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Bridging the Gap in Customized Medicine: Navigating the Regulatory Landscapes of Compounding Pharmacies of India and the USA

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KEYWORDS

Compounding Pharmacies; Personalized Medications; Drug Quality and Security Act; 503A and 503B Facilities; United States Pharmacopeia Convention (USP)

ABSTRACT:

Compounding pharmacies in India compounding pharmacy and the US are a vital service to cater customised medicines made as per individual patient requirement. This paper hence intends to bridge a gap by exploring this function — such work has so far not been published on compounding pharmacies of India and their comparison with those in the USA. The pharmacies have a great significance and importance when the prescription or common medications are not available, do not work as per their effectiveness. The 2013 Drugs Quality and Security Act (DQSA) was developed in response to an outbreak of fungal meningitis related to the use of contaminated compounded medications and it regulates compounding pharmacies within the United States. The act divided compounding pharmacies into two types i.e., 503A and 503B facilities. There are pharmacies authorized to fill prescriptions which are 503A facilities, and those that create more compounded meds — meaning they mix or alter existing medicines in some way before handing them off for sale; these shops have FDA regulations up the wazoo. To ensure that the potency and quality is maintained, they also published the major recommendations which were established by The United States Pharmacopeia Convention (USP). In India, compounding pharmacies are under a variety of strict operating and licensing requirements. Although India's regulatory processes have well advanced, this paper examines how enforcing international standards could still provide additional safety and efficiency in the compounding of active pharmaceutical ingredients. The paper is concluding with saying that for compounded drugs both India and United States have developed regulatory frameworks. But there is requirement of cross-bordered cooperation and continued innovation so that the growing demand can be met for customized pharmaceuticals in the present global healthcare environment.

1. Introduction

Personalized medicine is application of individualized or customized medicine. It is considered an emerging area, heralded as a game changer in medical treatment, tailoring it according to the specific genetic, environmental, and lifestyle characteristics of each individual patient. Personalized or precision medicine is one such rapidly evolving field that tends to make therapeutic interventions safer and more effective by moving from the one-size-fits-all approach to that of individual patient needs. An increasing number of people are coming to understand that treatment should be individualized, as is widely noticed with the growing interest in personalized medicine. Compounding pharmacies represent the missing link in the provision of personalized medicine, by being a conduit for individual needs communicated by patients and responded to from the perspective of modern pharmaceutical possibilities. In this way, compounding pharmacists can meet certain unmet medical needs, promote patient compliance, and assist with individualized treatment programs by using their expertise to offer personalized remedies. This becomes very important in the treatment of complicated medical diseases that conventional therapies cannot address.

Most medications with FDA approval marketed by community chemist are available for commercial use as final dosage formulations [1]. Retail pharmacists sell this medication in fixed doses. These doses may either be too high or too low to treat the symptoms of certain chronic illnesses. Medication might be readily available at a neighbourhood pharmacy, but the results might not be to par. However, in cases when such medications are unavailable or a patient shows intolerance to a component in a completed pharmaceutical product, a chemist may prepare a substitute. In turn, compounding pharmacies have access to raw ingredients. Compounding pharmacies will make a similar drug but, of course, in a particular dose

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according to the patient's need. This review is thus set to observe the most critical role that compounding pharmacies play in meeting the rising demand for specialty medications. p These pharmacies, therefore, offer an integral part of the pharmacists' practice in the knowledge that in many cases, traditional pharmaceutical products are insufficient to cater for the needs of tailored health care. Being in a position to perform dosage form modification, eliminate allergens, and combine more than one medication into a single preparation puts a compounding pharmacy in a unique position to develop customized treatment in accordance with patient-specific requests, which otherwise would not be satisfied with over-the-counter drug products. Pharmacists, working alongside physicians, have been involved in maintaining these services as part of their professional practice.

It focuses on the regulatory systems overseeing the activities of compounding pharmacy in India as well as the US. Understandably, such a landscape will also be necessary to understand what measures of safety and effectiveness have been brought in to check drug compounding in the two countries. The paper also describes how current regulations in the United States and India address opportunities and challenges that compounding pharmacies face. The present comparative analysis, thus, seeks to shed light on regulatory strategies that best enable customized treatment integrated with or more efficiently and effectively providing treatment that is patient-centered. The objective of this study aims to examine the link between compounding pharmacy, customized medicine, and the current regulatory setup with special emphasis to be laid on fulfilling the dire need of customized therapies between India and the U.S.

4. Compounding Pharmacies

In compliance with a licensed practitioner's prescription, compounding is "the preparation, mixing, assembling, altering, packaging, and labelling of a drug," according to the United States Pharmacopoeia (USP), which establishes quality standards for pharmaceuticals. It is, in essence, the development of a pharmaceutical that is not marketed commercially.

The FDA defines compounding as "combining, mixing, or altering the ingredients of a drug to create a medication tailored to a patient".

Compounding is done in outpatient pharmacies and inpatient hospital settings in the United States, with a tendency towards larger-scale outpatient production in recent decades. Compounding may now take place at recently described "outsourcing facilities," which are made to compound in large quantities, as will be covered later in this paper; Leiters and QuVa Pharma are a couple of these establishments.

Table 1. Compounding Medication Solutions for Customized Care

Customized medical care	By using personalized medicine compounding, health care providers can make drugs that are especially suited to the needs of each patient. This is especially beneficial for those with specific allergies, sensitivities, or intolerances to specific components commonly found in over-the-counter drugs. By tailoring the drug to each patient specifically, personalized compounding enhances treatment results and lowers the possibility of negative responses.
Dosage customization	Store-bought medication typically comes in pre-measured doses that may not be quite right for the patient. Drugs can be prepared at dosage strengths not seen in stores thanks to compounding. This increases the effectiveness of the treatment by enabling medical practitioners to accurately adjust the dosage to the patient's needs.
Choices for Administration in Many Formats and Forms	Personalized compounding allows patients who have trouble swallowing pills or who need medication in formats that are not easily accessible to take their prescriptions in different ways. To accommodate different preferences and needs, enhanced medications can be prepared as transdermal creams, gels, suppositories, sublingual tablets, lozenges, or other appropriate forms.
Combinations of Medications	Some patients require more than one drug to treat their diseases, which can be cumbersome and increase the risk of dosing errors. Combining many medications into one dosage form is possible with personalised compounding.

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	This facilitates and eases adherence to the prescription schedule. The patients who will benefit from this the most are those who have trouble managing many drugs or who need specific drug combinations that aren't accessible in a single commercial product.
Medicants, Youngsters and elderly people	Children and older individuals often have specific drug needs because of things like limited dosage alternatives, taste preferences, and trouble swallowing. Compounding drugs can be converted into chewable tablets or flavour-infused solutions for children, and smaller, dose-specific versions for elderly patients.
Removing Prescription Drugs	Even though the use of compounding in pharmaceutical treatment was known already in the 19th century, at those years, such technique was mostly used by apothecaries and wasn't considered to be a substitute to the original. In the event that companies stop manufacturing drugs, compounding pharmacies can fill this gap and allow patients to continue receiving the right therapy.
Science of Veterinarians	Personalized compounding also applies to veterinary care, where animals are provided with tailor-made drugs. The customization possible in changing dosages, flavours, and alternative forms acceptable among the various animal species makes veterinary compounding that much easier for pet owners to dose their animal patients.
Creative Remedies	Customized compounding allows both the practitioner and patient to explore new treatment options not provided in commercial medication. Examples include novel combinations of medicines, hormone replacement therapy, unique pain formulations, and many more customized treatments. These advanced techniques are used by compound pharmacies in collaboration with physicians to help develop individualized medications for patients.
Patient compliance and satisfaction	Compounded medications enhance the satisfaction and compliance of patients due to the provision of prescriptions that best meet personal needs. Patients appreciate that the medication is convenient, easy to use, and allows them to avoid components that trigger allergies or intolerances. Personalized compounding increases patient pleasure and compliance, which enhances treatment outcomes and patients' overall quality of life.
Steer Clear of Allergies	Among the substances that may trigger allergic responses or sensitivities in certain people are colorants, preservatives, and fillers. Personalized compounding allows doctors to create medications without any allergenic chemicals, improving patient safety and lowering the chance of adverse responses [2].

Compounding can occur for a variety of causes and symptoms. (**Table 1**). Certain patients, such as young children receiving antibiotics, patients dependent on feeding tubes, or patients experiencing dysphagia due to neurologic deterioration such as a stroke, may not be able to take pills and may instead need a compounded liquid medicine formulation. Patients may have allergies to inactive chemicals found in commercially available formulations, such as diluents, binding agents, or colours. Compounding sugar-free drugs may be necessary due to dietary limitations, such as a ketogenic diet for children with epilepsy. Compound analgesic topical creams that combine several drugs not commercially available together, such as ketamine, baclofen, gabapentin, amitriptyline, bupivacaine, and clonidine, may be helpful for refractory neuropathic pain. "Magic mouthwash" is used to cure painful oral lesions, while "gastrointestinal (GI) cocktail" is used to treat dyspepsia; these words really refer to a variety of compounded treatments.

For patients who cannot consume enough food orally, total parenteral nutrition (TPN) is required, and many

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chemotherapy regimens need to be combined in order to treat cancer. For specialised operations like intraarticular or intravitreal injections, healthcare providers might require compounded drugs. Commercial preparations may be available in some cases, although they are likely to be costlier than a compounded equivalent [1].

Types of Compounding Pharmacies

The most common people that perform compounding are licensed physicians, licensed pharmacists, or individuals working under a professional pharmacist's supervision. The typical compounding procedure begins with prescribers creating prescriptions based on patient needs. Prescribers frequently choose the active ingredient or ingredients' dosage form, dose, intervals between doses, and mode of administration when writing prescriptions. Additionally, the prescriber has the option to select inactive substances, particularly if the patient has a history of allergies to an inactive ingredient (like peanut oil). The compounding chemist next gets to work on preparing (also known as formulating) and giving the patient their medication.

It's crucial for understanding the various forms of compounding and the associated risks to patient safety and public health [3].

I.Non-Sterile Compounding:

The United States Pharmacopoeia (USP) started adopting significant amendments to Chapter 795 in November 2023, which had an impact on the practice of non-sterile compounding (Table 2).

Making compounded medications without needing sterility for safety is known as non-sterile compounding. This covers a wide range of oral and topical medications. The skin typically acts as a strong enough barrier to shield the body from the environmental microbiological contamination that is present everywhere. Similar to this, the stomach's pH acts as a barrier to keep most microbes out. For these reasons, it is not necessary to make compounded products in a buffer room or to prove that the finished product is sterile when taken orally or administered topically. It is important to clarify that this does not mean that, in terms of non-sterile compounding, there are no controls on the production environment or outcome; rather, it only means that the regulations are less onerous.

Sterile hazards in non-sterile compounding are almost non-existent due to the body's natural defences. This mainly restricts the excipients, or potency, which can also raise efficacy concerns, as the source of safety hazards for non-sterile products. The amount of API in the product is referred to as its "potency". When an API is present in a non-sterile product in greater amounts than are conventional for a certain therapy, it may become poisonous or have adverse effects that are more severe. Too little API in a non-sterile product could prevent it from having the intended effect.

Non-sterile compounds can be manufactured solely from API or from commercially available, FDA-approved finished medicines, or from a combination of the two [4].

Table 2. USP non-sterile compounding practice

Sr. No	Documentation on	Features
1.	**Education and Proficiency**	Every employee needs to go through an orientation and show that they are capable of meeting the standards. Must recruit Department Head, Registered Pharmacist and Non-pharmacist personnel.
2.	**Personal Care and Clothes**	Personnel with open wounds, rashes, or recent tattoos that could be sources of contamination now need to notify the authorised responsible person in order to lower the possibility of contamination. Furthermore, all compounding procedures now require the use of gloves; the former "as needed" policy has been replaced.
3.	**Observation and Maintenance**	There is a table in USP Chapter 795 that shows how often work surfaces, floors, walls, and ceilings should be cleaned and sanitised. Compounding environments are kept clean and free of possible pollutants thanks to this instruction.
4.	**Equipment and Components**	Compounding areas need to be sufficiently big so that compounding staff members can work securely and comfortably. The designated area must have proper heating, lighting, ventilation and air conditioning systems. In order to guarantee consistency and quality in compounded preparations, the require-

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		ments cover equipment usage, cleaning, and maintenance.
5.	**Compounding Records for Master Formulations**	Formulation Master Record (MFR) According to the amended USP795, each fresh batch must have both MFRs and Compounding Records (CRs) recorded before a preparation is compounded for the first time. The compounding process is made more traceable and accurate by this documentation.
6.	**Dates Beyond Usage**	In order to determine acceptable Beyond-Use Dates (BUDs) for preparations that are compounded, the word "water-containing" preparations has been eliminated from Chapter 795 and replaced with the idea of water activity levels. Updates like this one guarantee the stability and safety of compounded products while also keeping up with the rapid advancement of science [5].

II.Sterile Compounding

The process of creating compounded medications that need to be sterile is called sterile compounding. Injectable medications and ocular drops are a couple of examples of these items. The GI tract is avoided by injectable preparations meant to be injected intravenously, intramuscularly or subcutaneously and the skin's protective layer to reach parts of the body that are typically uncontaminated by microbes. Therefore, more stringent environmental requirements must be met during the production of injectable compounded goods. Similarly, the sterile production of eye drops is required due to the mucosal sensitivity and internalisation.

Sterile to Sterile

The process of changing an FDA-approved sterile dosage form to produce a different product while maintaining its sterility is known as "sterile to sterile compounding." The procedures are performed in a primary engineering control (such as a laminar airflow hood) that provides an ISO-class 5 environment, in a buffer room with a scrubbed and garbed operator utilising aseptic technique to assure sterility. In terms of safety, there is some possibility that sterile compounds created using a sterile-to-sterile technique won't be completely sterile since sterility may have been compromised during manipulation. But compared to non-sterile to sterile preparation, the chance of infection is reduced. Similarly, potency concerns as those associated with nonsterile compounding—namely, excess or insufficiency of the active component and possible chemical incompatibilities between ingredients—also apply to compounding from sterile to sterile.

Nonsterile to Sterile

Nonsterile-to-sterile compounding is the process of converting a bulk drug substance—an API, typically a powder—that is by definition nonsterile into sterile by dissolving it in a solvent and then sterilising the resulting solution. Filtration and terminal sterilization methods such as heat or radiation can be used to achieve sterilization. Similar to sterile-to-sterile procedures, these operations are carried out in a buffer room in a primary engineering control by an operator who has been washed and dressed and who uses aseptic technique to achieve sterility. From non-sterile to sterile products, the greatest risk is a lack of sterility associated with this type of compounded preparation. The strength hazards related to nonsterile and sterile to sterile compounding still exist with such type of sterile compounding [4].

5. US Regulatory Bodies That Oversee the Safety of Compounded Drugs

The 2013 Drug Quality and Security Act (DQSA) provides requirements that compounding pharmacies in the United States must follow in order to ensure the highest standards of safety and quality when preparing medications. Following an outbreak of fungal meningitis linked to contaminated medications being compounded, the DQSA was passed into law; since this time, compounding has been under greater regulation. State-to-state, regulation may differ with regard to compounding pharmacy and usually adheres to the United States Pharmacopeia (USP) compounding standards for quality and safety. However, "Compliance with the United States Pharmacopeia standards is no assurance of the safety or quality of compounded drug products," and compounding pharmacies need more serious examination to secure the integrity of these products. After the DQSA, the adoption of USP standards has increased significantly and pharmacy boards are also keen on these standards. This proves that the safety and efficacy of these drugs are not directly evaluated by the FDA. However, for cases of medical necessity, the FDA permits the community pharmacist to compound medications.

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In general, three entities ensure compounded medications are quality. They include the United States Pharmacopeia (USP) Convention, state boards of pharmacy as well as the FDA. Regulations have also been put in place, which guarantee the safety of compounded medications. These drugs may only be prepared by select qualified individuals including licensed pharmacists or physicians. USP also published provisions to maintain high quality of compounded drugs. Quality standards of ingredients used to formulate compounds are dictated by the standards set in guidelines developed by USP. They also offer guidelines for the compounding process, as well as testing and analysing of the products.

The compounding pharmacies must abide by the USP set standards. This is statutory in most states. The state board of pharmacy regulates compounding pharmacies. It also inspects them so that they comply with all such requirements. A compounding pharmacy may face a corrective action if these quality standards are not met by it. Some compounding pharmacies are also inspected by the FDA. In addition to that, FDA also inspects the companies that produce ingredients, which compound pharmacies use. Unlike old compounding pharmacies 503B outsourcing establishments need to have registration from FDA. The FDA also inspects them under cGMP, known as current Good Manufacturing Practices, for more rigorous standards of quality. This is to ensure that there are quality assurance processes in place [6].

5.1. Drug Quality and Security Act (2013)

Enacted in 2013, the Drug Quality and Security Act had arisen from safety concerns with regard to compounded drugs, particularly after incidents such as the New England Compounding Centre contamination. The DQSA made compounding pharmacies more accountable; 503A pharmacies were to be state-regulated, and 503B pharmacies were supposed to be regulated by the FDA according to their identified risk level. Compounded drugs do not subject the same safety and quality assurance regulations that approved drugs by the FDA do, hence the need for modernized guidance and standards such as those set out in United States Pharmacopeia (USP) guidelines. The FDA's Compounding Incidents Program plays a very important role in monitoring adverse events and complaints related to compounded drugs for the purpose of protecting public health. In general, the DQSA has radically changed the regulation of compound pharmacies in the USA with the goal of ensuring safety and quality of compounding medications [7].

The Drug Quality and Security Act was enacted in November of 2013 to empower the Food and Drug Administration with more power in regulating and overseeing compounding pharmacies to heighten oversight and thus heighten product safety **(Fig.1)**. According to a statement by the FDA, after an outbreak of a rare fungal meningitis in 2012, activities at compounding pharmacies, especially those that involved sterile products, were under a lot of observation and concerns. This disease outbreak caused 750 infections in 20 states where these compounding pharmacies were located and resulted in 64 deaths. It was not long before it was discovered that the source of the outbreak was injection steroidal medications that had been tainted during compounding at the Compound Pharmacy in New England. The epidemic was viewed as proof that compounding pharmacies were not adequately regulated.

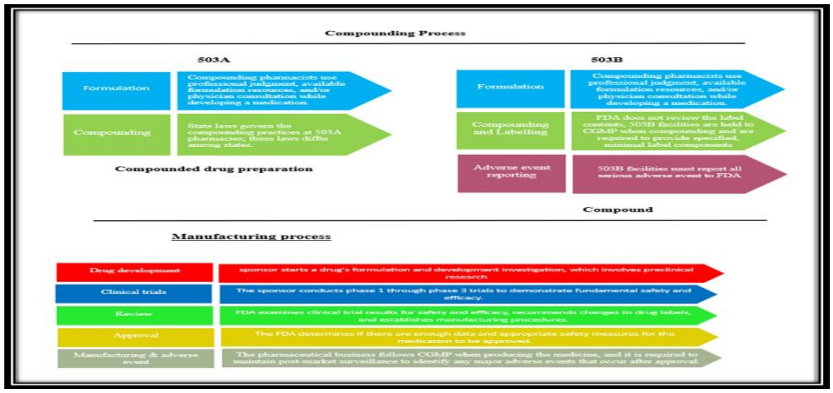

Fig 1. Overview of the legal and regulatory procedures that FDA-approved pharmaceutical products and compounded medicinal preparations must follow in general [11]

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Compounding pharmacies in the United States are categorized into two main types: 503A and 503B facilities. These classifications were established following the 2012 meningitis outbreak to enhance the safety and regulation of compounded medications.

Pharmacists and healthcare practitioners must understand the differences between these institutions and their roles in the medication supply chain**.** This legislation defined two categories of compounders **(Table 3)** [8].

503A Facilities

Traditional compounding pharmacies were defined as '503A' pharmacies. They can only combine medications for specific prescriptions; they cannot produce pharmaceuticals in large quantities. USP <795> criteria as well as state boards of pharmacy laws must be followed by a 503A compounding pharmacy. USP <797>: Pharmaceutical Compounding-Nonsterile Preparations Sterile Preparations for Pharmaceutical Compounding and any related standards mentioned in those chapters. The current Good Manufacturing Practice (cGMP) rules are not mandatory for them to follow [9].

503A compounding pharmacies are 'traditional' patient-focused compounding facilities in that they:

1. Complete prescriptions that have been authorized by a prescribing physician and are written especially for each patient.
2. Ensure that a licensed pharmacist with further training in compounding in a licensed establishment is on staff.
3. Every compounding procedure needs to be carried out in a federal facility or licensed pharmacy, overseen by a qualified pharmacist.
4. Adhere to the rules set forth by state boards of pharmacy.
5. Create substances that adhere to the National Formulary (NF) monograph or United States Pharmacopoeia (USP) chapters. In addition to maintaining medicine quality and purity, these compliance standards guarantee patient safety. USP <797> and <795> refer to these chapters on sterile human pharmaceuticals. Each and every bulk material (i.e., essential component of pharmaceuticals) utilised in the compounding procedure ought to be:

a. Produced in a facility registered with the FDA
b. Having a current Certificate of Analysis (COA)

6. Do not compound drugs that the FDA has withdrawn, removed from distribution, or found to be unsafe or ineffective in any other manner. [10].

503B Facilities

The CQA also defined an additional category of business: "503B" outsourcing facilities. Following their voluntary registration with the FDA, outsourcing facilities classified as 503Bs come under FDA authority and are required to abide by the 21 CFR Parts 210 and 211 cGMP requirements as well as the FDA guidance papers specifically related to 503B cGMPs. The provisions of the Food, Drug, and Cosmetic Act for drug makers may apply to any compounding pharmacy that violates relevant laws or neglects to register as an outsourced facility [9].

Outsourcing facilities are pharmacies which combine sterile drugs in large numbers that aren't usually in response to a prescription from a single patient. The FDA inspects and monitors them, and they are required to pay an annual fee that is determined by their total yearly sales values. Outsourcing facilities are required to report the pharmaceuticals they compound twice a year. Using a risk-based timetable, the FDA inspects outsourcing facilities with a higher likelihood of inspection for the highest-risk facilities. Establishments that are shown to be engaging in hazardous procedures or producing impure mixes face penalties, and if the FDA needs to visit them again, they can also have to pay for another inspection. Recalls of tainted or otherwise useless goods can also contribute to the public's safety when it comes to compounding pharmacy products [8].

503A facilities are conventional compounding pharmacies that assemble drugs in accordance with specific prescriptions for specific patients. In contrast, 503B facilities, also known as outsourcing facilities, can compound large quantities of medications without patient-specific prescriptions, provided they adhere to stringent regulatory standards.
Unless these compounds are on the FDA's drug shortage list or the 503B Bulk Drug Substance list, which is still being developed, 503B establishments are prohibited from utilising bulk drug substances. Recent FDA audits indicate increased scrutiny of 503A facilities, with practices and observations similar to those for 503B facilities and other drug manufacturing plants. This shift aims to prevent medical outbreaks and ensure higher safety standards. Compliance with regulatory standards is becoming a key factor for 503A facilities to gain market share, as those maintaining good standing with the FDA are better positioned in the market [12].

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5.2. United States Pharmacopeia Convention.

Predating the FDA, the USP is a private organisation that had a significant impact on the US healthcare system. The USP's primary function is to publish comprehensive, significant information about all drug products and to update it periodically. On the other hand, the FDA, a government agency, regularly references the USP in its recommendations and regulations. One example of this is the FDA's listing of drug compounds that are legally allowed to be used in compounding as well as those that are prohibited; this list is updated and reviewed on a regular basis. Comprehensive information regarding compounding pharmaceuticals, including sterility, responsibilities, safety, storage, and other standards, can be found in the USP General Chapter <797>.

A systematic and well-organized methodology can be used to implement USP chapter 797 for compounding sterile preparations; quality cleanroom design, installation, and management will raise the quality of the finished product [13].

USP 797 Non-Hazardous Cleanroom Design:
Non-hazardous compounding and storage areas must be pressurized in accordance with USP Chapter 797 cleanroom design requirements. Primary engineering controls, buffer rooms, and ante-rooms are supported by the ISO 5, 7, and 8 settings.

- Primary Engineering Control ISO Class 5 (no need for external venting)
- ISO Class 8 Positive Pressure Ante Room;
- Positive Pressure in ISO Class 8 Buffer Area

The presence of positive pressure guarantees that the region remains sterile even in the case of a barrier being broken. Positive pressure rooms can be used for compounding Syringes, salves, oils, injections of antibiotics, eye drops, infusion, TPN (Total Parenteral Nutrition), and more.

USP 797 Hazardous Cleanroom Design (USP 800):

USP Chapter 800 lays out new guidelines for hazardous medication compounding, superseding USP 797's existing guidelines. The most recent version to the United States Pharmacopoeia (USP) addresses hazardous medication compounding (both sterile and non-sterile), and it is known as USP 800. When handling, combining, and packing hazardous materials, enhanced engineering and procedural controls (including the 2018 changes to the NIOSH list) provide additional protection for operators and environments. Negative pressure, engineering controls, storage, and updated equipment settings are just a few of the new concessions that USP 797 establishments handling or synthesising hazardous pharmaceuticals may need to make **(Table 3).**

What changes must a USP 797 plant make in order to comply with USP 800? (Fig. 2)
• Positive Pressure Ante-Room ISO Class 8;
• Negative Pressure Buffer Area, ISO Class 7 (S-PEC);
• Primary Engineering Control (PEC) in ISO Class 5.
• Water column of 0.01 inches in comparison to the surrounding area.

OR an equivalent CACI for both non-sterile and sterile criteria

Table 3. The requirements for primary engineering control, or PEC:

System of laminar airflow	Workbench for Laminar Airflow, Class II Biological Safety Cabinet (BSC), and Integrated Vertical Laminar Flow Zone (IVLFZ)
System of restricted access (RABS)	Aseptic Compounding of Isolators (CAI) Making Aseptic Containment Isolator (CACI) Compound [14]

Risk Determination

USP 797 describes requirements for CSPs at three different risk levels. It is essential to understand that these requirements are not complete; instead, they have been developed to serve as a reference for assessing a CSP's risk level in order to create appropriate protocols and practice for handling CSPs.

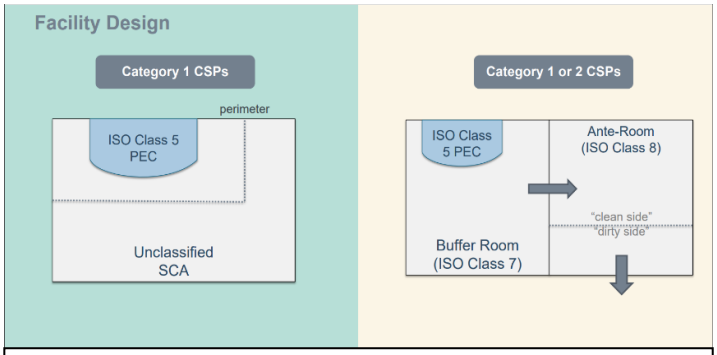

Fig.2 Illustration of Cleanroom Design [14]

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Risk levels

❖ **CSPs at Low-Risk Levels: CSPs with little chance of contamination**

- Maintained exclusively in Class 5 ISO setting
- Transferring sterile dosages in single volumes
- Simple aseptic measurement and transfer requiring a maximum of three sterile, manufactured packages

❖ **CSPs with Low-Risk Levels that meet one of the following criteria are classified as Medium-Risk Level CSPs:**

- Sterilised materials in small doses to be given repeatedly to one patient or to several patients at a time
- Complex aseptic manipulations, not-single volume transfers

❖ **High-Risk Level CSPs: When CSPs are combined with the following elements, it indicates that they are polluted or could get contaminated**.

• Manufactured outside of an ISO Class 5 environment;
• Contains non-sterile ingredients or non-sterile equipment;
• Personnel not wearing appropriate personal protective equipment;
• Assumed and unverified component strength and purity [15].

Sterilization and depyrogenation

Section 10 of USP 797 describes the steps involved in sterilisation and depyrogenation. It specifies that the sterilisation process employed must sterilise the CSP without compromising its chemical and physical stability or the integrity of the packaging. Filtration and terminal sterilisation, which involves autoclaving or dry heat, are the main methods for sterilising compounded preparations. We intend to change the particular compounding sterilisation procedure in order to align with the updated USP 797.

FILTRATION

❖ **Sterilization Procedure for Aqueous Solutions:**

Pour the mixture into a suitable depyrogenated and sterile container-closure system after filtering it through a sterile, depyrogenated filter (fit for pharmaceutical use) having a nominal pore size of at least 0.22 microns. As per USP rules, the utilised filter needs to undergo a bubble point test to guarantee its integrity. Please refer to the product specifications for the minimum pressure required.

❖ **Sterilization Procedure for Oil or Alcohol Solutions:**

Filter the solution through a sterile and depyrogenated Teflon® filter (appropriate for pharmaceutical use) Using a 0.2 micron or less nominal pore size into a suitable container-closure system that has been depyrogenated and sanitised. As per USP rules, the utilised filter needs to undergo a bubble point test to guarantee its integrity. Please refer to the product specifications for the minimum pressure required.

AUTOCLAVE

❖ **Sterilization Procedure for Solutions**

To remove any possible particulate debris, strain the mixture through a sterile, depyrogenated filter (fit for pharmaceutical use) with a nominal particle size of no more than 1.2 microns. Transfer the mixture to a suitable, depyrogenated, and sterile container-closure system.

Seal the serum bottle by crimping it. For the amount of time required to make the preparation sterile, autoclave it until the contents of the vial reach 121°C and 15 pressure.

This process can take anywhere from 20 to 60 minutes, depending on the volume of preparation and the arrangement of the load.

In accordance with USP recommendations, this procedure needs to be confirmed and recorded for every sterilisation run or load using Sterilisation Integrators, Steam, and SporeView® Steam Biological Indicators. For further details, see USP 1229, Sterilisation of Compendial Articles.

❖ **Sterilization Procedure for Suspensions**

Compound suspensions are autoclaved without the first filter step. To keep the suspension from clumping after the autoclave procedure, it's critical to keep the preparation moving constantly while it cools.

Fig. 3 Principles of Current Good Manufacturing Practices [16]

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DRY HEAT/CONVECTION

❖ **Sterilization Procedure for Solutions**

To remove any possible particulate debris, strain the mixture through a sterile, depyrogenated filter (fit for pharmaceutical use) with a nominal particle size of no more than 1.2 microns. Transfer the mixture to a suitable, depyrogenated, and sterile container-closure system.

Crimp and seal the serum bottle. Dry heat the oil solution in a convection oven until the contents of the Seal the serum bottle by crimping it. The oil solution should be dry heated in a convection oven for long enough to keep the preparation sterile, or until the vial's contents are at least 160°C.

This process can take a variety of times, depending on the volume of preparation and load setup. With every sterilisation cycle or load, this procedure needs to be confirmed and recorded using SporeView® Culture Set Biological Indicators and temperature monitoring in accordance with USP recommendations. For further details, see USP 1229, Sterilisation of Compendial Articles. Take out of the oven right away, then let cool to room temperature.

❖ **Sterilization Procedure For Suspensions**

The first filter stage is eliminated when sterilising compounded oil suspensions using dry heat. To keep the suspension from clumping after the dry-heat procedure, it's critical to keep agitating the preparation continuously while it cools.

❖ **Multiple Dose Compounded Preparations**

USP 797 revisions additionally specify that preserved multi-dose CSPs are necessary. A multi-dose CSP needs to be produced as a Category 2 or Category 3 CSP, per USP 797. In compliance with USP 51 Antimicrobial Effectiveness Testing (AET) guidelines, a multiple-dose aqueous CSP also needs to pass the test for antibacterial efficacy. Following the dispense of a multiple-dose CSP (aqueous or nonaqueous), the preparation's beyond-use date (BUD) is reduced to 28 days or fewer upon first entering or puncturing the container [16].

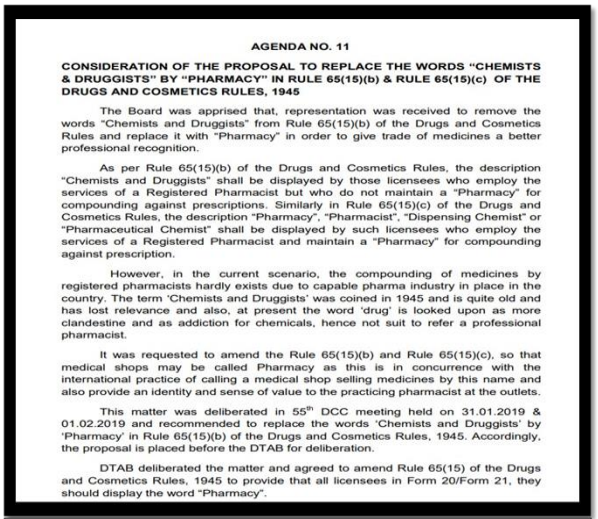
6. cGMP – Current Good Manufacturing Practice (Usfda 21 Cfr Part 210 And 211)

The 503As, or traditional compounding pharmacies, are exempt from cGMP regulations. This means the medications to the patients receive from a 503A pharmacy can vary in qualities such as potency and sterility from batch to batch. Medication that has expired or been tampered with may have negative repercussions, including sickness and/or death. The manufacturing facility or a pharmacy that dispenses drugs manufactured under cGMPs means to receive reliable medications and the patients receive the best treatment.

Under 21 CFR Parts 210 and 211, the FDA implements Current Good Manufacturing Practice, or cGMP, to ensure that the facilities, procedures, and controls utilised in the drug manufacturing process adhere to basic requirements. This is employed in the production of pharmaceuticals for both humans and animals, with the aim of verifying the efficacy of the medication and ensuring its safety for ingestion. Pharmaceutical manufacturers are given a basic framework (**Fig. 3**) by cGMP to guarantee that quality requirements are monitored and upheld for the following, among other things:

- Personnel
- Facility design and function
- Equipment
- Procurement from qualified suppliers
- Tracking and traceability of product and components
- Documentation
- Final product requirements are a crucial component of cGMP. These specifications demand results from validated testing that guarantee each batch of product satisfies all quality standards before it is released.

When a business adheres to cGMPs, quality is integrated into the workflow and is confirmed by a separate quality department. These procedures regulate each and every stage of their production process, which is why items that must adhere to cGMPs are of higher quality [17].



AGENDA NO. 11

CONSIDERATION OF THE PROPOSAL TO REPLACE THE WORDS "CHEMISTS & DRUGGISTS" BY "PHARMACY" IN RULE 65(15)(b) & RULE 65(15)(c) OF THE DRUGS AND COSMETICS RULES, 1945

The Board was apprised that, representation was received to remove the words "Chemists and Druggists" from Rule 65(15)(b) of the Drugs and Cosmetics Rules and replace it with "Pharmacy" in order to give trade of medicines a better professional recognition.

As per Rule 65(15)(b) of the Drugs and Cosmetics Rules, the description "Chemists and Druggists" shall be displayed by those licensees who employ the services of a Registered Pharmacist but who do not maintain a "Pharmacy" for compounding against prescriptions. Similarly in Rule 65(15)(c) of the Drugs and Cosmetics Rules, the description "Pharmacy", "Pharmacist", "Dispensing Chemist" or "Pharmaceutical Chemist" shall be displayed by such licensees who employ the services of a Registered Pharmacist and maintain a "Pharmacy" for compounding against prescription.

However, in the current scenario, the compounding of medicines by registered pharmacists hardly exists due to capable pharma industry in place in the country. The term 'Chemists and Druggists' was coined in 1945 and is quite old and has lost relevance and also, at present the word 'drug' is looked upon as more clandestine and as addiction for chemicals, hence not suit to refer a professional pharmacist.

It was requested to amend the Rule 65(15)(b) and Rule 65(15)(c), so that medical shops may be called 'Pharmacy' as this is in concurrence with the international practice of calling a medical shop selling medicines by this name and also provide an identity and sense of value to the practicing pharmacist at the outlets.

This matter was deliberated in 55th DCC meeting held on 31.01.2019 & 01.02.2019 and recommended to replace the words 'Chemists and Druggists' by 'Pharmacy' in Rule 65(15)(b) of the Drugs and Cosmetics Rules, 1945. Accordingly, the proposal is placed before the DTAB for deliberation.

DTAB deliberated the matter and agreed to amend Rule 65(15) of the Drugs and Cosmetics Rules, 1945 to provide that all licensees in Form 20/Form 21, they should display the word "Pharmacy".

Fig. 4 82nd DTAB Draft Agenda No. 11: Examining the Request to Modify the 1945 Drugs and Cosmetics Rules, Rules 65(15)(B) and 65(15)(C). By Putting "Pharmacy" in Place of "Chemists &

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7. REGULATORY AGENCIES THAT ENSURE SAFETY OF COMPOUNDED MEDICINES IN INDIA

7.1. Section 65 of Drug and Cosmetic Rule 1945

The Drug and Cosmetics Rules, 1945, Section 65, addresses the distribution of pharmaceuticals and cosmetics. It describes the requirements for drug supply, such as the requirement for a prescription from a licensed medical professional and the participation of a registered pharmacist in the supply chain.

It helps to ensure the safe and responsible supply of drugs, and provides a paper trail for auditing and quality control purposes **(Fig. 4).**

Condition of Licenses: Licenses for medications that are compounded or manufactured on the licensee's premises must be issued in Form 20, 21 in accordance with the requirements of Section 65 of the Drug and Cosmetics Act. [Forms 20, 20-A, 20-B, 20-F, 20-G, 21 and 21-B] and need to be closely looked after by a registered pharmacist in person [18].

7.2 GOOD PHARMACY PRACTICE GUIDELINES 2002

The recommendations for the provision of pharmaceutical care and services in Indian community pharmacy settings were developed by the Indian Pharmaceutical Association in March 2002.

Establishing guidelines for the pharmacy profession in India is the aim of the Good Pharmacy Practice Guidelines. Additionally, it is an affirmative statement that we, and no one else, determine the standards for our profession. The recognition and acknowledgement that pharmacy practice circumstances can differ across the nation is reflected in the documentation of these standards.

The pharmaceutical services provided in our rural and urban locations most certainly will continue to being different, but most cities still have an excessive number of retail pharmacies that provide a wide range of services at varying levels.

The Drugs and Cosmetics Rules define that establishments that adhere to Schedule N (which deals with the compounding of medicines) must display the word "Pharmacy." Nevertheless, regardless of whether they compound or not, the term "pharmacy" has been used here to refer to all retail pharmacies. Compounding pharmacies should be referred to as such, it is suggested.

Within the next few years, all Indian pharmacies should adhere to the GPP Guidelines for India, which have been developed and put into effect. This is only possible with the determination of the chemists, their continued education, and the backing of professional associations.

Table 4 Pharmacy Structure Guidelines in India

1. Facilities	
a) Premises	A compounding pharmacy should not only have the equipment it needs, but also enough extra room to make last-minute preparations. It is recommended that distinct containers for collecting waste be made available to both employees and customers.
b) Furnitures and Fixtures	The following items should be included in the counselling area's furnishings: **(i)** A table. **(ii)** A chair for a few patients and the chemist. **(iii)** Medication records (PMRs) cabinet for patients
c) The Equipment	According to Schedule N of the Drugs and Cosmetic Rules, the pharmacy's compounding department needs to be furnished. There should also be additional equipment available if needed for operations.
2. Personnel	A pharmacist who works in a drugstore should: **1.** Have a pharmacy degree, but even a diploma is acceptable. **2.** Be registered with the pharmacy council in the state where they work, as of right now. **3.** Possess sufficient hands-on experience in a neighbourhood pharmacy. **4**. Complete internal training in accordance with the staff training policy of the organisation. **5.** Have the capacity to interact with people in an efficient manner and advise them on

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	how to take drugs, treat ailments, etc. in order to improve patient compliance.
3. Systems	
a) Quality policy	A quality manual should be kept at the pharmacy, describing exactly what needs to be done to meet the predetermined standards for quality. The handbook must provide information on the tasks, schedules, task delegation, protocols, and guidelines required to accomplish the quality objectives in the daily operations of the pharmacy. Pharmacy employees should have easy access to the Quality Manual so they can refer to it whenever needed.
b) Service Policy	The steps required to provide each service provided by the pharmacy should be outlined in detail in the service manual. The handbook should also contain all of the specifics of the pharmacy daily operations, including routines, responsibility assignments, work processes, and guidelines necessary for providing the services.
c) Self training Policy	Training policies need to consider the pharmacy's adjusting out-of-service policies. The training frequency, content, and resources should all be specified in the policy. A training policy should guarantee that all pharmacy staff members are informed about advancements in their respective fields.
d) Complaints Policy	The pharmacy must to have a complaints procedure that is periodically examined. Any concerns raised by the chemist, whether expressed verbally or in writing, must be addressed immediately, and the necessary steps need to be done to correct the situation.
e) Policy for Drug Recalls	The Pharmacist must to have a meticulously recorded recall procedure.
f) Audit Policy	Audits are carried out to verify that the pharmacy's goals are being met to see if the Quality Management Systems are operating correctly and in accordance with the Quality Manual's guidelines. A Quality Audit allows the senior chemist of the pharmacy to assess the various standards operating procedures and quality control systems to determine whether they are meeting the necessary standards.
g) Documentation System	Protocols, Standard Working Procedures, Operation Instructions, Quality Manual, Cleaning and Maintenance Processes and Records, Complaint Records, and Internal and External Audit Records, Documents outlining policy, Individual information are a few of the required documents. Furthermore, it is imperative to retain and store pharmaceutical care procedure papers appropriately. These records consist of: **(i)** the health profile of the patient; **(ii)** the medication records of the patient; **(iii)** the records of follow-up counselling, etc. [20]

Table 5 ***cGMP Guidance for Human Drug Compounding Outsourcing Facilities***

Facility	**cGMP Guidelines for Outsourcing Facilities that Compound Human Drugs**

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A) Activities for Quality Assurance	Drug manufacturers must set up a quality control unit to monitor many elements of production, including microbiological quality for non-sterile medicines, in order to verify that protocols are followed and a quality drug product is created.
B) Facilities layout	The guidelines for designing structures used for manufacturing, processing, packing, or storing pharmaceutical items are outlined in Part 211 of the Guide. The products that a facility produces must be considered, and the necessary level of control must be provided to prevent contamination and mix-ups. To avoid undesirable microorganisms in non-sterile drug products, the production areas where parts, drug products, in-process materials, equipment, and containers or closures are prepared, held, or transported must be built to reduce the level of contaminants.
C) Control Systems and Procedures for Maintaining Suitable Facilities	It is necessary to have distinct spaces for operations, control systems of a similar nature, or both to avoid contamination or confusion during operations. A facility's layout must consider the products it produces and offer the required degree of control to avoid contamination and mix-ups. For a facility to function, procedures that designate who is responsible for sanitation and give a thorough explanation of the cleaning schedules, methods, equipment, and materials to be used in cleaning buildings and facilities must be created and followed. Water used as a final rinse agent for any equipment or utensils that come into direct contact with the drug product during non-sterile drug production should either be filtered water or fulfil USP criteria for higher quality.
D) Personnel and Environmental Monitoring	The frequency and methods of environmental and personnel control and monitoring should be determined with the product's quality in mind. The majority of non-sterile drugs provide a microbiological risk to patients, including those based on aqueous solutions. Therefore, more frequent water system & environmental monitoring should be carried out for the manufacturing of aqueous non-sterile pharmaceuticals than for non-aqueous non-sterile drugs. Monitoring humidity, temperature and air and surfaces (viable particles) have to be carried out every day and periodic basis during the manufacture of non-sterile aqueous drugs.
E) Equipment	Before being used for the first time, any equipment—mechanical, electrical, or automated—must be certified to be able to carry out its intended tasks. Additionally, regular maintenance and calibration protocols must be set up and followed to.
F) Containers and Closures	Testing the drug product container-closure system under the suggested storage circumstances for the final product is a necessary step in the selection process since it confirms the system's ability to maintain the finished product's quality standards beyond the expiration date. Before being used, appropriate protocols must be set up for testing or validating the testing, if necessary, of the containers and closures to make sure they match the requirements for use; the tests and outcomes must be recorded.
G) Components	It is necessary to have control over the components' quality and supply. One component of such controls in the production of sterile pharmacological products is determining whether the incoming components are non-sterile [21]

7. Conclusion

In conclusion, the regulatory frameworks pertaining to compounding pharmacies in established and developing nations exhibit substantial distinctions as well as commonalities, highlighting the variety of procedures uti-

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lized to guarantee the safety and effectiveness of pharmaceuticals. Strict regulatory regimes in industrialized nations frequently entail thorough oversight, exacting standards, and copious paperwork to reduce the hazards connected to compounding techniques. These precautions are intended to maintain strict safety guidelines and guarantee uniform pharmaceutical quality.

While India has improved its regulatory environment for compounding pharmacies, there are still several areas where further alignment with international norms could be beneficial. In the end, the contrast emphasizes how crucial it is for regulatory standards to continuously evolve and develop. India and developed nations alike stand to gain from exchanging experiences and working together to fortify their regulatory structures. Through mutual learning, regulators and stakeholders can work to achieve a balance that ensures the safety and quality of compounded medications while satisfying the unique needs and capacities of their respective healthcare systems.

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