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Pharmacopoeial Comparison of In-process & Finished Product Quality Control Tests for Parenterals: IP, BP & USP

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ABSTRACT

The present study deals with the comparative study of the quality requirements for the drugs that are injected into the body; during their production and for finished drugs. The concept of total quality control test refers to the process of striving to produce a quality product by a series of measures, requiring an organized effort in order to eliminate errors at every stage in the production. Product testing during the production is done in order to check the conformance of the final product with the standards as specified in the official book of drugs (pharmacopoeias) specific to each country. The test parameters have been discussed and taken from the official book of drugs issued by the respective authorities for India, US and UK. However, the parameters and standards differ from each other to some extent. Hence, an attempt is made to bring out the harmonized standards for a product so that it satisfies the quality requirements for many regions. The parameters as per the standards were compared and certain similarities and differences were observed. It was noted that except for a few parameters, the quality control tests were broadly similar.

Introduction

In the pharmaceutical industry, total quality of the product must be ensured in order to prevent the kind of product which does not comply with the specifications laid down by the Pharmacopoeias, and at the same time it is also necessary for controlling the errors during the production process. Quality can be defined as the suitability of the goods or service to the determined qualifications. Quality control emphasizes testing of products for defects and reporting to management who makes the decision to investigate or deny the release. Both the in process and finished product quality control tests help to ensure the total quality of the product. The entire dealing process (In process and finished product quality control tests) involves stringent quality control tests to make products totally flawless before they are released into the market.

In-process tests may be performed during the manufacture of either the drug substance or drug product, rather than as part of the formal battery of tests which are conducted prior to release.

In-process controls (IPC) are checks that are carried out before the manufacturing process is completed. The function of in process controls involves monitoring and if necessary, adaptation of the manufacturing process in order to comply with the specifications. This may include control of equipment and environment too.

In-process materials should be tested for their physical parameters and its quality attributes which are later approved or rejected by the quality control department based on the results obtained during the manufacturing process. Rejected In process materials should be identified and controlled under a quarantine system designed to prevent their use in manufacturing.

Standard operating procedures should be established and followed that describe the in process controls and tests. Certain tests conducted during the manufacturing process, where the acceptance criterion is identical to or narrower than the release requirement, (e.g., pH of a solution) which may satisfy requirements when the test is included in the specification.

References to certain procedures are quite similar in pharmacopoeias in each region even though there are minor changes within each of them. Wherever and whichever procedures are appropriate, pharmacopoeial procedures should be utilized. Whereas differences in pharmacopoeial procedures and/or acceptance criteria have existed among the regions, a harmonized specification is possible only if the procedures and acceptance criteria defined are acceptable to regulatory authorities in all regions.

In process controls may be performed at regular intervals during a process or at the end of the process. The objectives of in process control are both quality control and process control. The classic interpretation of the term in process control includes the recording of measured values by members of the in process control group.

Finished product controls (FPC) are checks that are carried out after the manufacturing process is complete with respect to qualitative and quantitative characteristics along with test procedures and their acceptance limits, with which the finished product must comply throughout its valid shelf life.

In order to determine the specifications of the finished product, the quality characteristics related to the manufacturing process should be taken into account. An appropriate specification for each aspect of quality studied during the phase of development and during the validation of the manufacturing process should be determined. At least those aspects considered to be critical should be the object of specifications routinely verified. The specification limits of the finished product at the time of batch release are set by the marketing authorization applicant such that the specifications proposed at the end of shelf life are guaranteed and are established on the basis of a

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Table 1: Test procedures for Parenterals preparations

Reference code	Test procedure
PQC 1	**Uniformity of content:** **As per IP: -** Determine the content of active ingredient(s) of each of 10 containers taken at random, using the method given in the monograph or by any other suitable analytical method of equivalent accuracy and precision. The preparation under examination complies with the test if the individual values thus obtained are all between 85 and 115 per cent of the average value. The preparation under examination fails to comply with the test if more than one individual value is outside the limits 85 to 115 per cent of the average value or if any one individual value is outside the limits 75 to 125 per cent of the average value. If one individual value is outside the limits 85 to 115 per cent but within the limits 75 to 125 per cent of the average value, repeat the determination using another 20 containers taken at random. The preparation under examination complies with the test if in the total sample of 30 containers not more than one individual value is outside the limits 85 to 115 per cent and none is outside the limits 75 to 125 per cent of the average value. **NOTE — The test for Uniformity of content is not applicable to suspensions for injection containing multivitamins and trace elements.** **As per BP *:***- **TEST A** Tablets, powders for parenteral use, ophthalmic inserts, suspensions for injection. The preparation complies with the test if each individual content is between 85 per cent and 115 per cent 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 per cent to 125 per cent of the average content. If one individual content is outside the limits of 85 per cent to 115 per cent but within the limits of 75 per cent to 125 per cent, 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 per cent to 115 per cent of the average content and none is outside the limits of 75 per cent to 125 per cent of the average content. **TEST B** Capsules, powders other than for parenteral use, granules, suppositories, pessaries. The preparation complies with the test if not more than one individual content is outside the limits of 85 per cent to 115 per cent of the average content and none is outside the limits of 75 per cent to 125 per cent of the average content. The preparation fails to comply with the test if more than 3 individual contents are outside the limits of 85 per cent to 115 per cent of the average content or if one or more individual contents are outside the limits of 75 per cent to 125 per cent of the average content. If 2 or 3 individual contents are outside the limits of 85 per cent to 115 per cent but within the limits of 75 per cent to 125 per cent, determine the individual contents of another 20 dosage units taken at random. The preparation complies with the test if not more than 3 individual contents of the 30 units are outside the limits of 85 per cent to 115 per cent of the average content and none is outside the limits of 75 per cent to 125 per cent of the average content. **As per USP**:- **Stage1**: Take 10 units randomly and perform the assay. It passes the test if the relative standard deviation (RSD) is less than 6% and no value is outside 85-115%. Fails the test if one or more values are outside 75-125%. **Stage2**: Take 20 more units and perform the assay procedure. Passes the test if RSD of all the 30 tablets is less than 7.8%, not more than one value is outside 85-115%, and no value is outside75-125%. Or else the batch fails the test. **GENERAL PROCEDURE** : Determine the content of the active ingredient of each of 10 containers taken at random. The preparation under examination complies with the test if the individual values thus obtained are all between 85 and 115 percent of the average value. The preparation under the examination fails to comply with the test if more than one individual value is outside the limits 85 to 115 percent of the average value or if any one individual value is outside the limits 75 to 125 percent of the average value. If one individual value is outside the limits 85 to 115 percent but within the limits 75 to 125 percent of the average value, repeat the determination using another 20 containers taken at random. The preparation under examination complies with the test if in the total sample of 30 containers, not more than one individual value is outside the limits 85 to 115 percent and none is outside the limits 75 to 125 percent of the average value.
PQC 2	**Uniformity of weight:** Remove labels and wash the container and dry. Weigh the container along with its contents. Empty the containers as completely as possible. Rinse with water and with ethanol and dry at 100^0C to a constant weight. Allow to cool in desiccators and weigh. The difference between the weights represents the weight of the contents. Repeat the procedure with further 19 containers and determine the average weight. Not more than two of the individual weights deviate from the average weight by more than 10% and none deviates by more than 20%. **As per IP**:- This test is applicable to capsules that contain less than 10 mg or less than 10 per cent w/w of active ingredient. For capsules containing more than one active ingredient carry out the test for each active ingredient that corresponds to the afore-mentioned conditions. The test should be carried out only after the content of active ingredient(s) in a pooled sample of the capsules has been shown to be within accepted limits of the stated content. **NOTE** — **The test is not applicable for capsules containing multivitamins and trace elements.** Determine the content of active ingredient in each of 10 capsules taken at random using the method given in the monograph or by any other suitable analytical method of equivalent accuracy and precision. The capsules comply with the test if not more

than one of the individual values thus
obtained is outside the limits 85 to 115 per cent of the average value and none is outside the limits 75 to 125 per cent. If two or three individual values are outside the limits 85 to 115 per cent of the average value repeat the determination using another 20 capsules. The capsules comply with the test if in
the total sample of 30 capsules not more than three individual values are outside the limits 85 to 115 per cent and none is outside the limits 75 to 125 per cent of the average value.

Test Procedure

Weigh individually 20 units selected at random and calculate the average weight.Not more than two of the individual weights deviates from the average weight by more than the percentage given in the pharmacopea and none deviates by more than twice that percentage.IP/BP & USP limits for tablet weight variation is given below.

IP/BP	LIMIT	USP
80 mg or less	± 10%	130mg or less
More than 80mg or Less than 250mg	± 7.5%	130mg to 324mg
250mg or more	± 5%	More than 324mg

PQC 3

Particulate matter:

For sub-visible particles: Two methods are specified, one involving the counting of particles viewed under the microscope and the other based on the count of particles causing light obscuration. Both methods are applied on small samples.

Method 1:

Microscopic particle count test:

This method is suitable for revealing the presence of particles the longest axis or effective linear dimension of which is 10m or more.

Method:

Invert the container of the preparation 20 times. For large volume Parenterals, single units should be tested.

For small volume Parenterals less than 25 ml in volume, the contents of 10 or more units should be combined in a clean container. Where the volume of liquid in a container is very small, the test solution may be prepared by mixing the contents of a suitable number of containers and diluting to 25 ml with particle free water. Small-volume Parenterals having a volume of 25 ml or more may be tested individually. Powders for Parenteral use should be constituted with particle free water.

Fit the membrane filter on to the membrane filter holder. Filter under reduced pressure 200 ml of the purified water for particulate matter test at the rate of 20 to 30 ml per minute. Apply the vacuum until the surface of the membrane is free from water and remove the membrane and dry it carefully below 50° C.

After the filter is dried, place it under the microscope. Adjust the microscope to get the best view of the particles that are equal to or greater than 150µm.

Ascertain that the number is not more than 1.

Fit another membrane filter and wet it with purified water for particulate matter test. Pour the sample solution into the filter. For viscous solutions dilute suitably with purified water for particulate matter test and filter.

When the amount of solution on the filter becomes small, add 30 ml of water. Repeat the process 3 times with 30 ml of the water. Apply the vacuum gently until the surface of membrane filter is free from water. Dry it and observe under microscope. Count the number of particles that are equal to or greater than 10 µm, the number of particles equal to or greater than 25µm and the particles equal to or greater than 50 µm.

Method 2:

Light obscuration particle count test.

Use a suitable apparatus based on the principle of light blockage which allows an automatic determination of particle size and the number of particles according to size.

Method:

Invert the container of the preparation 20 times. For large volume Parenterals, single unit should be tested. For small volume Parenterals less than 25 ml in volume, the contents of 10 or more units should be combined in a clean container. Where the volume of liquid in a container is very small, the test solution may be prepared by mixing the contents of a suitable number of containers and diluting to 25 ml with particle free water.

Small-volume Parenterals having a volume of 25 ml or more may be tested individually. Powders for Parenteral use should be constituted with particle free water. Remove 4 portions, each of not less than 5 ml, count the number of particles greater than 10 µm and 25µm.

Table 3(A): Limits for Microscopic particle count test as per IP, BP, USP

Volume of solution	≥ 10 µm particle size	≥25 µm particle size
Small volume injections	3000 per container	300 pe container
Large volume injections	12 per ml	2 per ml

Table 3(B): Limits for Light obscuration particle count test as per IP, BP, USP

Volume of solution	≥ 10 µm particle size	≥25 µm particle size
Small volume injections	6000 per container	600 per conta ner
Large volume injections	25 per ml	3 per ml

PQC 4

Extractable volume:

Suspensions should be shaken before the contents are withdrawn. Oily injections may be warmed but should be cooled to 25°C

before carrying out the test.

Single dose containers: for IP :-

Method I:

Where the nominal volume does not exceed 5ml.

Use 6 containers, 5 for the tests and 1 for rinsing the syringe used. Using a syringe with appropriate capacity, rinse the syringe and 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% 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% of the nominal volume.

Alternatively the volume of contents in milliliter can be calculated as mass in grams divided by the density.

Method II:

Nominal not less than 3 containers separately to dry graduated cylinders such that the volume to be measured occupies not less than 40% 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% of the nominal volume.

Multi dose containers: Same as single dose containers

Table 3(C): Limits for Extractable volume as per BP, USP

Volume of the solution	No of containers to be used for the test
≥ 10 ml	1
3-10 ml	3
<3 ml	5

PQC 5

Sterility Test:

Culture media:

1. Fluid thioglycollate medium:

For anaerobic bacteria. Use fluid thioglycollate medium by incubating it at 30° to 35°C.

2. Soyabean-casein digest medium:

Fungi and aerobic bacteria. Use soybean- casein digest medium by incubating it at 20° to 25°C under aerobic conditions.

3. Alternative Thioglycollate Medium:

For use with turbid and viscid products and for devices having tubes with small Lumina.

Table 3(D): Strains of the micro organisms used for the test as per IP, BP, USP

Medium	Test micro organism	Incubation		
		Temp. (^{0}C)	Duration	Type of micro organism
Fluid thioglycollate	*Bacillus subtilis*	30-35	3 days	Aerobic
	Staphylococcus aureus	30-35	3 days	Aerobic
	Pseudomonas aeruginosa	30-35	3 days	Aerobic
Alternate thioglycollate	*Bacterides vulgates*	30-35	3 days	Anaerobic
	Clostridium sporogenes	30-35	3 days	Anaerobic
Soya bean casein digest	*Asperigillus niger*	20-25	5 days	Aerobic
	Candida albicans	20-25	5 days	Aerobic

Test procedure:

Method A (Membrane filtration) is preferred where the substance under examination is

1. An oil,
2. An ointment that can be put into solution.
3. A non bacteriostatic solid not readily soluble in the culture medium, and
4. A soluble powder or a liquid that possesses bacteriostatic and /or fungistatic properties.

For liquid products where the volume in a container is 100 ml or more, method A should be used.

Method A – Membrane Filtration

The method calls for the routine use of positive and negative controls.

Apparatus:

Cellulose nitrate filters are used for aqueous, oily and weakly alcoholic solutions and cellulose acetate filters are recommended for strongly alcoholic solutions.

Diluting Fluids: (IP, BP):

Fluid A: Dissolve 1 g of peptic digest of animal tissue (such as bacteriological peptone) or its equivalent in water to make 1 liter, filter or centrifuge to clarify, adjust to pH 7.1 ± 0.2, dispense into flasks in 100-ml quantities and sterilize at 121^0 C for 20 minutes.

Fluid B: If the test sample contains lecithin or oil, use fluid A to each liter of which has been added 1 ml of polysorbate 80, adjust to pH 7.1± 0.2, dispense into flasks and sterilize at 121^0 C for 20 minutes.

Quantities of sample to be used:

For Parenteral preparations:

Whenever possible, use the whole contents of the container, but in any case not less than the quantities prescribed in Table 3(E), diluting where necessary to about 100 ml with a suitable diluents such as fluid A.

For ophthalmic and other non-Parenteral preparations:

Take an amount within the range prescribed in column (A) of Table 3(E), if necessary, using the contents of more than one container, and mix thoroughly. For each medium use the amount specified in column (B) of Table 3(E), taken from the mixed sample.

Test method:

For aqueous solutions:

Aseptically transfer a small quantity of fluid A on to the membrane and filter it. Transfer aseptically the combined quantities of

the preparation under examination prescribed in the two media onto one membrane.
If the solution under examination has antimicrobial properties, wash the membrane(s) by filtering through it (them) not less than three successive quantities, each of 100 ml, of sterile fluid A.
Do not exceed a washing cycle of 5 times or 200 ml, even if it has been demonstrated during validation that such a cycle does not fully eliminate the antimicrobial activity. The quantities of fluid used should be sufficient to allow growth of a small inoculum of organisms (approximately 50 CFU) sensitive to the antimicrobial substance in the presence of the residual inhibitory material on the membrane.
After filtration, aseptically remove the membrane(s) from the holder, transfer the whole membrane or cut it aseptically into 2 equal parts. Transfer one half to each of two suitable media. Incubate the media for not less than 14 days.
Observe the containers of media periodically during the 14 days of incubation. If the test specimen is positive before 14 days of incubation, further incubation is not necessary. For products terminally sterilized by a validated moist heat process, incubate the test specimen for not less than 7 days.

For liquids immiscible with aqueous vehicles, and suspensions:

Carry out the test described under for aqueous solutions but add a sufficient quantity of fluid A to the pooled sample to achieve rapid filtration. Sterile enzyme preparations such as penicillinase or cellulose may be added to fluid A to aid in dissolving insoluble substances. If the substance being examined contains lecithin, use fluid B for diluting.

For oils and oily solutions:

Filter oils or oily solutions of sufficiently low viscosity without dilution through a dry membrane. Dilute viscous oils as necessary with a suitable sterile diluent such as isopropyl myristate that has been shown not to have antimicrobial properties under the conditions of the test.
Allow the oil to penetrate the membrane and filter by applying pressure or by suction, gradually. Wash the membrane by filtering through it at least three successive quantities, each of approximately 100ml, of sterile fluid B or any other suitable sterile diluent.
After filtration, aseptically remove the membrane(s) from the holder, transfer the whole membrane or cut it aseptically into 2 equal parts. Transfer one half to each of two suitable media**.** Incubate the media for not less than 14 days.
Observe the containers of media periodically during the 14 days of incubation. If the test specimen is positive before 14 days of incubation, further incubation is not necessary. For products terminally sterilized by a validated moist heat process, incubate the test specimen for not less than 7 days.

For ointments and creams

Dilute ointments in a fatty base and emulsions of the water-in-oil type to give a fluid concentration of 1 per cent w/v, by heating, if necessary, to not more than 40ºC with a suitable sterile diluent such as isopropyl myristate previously rendered sterile by filtration through a 0.221 m membrane filter that has been shown not to have antimicrobial properties under the conditions of the test. Filter as rapidly as possible and complete the test as described under for oils and oily solutions. In exceptional cases, it may be necessary to heat the substance to not more than 44ºC and to use warm solutions for washing the membrane.

For soluble solids:

For each medium, dissolve not less than the quantity of the substance under examination, as prescribed in Table 3(E), in a suitable sterile solvent such as fluid A and carry out the test described under for aqueous solutions using a membrane appropriate to the chosen solvents.

For solids for injection other than antibiotics:

Constitute the test articles as directed on the label, and carry out the test as described under for aqueous solutions or for oils and oily solutions, as applicable.

Table 3(E): Minimum quantity to be used for each medium

Quantity in each container of injectable preparation	Minimum quantity to be used for each culture medium
For liquids	
Less than 1 ml	Total contents of the container
1 ml or more but less than 40 ml	Half the contents of the container
40 ml or more but less than 100 ml	20 ml
100 ml or more	10% of the contents of 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.	The whole contents of each container to provide not less than 200 mg
For solids	
Less than 50 mg	Total contents of the container
50 mg or more but less than 300 mg	Half the contents of the container
300 mg or more	100 mg
For catgut and other surgical sutures for veterinary use	3 sections of the strand
For surgical dressings/cotton/gauge	100 mg per package
For sutures and other individually packed	The whole device or materials, cut into pieces or

		single use materials	disassembled.

Method B: Direct inoculation method

The quantity of the substance or preparation under examination to be used for inoculation in the culture media varies according to the quantity in each container. Follow the directions given in the Table 3(E).

Test method:

For aqueous solutions and suspensions:

Remove the liquid from the test containers with a sterile pipette or with a sterile syringe or a needle. Transfer the quantity of the preparation under examination prescribed in Table 3(E) directly into the culture medium so that the volume of the preparation under examination is not more than 10 per cent of the volume of the medium, unless otherwise prescribed. When the quantity in a single container is insufficient to carry out the tests, the combined contents of two or more containers are to be used to inoculate the media.

If the preparation under examination has antimicrobial activity, carry out the test after neutralizing this with a suitable neutralizing 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.

Incubate the inoculated media for not less than 14 days. Observe the cultures several times during the incubation period. Observe the containers of media periodically during the 14 days of incubation. If the test specimen is positive before 14 days of incubation, further incubation is not necessary. For products terminally sterilized by a validated moist heat process, incubate the test specimen for not less than 7 days.

For oils and oily solutions:

Use media to which has been added a suitable emulsifying agent at a concentration shown to be appropriate in the validation of the test, for example, polysorbate 80 at a concentration of 10g/liter and which has been shown not to have any antimicrobial properties under the conditions of the test. Carry out the test as described under for aqueous solutions and suspensions.

During the incubation period shake the cultures gently each day. However, when thioglycollate medium or other similar medium is used for the detection of anaerobic micro-organisms keep shaking or mixing to a minimum in order to maintain anaerobic conditions.

For ointments and creams:

Prepare by diluting to about 1 in 10 by emulsifying with the chosen emulsifying agent in a suitable sterile diluent such as fluid A. Transfer the diluted product to a medium not containing an emulsifying agent. (Before use, test the emulsifying agent to ascertain that in the concentration used it has no significant antimicrobial effects during the time interval for all transfers). Mix 10 ml of the fluid mixture so obtained with 80 ml of the medium and proceeds as directed under for aqueous solutions and suspensions.

For solids:

Transfer the quantity of the preparation under examination to the quantity of medium specified in Table 3(E) and mix. Proceed as directed under for aqueous solutions and suspensions.

Observation and Interpretation of Results:

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 easily 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.

If no evidence of microbial growth is found, the preparation under examination complies with the test for sterility. If evidence of microbial growth is found, the preparation under examination does not comply with the test for sterility. Do not repeat the test unless it can be clearly shown that the test was invalid for causes unrelated to the preparation under examination. The test may be considered invalid only when one or more of the following conditions are fulfilled:

a) Microbial growth is found in negative controls.
b) Data on microbial monitoring of the sterility testing facility show a fault.
c) A review of the testing procedure used for the test in question reveals a fault.
d) After identifying the microorganisms isolated from the containers showing microbial growth may be as scribed without any doubt to faults with respect to the materials and/or technique used in conducting the test procedure.

If the test is declared to be invalid, repeat with the same number of units as in the original test. If no evidence of microbial growth is found in the repeat test, the preparation under examination complies with the test for sterility. If microbial growth is found in the repeat test and confirmed microscopically, the preparation under examination does not comply with the test for sterility

Table 3(F): Minimum of items to be tested

Number of items in the batch	Minimum number of items recommended to be tested
Parenteral Preparations	
Not more than 100 containers	10% or 4 containers
More than 100 but not more than 500 containers	10 containers
More than 500 containers	
For large volume parenterals	2% or 20 containers whichever is less
	2% or 20 containers whichever is less

Specifications For Irrigations According to BP

Tests	Reference codes	BP
Pyrogen	IQC-1	Summed temperature of 3 rabbits should not be more than 1.150 C
Particulate matter	IQC-2	≥ 25 µm can be present

Extractable value	IQC-3	-
Deliverable mass/ volume	IQC-4	-
Sterlity	IQC-5	No growth in 14 days.

PQC 6

Pyrogen test:

The test involves measurement of the rise in body temperature of rabbits following the intravenous injection of a sterile solution of the substance under examination.

Do not use animals for Pyrogen tests more frequently than once every 48 hours. After a Pyrogen test in the course of which a rabbit's temperature has risen by 0.6°C or more, or after a rabbit has been given a test substance that was adjudged pyrogenic, at least 2 weeks must be allowed to elapse before the animals is used again.

Test animals:

Healthy adult rabbit of either sex (1.5 Kg)

Recording of Temperature:

Use temperature-sensing device such as a clinical thermometer or thermistor or other suitable probes (accuracy of 0.10). Insert the thermometer or temperature-sensing probe into the rectum of the test rabbit to a depth of about 5 cm **{7.5 cm –USP}**

Preliminary Test (Sham Test)

Injecting intravenously 10 ml per kg body weight of a pyrogen-free saline solution warmed to about 38.5^0 C. Record the temperatures of the animals, beginning at least 90 minutes before injection and continuing for 3 hours after injection of the test solution. Any animal showing a temperature variation of 0.6°C or more must not be used in the main test.

Main Test:

Carry out the test using a group of three rabbits.

Preparation of the sample:

Dissolve the substance with pyrogen-free saline solution. Warm the liquid under examination to approximately 38.5°C before injection.

Procedure:

Record the temperature of each animal 90 minutes before the injection and continue for 3 hours after the injection for every 30 minutes. Record the "initial temperature" of each rabbit and temperature after 30 minutes. Rabbits showing a temperature variation greater than 0.2°C between two successive readings in the determination of "initial temperature" should not be used for the test. Do not use any rabbit having a temperature higher than 39.8°C and lower than 38°C.

Inject the solution slowly into the marginal vein of the ear of each rabbit over a period not exceeding 4 minutes. The volume of injection is not less than 0.5 ml per kg and not more than 10 ml per kg of body weight. The difference between the "initial temperature" and the "maximum temperature" which is the highest temperature recorded for a rabbit is taken as its response. When this difference is negative, the result is counted as a zero response.

Interpretation of results:

Having carried out the test first on a group of three rabbits, repeat if necessary on further groups of rabbits given in the Table 3(G), depending on the results obtained.

If the summed response of the first group does not exceed the figure given in the third column of the Table 3(G), the substance passes the test. If the response exceeds the figure given in the third column of the table 3(G) but does not exceed the figure given in the fourth column of the Table 3(G), repeat the test as indicated above.

If the summed response exceeds the figure given in the fourth column of the Table 3(G), the product fails the test.

Table 3(G): Results of pyrogen test according to IP, BP, and USP.

Pharmacopeia	No. of rabbits in a group	Passes if temp. is not more than	Fails if temp. is more than
IP	3 8	1.4 3.7	Each rabbit temp raise should not be more than 0.6^0C
BP	3 6 9 12	1.15 2.80 4.45 6.6	2.65 4.30 5.95 6.6
USP	3 8	---- 3.3	Each rabbit temp raise should not be more than 0.6^0C

PQC 7

Clarity of solution

General procedure :-

Constitute the injection as directed on the label.

1) The solid dissolves completely, leaving no visible residue as undissolved matter.
2) The constituted injection is not significantly less clear than an equal volume of diluents for water for injections contained in a similar container and examined in the same manner.

PQC 8

Bacterial Endotoxin Test:

The test for bacterial endotoxins (BET) measures the concentration of bacterial endotoxins that may be present in the sample or in the articles to which the test is applied using alysate derived from hemolymph cells or amoebocytes of horse shoe crab, limulus polyphemus.

The endotoxin limit for a given test preparation is calculated from the expression K/M, where M is the maximum dose administered to an adult (taken as 70 Kg for this purpose) per kg hour.

The following methods can be used to monitor the endotoxin concentration:

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

Gel- Clot Limit Test Method:

Prepare the solutions and dilutions with water BET. If necessary, adjust the pH of the solution to 6.0 to 8.0 using sterile 0.1M hydrochloric acid BET, 0.1M sodium hydroxide BET of suitable buffer prepared with water BET.

Prepare the sample solution at any dilution at or below MVD. Use two positive controls, one having the concentration of 2λ and other is spiked to get the concentration of 2λ.

Add an appropriate volume of negative control (NC), standard CSE solutions in water BET, test solution and positive control (PPC). At regular intervals add an equal volume of the appropriately constituted lysate unless single vial is used. Mix it and place it in an incubator. Incubation should be done at 37º±1º undisturbed for 60±2 minutes. Remove and examine the receptacles carefully. A positive reaction is recorded when firm gel is formed that retains the integrity when inverted through 180º in one smooth motion. If no firm gel is formed then it is a negative reaction.

Calculation:

Calculate the average of the logarithms of the lowest concentrations of endotoxin in each series of the lowest concentration of endotoxin in each series of dilutions.

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

Where, Σe = sum of the log end point concentration of the series of dilutions used;

f = number of replicate test- tubes.

The value must be in between 0.5λ and 2.0λ

Interpretation of results:

The product under examination complies with the test if the negative control and test solutions are negative, and if the positive control is positive.

Retests:

If a positive control is found for one of the test solution duplicates and a negative result for the other, the test may be repeated as described above. Results of the retest should be interpreted as for initial test.

Semi Quantitative Gel Clot Method

Preparation of the test solutions:

Prepare the test solutions at concentrations of MVD, 0.5MVD, 0.25MVD.

Procedure:

Same as Method A

Calculation and interpretation of results

To calculate the endotoxin concentration in the product, determine for the series of test solutions the lowest concentration or the highest dilution giving a positive (+) reaction. Multiply this dilution with λ to obtain the endotoxin concentration of the product. For instance, if MVD is equal to 8 and the positive reaction was obtained at 0.25 MVD and 1 was equal to 0.125EU/ml

Calculate the endotoxin content of the product under examination from endotoxin concentration. The product under examination meets the requirements of test if the endotoxin content of less than endotoxin limit stated in the individual monograph.

Kinetic Turbidimetric Method & Kinetic Chromogenic Method

Using CSE, prepare solutions of not less than 3 endotoxin concentrations to get a standard curve. Carry out the procedure in duplicates, of each standard endotoxin solution in accordance with the instructions of the lysate manufacture.

Preparation of test solutions:

Solution A: Solution of the product under examination at the initial dilution (test solution)

Solution B: Test solution spiked with CSE at a concentration at or near the middle of the standard curve (PPC)

Solution C: Standard solutions of CSE in water BET covering the linear part of the standard curve

Solution D: water BET (NC)

Method:

Add solution D, followed by solutions C, A, B. Add lysate and carry out the assay solution in accordance with the instructions of the lysate manufacture.

Calculation:

Calculate the endotoxin concentration of solutions A and B from the regression equation obtained with solutions of series C. Calculate the mean percentage recovery of the added endotoxin by subtracting the mean endotoxin concentration in solution A from the mean endotoxin concentration in solution B

Interpretation of results:

The assay is valid only if

1) The standard curve is linear for the range of CSE concentrations used
2) The coefficient of correlation r, is not greater than 0.980;
3) The mean % recovery of the added endotoxin in the positive product control is between 50% and 150%

End Point Chromogenic Method

Add solution D, followed by solutions C, A, B. The chromogenic substrate and lysate are added to the solution and incubated for the recommended time. Stop the reaction and measure the absorbance at the specified wavelength in accordance with the instructions of the lysate manufacture.

Interpretation of results:

The assay is valid only if

1) The standard curve is linear for the range of CSE concentrations used
2) The coefficient of correlation r, is not less than 0.980;
3) The mean % recovery of the added endotoxin in the positive product control is between 50% and 150%.

critical detailed review of the data gathered from the batches analyzed.

The concept of total quality control test refers to the process of striving to produce a perfect product by a series of measures requiring an organized effort in order to eliminate errors at every stage in the production. In process product testing is required in order to check the conformance of the product with the compendial standards as specified in the pharmacopoeias. The pharmacopoeias have laid down the specified limits within which the value should fall in order to be compliant as per the standards. As the final samples taken for the finished product testing is only a representative of a large batch, a significant difference still remains because of minor variation in the specified limits in different pharmacopoeias. Since the markets have opened up due to globalization it is necessary for a product to comply with the standards of the place where it is to be marketed.

As the official pharmacopoeias are different in different parts of the globe, there is a need for the harmonized limit within which a product should fall in order to meet the pharmacopoeial specifications of that region. The aim of the study is quality control tests for some conventional dosage forms and to list down the similarities and differences as per various Pharmacopoeias.

In-process and finished products quality control Tests for Parenterals

Parenteral products are unique dosage forms of drugs because they are injected through the skin or mucous membranes into the internal body compartments. Thus, because they have circumvented the highly efficient first line of body defence, the skin mucous membranes, they must be free from microbial contamination and from toxic compartments as well as possess an exceptionally high level of purity. All components and processes involved in the preparation of these products must be selected and designed to eliminate, as much as possible, contamination of all types, whether of physical, chemical or microbiologic origin. Parenteral preparations can be given by various routes such as intravenous, intraspinal, intramuscular, subcutaneous and intradermal.

The Parenterals quality control (PQC) tests are

- Uniformity of content.
- Uniformity of weight.
- Particulate matter.
- Extractable volume.
- Sterility test.
- Pyrogen test.
- Clarity of solution.
- Bacterial endotoxin test

Summary

The available QC tests from various pharmacopoeias supplement each other and each pharmacopoeia gives more details on a special issue than the other. Each pharmacopeia has its own specifications for each test.

Conclusion

From the above review it can be concluded that though IP, BP and USP included most of the in process and finished products QC tests for some conventional dosage forms. However some difference was observed. Some of the tests are available only in some pharmacopoeia. The differences in the tests and their limits as specified in the different pharmacopoeias needs to be harmonized and streamlined in such a way that if the test meets the specified limit as per harmonized one, it meets all the requirements of all the pharmacopoeias and later the regulatory requirements of that particular country. This is important for the products which are marketed globally. Because of this a huge amount of time, money and man power can be minimized.

References

[1] Indian Pharmacopoeia. The controller of publication, New Delhi; Ministry of health and family welfare. India. 5th ed. 2007. Volume I.

[2] Indian Pharmacopoeia. The controller of publication, New Delhi; Ministry of health and family welfare. India. 5th ed. 2007. Volume II.

[3] Indian Pharmacopoeia. The controller of publication, New Delhi; Ministry of health and family welfare. India. 5th ed. 2007. Volume III.

[4] British Pharmacopoeia. Published on behalf of Medicines and Health care products Regulatory Agency; The department of Health, social services and public safety. Great Britain sixth ed. 2010, volume II.

[5] British Pharmacopoeia. Published on behalf of Medicines and Health care products Regulatory Agency; The department of Health, social services and public safety. Great Britain sixth ed. 2010, volume III.

[6] British Pharmacopoeia. Published on behalf of Medicines and Health care products Regulatory Agency; The department of Health, social services and public safety. Great Britain sixth ed. 2010, volume IV.

[7] United States of Pharmacopoeia 29 National formulary 24 (USP29–NF24) Supplement 1, is current from April 1, 2006 through July 31, 2006.