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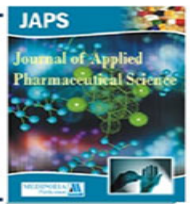


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# Process validation of Amoxicillin and Clavulanic acid

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**ABSTRACT**

As per requirement of Export Order, validation of product should be performed as per guideline. The protocol describes the process stages, control with justification, sampling plan, acceptance criteria, summary & conclusion. During validation samples with draw according to sampling plan. The Manufacturing of Amoxicillin and Clavulanic acid are validated successfully. All the data and inprocess derived during process validation of Amoxicillin and Clavulanic acid are complied with technical manufacturing document. Hence process is validated.

**Keywords:** Amoxicillin, Clavulanic acid, GMP, Process validation.

## INTRODUCTION

Validation is a concept that is fundamental to GMP's and any quality assurance program. There is no effective quality assurance program without validation. Validation study in evitably leads to process optimization, better productivity and lower manufacturing cost. The investment made in validation, similar to the investment made in qualified people can only provide an excellent return (WHO, 1997).

FDA definition of validation "There shall be written procedures for production and process control designed to assure that the drug products have their identity, strength, quality, and purity they purport or are represented to possess." FDA guidelines "general principle of validation" MAY 1987 **"**Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specification and quality attributes."According to the FDA's current Good Manufacturing Practices (cGMP) control procedure shall be established to monitor output and to validate performance of the manufacturing processes that may be responsible for causing variability in the characteristics of In-process materials and the drug product (Chows, 1997; WHO, 1992; Manohar, 2007; US FDA, 1987).

## MATERIALS AND METHODS

### Instrument Used

Stem Sterilizer, Vial Washing Machine, Sterilizing Tunnel, Powder Filling Machine, Vial Sealing Machine, Vial Inspection Machine all equipments are perfectly qualified.

### Batch Operation

The batch operation validation approach means a plan to conduct process validation on different products manufactured with the same processes using the same equipment. The validation process using these approaches must include batches of different strengths or products which should be selected to represent the worst case conditions or scenarios to demonstrate that the process is consistent for all strengths or products involved.

In process validation three consecutive batches are used for manufacturing operation these batches are of the size which will be produced during the routine marketing of the product.

The given Batch operation is for sterile products, to be performed in various stages (Table-1).

## RESULTS AND DISCUSSION

The process validation was started at the qualification of equipment all the equipment was qualified at the time of process validation. Environmental condition monitoring of manufacturing area is critical process parameter for process validation. In environmental monitoring critical parameter like, temperature, relative humidity, and differential pressure, viable or non-viable particles are generally monitored. The maximum and minimum temperature was found to be 22.44ºC and 19.21ºC respectively in different processing area. The maximum and minimum relative humidity % was found 27.50% and 18.23% respectively in different processing area. The maximum and minimum differential pressure was found to be 3.4 mm of WC and 1.8 mm of WC respectively depends on different processing area. The viable particles were not found during observation. The maximum non viable particles of ≥0.5µ were found to be 536 and 1645 per $m^3$ respectively in sterile filling area and area adjacent to sterile area. Similarly, the maximum non viable particles of ≥5.0µ were found to be 5 and 329 per $m^3$ respectively in sterile filling area and area adjacent to sterile area. The visible and non visible particulate matter was checked during vial washing, sterilization and filling stages, the particulate matter was found to be as per acceptance criteria. During vial filling and stoppering the weight variation and content uniformity of dosage unit was also calculated / checked. The result was found under acceptance criteria.

Sealing integrity test was performed after vial sealing with the help of sealing integrity test apparatus no defects was observed in this test. Analytical test and sterility test of finished product was performed by quality control and microbiology department both test were complies. All about the calculation the batch yield of three consecutive batches were found to be 95.14%, 95.67% and 95.53% respectively.

So the data of all three batches were complying with its acceptance criteria. Hence the product can be successfully manufactured at the commercial scale and the sterile manufacturing process is validated.

Where the result obtained show significant deviations from those expected, the regulatory authorities need to be informed immediately. In such cases corrective action should be proposed and any changes proposed in the manufacturing process should receive prior regulatory approval by way of variation.

**Table. 1:** Batch Operation Details.

| S. no. | Unit operation | Parameters | Limit/operating range for all three batches. |
|---|---|---|---|
| 1 | Water Purification | PH | 5 to 7 purified water, & Water for injection |
| | | Conductivity | WFI: NMT 1.3µs/cm |
| | | Toc/ Oxidisable substance. | NMT 500 PPb |
| | | Particulate matter | WFI:≥ 10µ:NMT 100/10ml≥25µ: NMT 10/10ml |
| | | Endotoxins | WFI & UF:NMT 0.25 EU/ml WFI 06≤125EU/ml |
| 2 | Steam Sterilization of Machine Parts, Garments and Rubber Stopper. | No. of steam pulses | 03 |
| | | Stem pressure for pulsing | 0.700Kg/cm² |
| | | Vacuum for pulsing | -0.700Kg/cm² |
| | | Sterilization temperature range during sterilization | 121ºC to 123ºC |
| | | Standard sterilization period | 25 min |
| | | Vacuum cycle | 45 min |
| 3 | Drying of Rubber Stopper. | Photohelic reading of sterilization chamber | Sterilization 5mm to 35mm to water column |
| | | Drying time | 120 min |
| | | Temperature range during hold period | 100-120 ºC |
| 4 | Vial Washing | Compressed air pressure | |
| | | Control air | NLT 5.0Kg/cm² |
| | | Process air | NLT 3.5Kg/cm² |
| | | Pressure of water | |
| | | Purified water | NLT 2.5 Kg/cm² |
| | | Water for injection | NLT 2.5 Kg/cm² |
| | | RE-circulated water wash time and WFI wash time | 10ml vials 1.5sec |
| | | Compressed air blowing time | 10ml vials 1.8sec |
| 5 | Sterilization and Depyrogenation of Vials | Sterilization zone temperature range | 320 to 360ºC |
| | | Conveyor speed | 10ml vial 119 ± 1RPM |
| | | Total travel time | 10ml vial 22-24min |
| | | Vacuum available | NLT 0.5 bar |
| 6 | Vial Filling and Stoppering | Compressed air pressure | NLT 3.0Kg/cm² |
| | | Dosing cycle | Single/Double dosing |
| | | Nitrogen pressure (Dosing) | NLT 3.0Kg/cm² |

**Sterile Process Flow Chart**

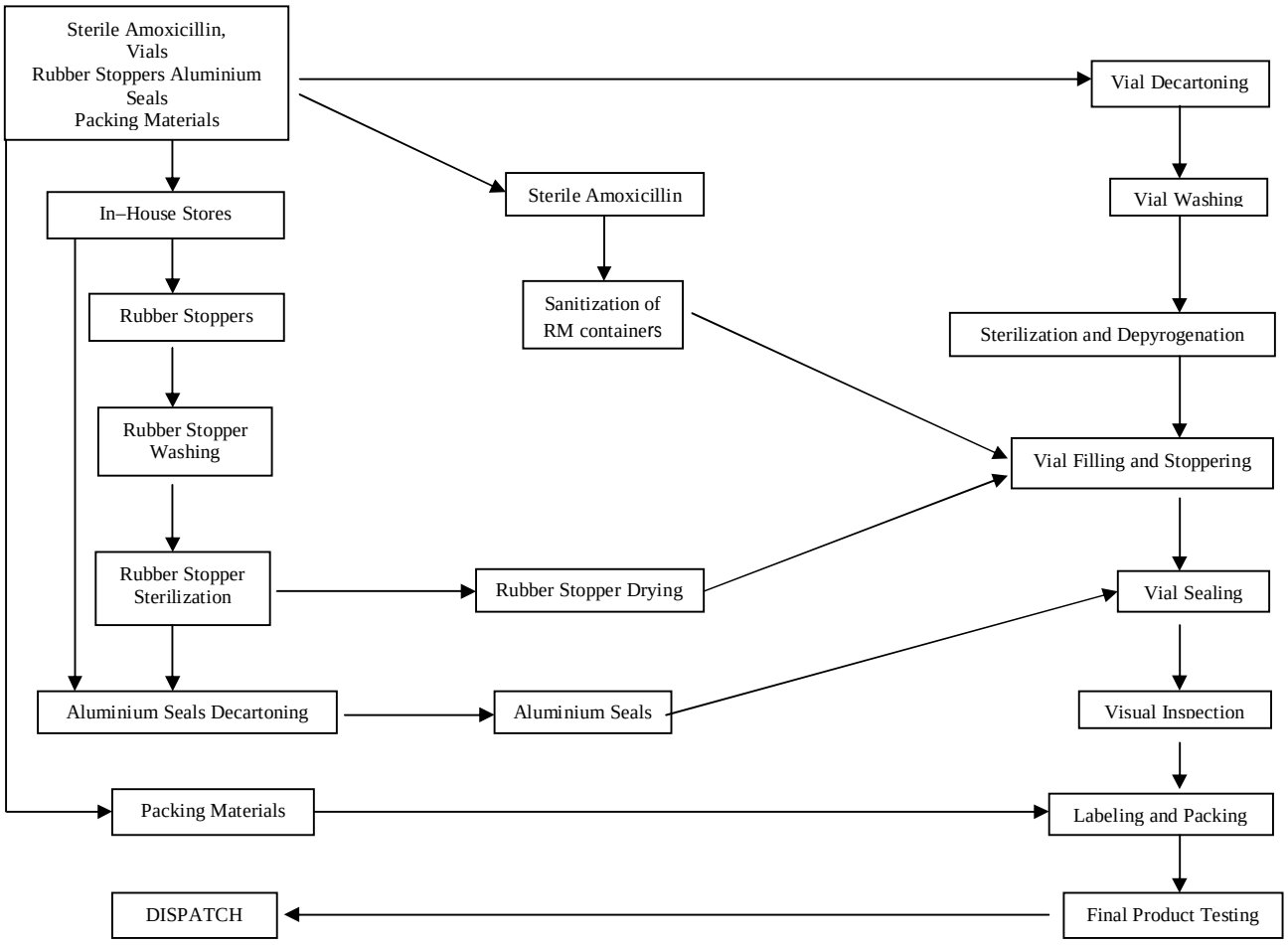


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**Table 2:** Equipment Details.

| S. No. | Equipment | Make | Equipment no. |
|---|---|---|---|
| 1. | Stem Sterilizer | Machine Fabric | SST-01 |
| 3. | Vial Washing Machine | Macofer | VWM-01 |
| 4. | Sterilizing Tunnel | Klinzaids | ST-01 |
| 5. | Powder Filling Machine | Macofer | PF-01 |
| 6. | Vial Sealing Machine | Macofer | VSM-01 |
| 7. | Vial Inspection Machine | Amba | VI-01 |

**Table 3:** Equipment Qualification Details.

| S. no. | Equipment name | Qualification |
|---|---|---|
| 1 | Autoclave | Qualified |
| 2 | Vial Washing Machine | Qualified |
| 3 | Sterilizing Tunnel | Qualified |
| 4 | Powder Filling Machine | Qualified |
| 5 | Vial Sealing Machine | Qualified |
| 6 | Vial Inspection machine | Qualified |

**Table 4:** Environmental Condition of Manufacturing Area.

| S. no. | Parameters | Area | Acceptance criteria | Observation | | | Comply / Not comply |
|---|---|---|---|---|---|---|---|
| | | | | B.NO-01 | B.NO-02 | B.NO-03 | |
| 1. | Temperature (◦c) | Vial filling area | NMT 24ºC | 19.21 ºC | 19.23ºC | 19.24ºC | Comply |
| | | Cooling zone | NMT 24ºC | 20.24ºC | 21.0ºC | 20.26ºC | Comply |
| | | Vial washing room | NMT 26ºC | 22.40ºC | 22.44ºC | 22.35ºC | Comply |
| | | Vial sealing room | NMT 26ºC | 23.10ºC | 22.40ºC | 23.23ºC | Comply |
| 2. | Relative Humidity (%) | Vial filling area | NMT 30% | 18.40% | 18.23% | 19.0% | Comply |
| | | Cooling zone | NMT 45% | 27.1% | 27.5% | 27.3% | Comply |
| 3. | Differential Pressure (mm of wc) | Vial filling vs Vial washing | NLT 10 pascal | 2.6mm of wc | 2.4 mm of wc | 2.3 mm of wc | Comply |
| | | Vial filling vs Cooling zone | NLT 10 pascal | 2.7 mm of wc | 2.8 mm of wc | 2.4 mm of wc | Comply |
| | | Vial filling vs Air lock | NLT 10 pascal | 1.8 mm of wc | 1.8 mm of wc | 1.8 mm of wc | Comply |
| 4. | Sterile Filling Area Particle Count | Viable particle count | 1 CFU/m³ | Nil | Nil | Nil | Comply |
| | | Non viable particle count | ≥0.5µ=NMT 3520 /m³ | 400/ m³ | 536 /m³ | 454/ m³ | Comply |
| | | | ≥5µ= NMT 20 /m³ | 4/ m³ | 5/ m³ | 5 /m³ | Comply |
| 5. | Area Adjacent to Sterile Area Particle Count | Viable particle count | 2CFU/m² | Nil | Nil | Nil | Comply |
| | | | ≥0.5µ=NMT 352000/ m³ | 1700/m³ | 1743/m³ | 1645/m³ | Comply |
| | | Non viable particle count | ≥5µ= NMT 2900 /m³ | 225/ m³ | 322 /m³ | 329/ m³ | Comply |

**Table 5:** Observation Report.

| S.no. | Test | Acceptance criteria | Observation comply / Not comply | | |
|---|---|---|---|---|---|
| | | | B.NO-01 | B.NO-02 | B.NO-03 |
| 1. | Particulate matter | Visible particulate matter: Vials should be free from visible particulate matter. | Comply | Comply | Comply |
| | | Sub-visible particulate matter: ≥10µ:NMT600 ≥25µ:NMT60 | Comply | Comply | Comply |
| 2. | Particulate matter | Visible particulate matter: Vials should be essentially free from visible particulate matter. | Comply | Comply | Comply |
| | | Sub-visible particulate matter: ≥10µ:NMT600 ≥25µ:NMT60 | Comply | Comply | Comply |
| 3. | Weight variation | Individual weight ±5% of target fill weight average fill weight: ±2% of target fill weight. RSD: NMT 6.0% | Comply | Comply | Comply |
| 4. | Uniformity of dosage units (By weight variation) | Meets the requirement.(NMT 15.0%) | Comply | Comply | Comply |
| 5. | Particulate matter | Visible particulate matter: Vials should be essentially free from visible particulate matter. | Comply | Comply | Comply |
| | | Sub-visible particulate matter: ≥10µ:NMT600 ≥25µ:NMT60 | Comply | Comply | Comply |
| 6. | Sealing of vials. | No. defects should be observed. | Comply | Comply | Comply |

**Table. 6:** Critical Process Parameters.

| S. no. | Parameters | Remark B.NO-01 | B.NO-02 | B.NO-03 |
|---|---|---|---|---|
| **Steam sterilization of machine parts, garments & rubber stoppers** | | | | |
| 1. | Loading pattern of vials filling machine parts, garments & rubber stoppers as per 5.2. | Comply | Comply | Comply |
| | **Drying of stoppers** | | | |
| 2. | Loading pattern should be as per 5.3. | Comply | Comply | Comply |
| | **Vial washing** | | | |
| 3. | Particulate matter in compressed air, purified water, and water for injection as per 5.4. | Comply | Comply | Comply |
| | **Vial sealing** | | | |
| 4. | Container closure integrity test as per reference 5.7. | Comply | Comply | Comply |
| | **Vial inspection** | | | |
| 5. | Defective vials (glass defects, sealing defects, foreign particles and others) and any extra matter embedded in powder as per reference 5.8. | Comply | Comply | Comply |

**Table. 7:** Analytical Results of Finished Product.

| S. no. | Test | Specification | Observation | | |
|---|---|---|---|---|---|
| | | | B.NO-01 | B.NO-02 | B.NO-03 |
| 1. | Description | White crystalline powder. | Comply | Comply | Comply |
| 2. | Identification by | | | | |
| | a) IR | IR spectrum of test is concordant with the spectrum of standard Amoxicillin sodium. | Comply | Comply | Comply |
| | b) HPLC | In the assay the retention time of test peak corresponds to that obtained with standard preparation of Amoxicillin sodium. | Comply | Comply | Comply |

## CONCLUSION

All the test result was found to be as per acceptance criteria or compiled. Based on observation of three batches it was concluded that the product can be successfully manufactured and the sterile manufacturing process is validated.

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