Regulatory Affairs in Industrial Pharmacy in India

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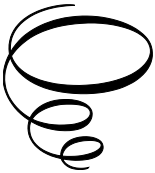
Edited by

Madhu Verma and Iti Chauhan

Cambridge Scholars Publishing



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PREFACE

The pharmaceutical industry is crucial for public health, and in India's fast-changing landscape, regulatory affairs are more important than ever. The dynamic interplay between regulatory frameworks, quality assurance, and drug safety has far-reaching implications for both healthcare providers and consumers. This book, *Regulatory Affairs in Industrial Pharmacy in India*, is intended to serve as a comprehensive guide in understanding the regulatory environment governing the pharmaceutical industry in India, addressing the challenges, complexities, and opportunities it presents.

With India emerging as a global hub for pharmaceutical manufacturing, there is a pressing need for professionals, students, and stakeholders to be well-versed in regulatory standards, guidelines, and processes. From ensuring the efficacy and safety of products to navigating the intricate pathways of drug approval, compliance with national and international standards is essential. This book is organised into fourteen chapters covering essential aspects of pilot plant scale-up considerations, SUPAC, technology transfer, drug regulation, quality management system, and Indian regulatory requirements.

This book aims to bridge the gap between theory and practice, offering readers both foundational knowledge and current insights into regulatory affairs. It is designed for pharmaceutical professionals, regulatory affairs specialists, students, and academicians who seek to deepen their understanding of the regulatory landscape that governs the pharmaceutical industry in India. By equipping readers with this knowledge, the book aspires to contribute to a more robust, transparent, and efficient regulatory ecosystem.

I would like to express my gratitude to all those who have contributed to this book, including industry experts, academic mentors, and colleagues. Their insights and experiences have been invaluable in shaping this work. I hope that this book will serve as a valuable resource for professionals and students alike, helping them navigate the complex regulatory environment with greater confidence and clarity.

Dr. Madhu Verma
Dr Iti Chauhan

CHAPTER 1

AN INTRODUCTION TO PILOT PLANT SCALE-UP TECHNIQUES

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Abstract

The Research and Development (R&D) division in Pharmaceutical Sciences is essential for developing dosage forms that meet desired specifications, ensuring they are chemically and physically stable, and delivering the drug at a controlled rate. The scale-up from laboratory to industrial production requires careful consideration of personnel, space, and raw materials. In the R&D phase, experiments are conducted using laboratory-scale equipment or intermediate-sized pilot plants, which help optimize processes and facilitate scaling. This chapter explores the key challenges and techniques involved in scaling up pilot plants for pharmaceutical manufacturing, focusing on the need for skilled personnel, including operators, engineers, and safety experts, as the complexity of operations increases. Space requirements are examined for accommodating larger equipment, expanding support systems, and ensuring safety and maintenance. The efficient procurement and management of raw materials are crucial for meeting the demands of scaled-up production. Additionally, it highlights the importance of integrating these elements to ensure a smooth transition to commercial-scale manufacturing while maintaining process consistency, quality, and safety. This study provides valuable insights into the operational and

logistical challenges faced during the pilot plant scale-up, contributing to more efficient and cost-effective pharmaceutical production processes.

Keywords: Commercialization, Lab scale, Research and development, personnel requirements, Batch scale, manufacturing.

1.1 Introduction

Research and development is a multidisciplinary field involving:

1. **Basic Research**: This initial phase involves fundamental research into diseases and potential treatment options.
2. **Drug Discovery**: Identification of promising compounds that could become new drugs.
3. **Preclinical Testing**: Early-stage testing on cells and animals to assess safety and efficacy.
4. **Clinical Trials**: Rigorous testing on humans in multiple phases to ensure safety and effectiveness.
5. **Regulatory Approval**: Gaining approval from regulatory bodies like the FDA.
6. **Manufacturing**: Scaling up production processes to meet the demands of mass production while maintaining consistent quality and adherence to regulatory standards.
7. **Post-Market Surveillance**: Monitoring drug safety and efficacy in the real-world scenario.

Each of these components plays a critical role in the successful development of new pharmaceutical products [Doroshenko, 2024]. R & D personnel develop a dosage form with desired specifications during manufacturing. The formulations should be physically and chemically stable and must release the drug at a predetermined rate. In R & D, experimentation uses equipment suited to laboratory-scale operations or intermediate-sized pilot plant facilities, facilitating process optimization and scale-up. Access to such equipment is widespread across laboratories, ensuring consistency in research and development practices and facilitating innovation in pharmaceutical manufacturing.

At this level a need of successful marketed product which is clinically efficient and safe in a cost-effective manner. The product should display reproducible manufacturing at high-speed commercial level equipment [Lachman, Lieberman and Kanig 1976].

1.1.1 Pilot plant

A pilot plant is a pivotal landmark in a drug's commercial development. Here, drug sponsors or manufacturers address issues related to engineering, commercialization, clinical, regulatory, and process which pose a challenge beyond the controlled environment of laboratory scale (R & D). Additionally, the pilot scale serves as a testing ground for assessing a product's manufacturability and is frequently revisited by sponsors to resolve production bottlenecks or unforeseen issues [DePalma, n.d.]. It is part of the pharmaceutical industry where a lab-scale formula is transferred into a viable robust product by developing a liable and practical procedure of manufacture. It's a step-by-step process that ensures the smooth progression from small-scale experimentation to routine processing and ultimately to large-scale manufacturing facilities (**Fig. 1-1**) [Rane et al., 2023]

Fig. 1-1 Stages of Scale-Up in Pharmaceutical Development

1.1.2 Importance of pilot plant

Pilot plant studies in the pharmaceutical industry encompass several essential components. These include a meticulous examination of the formula, adjustments to batch scale and processes, and a thorough review of relevant processing equipment to ensure compatibility with the formula. The aim is to develop procedures that are economical, simple, and reliable, while also ensuring consistency by checking raw materials against specified standards. Additionally, production rates are assessed in alignment with market demands, and considerations are made regarding physical space and layout. Personnel requirements, training, reporting structures, and responsibilities are defined. Process and production controls are rigorously evaluated, validated, and finalized, with comprehensive documenta-

tion maintained to support Good Manufacturing Practices (GMP). Ultimately, these studies result in detailed records covering production formulation, processes, equipment training, and specifications [Rane et al., 2023].

1.1.3 Objectives of pilot plant scale up

1. Designing a large-scale processing plant solely based on laboratory data lacks a reliable degree of success.
2. To investigate a product and process before large amounts of money are committed to full scale production.
3. Investigation of the formula to explore its adaptability to batch scale and process adjustments.
4. Assessment and validation of Process and equipment.
5. To identify essential characteristics of the process.
6. To establish production and process control guidelines.
7. To provide manufacturing technique guidance to master manufacturing.
8. To prevent issues with scaling up [Bandarapalle et al., 2024].

1.2 General considerations

Although commercialization primarily drives pilot plant projects, they encompass diverse objectives shaped by organizational goals. These facilities integrate the 5M's (Money, Material, Man, Method, and Machine) for manufacturing. NDAs and ANDAs are at peak levels, prompting laboratories to adopt new processes and technologies for scientific advancement. Considerations for scaling up pilot plants vary by dosage form, but overarching factors apply (**Fig.1-2**) [Kiran et al., 2022].

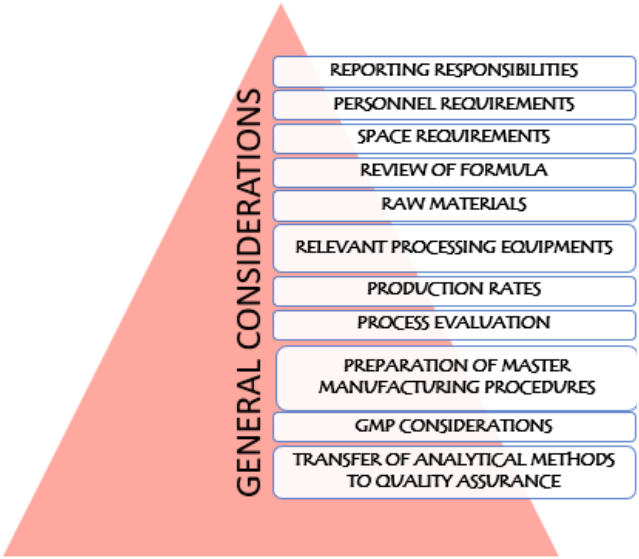

Fig. 1-2 Scaling Up Pilot Plants: Key Considerations

1.2.1 Reporting responsibilities

The goal of the reporting responsibility in the pilot plant is to streamline the transition of a product from the laboratory to production. This function can be part of a distinct department or an R&D team with its own staff. Some companies maintain both a pilot plant and a technical service group. The success of the pilot plant is measured by how smoothly new products or processes are integrated into regular production. This success is achievable if there is a strong collaborative relationship between the pilot plant team and other departments, such as Research & Development, Processing, Packaging, Engineering, Quality Assurance, Quality Control, and Regulatory. The product formulator, who developed the product, can oversee its production and continue to support other departments even after the product has entered production [Uberuser 2024].

1.2.2 Personnel requirements

Those employed during the scale up process should be individuals with qualifications required for position in a pilot plant organization. It should be a blend of good theoretical knowledge of pharmacy and some practical ex-

perience in the pharmaceutical industry. They should possess good communication and written skills. Scientists with experience in pilot plant operations as well as in actual production area are the most preferable as they have to understand the intent of the formulator as well as understand the perspective of the production personnel. The group should have some personnel with engineering knowledge as well as scale up also involves engineering principles. The number of people in a pilot plant depends on the number of products and the required level of support [Bhendale et al. 2021].

1.2.3 Space requirements

The space required in pilot plant is divided into 4 areas that are shown in **Fig. 1-3**.

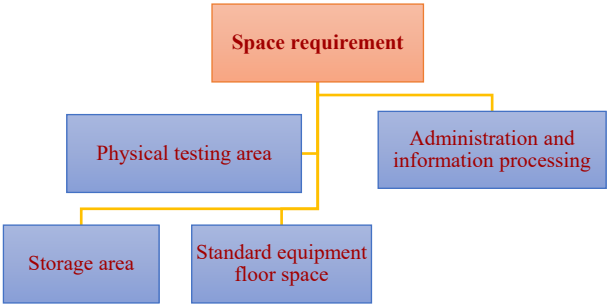

Fig. 1-3 Space requirement in pilot plant

1.2.3.1 Administration and information processing area

Adequate office and desk space should be provided for both scientists and technicians, ensuring they have a comfortable and efficient working environment (**Fig.1-4**). This space should be adjacent to the working area to minimize unnecessary movement and avoid distractions. Additionally, there should be designated space for conducting meetings with personnel from various fields, facilitating collaboration. A computer terminal should also be available for the storage of data, enhancing the organization and accessibility of information.

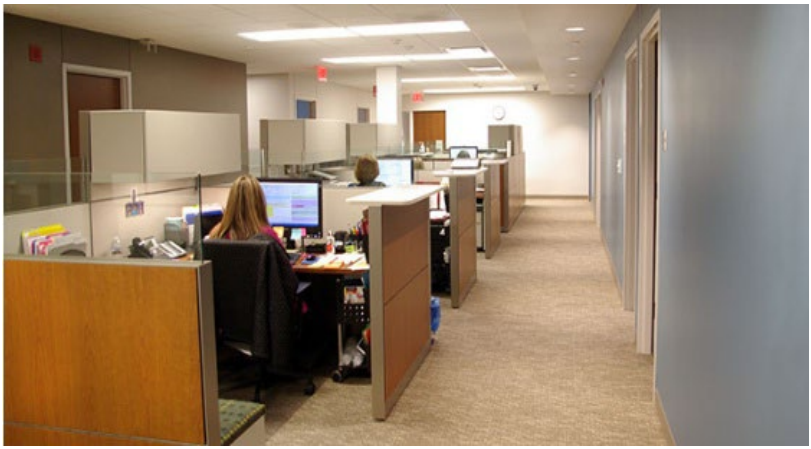

Fig. 1-4 An illustration of administration area.
PIC Credit: https://www.mortenson.com/company/news-and-insights/2014/advocate-good-shepherd-hospital-completes-phase-2

1.2.3.2 Physical testing area

An adequate working area should be provided for the analysis and physical testing of samples (in-process quality control analysis) to enable early identification of production errors. This area should include permanent benchtop space for routinely used physical testing equipment such as balances, pH meters, and viscometers (**Fig. 1-5**).

Fig. 1-5 An illustration of physical testing area.
PIC Credit: South west solutions

1.2.3.3 Standard equipment and floor space

The sufficient specified space must be there for free installation, operation and easy maintenance of the equipment. Further explanations are provided in **Fig. 1-6**.

Fig. 1-6 Standard details of equipment and floor space

1.2.3.4 Storage area

A designated storage area should be provided for in-process materials, finished bulk products, retained samples, experimental production batches, and packaging materials, with segregation into approved and unapproved areas (**Fig. 1-7 & 1.8**). Additionally, there should be a controlled environment space allocated for the storage of stability samples. Separate provisions should also be made for APIs and excipients, further segregated into approved and unapproved areas in accordance with GMP.

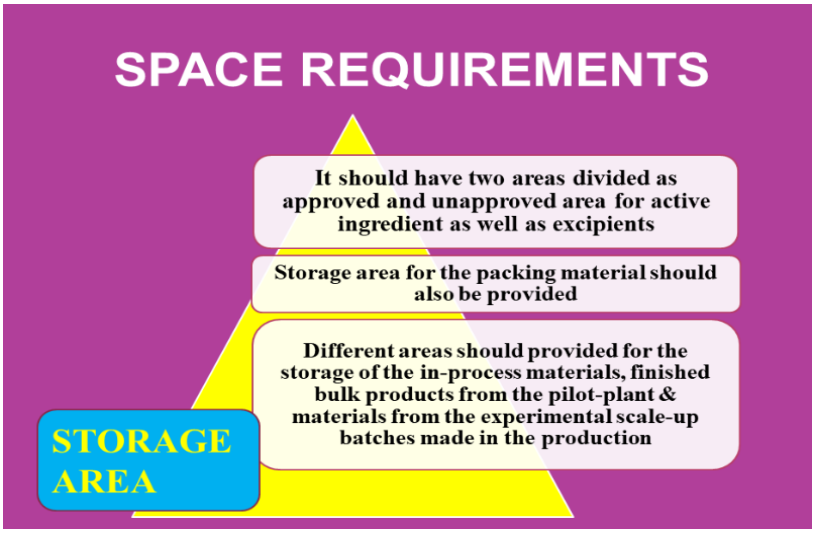

Fig. 1-7 Storage Requirements for Pilot Plant Operations

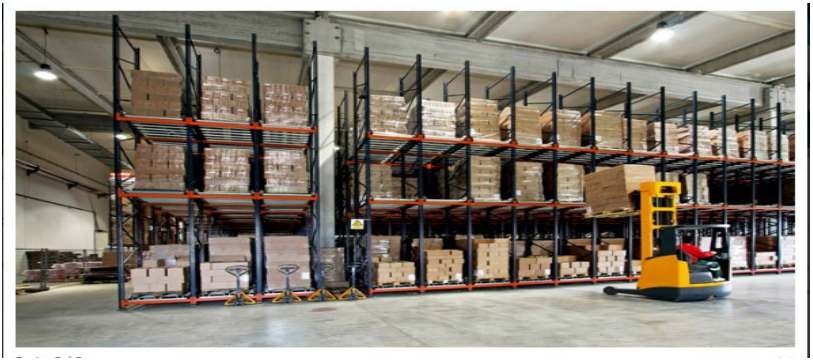

Fig. 1-8: An illustration of storage area
PIC credit: http://www.hursanlojistik.com/en/Storage.html

1.2.3 Review of formula

A thorough review of each aspect of formulation is important. Understanding the purpose of each ingredient and its csontribution to the final product manufactured on small-scale laboratory equipment is essential. This knowledge allows for better prediction or recognition of the

effects of scale-up using equipment that may subject the product to various types and degrees of stress.

1.2.4 Raw materials

One responsibility of the pilot plant is the approval and validation of the active ingredient and excipient raw materials. Raw materials used in small-scale production cannot necessarily be representative of those used in large-scale production. Even if analytical specifications are met, the API may vary in particle size, shape, and morphology, which can affect handling, bulk properties, and color. Quality should be verified, as having an alternate supplier is desirable for both supply reliability and acquisition cost [Lachman, Lieberman and Kanig 1976].

1.2.5 Relevant processing equipment

The selection of equipment prioritizes both economy and efficiency, opting for the simplest and most cost-effective options capable of meeting proposed specifications. The equipment's size must align with the scale of production, ensuring that experimental trials accurately reflect production-sized batches. If the equipment is too small, the developed process won't scale up effectively, whereas oversized equipment risks wastage of expensive active ingredients.

1.2.6 Production rates

The immediate as well as the future market trends/requirements are considered while determining the production rates. The equipment's size and use should be proportionate to one another. The number of batches required for testing, the amount of time needed to clean up equipment between batches, and product loss in equipment during the manufacturing process all influence the choice of equipment and procedure to be employed.

1.2.7 Process evaluation

This step critically evaluates the manufacturing process and optimizes its performance based on that evaluation. The processes to be examined include:

- Order of addition of components, including adjustments to their amounts.
- Mixing speed and mixing time.
- Rate of addition of granulating agents, solvents, drug solutions, slurries, etc.
- Heating and cooling rates.
- Filter sizes for liquid preparations.
- Screen sizes for solid preparations.
- Drying temperatures and drying times.

Understanding the impact of these crucial process parameters on both in-process and finished product quality forms the foundation for process optimization and validation. This is achieved by monitoring the within-batch variation of measurable parameters such as content uniformity, moisture content, and compressibility. Collecting this data helps in assessing and identifying where the process is performing as intended and where potential problem areas may be located [Liu, Levin and Sheskey 2009].

1.2.8 Master manufacturing procedure

This focuses on presenting the manufacturing procedures in a way that ensures easy compliance and understanding by processing technicians. These procedures encompass manufacturing directives, the chemical weight sheet, sampling directions, and specifications for both in-process and finished products.

1.2.8.1 Chemical weight sheet

The chemical weight sheet serves as an essential document that guides the technician through the batching process, ensuring consistency and quality control in the production. The chemical weight sheet helps the technician clearly identify each chemical used in the batch by its exact name and number on the raw material containers and in the batch records. The sheet indicates the specific order in which chemicals should be added to the batch, ensuring the correct chemical reactions and optimal product quality. Any special handling instructions or observations related to specific chemicals are noted to ensure safe and effective processing.

1.2.8.2 Processing directions

The processing directions must be precise and explicit to ensure clarity and avoid any misinterpretation during operations. Directions should be written in language familiar to the operators to facilitate understanding and accurate execution of tasks. Input for these directions should come from actual operators or individuals with current knowledge of weighing and processing operations to ensure relevance and accuracy. When maintaining batch records or standard operating procedures (SOPs), excessive signatures and overly detailed directions can be cumbersome and counterproductive.

1.2.8.3 Batch record directions

Addition rates, mixing time, mixing speed, heating and cooling rates, and temperature must be specified in the processing directions to ensure precise control over the production process. Appropriate ranges should be given for each parameter to allow for slight variations while maintaining product quality. The actual time, temperature, and speed used during processing should be clearly mentioned to provide an accurate record of the conditions under which the batch was produced. These parameters must be monitored and recorded by appropriate controller recorders to ensure compliance with specified ranges and maintain consistency. It is essential to verify that all equipment is functioning properly to prevent any deviations that could affect the quality of the final product.

1.2.8.4 Manufacturing procedure

The time, manner, handling, and storage of samples for both in-process and finished products should be clearly mentioned in the manufacturing procedure to ensure accurate data collection. Improperly taken samples can provide unreliable data, compromising the quality control process. In-process specifications should be realistic but narrower than those for finished products to ensure that any deviations are detected early and corrective actions can be taken promptly. Finished product specifications are essential for evaluating the product's quality and ensuring it meets the required standards. The manufactured finished product should release the drug at the specified dose within the prespecified timings to ensure efficacy and safety. Periodic revalidation, adherence to Good Manufacturing Practices (GMPs), and monitoring of finished product test results via control charts are required to maintain consistent product quality [Gad 2008].

1.2.9 GMP considerations

Equipment Qualification: Ensure that all equipment is properly qualified for its intended use.

Process Validation: Validate manufacturing processes to guarantee consistent product quality.

Regular Process Review & Revalidation: Conduct regular reviews and revalidations of processes to maintain standards.

Relevant Written Standard Operating Procedures: Maintain up-to-date SOPs to guide operations and ensure compliance.

Regularly Scheduled Preventative Maintenance: Implement scheduled maintenance to prevent equipment failures.

Use of Competent, Technically Qualified Personnel: Employ personnel who are technically qualified and competent.

Well-Defined Technology Transfer System: Establish a clear system for transferring technology between departments.

Adequate Provision for Training of Personnel: Provide thorough training programs for all personnel.

Orderly Arrangement of Equipment: Arrange equipment to ensure easy workflow and prevent cross-contamination.

Validated Cleaning Procedures: Validate cleaning procedures to ensure equipment is properly sanitized.

Although the FDA sets guidelines, interpretations may vary between FDA officials and industry professionals. So, include a checklist of GMP items as part of scale-up specifications to ensure comprehensive compliance [Anon 2024].

1.2.10 Transfer of analytical methods to quality assurance

During scale-up, the analytical methods developed in research should be transferred to the Quality Control (QC) department to ensure consistency in testing. Early in the transfer process, the QC department will ensure they have the appropriate analytical instrumentation and trained personnel

to perform the necessary tests. Validation studies for reliability, precision, accuracy, and recovery should be conducted over several weeks to test the comparability with the research method. If necessary, the assay method should be rewritten and reformatted to ensure clarity and usability in the QC department. To complete the transfer, an R&D professional should review the assay procedure and the data obtained during validation studies to verify the analytical method's accuracy and reliability [Lachman, Lieberman and Kanig 1976].

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CHAPTER 2

PILOT PLANT SCALE-UP CONSIDERATIONS FOR DOSAGE FORMS

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Abstract

The transition of a pharmaceutical formulation from a laboratory scale to commercial production is a critical and transformative stage in the drug development lifecycle. The scale-up process, conducted within a pilot plant, serves as a bridge between research and full-scale manufacturing. This phase involves scaling up the formulation to evaluate its feasibility, optimize production parameters, and identify potential challenges that may arise during commercial manufacturing. This chapter delves into the fundamental considerations, methodologies, and challenges associated with the scale-up of various pharmaceutical dosage forms, encompassing solid dosage forms (such as tablets and capsules), liquid dosage forms (including solutions, suspensions, and emulsions), as well as semi-solid dosage forms. This comprehensive overview serves as a practical guide for pharmaceutical professionals involved in pharmaceutical process development and scale-up.

Keywords: Pilot plant scale-up, dosage forms, scale-up challenges, process parameters, pharmaceutical formulation, drug development