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QUALITY CONTROL PARAMETERS OF PARENTERAL PHARMACEUTICALS BASED ON PHARMACOPOEIAS

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Abstract:

Quality control is an essential operation of pharmaceutical industries. Drugs must be marketed as safe and therapeutically active formulations whose performance is consistent and predictable. New and better medicinal agents are being produced at an accelerated rate. At the same time more exacting and sophisticated analytical methods are being developed for their evaluation. Currently, world-wide efforts have been made to ensure the practice of quality along with coast effective good quality medicines. Parenterals are the sterile preparation that is directly administered into the circulatory system avoiding the enteral route. These preparations provide rapid onset of action compared to others, but the most concerning topics related to this, is their stability problem that arises from microbial contamination of the products. Therefore, to ensure their sterility and stability, regulations regarding to quality control through pharmacopeial specifications has a great importance. Pharmacopeias provides an effective guideline to overcome those problems by following current good manufacturing practices and establishing standard operating procedures. In-process quality control tests are done with a motive to remove error from every stage in production and maintain the quality of the final product with the compendial standards as specified in the pharmacopoeias. The quality of final products depends on in-process control tests, because it helps to incorporate excellence within the products. The qualitative and quantitative parameters of pharmaceutical products are checked by finished product quality controls tests. Therefore, the drive of this study is to provide concise information on the in-process and finished product quality control tests for parenteral preparations as per different pharmacopoeias.

Keywords: *Parenteral pharmaceuticals, Pharmacopoeia, Specification, In-process quality control, Finished product quality control.*

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INTRODUCTION:

Quality control (QC) is a part of good manufacturing practice (GMP) that is concerned with checking and directing the degree of excellence in order to obtain the best quality product by maintaining their proper sampling, specifications, testing, inspection, documentation and release [1]. QC authorized that the products are satisfactory according to specifications, by being truly carried out the peremptory tests [2]. It has abundant important in building high customer satisfaction and loyalty as well as reduce the risk and effect related to faulty goods [3].

Although quality is doubtlessly important for all products, but in some particular cases like pharmaceuticals (i.e., medicines), quality has a greater impact. As pharmaceuticals are the most important thing dealing with mammalian life, their quality which represents their safety and efficacy has become the most concerning global issues [4]. So requirements related to the control of the quality of pharmaceuticals must be examined under considerable importance for the well-being of humanity. World regulatory authorities are continually working and upgrading their requirements for pharmaceutical manufacturing in order to provide safe, quality and effective drug to the patients [5]. In Europe, UK and USA this function is operated by the European Medicines Agency (EMA), Medicines and Healthcare products Regulatory Agency (MHRA) and Food and Drug Administration (FDA), respectively [6,7,8]. The FDA has issued regulatory guidelines known as current good manufacturing practice (cGMP) and good laboratory practice (GLP) which provides a system that assures proper design, monitoring and control of manufacturing processes and facilities. This includes establishing and maintaining a strong quality management system, obtaining appropriate quality raw material, establishing robust operational procedure, detection of product quality deviation and maintaining of reliable testing laboratories with a motive to ensure the public that the marketed drug product has been properly manufactured and clinically tested respectively [9,10].

Qualities of the pharmaceuticals are totally depends upon the success of two vital processes called in-process quality control (IPQC) and finished product quality control (FPQC) tests [11]. The function of IPQC involves monitoring and if necessary, adaptation of the manufacturing process with a view to consent with the pharmacopoeias [12]. IPQC tests are carried out at regular intervals according to the nature of each test and or the relevant guidelines until the manufacturing process is completed [13]. In-process testing enables easier identification and correction of problems by correcting the possible errors in the manufacturing process [14]. Failure to meet IPQC specification

indicates either those procedures were not followed or some factors were out of control [15]. Whereas, FPQC tests are performed when the manufacturing process is completed, in order to check qualitative and quantitative characteristics of the products according to specifications [16]. To maintain these specifications pharmacopoeia is a lawfully binding collection of standards and quality specifications for medicines. There are different types of pharmacopoeias such as Indian Pharmacopoeia (IP), British Pharmacopoeia (BP), United States Pharmacopoeia (USP), European Pharmacopoeia (PhEur), International Pharmacopoeia (PhInt) and Japanese Pharmacopoeia (JP) and those are followed in different parts of the world [17].

Parenteral preparations are sterile preparations containing one or more active ingredients. They are the most sophisticated pharmaceutical preparations as they are directly administered in the systemic circulation of the body [18,19,20,21]. Generally they are administered by injection, infusion or implantation using a syringe and a hollow needle piercing through the skin to a sufficient depth for the material to be administered into the body [22,23,24]. But maintain of their stability is a big problem, as they are very much susceptible to microbial attack. Therefor preparations should be carried out in clean areas by maintaining an appropriate standard of cleanliness and sterility [25]. Among all the injectable products, 95% of injections are administered in curative care, 3% are for immunization, and the rest for other purposes, such as blood transfusions. Approximately 40% of injections worldwide are administered with unsterilized, reused syringes and needles, and in some countries this proportion is 70%, exposing millions of people to infections [26,27]. So there quality maintenance is immensely important in term of safe medication therapy avoidance of infection.

Therefore the purpose of this study is to give an outline about the in-process and finished product quality control tests for parenteral preparation consistent with pharmacopoeial standards and specifications.

UNIVERSAL TESTS FOR PARENTERAL PREPARATIONS

Description

This test is often called appearance on a specification and is a qualitative description of the parenteral preparations. For example, the description of parenteral preparations on a specification may read: transparent preparation, proper labeling, imprinted with ‘‘Rx’’ [1,28,29].

Identification
The purpose of the identification or identity test is to verify the identity of the active pharmaceutical ingredient (API) in the parenteral preparations. This test should be able to discriminate between compounds of closely related structures that are likely to be present [1,28,29].

Assay
This test determines the strength or content of the API in the parenteral preparations and is sometimes called a content test [1,28,29].

Impurities
This test determines the presence of any component that is not the API or an excipient of parenteral preparations. The most common type of impurities that are measured is related substances, which are processed impurities from the new drug substance synthesis, degradation products of the API, or both [1,28,29].

QUALITY CONTROL PARAMETERS OF PARENTERAL PHARMACEUTICALS
QC tests are necessary to ensure the proper performance of parenteral preparations. IPQC and FPQC tests for parenteral preparations according to pharmacopoeial standards and specifications are listed below:

Test for Uniformity of Content
Consistent with BP, unless otherwise prescribed or justified and authorized, single-dose suspensions for injection with a content of active substance less than 2 mg or less than 2 percent of the total mass, or with a unit mass equal to or less than 40 mg comply with this test for uniformity of content of single-dose preparations. If the preparation contains more than one active substance, the requirement applies only to those substances that correspond to the above conditions [30].

Consistent with IP, unless otherwise stated in the individual monograph, suspensions for injection that are presented in single dose containers and that contain less than 10 mg or less than 10 percent of active ingredient comply with the following test. For suspensions for injection containing more than one active ingredient carry out the test for each active ingredient that corresponds to the above conditions [31].

In line with IP, unless otherwise stated in the individual monograph, powders for injection that contain 10 mg or less than 10 mg or less than 10 percent of active ingredient or that have a unit weight equal to or less than 50 mg comply with the test for uniformity of content described under Injections. For powders for injection containing more than one active ingredient carry out the test for each active ingredient that corresponds to the above conditions [31].

The test is not applicable to powders for injection containing multivitamins and trace elements. The test for uniformity of content should be carried out only after the content of active ingredient(s) in a pooled sample of the preparation has been shown to be within accepted limits of the stated content [30].

As per BP and IP, in this test using a suitable analytical method, determine the individual contents of active substance(s) of 10 dosage units taken at random. Parenteral preparation complies with the test if each individual content is between 85 percent and 115 percent of the average content. The preparation fails to comply with the test if more than one individual content is outside these limits or if one individual content is outside the limits of 75 percent to 125 percent of the average content [30,31].

If one individual content is outside the limits of 85 percent to 115 percent but within the limits of 75 percent to 125 percent, determine the individual contents of another 20 dosage units taken at random. The preparation complies with the test if not more than one of the individual contents of the 30 units is outside 85 percent to 115 percent of the average content and none is outside the limits of 75 percent to 125 percent of the average content [30,31].

Test for Uniformity of Mass
Powders for injections or infusions comply with the test for uniformity of mass of single-dose preparations. If the test for uniformity of content is prescribed for all the active substances, the test for uniformity of mass is not required [30].

For this test as per BP, remove any paper labels from a container and wash and dry the outside. Open the container and without delay weigh the container and its contents. Empty the container as completely as possible by gentle tapping, rinse it if necessary with purified water and then with ethanol (96%) and dry at 100-105 °C for 1 h, or, if the nature of the container precludes heating at this temperature, dry at a lower temperature to constant mass. Allow to cool in a desiccator and weigh. The mass of the contents is the difference between the weighings. Repeat the procedure with another 19 containers. Determine the average mass [30].

Consistent with IP, if not more than two of the individual weights deviates from the averag

Table 1. BP limits for uniformity of mass [30].

Dosage Form	Average Mass	Percentage Deviation
Powder for parenteral administration (single dose)	More than 40 mg	10
Note: When the average mass is equal to or below 40 mg, the preparation is not submitted to the test for uniformity of mass but to the test for uniformity of content of single dose preparations.		

weight by more than 10 percent and none deviates by more than 20 percent [31]. According to BP to comply with this test not more than 2 of the individual masses of parenteral preparations deviate from the average mass by more than the percentage deviation shown in Table 1 and none deviates by more than twice that percentage [30].

Test for Extractable Volume of Parenteral Preparations

For this test, suspensions and emulsions are shaken before withdrawal of the contents and before the determination of the density. Oily and viscous preparations may be warmed according to the instructions on the label, if necessary, and thoroughly shaken immediately before removing the contents. The contents are then cooled to 20-25 °C before measuring the volume [30,32].

Single-Dose Containers

In this test for single-dose containers as per BP and JP, select 1 container if the nominal volume is 10 mL or more, 3 containers if the nominal volume is more than 3 mL and less than 10 mL, or 5 containers if the nominal volume is 3 mL or less. Take up individually the total contents of each container selected into a dry syringe of a capacity not exceeding 3 times the volume to be measured, and fitted with a 21-gauge needle not less than 2.5 cm in length. Expel any air bubbles from the syringe and needle, then discharge the contents of the syringe without emptying the needle into a standardised dry cylinder (graduated to contain rather than to deliver the designated volumes) of such size that the volume to be measured occupies at least 40 per cent of its graduated volume. Alternatively, the volume of the contents in millilitres may be calculated as the mass in grams divided by the density [30,32].

For containers with a nominal volume of 2 mL or less, the contents of a sufficient number of containers may be pooled to obtain the volume required for the measurement provided that a separate, dry syringe assembly is used for each container. The contents of containers holding 10 mL or more may be determined by opening them and emptying the contents directly into the graduated cylinder or tared beaker [30,32].

The volume is not less than the nominal volume in case of containers examined individually, or, in case of containers with a nominal volume of 2 mL or less, is not less than the sum of the nominal volumes of the containers taken collectively [30,32].

Multi-Dose Containers

For injections in multidose containers labelled to yield a specific number of doses of a stated volume, as per BP and JP select one container and proceed as directed for single-dose containers using the same number of separate syringe assemblies as the number of doses specified. The volume is such that each syringe delivers not less than the stated dose [30,32].

Cartridges and Prefilled Syringes

For cartridges and prefilled syringes in accordance with BP and JP, select 1 container if the nominal volume is 10 mL or more, 3 containers if the nominal volume is more than 3 mL and less than 10 mL, or 5 containers if the nominal volume is 3 mL or less. If necessary, fit the containers with the accessories required for their use (needle, piston, syringe) and transfer the entire contents of each container without emptying the needle into a dry tared beaker by slowly and constantly depressing the piston. Determine the volume in millilitres calculated as the mass in grams divided by the density. The volume measured for each of the containers is not less than the nominal volume [30,32].

Parenteral Infusions

In accordance with BP and JP for this test for parenteral infusions select one container. Transfer the contents into a dry measuring cylinder of such a capacity that the volume to be determined occupies at least 40 per cent of the nominal volume of the cylinder. Measure the volume transferred. The volume is not less than the nominal volume [30,32].

According to IP for injections, where the nominal volume does not exceed 5 ml, the containers comply with the requirements of Method 1 and where the nominal volume is greater than 5 ml, the containers comply with the requirements of Method 2. Suspensions should be shaken before the contents are withdrawn; oily injections may be

warmed but should be cooled to 25 ºC before carrying out the test [30,32].

Method 1
Use 6 containers, 5 for the test and 1 for rinsing the syringe used. Inspect the 5 containers to be used in the test visually and ensure that each contains approximately the same volume of the preparation. Using a syringe with a capacity not exceeding twice the volume to be measured and fitted with a suitable needle, take up a small quantity of the liquid under examination from the container reserved for rinsing the syringe, and discharge it from the syringe whilst the needle is pointing upwards so as to expel any air. Withdraw as much as possible the contents of one of the containers reserved for the test and transfer, without emptying the needle, to a dry graduated cylinder of such capacity that the total combined volume to be measured occupies not less than 40 per cent of the nominal volume of the cylinder. Repeat the procedure until the contents of the 5 containers have been transferred and measure the volume. The average content of the 5 containers is not less than the nominal volume and not more than 115 per cent of the nominal volume [31].

Method 2
Transfer the contents of not less than 3 containers separately to dry graduated cylinders such that the volume to be measured occupies not less than 40 per cent of the nominal volume of the cylinder and measure the volume transferred. The contents of each container are not less than the nominal volume and not more than 110 per cent of the nominal volume. Multiple dose containers labelled to yield a specific number of doses shall contain a sufficient excess to permit the withdrawal of the designated number of doses [31].

Test for Particulate Contamination
According to BP, JP and USP for the determination of particulate contamination 2 procedures, Light Obscuration Particle Count (LOPC) test and Microscopic Particle Count (MPC) test, are specified [30,32,33].

When examining injections and infusions for sub-visible particles, LOPC test is preferably applied. However, it may be necessary to test some preparations by the light obscuration particle count test followed by the microscopic particle count test to reach a conclusion on conformance to the requirements [30].

Not all parenteral preparations can be examined for sub-visible particles by one or both of these methods. When LOPC test is not applicable, e.g. in case of preparations having reduced clarity or increased viscosity, the test is carried out according to MPC test. Emulsions, colloids, and liposomal preparations are examples. Similarly, products that produce air or gas bubbles when drawn into the sensor may also require microscopic particle count testing. If the viscosity of the preparation to be tested is sufficiently high so as to preclude its examination by either test method, a quantitative dilution with an appropriate diluent may be made to decrease viscosity, as necessary, to allow the analysis to be performed [30].

The results obtained in examining a discrete unit or group of units for particulate contamination cannot be extrapolated with certainty to other units that remain untested. Thus, statistically sound sampling plans must be developed if valid inferences are to be drawn from observed data to characterise the level of particulate contamination in a large group of units [30].

Light Obscuration Particle Count Test
Use a suitable apparatus based on the principle of light blockage which allows an automatic determination of the size of particles and the number of particles according to size [30]. According to BP and JP, mix the contents of the sample by slowly inverting the container 20 times successively. If necessary, cautiously remove the sealing closure. Clean the outer surfaces of the container opening using a jet of particle-free purified water and remove the closure, avoiding any contamination of the contents. Eliminate gas bubbles by appropriate measures such as allowing to stand for 2 min or sonicating [30,32].

For large-volume parenterals, single units are tested. For small-volume parenterals less than 25 mL in volume, the contents of 10 or more units are combined in a cleaned container to obtain a volume of not less than 25 mL; where justified and authorized, the test solution may be prepared by mixing the contents of a suitable number of vials and diluting to 25 mL with particle-free purified water or with an appropriate solvent without contamination of particles when particle-free purified water is not suitable. Small-volume parenterals having a volume of 25 mL or more may be tested individually [30,32]. Powders for parenteral administration are reconstituted with particle-free purified water or with an appropriate solvent without contamination of particles when particle-free purified water is not suitable [30,32].
The number of test specimens must be adequate to provide a statistically sound assessment. For large-volume parenterals or for small-volume parenterals having a volume of 25 mL or more, fewer than 10 units may be tested, based on an appropriate sampling plan [30,32]. Remove 4 portions, each of

Table 2. BP, JP and USP limits for particulate matters determined by LOPC test [30,32,33].

Nominal Volume	≥ 10 µm	≥ 25 µm
More than 100 mL	25 particles/mL	3 particles/mL
100 mL or less than 100 mL	6000 particles/container	600 particles/container

not less than 5 mL, and count the number of particles equal to or greater than 10 µm and 25 µm. Disregard the result obtained for the first portion, and calculate the mean number of particles for the preparation to be examined. The limit for this test as per various pharmacopoeias is given in Table 2 [30,32,33].

Microscopic Particle Count Test

Use a suitable binocular microscope, filter assembly for retaining particulate contamination and membrane filter for examination. According to BP, mix the contents of the samples by slowly inverting the container 20 times successively. If necessary, cautiously remove the sealing closure. Clean the outer surfaces of the container opening using a jet of particle-free purified water and remove the closure, avoiding any contamination of the contents [30].

For large-volume parenterals, single units are tested. For small-volume parenterals less than 25 mL in volume, the contents of 10 or more units are combined in a cleaned container; where justified and authorised, the test solution may be prepared by mixing the contents of a suitable number of vials and diluting to 25 mL with particle-free purified water or with an appropriate solvent without contamination of particles when particle-free purified water is not suitable. Small-volume parenterals having a volume of 25 mL or more may be tested individually [30]. Powders for parenteral administration are constituted with particle-free purified water or with an appropriate solvent without contamination of particles when particle-free purified water is not suitable [30].

The number of test specimens must be adequate to provide a statistically sound assessment. For large-volume parenterals or for small-volume parenterals having a volume of 25 mL or more, fewer than 10 units may be tested, based on an appropriate sampling plan [30]. Wet the inside of the filter holder fitted with the membrane filter with several millilitres of particle-free purified water. Transfer to the filtration funnel the total volume of a solution pool or of a single unit, and apply vacuum. If needed, add stepwise a portion of the solution until the entire volume is filtered. After the last addition of solution, begin rinsing the inner walls of the filter holder by using a jet of particle-free purified water. Maintain the vacuum until the surface of the membrane filter is free from liquid. Place the filter in a Petri dish and allow the filter to air-dry with the cover slightly ajar. After the filter has been dried, place the Petri dish on the stage of the microscope, scan the entire membrane filter under the reflected light from the illuminating device, and count the number of particles that are

equal to or greater than 10 µm and the number of particles that are equal to or greater than 25 µm. Alternatively, partial filter count and determination of the total filter count by calculation is allowed. Calculate the mean number of particles for the preparation to be examined [30].

The particle sizing process with the use of the circular diameter graticule is carried out by transforming mentally the image of each particle into a circle and then comparing it to the 10 µm and 25 µm graticule reference circles. Thereby the particles are not moved from their initial locations within the graticule field of view and are not superimposed on the reference circles for comparison. The inner diameter of the transparent graticule reference circles is used to size white and transparent particles, while dark particles are sized by using the outer diameter of the black opaque graticule reference circles [30].

In performing the microscopic particle count test do not attempt to size or enumerate amorphous, semi-liquid, or otherwise morphologically indistinct materials that have the appearance of a stain or discoloration on the membrane filter. These materials show little or no surface relief and present a gelatinous or film-like appearance. In such cases the interpretation of enumeration may be aided by testing a sample of the solution by the light obscuration particle count test. Table 3 represents the limit for this test according to various pharmacopoeias [30,32,33].

Table 3. BP, JP and USP limits for particulate matters determined by MPC test [30,32,33].

Nominal Volume	≥ 10 µm	≥ 25 µm
More than 100 mL	12 particles/mL	2 particles/mL
100 mL or less than 100 mL	3000 particles/container	300 particles/container

Table 4. Culture media suitable for the test for sterility [30,32,33].

Medium	Amount
Fluid Thioglycollate Medium	
l-Cystine	0.5 g
Sodium Chloride	2.5 g
Dextrose	5.5/5.0 g
Agar, granulated (moisture content not exceeding 15%)	0.75 g
Yeast Extract (water-soluble)	5.0 g
Pancreatic Digest of Casein	15.0 g
Sodium Thioglycollate or Thioglycolic Acid	0.5 g 0.3 mL
Resazurin Sodium Solution (1 in 1000), freshly prepared	1.0 mL
Purified Water	1000 mL
Soybean–Casein Digest Medium	
Pancreatic Digest of Casein	17.0 g
Papaic Digest of Soybean Meal	3.0 g
Sodium Chloride	5.0 g
Dibasic Potassium Phosphate	2.5 g
Dextrose ($C_6H_{12}O_6 \cdot H_2O$)	2.5/2.3 g
Purified Water	1000 mL
Alternative Thioglycollate Medium	
L-Cystine	0.5 g
Sodium chloride	2.5 g
Glucose, monohydrate/anhydrate	5.5/5.0 g
Yeast extract (water-soluble)	5.0 g
Pancreatic digest of casein	15.0 g
Sodium thioglycolate or Thioglycolic Acid	0.5 g 0.3 mL
Water	100 mL

In addition to this USP specifies that good manufacturing practice requires each final container of an injection be subjected individually to a visual inspection and containers in which visible particles can be seen should be discarded. This 100% inspection of a lot of product is designed to prevent the distribution and use of parenteral that contain particulate matter.

Therefore, all of the product units from a production line are currently being inspected individually, by human inspectors, under a good light, baffled against reflection into the eye, and against a black and white background [30].

Sterility Test

As stated by BP and USP the sterility test may be carried out using the technique of membrane filtration or by direct inoculation of the culture media with the product to be examined. Appropriate negative controls are included [30,33].

The following culture media have been found to be suitable for the test for sterility. Fluid thioglycollate medium is primarily intended for the culture of anaerobic bacteria; however, it will also detect aerobic bacteria. Soya-bean casein digest medium is suitable for the culture of both fungi and aerobic bacteria [30,32,33].

Membrane Filtration

The technique of membrane filtration is used whenever the nature of the product permits, that is, for filterable aqueous preparations, for alcoholic or oily preparations and for preparations miscible with or soluble in aqueous or oily solvents provided these solvents do not have an antimicrobial effect in the conditions of the test [30].

According to BP, use membrane filters having a nominal pore size not greater than 0.45 µm whose effectiveness to retain micro-organisms has been established. Cellulose nitrate filters, for example, are used for aqueous, oily and weakly alcoholic solutions and cellulose acetate filters, for example, for strongly alcoholic solutions. Specially adapted filters may be needed for certain products, e.g. for antibiotics [30].

The technique described below assumes that membranes about 50 mm in diameter will be used. If filters of a different diameter are used the volumes of the dilutions and the washings should be adjusted accordingly. The filtration apparatus and membrane are sterilised by appropriate means. The apparatus is designed so that the solution to be examined can be introduced and filtered under aseptic conditions; it permits the aseptic removal of the membrane for transfer to the medium or it is suitable for carrying out the incubation after adding the medium to the apparatus itself [30].

Aqueous Solutions

Consistent with BP, if appropriate, transfer a small quantity of a suitable, sterile diluent such as a 1 g/L neutral solution of meat or casein peptone pH 7.1 ± 0.2 onto the membrane in the apparatus and filter. The diluent may contain suitable neutralising substances and/or appropriate inactivating substances for example in the case of antibiotics [30].

Transfer the contents of the container or containers to be tested to the membrane or membranes, if necessary after diluting to the volume used in the method suitability test with the chosen sterile diluent but in any case using not less than the quantities of the product to be examined prescribed in Table 5. Filter immediately. If the product has antimicrobial properties, wash the membrane not less than 3 times by filtering through it each time the volume of the chosen

Table 5. In line with BP, JP and USP minimum quantity to be used for each medium [30,32,33].

Quantity per Container	Minimum Quantity to be Used for Each Medium Unless Otherwise Justified and Authorized
Liquids (other than antibiotics)	
Less than 1 mL	The whole contents of each container
1–40 mL	Half the contents of each container, but not less than 1 mL
Greater than 40 mL, and not greater than 100 mL	20 mL
Greater than 100 mL	10% of the contents of the container, but not less than 20 mL
Antibiotic liquids	1 mL
Other preparations soluble in water or in isopropyl myristate	The whole contents of each container to provide not less than 200 mg
Insoluble preparations, creams, and ointments to be suspended or emulsified	Use the contents of each container to provide not less than 200 mg
Solids	
Less than 50 mg	The whole contents of each container
50 mg or more, but less than 300 mg	Half the contents of each container, but not less than 50 mg
300 mg–5 g	150 mg
Greater than 5 g	500 mg

sterile diluent used in the method suitability test. Do not exceed a washing cycle of 5 times 100 mL per filter, even if during the method suitability test it has been demonstrated that such a cycle does not fully eliminate the antimicrobial activity. Transfer the whole membrane to the culture medium or cut it aseptically into 2 equal parts and transfer one half to each of 2 suitable media. Use the same volume of each medium as in the method suitability test. Alternatively, transfer the medium onto the membrane in the apparatus. Incubate the media for not less than 14 days [30].

Soluble Solids

In line with BP, use for each medium not less than the quantity prescribed in Table 5 of the product dissolved in a suitable solvent such as the solvent provided with the preparation, water for injections, saline or a 1 g/L neutral solution of meat or casein peptone and proceed with the test as described above for aqueous solutions using a membrane appropriate to the chosen solvent [30].

Oils and Oily Solutions

Along with BP, use for each medium not less than the quantity of the product prescribed in Table 5. Oils and oily solutions of sufficiently low viscosity may be filtered without dilution through a dry membrane. Viscous oils may be diluted as necessary with a suitable sterile diluent such as isopropyl myristate shown not to have antimicrobial activity in the conditions of the test. Allow the oil to penetrate the membrane by its own weight then filter, applying the pressure or suction gradually. Wash the membrane at least 3 times by filtering through it each time about 100 mL of a suitable sterile solution such as 1 g/L neutral meat or casein peptone containing a suitable emulsifying agent at a concentration shown to be appropriate in the method suitability test, for example polysorbate 80 at a concentration of 10 g/L. Transfer the membrane or membranes to the culture medium or media or vice versa as described above for aqueous solutions, and incubate at the same temperatures and for the same times [30].

Ointments and Creams

In relation to BP, use for each medium not less than the quantities of the product prescribed in Table 5. Ointments in a fatty base and emulsions of the water-in-oil type may be diluted to 1 per cent in isopropyl myristate as described above, by heating, if necessary, to not more than 40 °C. In exceptional cases it may be necessary to heat to not more than 44 °C. Filter as rapidly as possible and proceed as described above for oils and oily solutions [30].

Prefilled Syringes

According to USP, for prefilled syringes without attached sterile needles, expel the contents of each syringe into one or two separate membrane filter funnels or into separate pooling vessels prior to transfer. If a separate sterile needle is attached, directly expel the syringe contents as indicated above, and proceed as directed for Aqueous Solutions. Test the sterility of the needle, using direct inoculation under validation test [33].

Solids for Injection Other than Antibiotics

As said by USP, constitute the test articles as directed on the label, and proceed as directed for Aqueous Solutions or Oils and Oily Solutions, whichever applies [33].

Antibiotic Solids for Injection

Table 6. Composition and pH of diluting and rinsing fluids as per USP [33].

Diluting and Rinsing Fluids	Composition	pH
Fluid A	1 g peptic digest of animal tissue/1 L water	7.1 ± 0.2
Fluid D	1 g peptic digest of animal tissue + 1 mL polysorbate 80/1 L water	7.1 ± 0.2

Pharmacy Bulk Packages, < 5 g
According to USP, from each of 20 containers, aseptically transfer about 300 mg of solids, into a sterile 500-mL conical flask, dissolve in about 200 mL of Fluid A (Table 6), and mix; or constitute, as directed in the labeling, each of 20 containers and transfer a quantity of liquid or suspension, equivalent to about 300 mg of solids, into a sterile 500-mL conical flask, dissolve in about 200 mL of Fluid A, and mix. Proceed as directed for Aqueous Solutions or Oils and Oily Solutions, whichever applies [33].

Pharmacy Bulk Packages, ≥ 5 g
According to USP, from each of 6 containers, aseptically transfer about 1 g of solids into a sterile 500-mL conical flask, dissolve in about 200 mL of Fluid A, and mix; or constitute, as directed in the labeling, each of 6 containers and transfer a quantity of liquid, equivalent to about 1 g of solids, into a sterile 500-mL conical flask, dissolve in about 200 mL of Fluid A, and mix. Proceed as directed for Aqueous Solutions [33].

Antibiotic Solids, Bulks and Blends
According to USP, aseptically remove a sufficient quantity of solids from the appropriate amount of containers (Table 4), mix to obtain a composite, equivalent to about 6 g of solids, and transfer to a sterile 500-mL conical flask. Dissolve in about 200 mL of Fluid A, and mix. Proceed as directed for Aqueous Solutions [33].

Devices with Pathways Labeled Sterile
According to USP, aseptically pass not less than 10 pathway volumes of Fluid D through each device tested. Collect the fluids in an appropriate sterile vessel, and proceed as directed for Aqueous Solutions or Oils and Oily Solutions, whichever applies [33].

In the case of sterile, empty syringes, draw sterile diluent into the barrel through the sterile needle, if attached, or through a sterile needle attached for the purpose of the test, and express the contents into a sterile pooling vessel. Proceed as directed above [33].

Direct Inoculation of the Culture Medium
In line with BP, transfer the quantity of the preparation to be examined prescribed in Table 5 directly into the culture medium so that the volume of the product is not more than 10 percent of the volume of the medium, unless otherwise prescribed [30].
If the product to be examined has antimicrobial activity, carry out the test after neutralising this with a suitable neutralising substance or by dilution in a sufficient quantity of culture medium. When it is necessary to use a large volume of the product it may be preferable to use a concentrated culture medium prepared in such a way that it takes account of the subsequent dilution. Where appropriate, the concentrated medium may be added directly to the product in its container [30].

Oily Liquids
According to BP, USP and JP, use media to which have been added a suitable emulsifying agent at a concentration shown to be appropriate in the method suitability test, for example polysorbate 80 at a concentration of 10 g/L [30,32,33].

Ointments and Creams
As stated by BP, USP and JP, prepare by diluting to about 1 in 10 by emulsifying with the chosen emulsifying agent in a suitable sterile diluent such as a 1 g/L neutral solution of meat or casein peptone. Transfer the diluted product to a medium not containing an emulsifying agent [30,32,33].

In line with JP, the minimum quantity to be used for each medium is given in Table 8 [32].

Incubate the inoculated media for not less than 14 days. Observe the cultures several times during the incubation period. Shake cultures containing oily products gently each day. However when fluid thioglycollate medium is used for the detection of anaerobic micro-organisms keep shaking or mixing to a minimum in order to maintain anaerobic conditions [30,32,33].

Solids
According to USP, transfer a quantity of the product in the form of a dry solid (or prepare a suspension of the product by adding sterile diluent to the immediate container), corresponding to not less than the quantity indicated in Tables 5 and Table 7. Transfer the material so obtained to 200 mL of Fluid Thioglycollate Medium, and mix. Similarly, transfer the same quantity to 200 mL of

Table 7. According to BP and USP, minimum number of articles to be tested in relation to the number of articles in the batch [30,33].

Number of Items in the Batch*	Minimum Number of Items to be Tested for Each Medium Unless Otherwise Justified and Authorized[#]
Parenteral preparations	
Not more than 100 containers	10% or 4 containers, whichever is the greater
More than 100 but not more than 500 containers	10 containers
More than 500 containers	2% or 20 containers, whichever is less
For large-volume parenterals	2% or 10 containers, whichever is less
Antibiotic solids	
Pharmacy bulk packages (< 5 g)	20 containers
Pharmacy bulk packages (≥ 5 g)	6 containers
Bulk solid products	
Up to 4 containers	Each container
More than 4 containers, but not more than 50 containers	20% or 4 containers, whichever is greater
More than 50 containers	2% or 10 containers, whichever is greater
*If the batch is not known, use the maximum number of items prescribed. [#]If the contents of one container are enough to inoculate the 2 media, this column gives the number of containers needed for both the media together.	

Table 8. According to JP, minimum quantity to be used for each medium [32].

Quantity per Container	Minimum Quantity to be Used for Each Medium
Liquids	
Less than 1mL	The whole content of each container
1–40 mL	Half the contents of each container but not less than 1 mL
Greater than 40 ml and not greater than 100 mL	20 mL
Greater than 100 mL	10% of the contents of the container but not less than 20 mL
Antibiotic liquids	1 mL
Other preparations soluble in water or in isopropyl myristate	The whole contents of each container to provide not less than 200 mg
Insoluble preparations	
Creams and ointments to be suspended or emulsified	Use the contents of each container to provide not less than 200 mg
Solids	
Less than 50 mg	The whole contents of each container
50 mg or more but less than 300 mg	Half the contents of each container but not less than 50 mg
300 mg–5 g	150 mg
Greater than 5 g	500 mg

Soybean–Casein Digest Medium, and mix. Proceed as directed above [30].

In line with BP and USP, at intervals during the incubation period and at its conclusion, examine the media for macroscopic evidence of microbial growth. If the material being tested renders the medium turbid so that the presence or absence of microbial growth cannot be readily determined by visual examination, 14 days after the beginning of incubation transfer portions (each not less than 1 mL) of the medium to fresh vessels of the same medium and then incubate the original and transfer vessels for not less than 4 days [30,33].

If no evidence of microbial growth is found, the product to be examined complies with the test for sterility. If evidence of microbial growth is found the product to be examined does not comply with the test for sterility, unless it can be clearly demonstrated that the test was invalid for causes unrelated to the product to be examined. The test may be considered invalid only if one or more of the following conditions are fulfilled [30,33]:

□ The data of the microbiological monitoring of the sterility testing facility show a fault [30,33];
□ A review of the testing procedure used during the test in question reveals a fault [30,33];
□ Microbial growth is found in the negative controls [30,33];
□ After determination of the identity of the micro-organisms isolated from the test, the growth of this species or these species may be ascribed unequivocally to faults with respect to the material and/or the technique used in conducting the sterility test procedure [30,33].

If the test is declared to be invalid it is repeated with the same number of units as in the original test. If no evidence of microbial growth is found in the repeat test the product examined complies with the test for sterility. If microbial growth is found in the repeat test the product examined does not comply with the test for sterility [30,33].

Test for Bacterial Endotoxins

The test for bacterial endotoxins (BET) measures the concentration of bacterial endotoxins that may be present in the sample or on the article to which the test is applied using a lysate derived from the hemolymph cells or amoebocytes of the horseshoe crab, *Limulus polyphemus*. Other species of horseshoe crab namely *Tachypleus gigas*, *Tachypleus tridentatus* and *Carcinoscropius rotundicauda* also yield amoebocyte lysate having similar activity [31].

The addition of a solution containing endotoxins to a solution of the lysate produces turbidity, precipitation or gelation of the mixture. However, addition of a chromogenic substrate to a solution of the lysate results in development of colour due to release of chromophore from the substrate upon activation by the endotoxin present in the solution. The rate of reaction depends on the concentration of endotoxin, the pH and the temperature. The reaction requires the presence of certain bivalent cations, a clotting cascade enzyme system and clottable protein, all of which are provided by the lysate [31].

According to BP, There are 3 techniques for this test: the gel- clot technique, which is based on gel formation; the turbidimetric technique, based on the development of turbidity after cleavage of an endogenous substrate; and the chromogenic technique, based on the development of colour after cleavage of a synthetic peptide-chromogen complex [30]. The following 6 methods are described in the BP [30]:

□ Method A. Gel-clot method: limit test
□ Method B. Gel-clot method: quantitative test
□ Method C. Turbidimetric kinetic method
□ Method D. Chromogenic kinetic method
□ Method E. Chromogenic end-point method
□ Method F. Turbidimetric end-point method

According to IP, the following methods can be used to monitor the endotoxin concentration in a product official in the pharmacopoeia and to determine whether the product complies with the limit specified in the monograph [31].

□ Method A: Gel-Clot Limit Test Method
□ Method B: Semi-quantitative Gel-Clot Method
□ Method C: Kinetic Turbidimetric Method
□ Method D: Kinetic Chromogenic Method
□ Method E: End-Point Chromogenic Method

On the word of IP, when a monograph includes a test for bacterial endotoxins without mentioning a method, the test is carried out by Method A. Any one of the other four methods may be employed as an alternative method provided it yields results of equivalent reliability with the preparation under examination [31].

Consistent with IP, carry out the following procedure in receptacles such as tubes, vials or wells of micro-titre plates. Into each of the chosen receptacle, add an appropriate volume of negative control (NC), control standard endotoxin (CSE) solutions in water BET, test solution and positive product control (PPC). At intervals that will permit the reading of each result, add to each receptacle an equal volume of the appropriately constituted lysate unless single test vials are used. Mix the sample-lysate mixture gently and place in an incubating device such as a water-bath or a heating block, accurately recording the time at which the receptacles are so placed. Incubate each receptacle at 37º± 1º undisturbed for 60 ± 2 minutes. Remove the receptacles and examine the contents carefully. A positive reaction is characterised by the formation of a firm gel that retains its integrity when inverted through 180º in one smooth motion. Record this result as positive (+). A negative result is characterised by the absence of such a gel or by the formation of a viscous gel that does not maintain its integrity. Record such a result as negative (–). Handle the receptacles with care to avoid subjecting them to unwanted vibrations as false negative observations may result [31].

Consistent with IP, calculate the geometric mean end-point concentration of solutions of series B and C (Table 9) by using the following formula [31]:

Geometric mean end-point concentration = antilog ($\sum e/f$)

Table 9. According to IP, preparation of solutions for gel-clot techniques [31].

Solution	Final Concentration of Added CSE in the Solution	Number of Replicates
A = Solution of the product at a dilution at or below MVD (test solution)	–	4
B = Test solution spiked with indicated CSE concentrations (Positive Product Control; PPC)	21	4
	0.51	4
	0.251	4
C = Standard solution with indicated CSE concentrations in water BET	21	4
	1	2
	0.51	2
	0.251	2
D = Water BET(Negative Control; NC)	–	2

Table 10. According to BP and USP, preparation of solutions for gel-clot techniques [30, 33].

Solution	Endotoxin Concentration/Solution to which Endotoxin is Added	Diluent	Dilution Factor	Endotoxin Concentration	Number of Replicates
A	None/sample solution	–	–	–	4
B	2λ/Sample solution	Test solution	1	2λ	4
			2	1λ	4
			4	0.5λ	4
			8	0.25λ	4
C	2λ/Water for BET	Water for BET	1	2λ	2
			2	1λ	2
			4	0.5λ	2
			8	0.25λ	2
D	None/Water for BET	–	–	–	2
where, Solution A: Sample solution of the preparation under test that is free of detectable endotoxins. Solution B: Test for interference. Solution C: Control for labeled lysate sensitivity. Solution D: Negative control (water for BET).					

where, ∑e = sum of the log end-point concentrations of the series of dilutions used; f = number of replicate test-tubes [30, 31, 33].

This average gives the estimated lysate sensitivity which must lie between 0.5λ and 2λ [30, 31, 33].

The possibility of interference with the bacterial endotoxins test by certain factors should be borne in mind. For validation of the test results it must be demonstrated that the test preparation does not inhibit or enhance the reaction or otherwise interfere with the test. The validation must be repeated if the lysate vendor or the method of manufacture or the formulation of the sample is changed. Dilution of the test preparation with water BETis the easiest method for overcoming inhibition [31]. The allowable dilution level or Maximum Valid Dilution (MVD) is dependent on the concentration of the product, the endotoxin limit for the product and the lysate sensitivity. It is calculated by the following expression [30, 31]:
MVD = Endotoxin limit × Concentration of the test solution*/λ

where, λ is the labelled sensitivity of the lysate (EU/ml) [30, 31]. Note: *Concentration of the test solution is expressed as mg/ml in case the endotoxin limit is specified by weight (EU/mg), or as Units/ml in case the endotoxin limit is specified by Unit (EU/Unit), or as 1.0 ml/ml in case the endotoxin limit is specified by volume (EU/ml) [31].

According to BP the geometric mean end-point concentrations of solutions B and C (Table 10) are determined. The test for interfering factors must be repeated when any changes are made to the experimental conditions that are likely to influence the result of the test [30].

The test is considered valid when all replicates of solutions A and D show no reaction and the result of solution C confirms the labelled lysate sensitivity. If the sensitivity of the lysate determined with solution B is not less than 0.5l and

not greater than 2l, the test solution does not contain interfering factors under the experimental conditions used. Otherwise, the test solution interferes with the test [30].

If the preparation being examined interferes with the test at a dilution less than the MVD, repeat the test for interfering factors using a greater dilution, not exceeding the MVD. The use of a more sensitive lysate permits a greater dilution of the preparation being examined and this may contribute to the elimination of interference [30].
Interference may be overcome by suitable validated treatment, such as filtration, neutralisation, dialysis or heat treatment. To establish that the treatment chosen effectively eliminates interference without loss of endotoxins, repeat the test for interfering factors using the preparation being examined to which the standard endotoxin has been added and which has then been submitted to the chosen treatment [30].

Consistent with IP, the test for interfering factors is valid if [31]:

□ Solutions of series A and D give negative results [31];
□ The results obtained with solutions of series C confirm the labelled sensitivity of the lysate [31];
□ The geometric mean of the end-point concentration of solutions of series B is not more than 2l or not less than 0.5l [31].

If the result obtained is outside the specified limit, the test preparation under examination is acting as an inhibitor or activator. The interfering factors may be eliminated by further dilution (not greater than MVD), filtration, neutralisation, inactivation or by removal of the interfering substances. The use of a more sensitive lysate permits the use of greater dilution of the preparation under examination [31].

Ultrafiltration may be used, if necessary, when the interfering factor passes through a filter with a nominal separation limit corresponding to a molecular weight of 10,000 to 20,000, such as asymmetrical membrane filters of cellulose triacetate. Such filters should be checked for the presence of any factors causing false positive results. The material retained on the filter, which contains the endotoxins, is rinsed with water BET or tris-chloride buffer pH 7.4 BET. The endotoxins are recovered in the water BET or the buffer. The endotoxin concentration in the test volume and the final volume are determined for each preparation under examination [31].

Establish that the chosen treatment effectively eliminates interference without removing endotoxins by repeating the test for interfering factors using the preparation under examination to which the CSE has been added and which has been submitted to the chosen treatment [31].

The product under examination complies with the bacterial endotoxin test if the positive product control is positive and the negative control as well as the test solutions are negative. The test is not valid if the positive product control is negative or if the negative control is positive. The product under examination meets the requirements of the test if the endotoxin content is less than the endotoxin limit stated in the individual monograph. If a positive result is found for one of the test solution duplicates and a negative result for the other, the test may be repeated as described above. The results of the retest should be interpreted as for the initial test [31].

Safety Test
The National Institutes of Health requires, of most parenteral products, routine safety testing in animals. Under the Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetic Act, most pharmaceutical preparations are now required to be tested for safety. Because it is entirely possible for a parenteral product to pass the routine sterility test, pyrogen test, chemical analyses and still cause unfavorable reactions when injected, a safety test in animals is essential, particularly for biological products, to provide an additional assurance that the product does not have unexpected toxic properties [34].

CONCLUSION:

Quality is not an accident, this is the result of an intelligent effort. To get a product of a maximum quality, quality control tests for pharmaceuticals are barely needed. The quality of parenteral preparations is very important and sensitive issue, since these are immediately reached to the systemic circulation. From the present study it is clearly exposed that various pharmacopoeias suggest different quality parameters but the the main intention is to generate effective good quality products. So, the tests mentioned in pharmacopoeias for the parenteral preparations must strictly be performed to ensure the proper quality as well as secure human health.

AUTHORS' CONTRIBUTIONS:

This work was carried out in collaboration between all authors. Author MSU designed the study, wrote the protocol, managed the analyses of the study and prepared the draft of the manuscript. Authors MAS, MTI, TZ and AAM managed the literature searches

and participated in manuscript preparation under GMSU reviewed the scientific contents of the manuscript. All the authors read and approved the final manuscript.

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