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PROCESS VALIDATION OF CETIRIZINE HYDROCHLORIDE TABLETS

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Abstract: **Background and objective:** The objective of the study is to form a basis for written Procedures for production and process control which are designed to assure that the drug Cetirizine hydrochloride 10 mg coated tablet have the identity, strength, quality and purity they purport of are represented to possess. It is done by checking and controlling the critical in process parameters and by evaluation of finished product. So for that purpose a specific method is selected and performed the validation of preferred process. **Method:** Three consecutive batches of Cetirizine hydrochloride 10 mg tablet manufactured as per the Batch Manufacturing Record. Collected samples at different stages like for sifting, blending, compression and coating as mentioned in the sampling plan for individual process. Then sent for analysis, each parameter is analysed and tested as per specifications and recorded the results, which were found within the limits. **Results:** The results suggest that the all parameters are within the limits. The manufacturing process parameters like sieve integrity, appearance, bulk and tapped density, blend uniformity and assay, all physical parameters like weight variation, hardness and thickness, disintegration time, friability, coating parameters were found within the limits. So the manufacturing process intended for further batches. **Conclusions:** The process is validated as per specifications. Overall manufacturing processing parameters are analysed and compared with the standard specifications, found within the limit and it was concluded as the parameters mentioned above validated as per BMR and BPR. The process validation data of Cetirizine hydrochloride tablets reveals that there was no significant variation between batch to batch and all the process variables were studied. Therefore it can be concluded that the process of Cetirizine hydrochloride tablet for the batch size 3 Lac stands Validated.

Keywords: Cetirizine hydrochloride, Lactose monohydrate, Maize starch, Povidone 30, Magnesium stearate

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INTRODUCTION

Process validation is defined by various regulatory agencies as given below:

USFDA defined process validation as **"Establishing documented evidence (through protocols and master plans) which provides a high degree of assurance (repeated trials challenging full) that a specific process will consistently produce (range of process variables and collecting multiple samples) a product meeting its predetermined specifications and quality attributes (documented approved acceptance criteria and product/process specifications derived from R&D or revalidation work)."**

The WHO cGMP's defines process validation as **"Establishing documented evidence, which provides a high degree of assurance that a planned process will consistently perform according to the intended specified outcomes".**

Types of process validation

The various types of process validation are outlined below:

1) Prospective validation: Prospective validation is a requirement and therefore it makes validation an integral part of a carefully planned, logical product/process developmental program. In prospective validation an experimental plan called the validation protocol is executed (following completion of the qualification trials) before the process is put into commercial use. This is normally carried out in connection with the introduction of new drug products and their manufacturing processes.

2) Retrospective validation: For a product to be considered for retrospective validation it must have a stableprocess; that is one in which the method of manufacture has remained essentiallyunchanged for a period of time. The first step in the product selection process istherefore to obtain a summary of changes in the method of manufacture.

3) Concurrent validation: This involves in-process monitoring of critical processing steps and end producttesting of current production can documented evidence to show that themanufacturing process is in a state of control such validation documentation can be provided from the test parameter and data sources disclosed in the selection on retrospective validation.

4) Revalidation: Revalidation provides the evidence that changes in a process introducedintentionally/unintentionally do not adversely affect process characteristics andproduct quality.

Revalidation may be required in following cases:

1. Change in formulation, procedure or quality of pharmaceutical ingredients

2. Change in equipment, addition of new equipment and major breakdown

3. Major change of process parameters

4. Change in site

5. On appearance of negative quality trends

6. Significant increase or decrease in batch size

Revalidation remains an important validation option and should be considered whenever the continued state of control and reliable performance of the manufacturing process are in doubt.

Materials:

Cetirizine hydrochloride (API), Lactose monohydrate, Maize starch, Povidone 30, Hypermellose, Magnesium stearate, Macrogol 6000, Talc, Titanium dioxide, Semithicone emulsion, D. M.All raw materials used were of IP grade and chemicals used in the analysis were of analytical grade.

Machinaries

Machineries and equipments used were as Sifter, Scoops, Oscillating Granulator (CadmachMachinery co. pvt. ltd),Rapid mixing granulator [RMG] (250L, Kevin make), Tray Dryer (Manish Metal), Octagonal blender (240L,Ganson Ltd), Compression machine 45 station double rotatory (SHAMDEW), UVvisible spectrophotometer (Shimadzu), Weighing balance (Shimadzu), hardness tester (Vishal Hardness testing), Disintegration and Friability test apparatus (Electo lab),

Thickness tester, IR Moisture balance(Rajdhani Scientific Instts.co)

Experimental plan:

Validation Procedure:

➤ Three consecutive batches of Ibuprofen 400 mg tablet shall be manufacturedas per the Batch Manufacturing Record.

➤ Collect samples at different stages of processing as mentioned in the samplingplan for individual process.

➤ Send the samples to Quality Control Laboratory for analysis as per testingplan.

➤ Monitor and record the results of critical control variables and responsevariables as mentioned in the process parameter table for individual operation.

➤ During the processing of the batches, Current GMP shall be followed.

➤ Compression machine evaluation: Verify the tablets parameters at maximumand minimum speed of machine, then set the parameters for target speed andverify the parameters well within the limits, then check the physicalparameters of the tablets.

➤ In case any deviation(s) are observed they must be noted down in thedeviation report immediately. The deviation must be noted in

successionthroughout the process along with the corrective action.

➤ A validation report shall be prepared upon the execution of this protocol andtesting of the validation samples.

Evaluation of Tablet

The critical parameters considered during the process validation of Cetirizine hydrochloride tablets were

• Dry Mixing

• Wet granulation

• Drying

• Lubrication

• Compression

• Coating

• Strip Packing

• Weight variation, Hardness Test, Friability, Assay, Dissolution Study.

Dry Mixing

The dry-mixing step involves mixing of active ingredients with other additives using Rapid Mixer Granulator (RMG). The content of Cetirizine hydrochloride in the dry mix shall be tested, to validate dry mixing process. Mixing speed and mixing time are the critical variables that determine content uniformity.Mixing speed is kept constant, mixing time shall bestudied to validate dry mixing step. In dry mixing stage 3 batches like 02C041202, 02C041203 and 02C041204

are considered for validation. Each sides sampled fromtop (RS1T, RS2T, RS3T), middle (RS1M, RS2M, RS3M),bottom (RS1B RS2B RS3B) layer of RMG in polyethylene bag for QC analysis of assay. Refer sampling plan of RMG as shown in figure.1 Dry mixing results of all the batches are well within the acceptance criteria.

Fixed parameters

Time interval studies: after 30 minutes

Measured response: Description, blend uniformity

Acceptance criteria: Not less than 95% and not more than 105% of the Label claim

Spray Granulation

Binding solution was added in to sifted raw material and mixes it for 30 min in FBD. Finally complete the granulation by running impeller and Chopper at slow speed at till suitable dough mass is obtained.

Binder solution preparation: Takeout Povidone 30and hot water in S.S vessel and mix properly and prepared solution. In another vessel add Starch and D.M water and mix and make slurry, then add above solution in slurry and made a paste.

Drying

Drying of wet granules for 2 to 4 hours at 55-65°C till the loss on drying is NLT % w/w at 105°C. (Outlet temperature would be approx.30°C to 40°C). The level of moisture in the granules is important factor. If level

of moisture is more in granules then blend will have poor flow &distribution characteristics. If level of moisture in blend is less it will produce tablet with capping, high friability and chipping problems. During drying the desired LOD will be maintained in the granules which will influence the quality parameters like tablet hardness, flow properties, physical properties during compression. Drying of granules in Tray dryer controls the level of moisture. Inlet temperature of is most critical variable for the same. LOD is checked at regular interval to establish the correlation with outlet temperature. In dry stage of different time interval of each batch should be considered for validation.

After mixing completed of above material take 5 gm. sample material from three sides (starting from left corner, center and right corner). Drying results of the batches are well within the acceptance criteria.

Results of Loss on drying were shown in Table 5.

Acceptance criteria: NMT 2%w/w.

Lubrication

This step involves mixing of Lubricating agent with drug granules& other blending material. The purpose of blending is to get a uniform distribution of granules and lubricating agent. This is followedby mixing of the granules with lubricant to get good flow and anti-adhesion property of the blend. Mixing speed and time are critical variables in this process. Mixing speed is

kept constant & mixing time of blender should be studied for validate blending process. Mixing time is critical since under mixing would result in non-uniform distribution of drug and poor flow whereas over mixing will result affect the uniformity of mixing and leads to non-uniform distribution of drug.

Compression of Tablets

For compression of tablets involves consistent flow of properly lubricated granules in the hopper to dies where the granules were compressed in to tablets. Compression carried out as per batch manufacturing recorded. Collect the sample at various stage and speed. i.e. at maximum RPM, minimum RPM, optimum RPM and at start, middle and end of compression process and carry out testing of content uniformity and physical parameters such as hardness, thickness, friability etc. In compression stage three batches i.e. Batch No 02C041202, 02C041203 and 02C041204 shall be considered for validation. Compression results of all the batches are well within the acceptance criteria. Results of the compression at different speed, low weight at optimum speed, high weight at optimum speed, initial, middle and end of the compression were shown in table no.9 Tablets were compressed using 12.5mm, round Punch, Upper punch & lower Punches plain. Each 125 mg tablet contains 10 mg Cetirizine hydrochloride. The specifications for tablet was average weight 114-126mg(±5%) , hardness NLT 40 N,

thickness 2.70-3.10mm,friability NMT 1%w/w, DT NMT 15 min, Assay 95 -105% ,Dissolution NLT 80% .

Coating

Coating is to be carried out as per batch manufacturing record. Samples are collected at the end of coating stage and carried out the testing of content uniformity and identification tests, inlet temperature, outlet temperature, solid content, physical parameters such as hardness, thickness, friability, etc. In coating stage three batches i.e.Batch No 02C041202, 02C041203 and 02C041204should be considered for validation. Coating results of all thebatches are well within the acceptance criteria.Results are shown in Table no. 10 and 11.

Strippacking

Packing is to be done as per batch packing record. In packing stage three batches i.e. Batch No 02C041202, 02C041203 and 02C041204shall be considered forvalidation. Packing results of all the batches are well within the acceptance criteria.

Evaluation Parameters:-

Weight Variation

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if

not more than two of the individual tablet weight deviate from the average weight by more than the percentage shown in Table 12

Thickness

Twenty tablets were randomly selected from each batch and there thickness and diameter was measured by using digital verniercaliper. Results are shown in Table 13.

Hardness

The crushing strength Kg/cm2 of prepared tablets was determined for 10 tablets of each batch by usingVishal tablet hardness tester. The average hardness and standard deviation was determined. The results are shown in Table 14.

Friability

Twenty tablets were weighed and placed in the Electro lab friabilator and apparatus was rotated at 100 rpm. After revolutions the tablets were deducted and weighed again Table 12 The percentage friability was measured using the formula,

% F = {1-(Wt/W)} ×100

Where, % F = friability in percentage

W = Initial weight of tablet

Wt = weight of tablets after revolution.

Assay

Cetirizine hydrochloride was estimated by using U.V. Spectrophotometer as per the

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Indian pharmacopoeia method at 210nm - 350 nm formulation Samples was Subjected to U.V spectroscopy.

Weight and finely powder 20 tablets. Shake a quantity of the powdered tablets containing 0.1 g of Cetirizine hydrochloride with 50 ml of 1.03% Hydrochloric acid for 20 minutes, add sufficient 1.03% Hydrochloric acid to produce 100ml and filter (Whatman filter).Measured the absorbance of solution at the maximum at 210-350 nm, the resulting solution showed an absorption maximum at 231 nm. The specific absorbance at 231 nm was 361(359 to 381).

RESULTS

All the results are tabulated in Table 1-14

CONCLUSION

Quality cannot be adequately assured by in-process and finished inspections and testing but it should be built in to the manufacturing process. These processes should be controlled in order that the finished product meets all quality specifications. The quality system regulation defines process validation by establishing evidence that a process consistently produces a result or product meeting its predetermined specifications. The goal of quality system is to consistently produce products that are suitable for their intended use. In this study prospective process validation was carried out for one product. In tablet dosage form, critical parameters were taken up for validation studies.

In tablet dosage form, the critical parameters are

- Dry mixing
- Granulation
- Drying
- Lubrication
- Compression
- Coating

Dry Mixing

The dry-mixing step involves mixing of Cetirizine hydrochloride with other additives using Rapid mixer granulator. The content uniformity of Cetirizine hydrochloride has to be established during validation of dry mixing process. The mixing of the active ingredient depends on the mixing of drug during mixing. Hence it is a critical step to be validated.

Drying

The drying step involves drying of wet mass. Moisture in granules is important factor. If moisture is more in granules it will lead to poor flow and sticking problem. If moisture is less it will lead to capping, high friability and chipping. During drying the quality parameters like tablet hardness, flow properties of granules, physical properties of tablets during compression should be taken in to consideration. The inlet temperature of the Freeze dryer is controlled during the drying process and the outlet temperature is monitored and

correlated with the corresponding LOD of the granules under drying.

Lubrication

The blending of three batches was performed and the samples at the designated locations were drawn after 10, 15, 30 minutes of blending for determining the content uniformity and RSD values of Cetirizine hydrochloride. The RSD values meet the acceptance criteria at 8 minutes of blending. From the analytical results it is clear that the drug distribution pattern in the blend is almost homogeneous at 8 minutes of blending. Hence the blending time of 30 minutes as mentioned in the BMR stands was validated.

Compression

The compression for all the three batches has been validated for Startup, high RPM, low RPM, low weight at target speed, high weight at target speed, Initial, Middle, and End cycle of compression. The physical parameters, results of content uniformity and dissolution of the tablets were well within the acceptable limits. The results are comparable among all the three batches.

Coating

The coating of all three batches has been validated for Pan load, Pan RPM, Inlet & outlet temperature, Gun distance, Atomization air pressure and Spray rate. The results are comparable among all the three batches. Aqueous film coating of the tablets is multivariate process. Speed of pan

was taken 4, 5, 6 was effective for coating. Spray rate was maintained to between 16 to18 gm/min. Atomizing pressure 2 bars was constant maintained otherwise lower pressure sticking and picking was observedand higher pressure formation of dust. Rotating pan speed was improved the mixing of the tablet and distribution of the coating solution. Rotating pan speed was 4 to 6 rpm maintained otherwise sticking of the tablet. Higher pan speed problem of friability was observed. Film coating of the tablet direct related to the tablet parameter increased weight up to 1 to 3 % of specified weight, Disintegration time almost double after coating of tablets.

Strip packing

Here, various measured parameter for packing process are machine speed, sealing & forming, temperatures, knurling & cutting,pocket formation.Strip packing process involves packing of tablets in aluminium foil. Temperature of sealing rollers, speed of machine is critical variables. Adequate sealing roller temperature is essential to get proper sealing, less temperature will lead to improper sealing which cause leakage and higher temperature will result in burning or spoilage of aluminium foil. Speed of the machine is influenced by following parameters. Proper sealing of strip pack configuration of strip pack Leak test and strip appearance are carried out to establish the above variables during blister packing

operation. Calculated the % yield and   record.

Process control variables

Table 1

Process Control Variables

Process	Variable
Sifting	Sieve size
Dry Mixing	Load , Speed of Mixer , Mixing Time
Granulation	Speed of Mixer & chopper, Mixing Time,Temp. of Binder, Quantity of Purified Water used
Drying	Initial air drying , Inlet air temperature , Outlet temperature , Drying time
Dry Screening	Sieve size , Screen size , Milling speed
Blending& Lubrication	Load , Mixing Time
Compression	Speed of compression ,Compression force, Average weight, Uniformity of weight, Diameter, Thickness ,Hardness ,Friability, Disintegration time
Coating	Pan Load (Kg),Pan Speed, Inlet Temperature, Outlet Temperature, Tablet bed temperature ,Atomizing air pressure, Spray rate

Table 2

Details of Raw Materials

Sr. No.	Name	Grade	Qty/Tablet (mg)
1.	Cetirizine dihydrochloride*	API	10
2.	Lactose monohydrate	IP	73.40
3.	Maize starch	IP	33.00
4.	Povidone 30	IP	2.40
5.	Magnesium stearate	IP	1.20
6.	Hypromellose	IP	3.45
7.	Macrogol 6000	IP	0.35
8.	Talc	IP	0.35
9.	Titanium dioxide	IP	0.80
10.	Simethicone Emulsion SE4	IP	0.05
11.	Purified water	IP	--

Table 3

Equipments to be used During Validation

Processing Stage	Processing Equipment's
Weight verification	Weighing Balance
Sifting	Mechanical sifter
Dry Mixing	Rapid Mixer granulator
Drying	Fluidised Bed Dryer
Dry screening and Milling	Oscillating Granulator
(Sizing of dried granules)	Multimill
Blending & Lubrication	Octagonal Blender
	RMG
Compression	Double station rotary compression machine
Assay testing	U.V spectrophotometer

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Table 4

Dry Mixing Process results

	Batch 02C041202	Batch 02C041203	Batch 02C041204
	96.81	96.79	98.16
	101.2	96.41	98.57
	99.47	97.01	100.2
	99.08	98.06	98.24
	99.36	99.9	98.33
Assay results	99.51	99.07	98.29
after completion	99.27	101.79	98.44
of mixing process	99.83	99.57	98.14
	100.1	98.89	97.77
SD%	0.78526	1.701955	0.727181

Table 5

Wet Mixing Results

S.	Process	Batch no.		
No.	Parameter	02C041202	02C041203	02C041204
1	Impeller	Slow speed till wet dough Mass is obtained.		
2	Chopper			
3	Impeller motor amperage at the end of wet granulation	18A	18.2A	18.6A
4	Speed of Impeller during Discharging	Slow Speed	Slow speed	Slow speed
5	Total Granulation time (min)	30 min	30 min	30 min
6	% assay result after completion of process	98%	97.91%	98.58%

Table 6

Drying Stage Results

Loss on Drying LOD (%w/w)									
Time	**After 4 hours**			**After 5 hours**			**After 6 hours**		
Layer	T	M	B	T	M	B	T	M	B
02C041202	2.50	2.63	2.53	2.40	2.30	2.41	1.53	1.50	1.50
02C041203	2.60	2.56	2.56	2.15	2.35	2.40	1.53	1.50	1.56
02C041204	2.53	2.50	2.53	2.46	2.50	2.21	1.46	1.53	1.50

T = Top M = Middle B = Bottom

Table: 7

Lubrication Stage Result

Sample Location of octagonal blender	% Assay								
	After 20 min			After 25 min			After 30 min		
	02C041202	02C041203	02C041204	02C041202	02C041203	02C041204	02C041202	02C041203	02C041204
BS1	97.51	99.11	101.23	101.25	100.7	96.81	100.2	99.07	98.13
BS3	99.66	101.06	99.24	98.71	98.64	101.2	98.1	98.37	98.74
BS2	98.64	99.81	98.66	97.92	98.55	99.47	98.24	98.76	99.72
BS4	98.39	96.51	99.62	98.02	98.83	99.08	98.3	98.8	99.66
BS9	97.82	97.91	101.79	97.72	98.46	99.36	98.44	98.82	100.5
BS5	96.43	99.16	98.9	98.22	98.53	99.5	98.14	98.89	99.36
BS7	98.19	98.82	101.63	98.18	98.66	99.27	97.77	98.93	99.34
BS6	101.79	98.75	99.73	98.27	98.72	99.83	98.57	98.9	96.33
BS8	99.81	101.2	96.81	98.05	101.2	100.1	98.29	98.83	99.33
SD%	1.55	1.46	1.6	1.07	1.03	1.57	0.65	0.192	1.19
RSD%	1.57	1.47	1.61	1.08	1.04	1.61	0.70	0.194	1.20

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Table 8

Sizing Stage Result

Batch no:	% fine	Bulk Density
02C041202	40	0.9010
02C041203	40	0.8973
02C041204	40	0.8843

Table 9

Illustrated the Result of the Compression Process.

Parameter	Speed	02C041202	02C041203	02C041204	Specification
Appearance	Minimum	ok	ok	ok	Well compressed white to off white oblong tablets with score line on one side and plain on the other side
	Maximum	ok	ok	ok	
	Optimum	ok	ok	ok	
Uniformity of Weight (%)	Minimum	± 120	± 122	± 121	Select 20 tablets at random, weigh each one individually and obtain an average weight. Not more than two of the individual weights deviate from the average weight by more than ± 5%
	Maximum	± 120	±121	±123	
	Optimum	± 122	± 120	± 121	
Thickness (mm)	Minimum	2.90	2.91	2.92	2.70-3.10 mm
	Maximum	2.94	2.93	2.94	
	Optimum	2.92	2.93	2.91	
Hardness (N)	Minimum	70	70	71	NLT 40 N
	Maximum	71	72	74	
	Optimum	71	71	70	

Disintegration	Minimum	2.20	2.30	2.10	NMT 15 min
Time (min)	Maximum	2.30	2.40	2.25	
	Optimum	2.15	2.30	2.20	
Friability	Minimum	0.35	0.34	0.40	NMT 1.0 % w/w.
(%w/w)	Maximum	0.42	0.47	0.49	
	Optimum	0.25	0.24	0.26	
Assay (%w/w)	Minimum	98.45	97.95	97.76	95.00% to 105.00 %
	Maximum	97.25	97.48	98.02	
	Optimum	98.78	97.79	98.76	
Dissolution (%)	Minimum	89.71	85.54	86.28	Not less than 80 % of the labelled amount
	Maximum	89.36	89.41	84.60	
	Optimum	87.76	84.68	89.60	
Yield of batch		98.03	98.34	98.03	95.00% to 100.00%

Table 10

Coating Stage Result

S. No	Parameters	02C041202	02C041203	02C041204	Limits
1	Speed of pan	4	5	6	3- 10 RPM
2	Hot air temperature	47	46	47	45ºC ± 5ºC
3	bed temperature	38	42	41	40ºC ± 5ºC
4	Total Coating time	3 hours	3 hours	3 hours	To be recorded
5	Room Temperature	24	23	24	25ºC ± 2ºC
6	Relative Humidity	45	48	44	45% ± 5%

Table 11

Coating Stage Tablet Result

Parameter	02C041202	02C041203	02C041204	Specification
Appearance	Ok	Ok	ok	Well compressed white to off white oblong tablets with score line on one side and plain on the other side
Thickness (mm)	2.90	2.92	2.99	2.70-3.10 mm
Hardness (N)	70	75	71	NLT 40 N
Disintegration Time (min)	2 min 30 sec	2 min 20 sec	2 min 10 sec	NMT 15 min
Assay (%w/w)	99.25	97. 46	97.00	95.00% to 105.00 %
Dissolution (%)	94.56	93.13	94.15	Not less than 70 %

Table 12

Weight variation Results of Tablets

Sample. No.	02C041202	02C041203	02C041204
1	120	122	122
2	121	122	120
3	119	120	119
4	118	119	118
5	120	121	119
6	122	121	120
7	121	121	120
8	120	120	120
9	119	120	121
10	120	121	121
11	120	119	120
12	121	118	120
13	120	120	120
14	118	120	120
15	119	121	119
16	122	122	118
17	121	121	121

18	120	121	122
19	120	120	120
20	119	119	121
Maximum	122	122	122
Minimum	118	118	118
Average	119.85	120.1	119.85

Table 13

Thickness results

Sample. No.	02C041202	02C041203	02C041204
1	2.90	2.91	2.95
2	2.91	2.91	2.94
3	2.92	2.92	2.91
4	2.94	2.95	2.96
5	2.95	2.96	2.91
6	2.94	2.94	2.93
7	2.91	2.95	2.92
8	2.90	2.96	2.92
9	2.95	2.97	2.90
10	2.94	2.94	2.90
11	2.92	2.96	2.91
12	2.93	2.93	2.93
13	2.90	2.94	2.91
14	2.91	2.94	2.91
15	2.91	2.95	2.92
16	2.92	2.94	2.94
17	2.92	2.94	2.93
18	2.93	2.94	2.94
19	2.94	2.95	2.91
20	2.95	2.91	2.93
Average	2.92	2.94	2.91
Maximum	2.95	2.97	2.96
Minimum	2.90	2.90	2.90

Table 14

Hardness test results

Sample. No.	02C041202	02C041203	02C041204
1	70	75	70
2	72	74	73
3	75	73	74
4	74	72	75
5	76	74	74
6	72	75	72
7	74	74	70
8	73	71	71
9	70	70	73
10	72	72	75
Average	72.8	72.8	72.7
Maximum	76	75	75
Minimum	70	70	70

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