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Validation of moist and dry heat processes used for sterilization and depyrogenation during ampoules manufacturing

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Abstract
 Pyrogens are fever-producing substances, which are metabolic products of microorganisms. Endotoxins are the most potent pyrogens. Depyrogenation can be defined as the elimination of all pyrogenic substances which is an important part of the pyrogen-free pharmaceutical products. This study investigated sterilization and depyrogenation using moist heat by autoclave, as well as dry heat. After incubation period (24 hours) at 55 °C-60 °C the color of *Groebachiller steurothermophilus* spores' control vial which didn't sterilized in autoclave changed from blue to yellow color representing the (over) result, while the other sterilized vials have no color change (-ve). In addition, all examined endotoxin containing ampoules showed gel formation (+ve) when examined by Limulus Amoebocyte Lysate (LAL). All ampoule groups that have autoclaved for periods of 1 hour to 4 hours showed gel formation (+ve) after LAL test, while only the last group which have autoclaving periods of 5 hours (5 cycles) showed no gel formation (-ve). Sterility of vials that contained spores of *Groebachiller steurothermophilus* after dry heating at 250 °C for 30 min showed no color change (-ve). In addition, LAL test for endotoxin containing ampoules after dry heating at 250 °C for 30 min showed no gel formation representing (-ve) pyrogens. So, moist heat is effective in sterilization and not for depyrogenation, whereas, dry heat is effective in sterilization as well as depyrogenation.

Key words
 Sterilization, Dry and Moist heat, Depyrogenation, Ampoule, Endotoxin

1. Introduction
 The most effective way to destroy microorganisms is through "heat", as it coagulates their proteins as well as the enzymes present in them. So sterilization (destroying or killing the microorganisms) process follows this principle of killing microorganisms, which can be either by giving wet (moist) heat or dry heat [1]. Heat sterilization methods using moist heat or dry heat sterilization technique are the effective methods used to sterilize pharmaceutical products which are heat stable (thermostable) products while thermolabile products sterilized with other methods like radiation sterilization or chemical gases sterilization [2]. Thermolabile pharmaceutical products are those products, which require special storage conditions (cold storage) at specific temperatures below room temperature. Moist heat sterilization methods are important for sterilizing instruments, tools and pharmaceutical products. The autoclave with steam pressure and relatively high temperature lower than that of dry heat sterilization is used in moist heat sterilization [1]. Moist heat sterilization mechanism in sterilizing the equipment and pharmaceutical products is the denaturation of the microorganism's protein structure and the enzymes of microorganisms present on the equipment or pharmaceutical product and thus killing them. Moreover, the required time for moist heat sterilization is about 15-20 minutes with the temperature of 121 °C [3]. Dry heat sterilization is one of the oldest techniques used to sterilize the glassware and other equipment. In this method, dry heated air of high temperature is used. Heat is moved through air from the surrounding area of the equipment and transferred to the next layer, whereas, slowly the whole equipment gets heated and sterilization is achieved. The sterilization time may be last from 1 to 2 hours period with the temperature of the 160 °C to 170 °C sequentially [4]. Dry heat sterilization temperature is higher than that of moist heat sterilization process; there are more chances for destroying the microorganisms. Pyrogens are fever-inducing substances, which considered as a metabolic byproducts of microorganisms. Chemically, they are lipid in nature and associated with a polysaccharide carrier molecule (S) these polysaccharide carriers enhance the lipid's solubility. Microorganisms including bacteria, yeasts and molds are producing pyrogens in surrounding media. Endotoxins are the most potent pyrogens, have a high molecular weight and produced from the cell walls of Gram-negative bacteria [5]. There are two phases of endotoxin's presence in environment it may be associated with live organisms or in a free form (unassociated). Endotoxin associated with microorganisms may be removed by bacterial filtration using micro porous sterilizing filters. However, the other free form of endotoxin can't be

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Depyrogenation of endotoxin	
Groebachiller steurothermophilus spores' color test	
1st	-ve
2nd	-ve
3rd	-ve
4th	-ve
5th	-ve
6th	-ve
7th	-ve
8th	-ve
9th	-ve
10th	-ve
11th	-ve
12th	-ve
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84th	-ve
85th	-ve
86th	-ve
87th	-ve
88th	-ve
89th	-ve
90th	-ve
91st	-ve
92nd	-ve
93rd	-ve
94th	-ve
95th	-ve
96th	-ve
97th	-ve
98th	-ve
99th	-ve
100th	-ve

System Dynamics Model of an Assembly System in Ramp-Up – Focusing Inspections

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This paper presents a System Dynamics (SD) model of an assembly system in ramp-up with special focus on inspections. The time between product development and stable series production is characterized by dynamically changing conditions referring to the product, processes and the assembly system's organization. Thus, SD serves as an efficient method to model the system's behavior within the ramp-up period. Based on a qualitative derivation of the system variables an explanation of their interconnection is provided in order to be able to model the system quantitatively and thereby to simulate effects which potential conditions have on the system's ramp-up time and on sales. A special focus is set on the role of inspections as they verify the product quality which is a precondition for achieving an as short as possible time to volume. So far the analysis of inspections has not been in the focus of the existing research on ramp-up.

Keywords: production ramp-up, inspections, system dynamics, assembly system

1. Introduction
 During the ramp-up of a production system two main activities are assembly system design and adaptation of the system are performed in order to reach the indicated peak production. Thus, the system shows a dynamic behavior over time (Lüdtgen 2009; Lüdtgen and Lütjens 2009; Lüdtgen 2012). The dynamics are on the one hand required by the continuous operation of the system referring to output and quality but on the other hand disturbances and unexpected changes of products and processes occur in the system as well as a result of the system (Lüdtgen 2012). Due to these interconnections between the system's elements changes of one element cause variations of other elements as well.
 Within this variable system inspections take a special role. They verify the product quality which is a precondition for generating more output. Especially in the early phases of the ramp-up inspections are necessary to get knowledge on the quality. During the progression of the ramp-up inspections may dynamically be adapted to the state of quality which should result in reduction of the inspection intensity. However, as a consequence of occurring disturbances and unexpected changes a continuous decrease of the inspection intensity is not completely reasonable. Each disturbance of



1. PROCESS VALIDATION PRESENTED BY- SALMAN LATIF ROLL NO.-27 M. PHARM DR. D.Y.PATIL COLLEGE OF PHARMACY 1 2. DE DEFINITION IMPORTANCE AMPOULES/VIAL VALIDATION i. WASHING ii. FILLING iii. SEALING iv. STERILIZATION v. INSPECTION vi. PACKAGING 2 3. VALIDATION OF OINTMENT " CREAM i. SAMPLING ii. TESTING iii. MOITORY VALVADATION OF LIQUID ORALS 1. CLASSIFICATION ii. TESTING iii. SAMPLING 4. VALIDATION REPORT 3 REFERENCE 3 4. DEFINITION 4. THE validation of the process is the establishment of documents tests that provide a high degree of security that are specific processes will consistently produce a product that meets its default specifications and quality. 5. The concept was first proposed by Food and Drug Administration (FDA) in 1970 to improve the quality of pharmaceutical products. 4 5. The definition can be simplified and explained by three main points: Documented Tests Guarantee Consistent quality 5 6 7. IMPORTANCIA: Quality assurance Process optimization Security Cost reduction Compliance Time frame 7 8. JUSTIFICATION OF THE PROCESS Identify Critical Quality Attributes (CQA) and Critical Process Parameters (CPP). To confirm that the process of filling of blisters/vials consistently produces quality finished products. To ensure that the sterile product after sterilization 8 9. VALIDATION REQUIREMENTS Equipment calibration Cleaning Validation Equipment classification Raw materials testing methods Change control Operator training 9 10. PROTOCOL The protocol should include the critical specifications and the operating parameters that were identified, such as the following: a. Purpose of validation b. Operation validated c. Heavy equipment involved d. Used components e. Parameters and ranges f. Sample and test g. senicoidsD senicoidsD h. ozahcer/nAicatpeca ed i. Review and adoption j. Measures to be taken by failure k. Responsible personnel and their function 10 11. AMPOULES The primary packaging material for injectors is the ampoules. Ampoules can be clear or amber, made of type I glass, type C (acc. to ISO 9187-2). Ampoules glass must meet the requirements of European Pharmacopea for type I glass containers and, if manufactured with amber glass, it must also meet the transmission of light. 11 12. Ampollas Wash Ampollas washing machine is made in a rotary washing machine. These CPP machines are: Water temperature This parameter can influence the efficiency of the washing; Water pressure This parameter will influence the correct and efficient washing of the ampoules; Washing hood this parameter can influence the efficiency of the washing as well as efficient processing, as if the washing machine is too fast, more ampoules can break in the process 12 13. REHING VIAL High-pressure water series wash and pressure should be maintained throughout the process. Pressure less = incorrect washing. Pressure more = breakage. The compressed air is used to dry the washed roads and moves to the tunnel. 13 14. Ampollas and frascos Depyrogenation After washing, the ampoules are continuously transmitted to the tunnel, sterilized, depyrogenated and then cooled before being transferred to the filling and sealing station. The key parameters are: 1) Speed of the conveyor belt this parameter can influence the efficiency of the ampoules in the tunnel and also in the time they pass in the tunnel, affecting exposure to sterilization temperature. 2) Camera temperature temperature should be high enough for the ampoules to be effectively sterilized and depyrogenated and the value of FH is high enough to ensure realization .51 51 41 .osecorp After cooling, the blisters are directed to the filling and sealing line. The filling process can be influenced by: 1) Solution flow the solution should flow correctly to be filled in the blisters. The filler needles depend on the product flow. 2) Filling volume The volume correction will influence the intended use of the dosing form, as it may influence the dosing uniformity 15 16. Sealing The sealing process can be influenced by: Flame temperature The flame will melt the glass and seal the blister. If the flame temperature is not adequate, the sealing can be compromised. Ampollas Altura is determined by the height of the flame and will influence the ease of opening. 16 17. Sterilization Ampoules are now placed in trays and, depending on the product, they can be sterilized in the autoclave by hot steam. This step ensures the use of the finished product. This parameter determines the time the product remains under temperature 121oC. Along with the temperature will influence the Fo of the sterilization process. According to the European Pharmacopea (EP), the process should take at least 15 minutes. Temperature This parameter is the key to the sterilization process, as high temperatures ensure the absence of microorganisms. According to the EP it must be at least 121oC, unless it is proved that the process has the same rate of lethality. 17 18. Visual inspection Visual inspection is performed on an automated machine. The machine contains a dual light transmission control system to detect particles in blisters. 18 11. Static Division system 2 Divides photo-detection system into individual parts, detection is done from base of ampoule. 3 The container rotates at specified speed. 4 Liquid forms a vortex imparts movement of the insoluble part 5 Virtual stops vortex aditmsnart aditmsnart zul al ne nAicairav nC atceyorp es negami 19. This minor inspects the following defects: particles, volume and cosmetic defects in the head of the ampoule. The inspection process can be influenced by: rotation speed: this paragraph is defined so that it can optimize the particles to suspend. Brake position: This signal affects the recovery of the meniscus and the moment between the end of the rotation and the inspection. A e a, ~ a^o Sensitivity: This parameter defines the intensity of the light that will illuminate the solution. A e a, ~ a^o Sensitivity: This parameter defines the particle detection threshold, differentiating the signal from the noise. 19 20. Integrity inspection The integrity inspection is carried out in an automated machine by detecting high voltage leaks (HVL). 20 High voltage is applied to the container. If the crack is present, the current will flow and detect by the detector. The difference in conductivity is measured. 21. Labeling The labeling is performed on an automated machine that prints the lot of lots and the expiration date on the label, as well as a sensor that detects the color of the ring code and the presence of the label. The parameters that can influence the labeling process are: a e a, ~ a A ~ The correction of the location of the label is essential for the identification of the product, influencing its quality. A e a, ~ a Quality and quantity of the creative: the correction of the ring color of the ring is essential for the identification of the product to be label, since the color of color is exclusive to the product. 21 22.7 A e a, ~ a ^o Batch & ExpiRY Print date 22 23. Packaging a e a, ~ The blisters in the ampoule tray and place the trays in the carton box with the adaninretdorp nAicacifpece v. otcdorp led sacitsAretcarC .iii ovitejbo abeup ed ortem,ArAp .ii nAicadilav al obac a (Aravell es omA^C .i .nAicudorp ed opiue le odiulcn. radlav a osecorp le ebriced es euq le ne otrice nalP ^a nAicadilav ed olcotorP .13 03 noitazilipoiL ^a odalles .gnippac .gnillif ^a nAicacifruP ^a lir oAtse onelleR ^a nAicacilreteR ^a nAicaneorypeD ^a oteimaenaS ^a azeipml ^a .nos acitu oAcamaraf nAicacirbaf al ne sodadilav res nebed osecorp sol. .03 92 .92 82 .aiortarig alczem ed acalp al ed nAicca al rop etnemacin^A atla etnemavitalar arutarepmet anu a abatnelac es euq cniz ed odixA^ ed odillupras ed amerC :airotsiH ^a ?onainotweN ojulf ed oteimaitroprec neneit sodotA^ ^a ?oduaceda sA^m ovitavreserp ametis nUzA^ ^a ?elpit^Am etnenopmoC ^a ?atla otcdorp ed oib ed agrac aLzA^ ^a ?amerco/otne^A^Agnu arap sosecorp ed nAicadilav ed dadisecc al oA^uq ropA^ ^a etneibma oidem le y oelpme le erbos nAicamrofni ed nAicualave al ed sodatuser sol ed nAicualavE .82 72 LAL ED OTSET eA TSET eA TSET eA TSETNEGORYP OTCEIRD N^ICALUONCI ed ODOTEM N^ICARTETED ed ODOTEM eA GNITSETYTLIRETS .72 62 NOITAUlave ETALUCITRAP TSET NEGORYP TSET EGAKAEL GNITSET DADILIRETS N^ICADILAV AL NE SODANIMRET .62 52 .etol ed orem^An le y otcdorp led atcerroc nAicacifmetl- ^a dadiitsE- ^a sanixotodnE- ^a :saluA^rapp ed nAicanimatmoC- ^a :sazerupml - ^a :oyasne- ^a :res nebed sodabeca otcdorp ed SAQC sol .PTTO led rargol arap .52 42 .etol led atcerroc dadilbazart al iArit^mrep nAiserpmI al ed nAiccerroc al a etad yripxE :touq& ozeAab led ahcef al ed nAiserpmI ^a :ejalabme led nAiccerroc al arap laicnese ne nAicamrof atcerroc us y)srrab ed ogid^Ac ed rosnes le rop odacteted(n^A^racc ed ajac al ed nAiccerroc al- n^A^racc ed ajac ^a .42 32 .ejalabme led dadirgetni al arap laicnese se nAicacolor us y)srrab ed ogid^Ac ed rosnes le rop odacteted(otellof led nAiccerroc al - telfael ^a .nos odateuqite ed osecorp le ne ruflni neduqp euq

