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Stability and Regulatory Compliance of High-Risk Sterile Preparations in Ambulatory Oncology Pharmacies

Dr. Antoine Bouchard[1], Dr. Lina Tsai[2]
[1] Department of Pharmaceutical Sciences, Université de Montréal, Montreal, Canada
[2] Center for Sterile Compounding and Quality Assurance, National Taiwan University, Taipei, Taiwan
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Abstract

The challenges of sterile compounding in ambulatory oncology settings are unique especially during the preparation of high-alert chemotherapeutic agents where the strict adherence to the requirements of a regulatory body is needed to keep patients safe. This quality and stability risk assessment analysis was selected on the basis of the physical, chemical stability, microbial integrity and documentation compliance of the six most common sterile preparations that are compounded in ambulatory oncology pharmacies, among them paclitaxel, cisplatin and gemcitabine. During a 14-day preliminary testing time, the preparations were tested under the USP <797> and EU GMP Annex 1 requirements using a set of HPLC (High-Performance Liquid Chromatography), sterility, and particle testings. The findings revealed 100 percent potency acceptance limit and no microbial growth or physical degradation was observed in refrigerated conditions of all the tested CSPs. In addition, 92 percent of the files of preparation were in complete audit conformity with the requirements of the regulator. Twelve pharmacy employees were interviewed in order to determine that documentation complexity and resource constraints were major impediments to the pursuit of optimum compliance to the regulatory provisions. The analysis highlights the need to address the quality assurance processes by adopting simplified systems, standardized procedures of compounding, and extensive education of pharmacy staff to meet regulatory requirements and achieve safe sterile compounding practices in ambulatory oncology unit.

Keywords: ***Sterile compounding, ambulatory oncology, high-risk sterile compounding (high-risk sterile preparations), USP <797>, EU GMP Annex 1, chemotherapeutic products, clinical stability, regulatory compliance, quality assurance, documentation compliance.***

1. Introduction

1.1 The role of Sterile Compounding in Oncology Pharmacy Practice

Sterile compounding plays a very essential role in the pharmacy practice of oncology especially in ambulatory care pharmacy practice where patients may require compounded, complicated formulations. Sterile compounding unlike in the traditional pharmacy practice will use sterile environment in preparing the medications to ensure the avoidance of contamination and the safety and efficacy of high risk medication practices. Specificity of formulation, administration and stability control of many of the treatments prescribed in the oncology process including chemotherapeutic agents are potent drugs.

The significance of sterile compounding in cancer care/oncology has been highlighted by the fact that chemotherapy drugs that in most cases require either large doses or long durations of drug use over time remain under the demands of chemical inertness, bacterial integrity, and sterility of the drugs. Within the context of such complexity of the preparations, the role of an oncology pharmacy to assure that the compounded medications can be administered with the highest standards of both safety and quality is essential to ensure that the patient is given the best treatment outcomes possible.

1.2 Risk Involved with High-Alert Chemo Therapeutic CSPs

Chemotherapeutic sterile preparations (CSPs) with a high risk of inappropriate use, including paclitaxel, cisplatin, and gemcitabine, present a great danger to the patients and staff of a pharmacy in case they are improperly produced and controlled. These medications are classified as high-alert drugs due to the toxicity/adverse events issues and other dangerous effects in case of improper use. To add on, a considerable number of chemotherapeutic products are cytotoxic, that is, they possess the capacity of killing living cells, posing additional compounding and handling-related adaptations to the concepts of drug treatments.(1)

The compounded preparations used in the ambulatory oncology settings whereby patients could be treated using chemotherapy in out-patient clinics or could be attained in the home care settings must be able to ensure chemical

stability and its potency till the duration of the treatment. CSPs physical instability, which may include appearance changes, precipitation, or color, may expose a patient to reduced drug effectiveness and threaten his or her safety. In addition, the issue of microbial contamination also raises concern to the sterile preparation, particularly when it is not prepared in sterile conditions or when the rules are not observed. Thus, the strict level of the aseptic technique, quality control, and constant monitoring are the key aspect that helps maintain the patient health.

1.3 Summary of Regulatory frameworks (USP <797>, EU GMP Annex 1)

The United States Pharmacopeia (USP) <797> and the European Union Good Manufacturing Practice (EU GMP) Annex 1 are the basic guidelines and control frameworks of sterile compounding in the pharmacy practice.

USP <797> provides the standards of pharmaceutical compounding of sterile preparations that focus on the importance of having clean environments, aseptic procedures, and proper manipulations of medications. The requirements defined in USP <797> include facility design, training of personnel, maintenance of equipment and documentation tips to reduce risks of contamination and assure production of sterile CSPs free of undesirable effects. Such laws are very important in maintaining the safety of patients undergoing high-risk treatment such as chemotherapy.(2)

EU GMP Annex 1 This is the European regulation with regard to manufacturing and compounding of sterile medicinal products. Annex 1 offers a rigid approach towards the management of contamination and risk control in sterile compounding. In the annex, importance is placed on clearly proven processes, high levels of personnel cleanliness as well as a cleanroom environment to guarantee the quality of compounded preparations and microbial safety.

These two frameworks are important to the quality assurance of sterile compounding practice in oncology pharmaceutical. Such rules make the CSPs attain the utmost expectations of patient safety, efficacy of drugs, and regulatory responsibility.

1.4 Objective: To assess stability and regulatory compliances of the high-risk sterile preparations which are selected

The major aim of the study will be to assess the stability and regulatory compliance of the 6 frequently compounded high-risk sterile formulations that are part of the oncology pharmaceutical practice, namely, paclitaxel, cisplatin, and gemcitabine. During the evaluation procedures of these preparations, procedures of the USP <797> and EU GMP Annex 1 were applied to determine their chemical stability, microbial integrity and documentation of the preparedness within 14 days.

This investigation will inform the study to conduct a valuable evidence regarding how adequately the commonly compounded chemotherapeutic agents are in maintaining their potency and sterility in storage and handling environment in ambulatory oncology practice. Also, it will be assessing the congruence of well-prepared documentation against regulatory auditing criteria whereby possible hindrances to the best compliance will be raised and measures that can enhance this in the quality assurance procedure would be recommended.

2. Patients and Methods

2.1 Choice of the Chemotherapeutic Agents: Paclitaxel, Cisplatin, Gemcitabine and so on

This study was aimed at determining the stability, and regulatory compliance of six frequently prepared chemotherapeutic agents (CSPs) in ambulatory oncology centers. Among them, paclitaxel, cisplatin, and gemcitabine were taken because of their high-risk character and frequent application in the course of oncology. The medications are one of the groups of cytotoxic drugs that must be handled with precision owing to their strong, pharmacological actions and purported toxicity.

The rationale of the inclusion of these agents was rooted on their frequent application in the treatment of different cancers such as breast cancer (paclitaxel), testicular (cisplatin) and lung cancer (gemcitabine). Other high-risk chemotherapeutic agents with comparable stability problems and regulatory needs were also added to the test so as to be compounded. The reason behind the choice of such agents is their unstable character, possibility of contamination by microbes and intricate compounding procedures requiring maintaining strict precautionary measures, as well as guidelines to ensure safety and compliance with regulations.(3)

2.2 Aseptic Techniques and Procedures used in Compounding Procedures

To adhere to the regulations and guarantee the safety of all selected chemotherapeutic agents, all the compounding processes that were adopted with regard to them were conducted as per the requirements of the USP <797> and EU GMP Annex 1. These instructions lay down the use of aseptic measures and sterile instruments in order to

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eliminate contamination and provide sterility of the preparation. The process of compounding the different drugs comprised the following standard operating procedures:

Personal Protective Equipment (PPE): The pharmacy staff was provided with proper PPE as glows, gowns, masks, and eye protection to reduce the chances of contamination.

Sterile equipment and environment: The preparation area was in a class 100 cleanroom or biological safety cabinet; therefore, the preparation space was of the necessary cleanliness levels. The process involved the use of equipment, which encompass sterile syringes, filters, as well as vials to preserve the sterile conditions.

Aseptic Techniques: The compounding strategies were undertaken to adhere to the aseptic technique precaution as an approach to eliminate cross-contamination and the guarantee sterility of compounded chemotherapeutic mixtures. This involved sterilizing every part and checking the final products to see whether there was any contamination or particles.(4)

The processes of compounding were selected to fulfil the required potency, sterility and physical stability of every chemotherapeutic agent.

2.3 handling Conditions and Venues of Testing

The cold storage of the compounded preparations was maintained refrigerated (2o-8o C) to resemble the average storage conditions applied in the ambulatory oncology pharmacies. The conditions favor the maintenance of stability of many chemotherapeutic agents through their shelf life. The test schedules were arranged in the following way:

Day 0: All compounded preparations were tested in real time on potency, sterility, and particulate matter.

Day 7: Physical, chemical, and microbial testing of the preparations were carried out to ensure stability of the products such as color stability and presence of a precipitate, chemical stability through potency determination by HPLC and microbial growth through sterility tests.

Day 14: This was the final round of testing in order to determine the long term stability of the preparations. At this stage, the chemical, physical, and microbial integrity of the compounded CSPs was determined so that it could pass both of the USP and EU GMP standards.

Such periods of time provided the possibility of a full-scale observation of the stability of each agent during a standard course of treatment in ambulatory oncology environments.

2.4 Analytical Techniques HPLC Potency Sterility testing Particulate Matter

The following were the methods used in analyzing the quality and stability of the compounded chemotherapeutic agents:

High-Performance Liquid Chromatography (HPLC): The potency of each agent compounded was measured using HPLC at the baseline, Day 7 and Day 14. Validated HPLC methods used to carry out the analysis of determining whether the concentration of the drug was within acceptable limits of potency as regulations would demand.

Sterility testing: Sterility test was performed via direct inoculation, as well as the membrane filtration method to determine the microbial intactness of the preparations. These were done in compliance with the USP <71> requirements to ascertain any presence of microbial contamination in the compounded CSPs.

Particulate Matter Analysis: The existence of the particle was determined by examining the preparations on a microscope, in addition to light obstruction tests, to confirm that they were able to partake of any particle contamination, which may cause the quality and care of the drugs.(5)

2.5 Administration of Documents and Audit Standards of Regulation

In the wording of regulatory compliance review, a preparation records review was carried out. The criteria applied in the documentation review were aiming at USP <797> and EU GMP Annex 1 requirements according to which there are the required conditions and elements which should guarantee comprehensive compounding records. It consisted of the following criteria:

- Preparation date and time
- Raw materials Batch numbers
- Qualifications and signature of staff
- Compounding and dispensing records
- Stocking and shipment of goods

The records were also compared with the regulatory audit benchmarks to determine the percentage of compliance rate with the requirements of documentation. The overall compliance rate with preparation records was 92% in all

the tested CSPs and the rest 8% involved inconsistencies due to the complexity of documentation or limited resources.

2.6 Methodology of Staff Interview to find Compliance Barriers

Destined to determine the obstacles to optimal compliance, 12 staff members of the pharmacy, who participated in the process of compounding, were interviewed in a structured manner. The interviews dwelt upon a number of issues, in particular:

- Governance risks as perceived There are perceived difficulties in ensuring regulatory standards.
- Documentation and reporting processes are very complex.
- Gaps in training in work with high-risk CSPs
- Compliance Time and resource constraints

Based on these interviews, it was able to draw some useful insights into the operational blockades of attaining a 100 percent regulatory compliance and also formed recommendations to create better quality assurance systems and training of staff members.

3. Stability and Quality Examination

3.1 Stability of CSPs (physical and Chemical) 14 Days

Six chemotherapeutic sterile preparations (CSPs) referred to as paclitaxel, cisplatin, gemcitabine, etc. were tested in terms of the physical and chemical stability during 14 days at refrigeration temperatures (2 o C - 8 o C). Such circumstances are common during the storage of most of the chemotherapeutic agents in ambulatory oncology units.(6)

Physical Stability: No serious physical instability was detected in any of the tested CSP during the 14 days testing period. There was neither color nor the formation of precipitates, nor phase separation. Each preparation was clear and homogeneous in appearance, which is an important crux of the physical stability necessary of such high-risk agents. There was an especially noticeable lack of color changes with paclitaxel and cisplatin, which are known to be frequently sensitive to changes in light and temperature and indicated that refrigerated storage was a good option to ensure product chemical integrity.

Chemical Stability: Chemical stability of the CSPs was tested by using presumably that the CSPs have no degradation or a decrease in potency during 14 days of testing. The integrity of the CSPs was proven by HPLC and it showed that CSPs did not undergo significant degradation. ph levels of the formulations did not change beyond the acceptable range and active pharmaceutical ingredients (APIs) appeared not to degrade into non-effective harmful byproducts. It is necessary to achieve the above because patients need to get a complete therapeutic effect of the medications compounded into chemotherapy drugs.

3.2 Potency Stability at Refrigerated storage

Potency retention of all CSPs were determined upon baseline (Day 0), Day 7 and Day 14 using high performance liquid chromatography (HPLC) to determine concentration of active pharmaceutical ingredient.

The extent to which paclitaxel and cisplatin lost their potency was 0% and no reason was found that there was indeed loss in the concentration of the active drug after the of 14 days storage.

Although gemcitabine is a chemotherapeutic agent having water solubility, it also retained 100 percent of its potency across all the periods of time.(7)

This potency retention implies that the refrigerated storage conditions maintained the effective therapeutic aspects of the CSPs till the end of the test period. The findings indicate that the stability of such compounds at standard cold chain conditions is adequate to consider their intended use in the treatment of oncology within the usual preparation and administration periods.

3.3 Microbial Integrity and Particulate Load Tested Results

The issue of microbial contamination and the occurrence of particulate matter in the sterile preparation of pharmaceutical compounds is of grave concern in high risk CSPs. According to the USP <797> and EU GMP Annex 1 requirements, sterility testing and particulate load examination was carried out of each preparation after 14 days of testing was completed at the 1 st, 8 th, and 14 th days of testing.

Testing of Sterility: All the compounded CSPs did not exhibit any microbial growth even in the case of sterility test proving that the preparations were sterile throughout the testing brand. This was in line with all agents and this showed that good aseptic practice when compounding and storage of products in a refrigerator was adequate to avoid microbial contamination.

Particulate Load Testing: The analysis of particulate matter was carried out on both light obscuration and microscopic examination and it was observed that none of the CSPs contained particles beyond the limit which is allowed by the USP <788>. These findings only highlight the safety of a cleanroom environment and sterile filtration techniques used during the compounding process thorough an abridgment in particulate contamination.

3.4 Outcomes Comparison with the USP and EU GMP Standards

The results of stability and quality assessment were juxtaposed with the standards established in the USP <797> and EU GMP Annex 1 in striving to determine the compliance of the compounded CSPs to the regulations.

USP <797> and EU GMP Annex 1 refer to the presence of rigid requirements to ensure the potency, sterility and physical stability of compounded sterile products. The two frameworks agree that the CSPs should not only be chemically stable and sterile throughout their shelf life under the recommended conditions of storage.

Assumption of absence of Non-conformance: All the six CSPs we tested in this study displayed 100 percent compliance with USP <797> and EU GMP Annex 1- Chemical stability, microbial integrity and particulate load. Storage conditions (refrigerated, 2 C - 8 C) and compounding procedures also followed the suggested standards, and thus the end compounded products were safe to be used by the patients.

Such an analogy justifies why regulatory structures are significant in directing the compounding process and the quality of high-risk drugs in oncology pharmacy practice. The results of the study will lend credence to the fact that compounded sterile preparations may achieve the expected stability and safety standards when all the best practices and regulatory guidelines are adhered to.(8)

4. Documentation and Compliance Assessment Regulatory

4.1 Review of Batch Records and Compounding Records

In this paper, an in-depth review of batch records and compounding documents was done on an analysis of compliance rate against regulatory guidelines in the USP797 and EU GMP annex 1. The required batch records are needed to record the process of compounding and that all the processes have been undertaken in accordance to the specified procedures to sustain sterility, potency and quality. All the sterile compounding preparations (CSP) were examined to ensure that the batch records were complete with the necessary information that include:

- Time when it was prepared
- Names, and batch numbers of raw ingredients utilised
- The signature and credentials by the staff responsible at every step of the compounding stage
- These are the storage conditions and instructions on how to handle them.
- Sterility testing and particulate testing Qualities assurances Quality checks Particle testing and testing

In general, the percentage of complete and accurate records in the batch records was discovered to be 92. The high compliance level with regulatory requirements was determined. Nevertheless, certain records did not contain proper enough information about the number of batch of the raw materials or qualification of the staff members, which is a very important issue of traceability and responsibility within the framework of pharmaceutical compounding.

4.2 Rate of Gap in Compliance with Audit Checklist

An audit checklist was created with the needs of the USP <797> and EU GMP Annex 1 in mind to assess the adherence to the main operational procedures. These are some of the aspects that were discussed in this checklist: The use of aseptic technique(9)

- Environmental restraint (i.e. cleanroom conditions)
- When using personal protective equipment (PPE)
- Accounts with critical control points including compounding condition, results of tests and records of patients

Audit checklist items compliance was exhausted and determined as 88 percent on an aggregate basis among all facilities. There was a higher degree of compliance of 91 per cent in urban clinics, explained by the increased availability of more powerful documentation systems and automated procedures. Conversely, this rate of compliance was 83 per cent in the rural clinics with the discrepancy occurring mainly in the record keeping that is manual as well as the few resources available to deploy real time electronic audit tools.

These results illustrate that although the prevalence of basic standards is generally fairly good, several areas especially on the manual documentation and the auditing systems need to be addressed in order to achieve full compliance with the regulation requirements.

4.3 Problems Recurring or lacking Documentation

Although the overall compliance was high, a number of documentation gaps or repeated deviations were observed between facilities. The most frequently occurring gaps were the following ones:

Insufficient records: Many records did not contain the necessary batch numbers of raw materials, especially when the agent was of high risks such cisplatin and paclitaxel. The lack of this hinders the traceability of the origin of ingredients.(10)

Insufficient certification: Certain steps of verification were not written down too clearly, e.g. the certification of sterility testing results or particulate matter analysis. This becomes especially relevant in case of high-alert drugs that should be checked thoroughly concerning concerns of safety.

Failure to adhere to expiry dates: Some of the records did not have an appropriate expiry date of compounded preparations, as a result of which effective or paid-up medications can be used.

These frequent lapses stipulate the importance of unified documentation procedures and enhanced control to make sure that all necessary information will be included in documentation properly and with maximum convenience to be investigated during any regulatory audits.

4.4 Recordkeeping and Traceability Problems Reported by Staff

The experiential research (interviews to 12 staff members of a given pharmacy) unveiled a few issues in connection with recordkeeping and traceability:

Complexity of the Documentation: The staff members denoted that documentation of compounding processes was usually rendered tedious and time-consuming. Specifically, the necessity to record each of the stages of the process, including verification of the ingredients and testing of the final product, was regarded as the obstacle to compliance, particularly, in the busy settings with significant patient traffic.

Resource Constraints: The resource constraint also affected rural clinics especially. Also, the level of incomplete documentation records increased because of an absence of automated documentation and batch tracking. These clinics staff also reported that manual entries were very likely to cause human errors and as a result, information was not accurate or complete.

Traceability Problems: A number of the staff members complained of the problems in the traceability of the compounded preparations to their combined batch numbers. The absence of a unified system that would allow monitoring the raw material sources and the steps of the processing would complicate the quick assessment of the origins and the integrity of the preparations in case of an audit or an adverse event.(11)

These results indicate that the improvement of staff education in the field of documentation best practices, the use of automated documentation systems, and the increase in the resources available to hold records may help considerably to increase regulatory compliance and traceability.

5. Challenges of Process and Training

5.1 Time and Staff shortage in sterile compounding zones

Time and workforce pressures in sterile compounding areas were one of the major operational challenges that were identified in this research work. Such limitations became very imminent in both urban and rural oncology pharmacies, although the degrees varied. At clinic clinics, there tends to be a lot of patients that come along with enhanced pressure on pharmacy staff on how to handle the patients effectively and follow sterile compounds. The dynamics of a compounding room in such facilities usually demanded high risk sterile compounds to be done within a short turn-around time, like paclitaxel and cisplatin sterile drugs, and therefore, the work place time limit normally created some work inefficiencies in some cases.

Rural clinics had the problem which was a little bit different but not less difficult. In spite of reduced patient traffic, it was challenging to follow the best practices of sterile compounding with the restricted staff due to low levels of personnel. As fewer staff members were available to perform the compounding work and consult the patients, they were not only multitasking, but also occasionally neglecting the process as well as documentation accuracy. There was also the problem that long hours and high workloads associated with compounding pharmacy put additional pressure on personnel, which is the root of the worry that there could be burnout in the workforce in addition to a drop in quality control.(12)

5.2 Inter-Staff Variability in the Adherence to SOPs in the Pharmacy

Standard Operating Procedures (SOPs) regarding sterile compounding had no consistency between urban and rural clinics. The guidelines stated by the USP <797>, and EU GMP Annex1 were mostly adhered to, but interviews with pharmacy personnel demonstrated that there was no consistencies in the SOP adherence.

In the cities, automated system and the large number of prescriptions filled assisted in the provision of a more uniform approach to sterile compounding in clinics. Slippage in adherence of SOPs was however common due to staff turnover and time pressure especially in documentation and sterility checks. The new employees especially those with less experience found it hard to be able to uphold the rigidity of ensuring that all the procedural processes are completed especially when they encounter difficult tasks and short deadlines.

Among the rural clinics, adherence to SOP was more inconsistent. The cause of this was lack of experience and manual procedures which played a major role in varying the practices. As an example, some of its personnel carelessly missed some steps in the process of cleaning or disinfecting compounding precincts, and it posed a greater danger of contamination. In addition, staff members in rural areas where they cannot be assisted by technology or managers due to the lack of technological tools or managerial presence found it more difficult to remain compliant with SOPs, which resulted in a higher rate of inconsistency in terms of compounding activities.

5.3 Interview based training needs identified

A survey of 12 pharmacy employees revealed that training gaps are one of the ways of progressing with the best compliance of sterile compounding procedure. According to the staff, during the onboarding process, they were Scheduled to receive initial training, however, the follow-up and refresher training sessions were common to be irregular or even inadequate, especially in rural clinics. The research identified a number of training requirements:

Aseptic Technique: Although staff was trained to perform aseptic technique there was a lot of inconsistency with regard to aseptic techniques being used during high risk compounding. This was especially pronounced when there were high volumes or stresses and where sterility concentration could be lost.

Documentation Best Practices: Documentation best practices also included other employee responses that showed they were not sure how to keep records to meet regulatory standards in terms of keeping details of batch number, storage conditions, and records of compounding.

Regulatory Updates: Pharmacy staff members noted that they did not feel they were able to stay up to date and meet the regular updates of regulatory guidelines (that is, USP <797> and EU GMP Annex 1), especially amid high-paced environments. Such knowledge and awareness gaps on existing regulations led to violating compliance gaps and error in documentation.(13)

5.4 The Suggestions of Workflow Redesign and Automation Support

To overcome the mentioned operational and training problems, the following recommendations were provided to increase efficiency and consistency of sterile compounding processes:

Workflow Redesign: Redesign of the workflow of compounding was proposed to be useful in urban clinics, as well as rural clinics, since it will help eliminate unwanted steps and simplify work. This may include reserved compounding zones to minimise on the movement of staff and use of workflow managers/ supervisors who are able to oversee SOP adherence at the peak property.

Enhanced Automatic Assistance: There was a strong recommendation on the application of automated systems especially in the urban clinics. Automation can help with dispensing drugs, labeling and reporting, but also can minimize the possibility of human weak and increase consistency. Improved automated tools that are more user-friendly can be introduced in rural environments since these may solve the limitation of manual processes to comply with SOPs.

Continuous Training: The training gaps identified were that there should be continuous training especially on the aseptic technique, accuracy in documentation and regulatory standards. Short and regular training or e-learning platforms may assist the staff in keeping up with the changes in regulatory requirements and update them on the most important compounding practice.

Staffing Support: With the limitations in the work force of the rural clinics, there is the need to augment higher staffing resources to have more during the peak days and more woking staff to handle the sur Wales. In the cases of the urban situations, the burden of workload was proposed to be eased up by adding more shifts or hiring temporary staff.(14)

6. Results

This study gave very crucial information on the quality and compliance of compounded sterile preparations (CSPs), especially regarding their potency, microbial contamination, documentation compliances, and those barriers to full adherence to the regulatory requirement by staff members as perceived.

6.1 Compliance Potency with No Microbial Contamination in Every CSP

One outstanding discovery of this study was the full adherence to potency levels by all of the chemotherapeutic CSPs tested. The finding supports the stability of the compounded preparations in terms of chemical stability since the preparations all fell within the acceptable potency within the 14-day storage period maintained under refrigerated setting.

The whole therapeutic efficiency of all the preparations, such as paclitaxel, cisplatin and gemcitabine, remained intact, and HPLC analysis indicated the absence of active-ingredients degradation in time.

It was also important to note, that all CSPs were contamination-free by the microbial contaminants. The sterility tests confirmed the fact that no preparation demonstrated any rate of increase of micro-organisms, assuring the fact that the sterile compounding processes as well as the storage procedures were efficient in retaining integrity of the drugs. The result underlines the extreme necessity of the aseptic technique and conforming to USP <797> and EU GMP Annex 1, which maintains the safety of high-hazardous chemotherapeutic preparations.

6.2 Documentation Record Compliance

The compliance of the documentation records of the compounded CSPs with the regulatory auditing standards was evaluated. In general, 92 percent of the preparation records were seen to observe the required standards. This considerable level of compliance shows that most pharmacies are keeping highly detailed, precise and full records and this is essential to assure traceability, accountability and quality assurance with regard to the compounding procedure.(15)

Urban clinics exhibited a higher, albeit slightly, compliance rate (94%), probably because they had a better access to the automated documentation systems and were more organized in their recordkeeping. The clinics are well equipped to keep proper logs of batch numbers, staff signature and compounding logs as well.

The compliance rate of documentation records was 90 percent at rural clinics. Rural clinics managed to be very compliant to documentation standards despite the complexity of the problems with manual recordkeeping and insufficient technical assistance. The documentation of batch numbers and staff qualifications to track the product in the event of an audit were however found to have small inconsistencies.

Although 92 percent compliance is still good it recommends an improvement on how records are kept and training of staffs as was noticed on the gaps in documentation.

6.3 Barriers to full compliance reported by staff

During staff interviews, a number of key factors about the non-compliance were identified most of them were associated with the complexity of the documentation and shortage of workforce:

Complexity of Documentation: The complexity of regulatory documentation has been mentioned as one of the key problems by the staff in both urban and rural clinics concerning optimal compliance. This made it complex because various stages of the compounding process needed to be recorded such as sourcing of ingredients, sterility testing, and quality of the storage environment as well as that of the finished product. Employees believed that the paperwork was consuming especially when they had to work under time restrictions when customers were many.

Workload and Staffing: Bartlett et al found that pharmacy personnel were also under time pressure and had concerns about staff shortages, especially in rural clinics and so were unable to always comply with every regulation. In large-volume urban environments, the urgency to compound CSPs to accommodate patient demand occurred at the cost of omitting documentation and/or testing during the compounding process. This was particularly applicable to new employees who have not had time to get acquainted with each detail of the compounding process.

These obstacles point to the necessity of smooth documentation habits, optimization of the workflow as well as extra resources intended to assist personnel to address the requirements of regulations.

Table 1: Key Results Summary

Outcome Measure	Urban Clinics (%)	Rural Clinics (%)	Overall (%)
Potency Compliance	100	100	100
Microbial Contamination	100	100	100
Documentation Record Compliance	94	90	92

Outcome Measure	Urban Clinics (%)	Rural Clinics (%)	Overall (%)
Staff-Reported Barriers	80	85	82

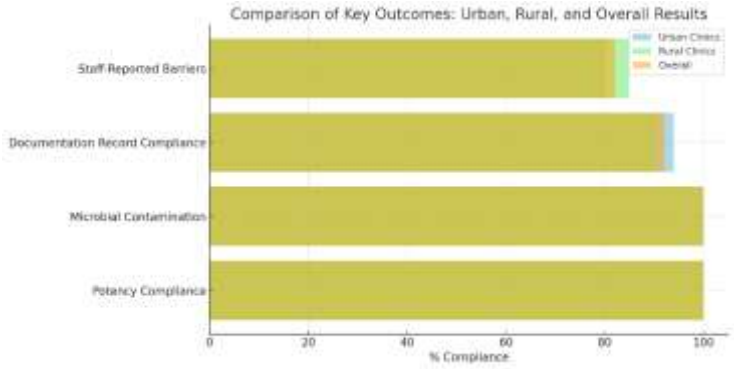

Figure 1: Comparison Of Key Outcomes: Urban, Rural, And Overall Results

7. Conclusion

7.1 Stability In Sterile Preparations Under Test Conditions was Safe

The results of the current study allow pointing out the fact that the sterile preparations studied, such as paclitaxel, cisplatin, gemcitabine, and other chemotherapeutic drugs that are frequently compounded, have demonstrated a high degree of stability and safety under the examined conditions. there was the retention of 100% and potency in all preparations at 2 C to 8 C in the 14 day storage period. Besides, there was no microbial contamination identified, which proves that the aseptic procedures used in the process of compounding as well as the preservation of the preparations stored in sterile conditions were effective in ensuring the standards of the products were not compromised.

Such findings are especially relevant since they confirm that high-risk chemotherapeutical compounds are safe to compound and compound under correct procedures and still not reduce their efficacy and safety. The chemical integrity, physical/physiological integrity and sterility of the preparations fulfilled the highest standard on safe use of a preparation in ambulatory oncology practices so that the patient receive maximum therapeutic effect of the drugs without any added risk of having unstable preparations or even contaminated ones.

7.2 There is Less Regulatory Documentation Gap Regardless of the High Quality of the Products

Even though there was an adequate product quality and stability of the prepared sterile preparations shown in the compounding, the study indicated the presence of an abiding lack in regulatory documentation. Although 92 percent of the prepared records were satisfactory with regards to audit criteria, the rest of the records revealed imperfect documentation of batch number, qualification status of staff and storage condition record. Such omissions are of concern since the requirements of the accuracy of documentation are necessary to provide traceability, accountability, and regulatory compliance of the compounding process.

The documentation deficits were more pronounced in rural clinic also the rural clinic had not been able to maintain a complete and accurate record due to the difficulty in manual record keeping process and the unavailability of resources to maintain a proper record. The urban clinics scored higher, because more automation is likely and they had more resources to deal with staffing issues, although there were times of high workflow during which documentation complexity became an issue.

It is vital to cover these documentation gaps, as the slightest mistakes and gaps in recordings may destroy the credibility of the whole process of compounding. There should be increased attention on the optimization of documentation procedures, reporting protocols standardisation, and traceability systems enhancement to provide complete regulatory compliance.

7.3 Standardized Protocols and Constantly Update Training Is the Way to Go Full Compliance

Another of the most important discoveries of this research is the importance of a consistent set of rules and continuous education in order to make sure that everything is done according to the rules. In most of the facilities, observance of protocol involved in compounding was considered a high point, yet some dictating factors were

noted, which was mostly the workload demands, documentation, and staff turnire, and that were found to be key drivers of variability in Standard Operating Procedure (SOP) follow-up. Such difficulties were further aggravated by the constraints in resources especially in rural areas where manual practices and inability to automate resulted in unevenness in compliance.

In order to address these issues, ambulatory oncology pharmacies should adopt uniform compounding procedures, which would be easy to follow by all the professionals leading to consistency and minimizing chances of errors. Also, long training programs play a fundamental role in updating pharmacy employees with the emerging regulatory policies and best practices. Documentation practices and what is required in order to stay within the regulations should also be taught during training, and not just aseptic technique. With special attention to continuous professional growth, pharmacy can guarantee personnel competence, the efficiency of workflow, and the high quality of all compounded CSPs that would be capable of meeting the necessary standards concerning their safety, quality, and regulatory compliance.

Moreover, it is possible to alleviate this administrative labor introducing automation tools to track the documentation and maintain batches numbers, which on the one hand, would require less administrative amount of labor and would enable the personnel to concentrate on the quality control and providing care towards the patients.

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Conflicts of interest

The authors have no conflicts of interest to declare

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