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A Literature Study of IPQC (In Process Quality Control) tests and FDF (Finished Dosage Form) tests for Parenteral Dosage forms taking Adicovil IV Ampoule as an Example.

Abstract

This study was conducted to evaluate both the in-process quality control tests as well as the finished dosage form tests for a parenteral product. Furthermore, all the processes from the purchase of API to marketing of product were studied. A batch of Adicovil was taken Adicovil was taken as an example, it is small volume parenteral of 2ml ampoule that is studied to evaluate its efficacy and stability by performing chemical and physical tests. IPQC tests for type I glass includes powder glass test, while for water for injection they are pH, acidity & alkalinity, non-volatile matter, ammonium ions, non-oxidizable matter, sterility and pyrogen test. Test for finished dosage form of Adicovil are identification, leaker test, clarity test, sterility, pyrogen test, BET, deliverable volume and determination of volume of injection for container. The selected batch of Adicovil passed all the IPQC and FDF tests in the procedure.

Key Words: Parenteral, IPQC, stability tests, FDF, physical tests, chemical tests.

Introduction

Parenteral preparations known as the sterile preparations consists of one or more active ingredients intend to administer other than oral route that is by injection, infusion or by implantation into the body. These preparations are packaged in single-dose or multidose containers. The *Small-volume Injection* is packaged in the containers which are labeled as containing 100 mL or less. Large volume parenteral provide electrolytes, dextrose solution has volume 101-1000ml. (Akers, Larrimore, & Guazzo, 2002)

Parenteral dosage forms must be stable, sterile, free from the pyrogens and toxins. They should also isotonic and chemically pure.

Different tests are performed for their evaluation like sterility test, leakage test, pyrogen test clarity test and assay are also performed to evaluate these preparations. (Awan, Raouf, Ahmad, Sparks, & Marketing, 2009)

Description

The product chosen is a 2ml ampoule of Adicovil, generic name is Pheniramine maleate, brand name is Adicovil, manufactured by *Ameer and Adnan Pharmaceutical Pvt Ltd.* for IV administration only.

The formats given below is acceptable for the contents which is of greater than 1 mL: API *(Pheniramine Maleate)* -------50mg

Water for injection----------q.s

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Strength and total volume format as per USP

(total------2ml) strength/volume: 50 mg/2 mL Strength/mL: 25 mg/mL

Purchase of API

API of Pheniramine maleate was purchased from *Biesterfield Pharma* at price of **1.5 lakh PKR per kg**. It was packaged in a fiber HDPE drum with double plastic bags inside and a capacity of 25kg and a shelf life of **5 years**, provided that it should be kept in a clean, dry, cool area that is away from direct sunlight and the moisture.

Physical properties of API

White colored powder, 134-135 C melting point,

Role of QA and QC inspector in industry

Role of QA Inspector

- First rule is to make and approve the Quality Policy, its Objectives, Manual and Validation Master Plan.
- Second is making of periodic planning of objectives of quality.
- All validation & stability activities are monitored and then completed according to the schedule.
- It is also made sure that all changes have impact on the product and the established systems are being regularly documented and reviewed.
- It is necessary to ensures that all market complaints are registered, investigated to find out the basic cause so as to take CAPA to stop recurrence.
- It is necessary to prepare Annual product quality reports, trending of the data, analyzing product and performance of process.
- Last step is to arrange and conduct the self-inspection, find out the gaps and then take CAPA, records of related batch manufacturing are reviewed and QC testing data is performed before to release of batch.

Line Clearance

Line clearance has importance in pharmaceutical manufacturing. It makes sure that the processes are according to the set the standard operating procedure. For the line clearance in preparation area quality assurance is required. It has following steps.

1. Dispensing
2. Separate clearance necessary for all those processes happening in manufacturing.
3. Filling
4. Batch production and packaging

Role of QC Inspector

- **Routine work:** He is responsible for daily RM & PM inspection, Intermediate stage inspection, Finished Products analysis and the Stability analysis.
- **Non-Routine:** Calibration & maintenance of instruments, Preparation of reference/ working standards and the Method of development are also performed by inspector.
- **Activities managed through:** Analysis of instruments, inspection of chemicals (RM & FG), Analysis of microbiological product and the inspection of packaging materials.
- Performing out Sampling and testing of products, Monitoring of environmental conditions, Conduction of stability studies, Investigation of test failures such as OOS / OOT / OOAC / OOAL, validation of Analytical method and then Evaluation of the complaint samples. (Banker, 1970)

Operational procedures

Physical facilities

Brick buildings, well lighted and air-conditioned areas, automated fire alarm, a raw material **quarantine** area.

Locked vaults for controlled substances. Separate rooms for different dosage forms. (Broadhead, Gibson, & Form, 2009)

QC Facilities

A bench, desk, hood must be provided to scientist or technician.

Receipt of Raw Material

When a raw material is received, it is assigned a receiving number, indicated on containers and in QC records and is tagged with a "Quarantine" label. It indicates product's identity, source, grade, quantity, and data received.

QC of Raw Material

A representative of each raw material received is withdrawn for analysis by the Raw Material Control department, the remaining is impounded in raw material quarantine area. **Passed** labelled items are accepted, while ones not meeting the requirement are labelled **Rejected.**

Master Formula File

A complete file for each product is maintained by quality control, containing master formula record, current label, and labeling copy, details about packaging, etc.

Master Formula Record

Prepared by technical committee with members from R&D, QC and manufacturing.

Batch Production Card

Initiated by director of QA. Lot number is assigned, and calculations of ingredients are made.

Issuance of Raw Material

Raw material department receives notification of lot number and product and prepares raw material requisition cards for rich ingredient.

Identification of Manufacturing Steps and Machines

Each is identified with a label, showing its name, lot number, batch size.
Sampling
Testing
Packaging

Different Portions of Industry

Area Planning and Environmental Control

Area planning is addressed to the basic functional groups ground. It is very critical area in which special attention is given to maintain the cleanliness.

Functional Groupings

Warehousing

- To store the spare parts, change parts, air filters, chemicals used in water treatment, office supplier, uniforms and so many might be handled by central storage or individual storage by that department.
- Finished product and other essential raw chemicals require particular environmental conditions for storage like temperature control and the humidity control.

Administrative Areas

- Administrative area planning needs particular analysis of direct and indirect requirements of specific plants.

Environmental Control Zone Grouping Zones

- White zone: it is last step (parenteral products are filled here)
- Grey zone: it includes weighing, filtration and dissolution.
- Black zone: it contains storage. It is the worst area according to contamination point.

Figure 1: Black, white & gray area

Zone 1

It consists of the maintenance of sterile areas.

Zone 2 plant exterior

It is the basic zone from which to we determine the requirements to do work for the various control barriers.

Zone 3 General Production and Administration Area

it is the third zone for environmental controls and it is made by the periphery of the general manufacturing area.

Zone 4 Clean Area

In this zone activities cleaning, washing and preparations of instruments or accumulation and finally sampling of the finished products is performed.

Zone 5 Weighing, Mixing, and Transfer Area

This Zone 5 ensures the activities of "balancing, mixing, filling ,weighing " addressed by c GMP section 212.81 that are not handled in zone 6 but they need a controlled environment.

Zone 6 Filling Area

it is very distinct zone for the controlled environment area where an aseptic filling function is carried out. It is not specific zone for non-aseptic filling function. (Ennis et al., 2001)

Wall & Floor Treatment

Requirements for cleanliness includes plain, cleanable walls, ceilings, fixtures, and separated exposed walls, studs, columns ,pipes and bracings are not acceptable. The requirement for cleanliness also removes the open floor system that is used for laminar air flow system.

Lightning Fixtures

Lighting fixtures must be less redden with the ceiling. Areas which have a full HEPA ceiling could not lodge dented lighting fixtures. These areas have special fixtures which are of a "tear drop" forms that reduces disturbance to the laminar airflow pattern.

Change Rooms

Personnel approach to all the controlled areas must be via changing rooms. These Changing rooms give ideas and setups that vary from a single size room to high-priced multi-room complexes. Vestibules are used as entry gate to enter the changing area, its doors are interlocked electrically such that both doors are not opened

at the same time, by maintaining the air pressure differential so that airborne contamination must be blocked. Wash skins are given to scrub hands and forearms after gaining entry into room. Filtered and heated compressed air is used further for drying purpose. When hands become dried, clothes taken from the dispensers and put on while moving across a dressing bench. In final step, aseptic gloves are worn . Exit is just like the entrance. (Haleem, Salem, Fatahallah, & Abdelfattah, 2015)

Personnel Flow

While making the design of individual plant areas motion of individuals must be planned. Each personal manufacturing are must have a plain and efficient flow pattern, it could develop a congested pattern. It is an inefficient way if flow of chemicals made through corridors and unsafe when different individual manufacturing area plants are combined.

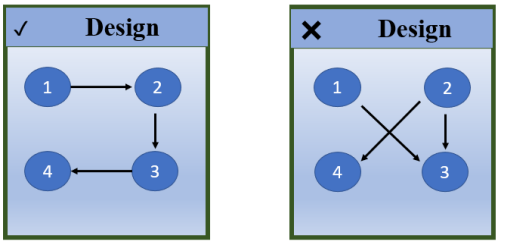

Figure 2: Correct design (left), incorrect design (right)

Utilities and Utility Equipment Location

Utilities

It is important to clean Piping system in particular initially and periodically. When it comes to exposed overhead then this kind of piping is not allowable from a cleanliness or contamination point because it gathers dust, so it is hard to clean and it might leak. Buried or enfold pipe might need unallowable destruction for cleaning or recovery. (Janodia & Udupa, 2015)

Utilities Equipment Location

Public services need space for dealing. Additionally, for switching devices and transformer electrical power system is needed. (Modgil & Sharma, 2016)

To make sure consistent quality treatment of water system is required. Plant generated services need steam boilers, pneumatic compressors, and distillation and the "boiler room" application. In foul weather, especially winter, maintenance of instruments is very hard. (Potdar, 2006)

Heavy instruments might cause harm to the roof-structure, especially when the instrument location needs much penetrations via the roof that is equipped with instrument vibration, will invariably lead to leakage.

Engineering and Maintenance

In view of engineering stand-point, any location if even it is exterior to the plant may serve good but approach to the manufacturing area by architects for field work must not too hard especially in small or less complex plants. (Schaut, Weeks, & technology, 2017)

Maintenance responsibilities include whole areas of the plant and may be divided into two forms: **plant maintenance and production maintenance.**

List of Equipment

Manufacturing Area

1. Storage instruments required for vials ,ampules ,bottles and closures
2. parching and washing instrument
3. Cabinet that is dirt proof

4. Blending and manufacturing tanks
5. Blending instruments where needed
6. Filtering instrument
7. Hot air cleaner

b) Aseptic filling and sealing room

8. Counters for lining and sealing
9. Filters for Bacteriological

C) General room

10. Examination table
11. Exude testing table
12. Benches for Labeling and packaging
13. For instruments storage consists of cold and refrigerators stockpile if needed

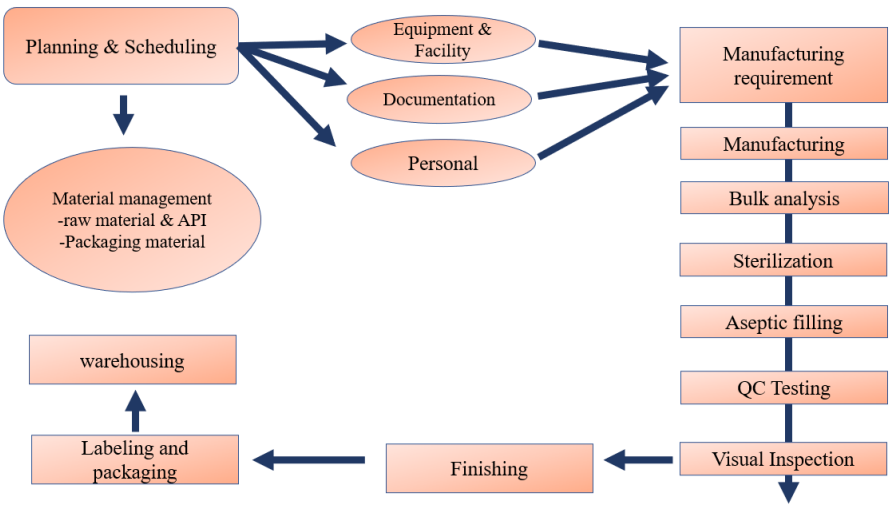

Figure 3: A Summary of Industrial Processing

Processing of type, I glass Ampoules

Purchase of Glass

The industry purchased glass from *Ganj Glass Works Ltd.* 12mm tempering glass was purchased at a price of PKR 800/sift with a bulk order of 5000 sift. The company has a production capacity of 200 tons glass per day.

Why use type I glass?

The best opposition to thermal shock is provided by type 1 borosilicate glass and it is higher chemical resistance. This type of glass shows the slightest reactive glass. It gives higher longevity, heat and the chemical resistance. It consists of notable quantity of aluminum oxide ,boric oxide and alkali and alkaline earth oxides.

Manufacturing Ampoules

Fabrication

In industry ampoules are formed from small lengths of glass tubing, that are made by warming with gas lamping and by the gravity in an automatic manufacturing lines. For the control of quality Computer vision techniques are used.

Ampoule code

Ampoules are basically in red color and are ringed along the neck so it becomes easy to find out the ingredient inside it. The rings which are machine-legible and permit for correct handling of the ingredient for the objective of labelling, storage, and secondary packaging.

Opening

they are unfastened by chalking up the neck and breaking the top off. In the "one-point cut" (OPC ampoules) a point overhead the neck finds out the place of a small slit in the glass for opening of the ampoule.

Filling and sealing

The filling and sealing of ampoules is done by the use of JLAB Ampoule Filling Machine with a production capacity of 1000. Before and after filling of liquid into ampoules nitrogen is purged in, so to eliminate atmospheric air present in it. Hermetic sealing is performed by a burner which is present in that device, it liquefies the things top and then break the neck. Overhead the device empty space left is filled with nitrogen. (Shirisha, Ghosh, Rajni, Banji, & Technology, 2014)

Labelling ampoules

Name of machine: ALPHARMA A
Specifications
150 products/min is the speed, power supply of 400 V, 50 Hz three-phase, power consumption of 1kW.

Labelling (USP 32 <1>)

The label on the container or device shows the name of the product, its drug percentage content of drug in a specific volume, conditions for storage and an expiry date, the location and name of business of the manufacturer, and lot number. The lot number is able to yield the full preparation history of the specified package, containing whole preparation, sterilizing, filling and labeling operations.

Table 1: Square Meter of Area Required in an Industry

Function	Area	
	Square meter	Percentage
Production	11,094	45.1
Warehouse	7,606	30.9
Utility	1,716	4.1
Quality control	1,716	7.0
Administration	1,018	4.1
Maintenance	1,014	4.5
Employee services	1,014	4.1
Security	39	0.9
Total	24,607	100.0

Qualitative Layout of Parenteral Manufacturing

Processing Of Water For Injection

USP 32 <1> shows that water for the injection has always been utilized as solvent unless specified in the individual monograph. There is no preservative less than the 5 ml.

Production

Single Effect Distillation

- BRAM-COR **Single Effect Distiller** Mod. **DPSG** is a Still along with a Pure Steam Generator. The manufacturing method contains evaporation of PW water by separation of pure steam and then condensation. By utilizing centrifugal and gravity processes this steam is refined. This instrument gives dried and saturated steam that is in in future utilized for sterilizing agent.
- pure steam fulfils the all conditions of international pharmacopoeias for Water for Injection. The system can therefore provide a simultaneous production of Pure Steam and Water for Injection by condensing it through the double sheet condenser.

Both BRAM-COR **CPSG and** Pure Steam Generator yields dry and saturated steam: this steam, by condensing ,fulfills USP conditions for **Water for Injection** (WFI).

Storage

The freshly prepared water is when stored and then sterilized in containers or devices that are hermitically sealed, it will be in very good condition. (Williams, 2004)

Table 2. Specifications of Water For Injection

S. No	Parameters	Specifications
1	Appearance	clear, colorless, no visible particles
2	Odor	Odorless
3	pH	5.0-7.0
4	Acidity or alkalinity	NMT 0.1 ml of 0.01M NaOH/Hcl
5	Chloride	0 ppm
6	Oxidizable Substances	0 ppm
7	Sulphate	0 ppm
8	Total hardness	0 ppm
9	Total dissolved solid (TDS)	NMT 10 ppm
10	Conductivity	NMT 0.1 ms
11	Microbial count	10 cru/100 ml

Water Supply to Industry

"(GMP) Water Distribution Pipe 14.40. The distribution of PW, HPW and WFI should be accomplished using a continuously circulating pipework loop. Proliferation of contaminants within the storage tank and distribution loop should be controlled. Filtration should not usually be used in distribution loops or at take-off user points to control bio-contamination. Such filters are likely to conceal system contamination."

Water from the Karachi sea is used by this industry. To get this water connection, attested photocopy of CNIC of owner, attested photocopy of sale proof/deed of ownership, copy of assessment, specification of departments using water, site plan to indicate location of property are to be provided to office of Sub Divisional Officer WASA in Karachi, and it is to specified that the connection is metered industrial one. A connection agreement is signed. An estimated bill for 6 months us included in the challan submitted which is later adjusted in monthly bills.

In Process Quality Control Tests

IPQC Test For Type I Glass

Table 3. Powdered Glass Test

Glass Type and Test Limit				
Type	**General Description**	**Type of test applied**	**Limits**	
			Size sq, ml	ml of cb 0.02N acid
I	Highly resistant, borosilicate glass	Powdered glass test	All	1.0

Tests for water for Injection

1) **pH:** Between 5-7, determined potentiometrically.
2) **Acidity or Alkalinity:** 1 drop of phenol red solution is added into 20ml of it. When it is of yellow, it changes into red on addition of 0.1ml of 0.01N NaOH; while when solution is red, it turns into yellow by addition of 0.1ml of 0.01N HCl.
3) **Copper, Iron and lead:** 1 drop of sodium sulfide solution is added to 100ml of it, then liquid keeps plain and clear.
4) **Chloride:** 1ml of Barium chloride solution is added to 100ml of it then after it make it almost to stand for five to six minutes; the liquid resets as clear and colorless.
5) **Ammonia:** 2ml of alkaline potassium mercuric iodide solution is added to 50ml of it then see in a Nessler cylinder that is ranking on the white side; yellow color generated quickly is not darker as compared to that formed by 50ml of ammonia-free water by adding dilute ammonium chloride solution.
6) **Calcium:** 2ml of ammonium oxalate solution is added to 100ml of it, there is no turbidity.
7) **Carbon Dioxide:** 25ml of calcium hydroxide solutions is added to 25 ml of it; the mixture remains clear.
8) **Oxidizable matter:** first Boil 100ml of it for almost three minutes with dilute sulphuric acid of 10ml; then add 0.1ml of 0.1N potassium permanganate and again boil it for 10 minutes, then pink color of it cannot completely disappear.
9) **Total solids:** first of all, 100ml is evaporated on a water bacth until it goes to dryness and dry the residue at about 105 degree for almost 1 hour, that is not more than 1 mg of residue remains. (10ppm)
10) **Non-volatile matter:** First of all, vaporize 100ml until to dryness on water bath, at 105 degrees for almost one hour dried the residues, that must not more than 2mg of residue remains (20ppm). In glass container WFI is packaged and then sterilized with a size of 30ml or less, the total solids content must not be over 40 ppm, and when in containers of more than 30ml but not more than 100ml volume, the total solids content must not excel 30ppm.
11) **Sterility:** it must fulfill the criteria for sterility.
12) **Pyrogen:** it must comply with the test for pyrogens.

Test for API

Assay: assay is carried out with Injection, to make the solution used to determine the absorbance, A_U, at the 264 nm wavelength. To determine A_S, we add about 25 mg of Adicovil, weighed correctly, in 20 mL of dilute sulfuric acid (1 in 350), and this solution is treated the same just like the portion of Injection is being assayed. At the end quantity is calculated in mg, of $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$ in each mL of the Injection by using the formula: $(C / V)(A_U / A_S)$

Finished Dosage Form Tests

Identification: (USP 32)

A: first volume of Injection is diluted equivalent to get about 50 mg of chlorpheniramine maleate, with dilute hydrochloric acid (1 in 1000) to 25 mL, and then we forwarded it as given specification.

B: a volume of Injection is vaporized on steam bath until to dried that is equivalent to about 25 mg of chlorpheniramine maleate, and then residue is dried at 105 for 1 hour: it liquefies between 128 and 135.

Leaker Test

It is utilized to identify incomplete closed containers or devices so they could be released. More chances are for tip sealed ampules to be closed incompletely as compared to pull-sealed ampoules. Leakers are identified by giving negative pressure inside in completed closed ampoules, mostly in a vacuum chamber, by immersing ampules in a deep colored dye solution (1% methylene blue).

Clarity test

Clarity is evaluated by individual human inspection of each container under good, and light bounces back to eyes, and is seen opposite to black and white background, by setting the contents in with a movement. A: The solid disperses fully, leaving behind no visible matter which is not dissolved.

B: The formed solution is not notably less plain and colorless as compared to an equivalent volume of the refined water that present in a similar bottle and examined as it is

Sterility test

For a batch containing 400 ampoules manufactured, 10 containers were used and half of the content of each container was tested. Method used was membrane filtration. This product meets the requirements for the test of sterility.

Pyrogen test

it is used to control to an allowable level the chances of burning reaction by injection in the patient, of the product that is concerned. This product fulfills the requirements for absence of pyrogens, none of the rabbits tested showed a rise of more than 0.5 degree.

BET

It contains not more than 8.8 USP Endotoxin Units per mg of chlorpheniramine maleate.

pH

between 4 to 5.2

Limits for the Particulate Matter Test:

Table 4. Limits for Particulate Matter Test

Method	Limits
Light blockage	≥ 10 um: max. 10,000/container
HIAC counter	≥ 25 um: max. 1000/container

Essentially free from visible particles.

Deliverable volume

Ten ampoules were taken from this batch, the AV10 for ten containers was less than 100% and none of the chosen containers had a volume less than 95% of the average volume, so batch was accepted.

Determination of volume of injection for containers

In case containers inspected individually the volume must not be less than the nominal volume,while in the case of containers which have their a nominal volume which is of 2 mL or less, it must not less than the total of the nominal volumes of the containers draw together.

Conclusion

After performing certain IPQC and finished dosage forms test on 10 containers of Adicovil this batch was accepted as no container had volume less than 95 percent and the average volume was less than 100 percent.

One container did not meet the all requirements but overall Batch of Adicovil fulfils the criteria of sterility, pyrogen and clarity test. So, it was accepted to release in market. Bacterial endotoxin content was not more than 8.8 USP endotoxin units per mg chlorpheniramine maleate.

References

Akers, M. K., Larrimore, M. K., & Guazzo, D. (2002). Parenteral quality control: sterility, pyrogen, particulate, and package integrity testing: CRC Press.

Awan, M. U., Raouf, A., Ahmad, N., Sparks, L. J. I. J. o. P., & Marketing, H. (2009). Total quality management in developing countries: A case of pharmaceutical wholesale distribution in Pakistan.

Banker, G. S. J. J. o. P. S. (1970). The theory and practice of industrial pharmacy. 59 (10), 1531.

British Pharmacopeia 2013

Broadhead, J., Gibson, M. J. P. P., & Form, F. A. P. G. f. C. D. S. t. C. D. (2009). Parenteral dosage forms. 331-354.

Ennis, R. D., Pritchard, R., Nakamura, C., Coulon, M., Yang, T., Visor, G. C., . . . technology. (2001). Glass vials for small volume parenterals: influence of drug and manufacturing processes on glass delamination. 6(3), 393-405.

Haleem, R. M., Salem, M. Y., Fatahallah, F. A., & Abdelfattah, L. E. J. S. P. J. (2015). Quality in the pharmaceutical industry–A literature review. 23(5), 463-469.

Janodia, M. D., & Udupa, N. J. T. P. R. (2015). Pharmaceutical Packaging–An Overview. 89-90.

Modgil, S., & Sharma, S. J. J. o. Q. i. M. E. (2016). Total productive maintenance, total quality management and operational performance: An empirical study of Indian pharmaceutical industry.

Pharmaceutical quality assurance in class, industry and market by Karamat A. Javid.

Potdar, M. M. A. (2006). Pharmaceutical quality assurance: Pragati Books Pvt. Ltd.

Schaut, R. A., Weeks, W. P. J. P. j. o. p. s., & technology. (2017). Historical review of glasses used for parenteral packaging. 71(4), 279-296.

Shirisha, V., Ghosh, S., Rajni, B., Banji, D. J. R. J. o. P., & Technology. (2014). An Updated Review on IPQC Tests for Sterile and Non Sterile Products. 7(2), 255-265.

United States Pharmacopeia 32

Williams, K. (2004). Microbial contamination control in parenteral manufacturing: CRC Press.