

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION							
DISTRICT ADDRESS AND PHONE NUMBER 12420 Parklawn Drive, Room 2032 Rockville, MD 20857		DATE(S) OF INSPECTION 8/12/2019-8/20/2019* FEI NUMBER 3006549835					
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED Sanjay Sharma, Executive Vice President, Global Manufacturing Operations							
FIRM NAME Dr. Reddy's Laboratories Ltd.		STREET ADDRESS P1 - P9 Vsez, Q1 - Q5 Phase Iii					
CITY, STATE, ZIP CODE, COUNTRY Duvvada, Andhra Pradesh, 530046 India		TYPE ESTABLISHMENT INSPECTED Manufacturer					
<p>This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.</p>							
<p>DURING AN INSPECTION OF YOUR FIRM WE OBSERVED: OBSERVATION 1 The quality control unit lacks authority to fully investigate errors that have occurred.</p> <p>Specifically,</p> <p>On 14/08/19 while observing the routine aseptic filling operations being performed in the (b) (4) at approximately (b) (4) we observed a small accumulation of liquid, pooling (approximately 5-10 ml) beneath a support structure that holds the (b) (4) in place. There appeared to be a small steady stream of liquid moving downward on the (b) (4) support. The Associate Director of Quality Assurance initially explained that this was due to condensate and the aseptic filling process and operations was not terminated. However, it was determined that the leakage was due to a hole in the (b) (4) tubing that is connected to the (b) (4). At approximately (b) (4) a production operator repositioning the (b) (4) tubing by pushing the (b) (4) tubing upward onto the connecting (b) (4) tube such that the hole stopped dispelling liquid out to the (b) (4) of the (b) (4) tube: there was an additional placement of a zip tie (now a third zip tie) to re-secure the (b) (4) tubing onto the (b) (4) tube. The repositioning of the (b) (4) tubing and the addition of a third zip tie appeared to address the leaking (b) (4) μ (b) (4) finished drug product. Not until after we communicated that it appeared that they were filling non-sterile finished drug product did the Associate Director of Quality Assurance state (at (b) (4)) they would "abort" the batch.</p>							
<p>OBSERVATION 2 Procedures designed to prevent microbiological contamination of drug products purporting to be sterile did not include adequate validation of the sterilization process.</p>							
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<p>Specifically,</p> <p>The "Performance Qualification Protocol for (b) (4)", document #FTAPROP366-00 dated 05/05/2016, includes the following documented objective: "To demonstrate that the (b) (4) is consistent and sufficient to (b) (4) the (b) (4) bearing equipment Id PR-E346". The scope of the qualification includes, but is not limited to, (b) (4) concentration verification during the (b) (4) cycle", (b) (4) component status during (b) (4) cycle" and "Microbiological monitoring data of pre & post (b) (4) study." The (b) (4) load configuration consisted of a number of items (e.g. equipment parts & utensils), specifically the protocol establishes, that it "...shall be (b) (4)". The current "Performance Re-Qualification Report for Line (b) (4) (PR-E346) document #VALRP-FT-07-000118 dated 27/03/2019 load configuration is not consistent with the validated load configuration performed in 05/05/2016, for example:</p> <table border="1" style="width: 100%; border-collapse: collapse; margin-top: 10px;"> <thead> <tr> <th style="width: 40%;">Brief description</th> <th style="width: 30%;">FTAPRPQP366-00; 05/05/2016 / location</th> <th style="width: 30%;">VALRP-FT-07-000118; 27/03/2019 / location</th> </tr> </thead> <tbody> <tr> <td>Rejection vial collection bin (b) (4)</td> <td>(b) (4)</td> <td>(b) (4)</td> </tr> <tr> <td>(b) (4) bags containing measuring cylinders - (b) (4) bags</td> <td>(b) (4)</td> <td>(b) (4)</td> </tr> <tr> <td>Tyvek bag containing non linting mops - (b) (4) bags</td> <td>(b) (4)</td> <td>(b) (4)</td> </tr> <tr> <td>(b) (4) - (b) (4) each</td> <td>(b) (4)</td> <td>(b) (4) unknown if (b) (4) or other (b) (4) locales</td> </tr> <tr> <td>Packs of sterile (b) (4) bags - 1 each (b) (4) tubes - (b) (4) each</td> <td>(b) (4)</td> <td>(b) (4) each - (b) (4) each in (b) (4)</td> </tr> <tr> <td>Media plates - (b) (4) each</td> <td>(b) (4)</td> <td>(b) (4) each - (b) (4)</td> </tr> </tbody> </table>			Brief description	FTAPRPQP366-00; 05/05/2016 / location	VALRP-FT-07-000118; 27/03/2019 / location	Rejection vial collection bin (b) (4)	(b) (4)	(b) (4)	(b) (4) bags containing measuring cylinders - (b) (4) bags	(b) (4)	(b) (4)	Tyvek bag containing non linting mops - (b) (4) bags	(b) (4)	(b) (4)	(b) (4) - (b) (4) each	(b) (4)	(b) (4) unknown if (b) (4) or other (b) (4) locales	Packs of sterile (b) (4) bags - 1 each (b) (4) tubes - (b) (4) each	(b) (4)	(b) (4) each - (b) (4) each in (b) (4)	Media plates - (b) (4) each	(b) (4)	(b) (4) each - (b) (4)
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Contact plates - (b) (4) each	(b) (4)	(b) (4) each - (b) (4)							
<p>In addition:</p> <p>a. There are no explicit details to describe the specific placement of the various items and equipment parts that are placed inside the (b) (4) during the 05/05/16 initial performance qualification. And, there is no manner with which the current 27/03/2019 load configuration can be compared to the original 2016 validated load configuration in support of the (b) (4) process. The Team Leader MSAT and Quality Assurance Team Leader Manufacturing & MSAT (b) (4) Team member confirmed there are no diagrams or photographs that assist to illustrate the (b) (4) load configuration;</p> <p>b. The (b) (4) Cycle Development for (b) (4) protocol dated 12/05/16 objective include but not limited to the "...develop parametric (b) (4) cycle parameters from a series of progressive studies" and "to qualify the developed cycle through biological indicator (BI) challenges." The acceptance criteria for the BI challenge consists of placement "where the CI's took the longest time to change", "where the temperature were both highest and lowest", "placed (b) (4) However, there were no other considerations with respect to determining or evaluating other possible (b) (4) locations to be (b) (4) via (b) (4); the current BI challenge locations may not represent the (b) (4) challenge locations and there may be other challenge locations that the firm may not be knowledgeable of with respect to where the (b) (4) did not contact, and/or the (b) (4) was less than adequate to penetrate the (b) (4) interior surfaces;</p>									
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<p>c. The "Assessment of Critical Locations Inside the (b) (4) During (b) (4) (b) (4) ' document #FT7MSATJST0041 dated 27/11/2018 objective is "To perform a thorough review of Biological indicator monitoring locations in (b) (4) and finding the additional possible worst case locations inside the (b) (4) The assessment describes the "BI monitoring locations has been rationalized based on below critical aspects" for example, (b) (4) as this could be the worst case and should be checked for distribution and shall be ensured that killing is occurring at this location." The Team Leader MSAT confirmed there is record to document the (b) (4) of the selected worst case locations in support of the (b) (4); and,</p> <p>The "Cleaning of Continuous Particle Monitoring System" document #SOP-FT07-PR-0107, dated 16/10/2018 establishes the cleaning procedure that includes, for example, to (b) (4) (b) (4) The (b) (4) of the (b) (4) (b) (4) is not subject to the (b) (4) via the (b) (4) validated process. There is no supporting data to document the manual cleaning with (b) (4) is comparable to the (b) (4) validated process.</p>			
<p>OBSERVATION 3</p> <p>Deviations from written production and process control procedures are not justified.</p> <p>Specifically,</p> <p>There is an "Incident Investigation Report" document #WI-DFTO-QA-0118 regarding the manufacture of (b) (4) Injection (b) (4) mg/vial B. No. (b) (4) in Line (b) (4). The incident consisted of a microbiological excursion dated 10/01/2019 had occurred at (b) (4) regarding (b) (4) L21SMG10 and L21SMG21 and at 15:43 from the (b) (4) (PR365A-1). For microbiological counts for (b) (4) L21SMG10 and L21SMG21 in Grade A area was TNTC and (b) (4) CFU, respectively. The</p>			
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<p>microbiological count in the (b) (4) was (b) (4) CFU/m³ (mold). The genus and species were identified as <i>Bacillus</i> species for (b) (4) L21SMG10 and <i>Sphingomonas paucimobilis</i> for the latter two locations. It was determined that the EM microbiological sampling swabs were not placed in the required configuration (i.e., individually placed (b) (4)), consequently they were not subject to (b) (4).</p> <p>In addition:</p> <p>d. There are several in-process control questionnaire checklists that require the In-Process Quality Assurance (IPQA) team to verify prior to commencing the aseptic fill operations. One of the questionnaire checklist is the "Check List for Review of Aseptic Operations, Practices in the Critical Area" document #FORM-DFTO-QA-0107 dated 03/08/2019. The checklist includes the following i.e., (b) (4) as per the validated (b) (4). The above observation document, despite the establishment of the IPQA checklist, there is a gap with the IPQA verification process;</p> <p>The "Operation of (b) (4) Integrity Tester (Skan Wireless GT) (Line (b) (4)), document #WI-FT07-PR-0202, dated 09/08/2019 establishes the visual verification process of the (b) (4) which includes a verification for (b) (4) rupture/puncture/pin hole) color change, cleanliness of (b) (4)". The visual verification is documented in the "Pre Check Points To Start (b) (4) Integrity Test (Line (b) (4))" Form-FT-07-PR-0298. The pre-checks are performed, however the Associate Director of Quality Assurance confirmed that QA does not review and approve the visual verification to assure that the requisite evaluation is performed and rightly obtained.</p>			
<p>OBSERVATION 4</p> <p>Aseptic processing areas are deficient regarding air supply that is filtered through high-efficiency particulate air filters under positive pressure.</p> <p>Specifically,</p>			
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<p>The "Performance Requalification Protocol of (b) (4) (b) (4) document #VALPR-FT07-000030 dated 27/03/2019 includes Non-Viable Particle (NVP) count monitoring. "The objective of this test is to verify that the concentration of airborne particles inside (b) (4) meet Grade A requirements." A "Rationale for the Selection of NVPC Location" establish, for example, the locations for (b) (4) includes (b) (4) (b) (4) the locations are near to (b) (4) the NVP (b) (4) is located before (b) (4) (b) (4) During routine aseptic filling operations, there are no NVP (b) (4) located between the (b) (4) and the (b) (4) The distance between the NVP (b) (4) near the (b) (4) In addition:</p> <p>a. Following the (b) (4) vial stoppering station the (b) (4) filled vials are automatically transferred to the (b) (4) via a conveyor system. There is no NVP monitoring performed during the transferring / conveying process of the (b) (4) vials to the (b) (4) and,</p> <p>b. There is no record to document that the (b) (4) filled vials are maintained in a Grade A (ISO-5) environment during the transferring process to the (b) (4) which precludes from substantiating that the Grade A environment is maintained to the requisite specification.</p> <p>The "Environmental Monitoring in Injectable of Block (b) (4) document #SOP-FT07-PR-0172, dated 02/11/2018 establish monitoring of NVP of critical area that include manufacturing room # (b) (4) The standard procedure defines an "In operation" state as, "...the conditions where the installation is functioning in the defined operating mode with the specified number of personnel working." The manufacturing room is a classified as Grade D during an "In operation" state. As established in the standard procedure, NVP monitoring is performed on a (b) (4) base. There is no document to describe the scientific rational that established the NVP monitoring (b) (4) frequency. In addition:</p>			
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<p>e. In 2018 and 2019 there were a total of (b) (4) patches of finished drug products manufactured in room # (b) (4) i.e. (b) (4) and (b) (4) batches, respectively. In 2018 and 2019 NVP monitoring of the manufacturing room was performed (b) (4) times, respectively;</p> <p>f. NVP measurements are taken from (b) (4) separate locations in manufacturing room (b) (4) (Grade D during in operation conditions). NVP sampling locations include (b) (4) of manufacturing room (b) (4) and from a (b) (4) between the (b) (4). The Associate Director of Quality Assurance confirmed there is no personnel activities that occur at (b) (4) of the (b) (4) sample locations of the room; and,</p> <p>g. The initial (b) (4) (b) (4) (b) (4) that is used to transfer the bulk solution to the (b) (4) and (b) (4) (b) (4) that is used to sterilize the finished drug product is manually connected next to the (b) (4) within a Grade D environment. As previously noted in the preceding observations, NVP monitoring locations do not include the personnel manual activities that occur within the area where the initial (b) (4) is connected.</p>			
<p>OBSERVATION 5</p> <p>Equipment for adequate control over air pressure, micro-organisms, dust, humidity and temperature is not provided when appropriate for the manufacture, processing, packing or holding of a drug product.</p> <p>Specifically,</p> <p>The "Air Flow Visualization for Clean Room / Zones" document #SOP-DFTO-QA-0041, dated 23 May 2019 defines Unidirectional flow as follows, "An airflow moving in a single direction, in a robust and uniform manner,</p>			
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<p>and at sufficient speed to reproducibly sweep particles away from the critical processing or testing area." In addition, the standard procedure establishes "Airflow should be unidirectional in nature and should show uniform flow patterns with minimum turbulence or eddies. Any turbulence or eddies should be justified with environmental monitoring studies or other justifications." Furthermore, the "study is to evaluate the impact of all the production interventions performed by human, machine during routine operation on air flow pattern demonstrated at operation." Despite the establishment of the standard procedure, the air flow pattern evaluations document a number of instances where the airflow does not demonstrate a "unidirectional" uniform manner of movement and/or the evaluations lack the ability to demonstrate the unidirectional airflow is appropriately achieved and maintained during the dynamic operations. This ultimately prevents the ability to "evaluate the impact of all the production interventions..." upon the "air flow pattern demonstrated at operation." Note: the summary information provided in the following table is not intended to be an all-inclusive and/or exhaustive list of concerns, for example;</p> <div style="background-color: #cccccc; width: 100%; height: 250px; margin-top: 10px; position: relative;"> (b) (4) </div>					
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**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT ADDRESS AND PHONE NUMBER

12420 Parklawn Drive, Room 2032
Rockville, MD 20857

DATE(S) OF INSPECTION

8/12/2019-8/20/2019*

FEI NUMBER

3006549835

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

Sanjay Sharma, Executive Vice President, Global Manufacturing Operations

FIRM NAME

Dr. Reddy's Laboratories Ltd.

STREET ADDRESS

P1 - P9 Vsez, Q1 - Q5 Phase Iii

CITY, STATE, ZIP CODE, COUNTRY

Duvvada, Andhra Pradesh, 530046 India

TYPE ESTABLISHMENT INSPECTED

Manufacturer

(b) (4)



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OF THIS PAGE**

EMPLOYEE(S) SIGNATURE

Bijoy Panicker, Investigator
Thomas J Arista, National Expert

Bijoy Panicker
Investigator
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Date Signed: 08-20-2019 07:38:49

X

DATE ISSUED

8/20/2019

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

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EMPLOYEE(S) SIGNATURE

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DATE ISSUED

8/20/2019

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION			
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CITY, STATE, ZIP CODE, COUNTRY Duvvada, Andhra Pradesh, 530046 India		TYPE ESTABLISHMENT INSPECTED Manufacturer	
<div style="background-color: #cccccc; height: 300px; width: 100%; position: relative;"> (b) (4) </div>			
<p>In addition:</p> <p>The "Handling of Alarms in EMS" document #SOP-FT-07-EN-0022, dated 16/04/2019 defines alarms and critical alarms as follows; an Alarm is an "...excursion in environmental conditions like Temperature, Relative Humidity and Room Differential Pressure" and a critical alarm as an "...excursion in environmental condition due to which there is an impact on system/product under manufacturing/holding." The standard procedure establishes "During excursion in Temperature, RH, POP UP will be displayed through EMS after a delay of ^{(b) (4)} from the time of excursion." "If same type of alarm for same area occurs more than ^{(b) (4)} for duration of</p>			
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<p>less than (b) (4) then incident shall be raised by User department and investigation shall be carried out. Only alarm which are crossed (b) (4) shall be considered in the report." When asked, if the above time lines have ever occurred, the Resource Manager of Engineering explained there were 27 and 3 separate occasion in 2018 and 2019, respectively, when there was a delay of >10 minutes. It was explained the occurrences were the exception rather than the rule. The time delay and noted considerations are not realistic limits and/or do they accurately reflect the EMS historical data.</p>			
<p>OBSERVATION 6</p> <p>Each lot of a component, drug product container and closure that is liable to microbiological contamination that is objectionable in view of its intended use is not subjected to microbiological tests before use.</p> <p>Specifically,</p> <p>The "Inspection of Microbial Growth" document #SOP-FT07-QC-0069, dated 27/08/2018 establishes "After an appropriate incubation period, remove the petri plates from the incubator and examine the plates for colonial growth using colony counter." On 12/08/2019 we observed an analyst perform a routine settle plate evaluation, which ultimately documented 3 bacteria and 4 fungi. We counted 4 bacteria and 5 fungi. There appeared to be one microorganisms, with mold like morphological growth, that was growing adjacent to another microorganism and a second contaminant (i.e., bacteria) that appeared to be growing over a separate microorganism. The microorganisms were not included with the colony forming unit (CFU) microbial count. In addition:</p> <p style="margin-left: 40px;">h. The standard procedure describes to "Recognize the difference between two or more colonies that have grown into contact with each other", which is not dissimilar to the concern noted above. However, when asked if this was ever encountered, documented and/or recorded in a</p>			
SEE REVERSE OF THIS PAGE		<div style="display: flex; justify-content: space-between;"> <div> <p>EMPLOYEE(S) SIGNATURE</p> <p>Bijoy Panicker, Investigator</p> <p>Thomas J Arista, National Expert</p> </div> <div style="border: 1px solid black; padding: 5px; text-align: center;"> <p style="font-size: small;">Bijoy Panicker Investigator Signed By: 2001908716 Date Signed: 08-20-2019 07:39:49</p> <p style="font-size: 2em; margin-top: 10px;">X</p> </div> <div> <p>DATE ISSUED</p> <p>8/20/2019</p> </div> </div>	

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<p>microbiological record, it was confirmed that this has never been captured;</p> <p>i. The "Microbiological Trend Analysis" document #SOP-FT-07-QC-0045, dated 23/04/2019 defines "Trend analysis is the science and (or) a mathematical technique of data collected from routine microbial monitoring and is related to time, shift, facility etc. studying changes in utility behavior, environmental data. This information is periodically evaluated to establish the status or pattern of that program to ascertain whether it is under adequate control." In addition, regarding a review of negative trends, the standard procedure establishes (b) (4)</p> <p>(b) (4) Mindful of the microbiological trend analysis, when asked if the above alert level excursions have ever occurred, the Resource Leader of Quality Control, confirmed they have not experienced the noted alert level considerations;</p> <p>j. The microbial contaminants and CFUs observed on the (b) (4) settle plates by the Analyst are documented in the microbiological records. It was explained that if the morphology of the microbial contaminant is similar to the color photographs of microorganisms in the "Album of Environmental Isolates" the contaminant would not be identified or further characterized to the genus and species level. It was described that if the colony morphology appears to be new then they would characterize to the genus and species level. When asked if there is a record to document the number of microorganisms that were discarded without further characterization or identified, the Team Leader of Quality Control confirmed that they did not have a record. The microbiology department and the Quality Unit does not know how many microbial contaminants have been discarded without further microbiological characterization;</p> <p>Regarding EM sampling in the (b) (4) Grade A area, we observed the manual operations and setup of the (b) (4) and the requisite manual connections of the (b) (4) product transfer hoses; the manual operations</p>			
SEE REVERSE OF THIS PAGE		<div style="display: flex; justify-content: space-between;"> <div style="width: 60%;"> EMPLOYEE(S) SIGNATURE Bijoy Panicker, Investigator Thomas J Arista, National Expert </div> <div style="width: 35%; text-align: right;"> DATE ISSUED 8/20/2019 <small>Bijoy Panicker Investigator Signed By: 2001956718 Date Signed: 08-23-2019 07:35:49</small> </div> </div>	

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<p>approximately (b) (4) accomplish. During this period of time there were no EM microbiological sampling performed. The Microbiologist confirmed there is no active or passive EM sampling performed during this period of time.</p> <p>OBSERVATION 7 Control procedures are not established which validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.</p> <p>Specifically,</p> <p>SOP-GLOB-QA-0043, version 3, entitled, "Stability Management of Drug Product" in section 3.2 states "QA to initiate the stability studies for commercial and validation batches, approval of protocol, compilation data and to ensure that the stability study is executed as per the approved protocol". The firm has performed a process validation study in 2018 (Protocol # VALPR-FT07-000044, Report # VALRP-FT07-000042) for (b) (4) Injection (b) (4) ng/vial, and none of the batches from this process validation study was placed under stability testing, and there is no written justification for not placing the validation batches under stability.</p> <p>OBSERVATION 8 There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed.</p> <p>Specifically,</p> <p>The OOS investigations (310016783, batch # (b) (4) 310013810, batch # (b) (4) 310013920, batch # (b) (4) attribute the OOS results obtained for the assay of (b) (4) Injection (b) (4) ng/vial, to the presence</p>			
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(b) (4) observed during the (b) (4) in-process check as one of the probable root causes, although the final in-process sample from the (b) (4) was clear and did not contain any API particles. In addition, the OOS investigations (#s 310013810 and 310013920) attribute the OOS results to the malfunctioning of (b) (4) that many have failed to reject the low fill vials as one of the probable root causes, however, the (b) (4) unit was not investigated for any malfunction during these investigations, and the investigation reports in page-10 state "Review of (b) (4) Sample [weight basis] results (b) (4) To ensure the consistency of dosage unit, the finished product sample for both batches was verified and no discrepancy was observed".

***DATES OF INSPECTION**

8/12/2019(Mon), 8/13/2019(Tue), 8/14/2019(Wed), 8/16/2019(Fri), 8/17/2019(Sat), 8/19/2019(Mon), 8/20/2019(Tue)

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