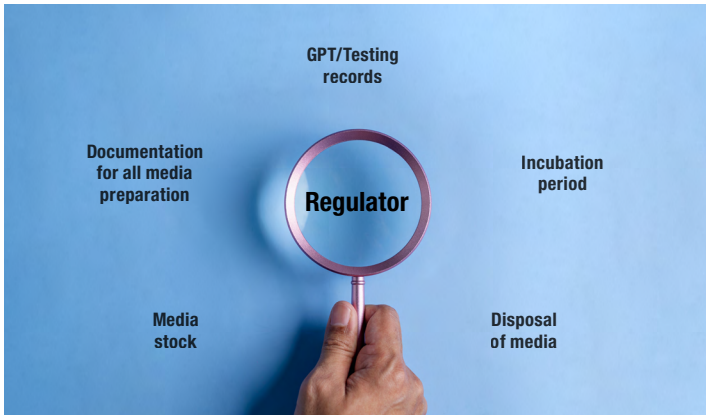
New broth

What do regulators look for related to GPT during a microbiology laboratory audit?

During microbiology laboratory audits, regulators focus on key aspects related to the GPT to ensure compliance with pharmacopoeia standards. Regulators typically look for evidence of GPT performance on all new batches of culture media used for microbial testing. They assess whether appropriate test organisms were selected and if the growth-promoting capabilities of the media were validated under specified conditions.

Furthermore, regulators examine documentation related to GPT protocols, including procedures for preparing inoculum, incubation parameters, and criteria for interpreting results.

Compliance with pharmacopeial requirements and internal specifications is crucial, and any deviations or non-conformities identified during the audit are examined thoroughly for corrective and preventive actions. Overall, regulators aim to verify that the GPT is conducted effectively to guarantee the reliability and accuracy of microbiological testing in pharmaceutical laboratories and complying to 21 CFR 211.160 of USFDA.



Regulators examine the qualification and training of laboratory personnel involved in performing the GPT. They look for evidence of competency in executing GPT procedures, handling microbial cultures, and interpreting test results accurately. Laboratory personnel's Proficiency Testing is evaluated by reviewing Training records, Microbiologist qualification done by handling of microbial culture, inoculation preparation, incubation and recording the results.

Case Study 1*

FDA audit has observation of the GPT for laboratory control system as follows:

Laboratory Control system:

Laboratory controls did not include scientifically sound and appropriate test procedures designed to assure that components, in-process materials, and drug products conform to appropriate standards of identity, strength, quality, and purity. 21 CFR 211.160

Growth promotion testing was not performed on microbiological testing media, there was no assurance that yeast and mold will grow at the [ ] incubation temperature used to detect bacteria growth, microorganisms found during environmental testing were not identified, and the [ ] analytical method used on eye drops and nasal spray was not fully validated. Your proposed corrections appear acceptable pending our receipt and review of supporting documentation.

In this scenario, there was a validation failure of the GPT for each dosage form, resulting in the absence of data during an audit at the auditor's request. This situation does not meet the requirements specified in 21 CFR 211.160.

Case Study 2*

Observation 9

The accuracy, sensitivity, specificity, and reproducibility of test methods have not been established.

1. Growth promotion testing for (b) (4) used in media fills and sterility testing does not include gram-negative bacteria. (b) (4) is prepared using (b) (4) for (b) (4), and is purchased as a pre-made (b) (4) for (b) (4). No documented scientific justification was provided to explain the exclusion of gram-negative bacteria in the different (b) (4) batches during growth promotion testing.

In this situation, there was a deficiency in conducting the GPT for the media intended for use in media fill and sterility testing of sterile dosage forms. Additionally, there was a lack of GPT performed on the pre-procured ready-made media intended for the media fill activity.

* Case studies are the references from the USFD site - ORA FOIA Electronic Reading Room.

Reference of warning letters for growth promotion test are as follows:*

January 22, 2020: Warning letter written to manufacturer of over-the-counter (OTC) products:

"You do not consistently perform growth promotion testing on the in-house media used for microbiological testing of your finished drug products and for water testing to ensure the media supports growth and acceptable recovery…As such each batch of media you use for microbiological testing has not been adequately verified for growth promotion. You cannot ensure that, upon release, your drug products meet acceptable microbiological specifications."

October 31, 2019: Warning letter written to manufacturer of OTC drug products:

"Your firm stated to our investigator that you do not perform growth promotion on each lot of prepared media to ensure your plates are suitable for use in microbial testing of incoming components, finished drug products, and your water system."

* References from the USFD site - ORA FOIA Electronic Reading Room.

9. Conclusion

The Growth Promotion Test is a critical quality control procedure in pharmaceutical microbiology, ensuring the reliability and accuracy of microbial testing. Compliance with regulatory standards and adherence to best practices are essential for successful GPT implementation. By validating the growth-supporting properties of culture media, the GPT contributes to the overall quality and safety of pharmaceutical products.

References

1. United States Pharmacopeia (USP) Chapter <61> Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests.
2. European Pharmacopoeia (Ph. Eur.) Chapter 2.6.1 Microbiological Examination of Non-Sterile Products: Microbial Enumeration Tests.
3. World Health Organization (WHO). Good Manufacturing Practices for Pharmaceuticals: Main Principles.
4. FDA Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice.
5. PDA Technical Report No. 33: Evaluation, Validation and Implementation of Alternative and Rapid Microbiological Methods.

This report provides a comprehensive overview of the Growth Promotion Test in pharmaceutical microbiology, covering its purpose, methods, regulatory aspects, and best practices. It serves as a valuable resource for pharmaceutical professionals involved in quality control, assurance, and regulatory compliance.