

**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 3/19/2018-3/27/2018*
	FEI NUMBER 3006370524

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Dr. Adil D. Billimoria, President-Quality & Compliance

FIRM NAME Alkem Laboratories Ltd	STREET ADDRESS 167 Mahatma Gandhi Udyog Nagar Road
CITY, STATE, ZIP CODE, COUNTRY Daman, Daman And Diu, 396210 India	TYPE ESTABLISHMENT INSPECTED Drug Manufacturer

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.

**DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:
OBSERVATION 1**

There is no quality control unit.

Specifically,

- A. Your Quality Unit confirmed an out-of-specification for assay testing on (b) (4) Tablets USP (b) (4) mg, Batch # (b) (4), and was signed by the Head of Quality Control and the Head of Quality Assurance on 08 November 2017. (b) (4) tablets of this product were distributed to the U.S., four (4) months prior to (b) (4) product testing release (24 July 2017). The Certificate of Analysis (COA) for this batch was approved on 13 November 2017. No Recalls were initiated.
- B. Your Quality Unit failed to track, trend, and investigate Invalid Analytical Results for system suitability. As of 20 March 2018, your firm had 259 system suitability failures since 1 January 2018. Your firm's QC Analyst Reviewer and QC Assistant Manager stated the previous logbook for January-Notification Record for Invalid Data, dated 11/12/17, was destroyed. An Investigation into these failures was not initiated and no corrective actions were taken to address these failures.

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In addition, your firm failed to maintain and retain logbooks that are not obsolete or outdated. For example, once completed your firm destroys logbooks from the following areas: (b) (4) Block Warehouse, Housekeeping (b) (4)-Block, (b) (4)-Block QC, (b) (4)-Block QA, (b) (4)-Block Manufacturing, (b) (4)-Block, QC, Warehouse, and Production-(b) (4) Block.

As recent as 2018, the destruction of logbook examples include, but are not limited to: Notification Record for Invalid Data, Line Clearance Checklist, Preventive Maintenance, Instrument Log books, training records, cleaning check lists.

- C. Your firm failed to prioritize in-process, stability, and finished product sample testing based on Quality. According to your firm's QC Manager, who is in charge of scheduling in-process and finished product sampling for QC analysis, scheduling priority is driven by the needs of your firm's Head of Production. For example, but not limited to, (b) (4) Tablets (b) (4) mg, Batch # (b) (4). According to your firm's Assistant Vice President of QC, this sample was pulled on 15 July 2017. However, this sample was not analyzed until 22 August 2017.
- D. Your firm's QC department deleted two-thousand one hundred one (2,101) files since 1 March 2018 on your network. These files names include, but are not limited to: OOS, OOT, Incidents, Method Verification Reports, chromatographs, calculations, and Stability Reports.

According to your Assistant Vice President of QC, your firm does not have any written procedures addressing the deletion of files from your firm's network. No investigations were initiated for the deletion of these files.

OBSERVATION 2

The quality control unit lacks the responsibility and authority to approve and reject all components, in process materials and drug products.

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THIS IS A REPEAT OBSERVATION

Specifically,

A. Your firm failed to conduct sample analysis in a timely manner for stability samples, in-process samples, and finished product samples. No FARS or recalls were initiated in the absence of timely results. For example, but are not limited to:

1. As of 23 March 2018, your firm had (b) (4) pending samples for analysis:
 - a. (b) (4) - Late and untested stability batches for (b) (4) °C/75%RH since January 2017.
 - b. (b) (4) -Reserve and Retain samples for February 2018
 - c. (b) (4) - Late and back logged In-process samples since January 2017
 - d. (b) (4) -Late and back logged stability samples for (b) (4) pending (b) (4)
 - e. (b) (4) -CQC (Central Quality Control/ (b) (4) Quality Control) back logged stability samples
 - f. (b) (4) - Distributed batches of US marketed products that are pending stability samples
 - g. (b) (4) - Finished Products since September 2017

2. In addition, commercial batch, (b) (4) Tablets (b) (4) mg Batch# (b) (4), was manufactured in November 2016. As of 19 March 2018, this batch is pending 2 month (2M) stability testing for storage condition 40 ±2 °C/ 75 ±5%RH. On (b) (4) (b) (4) tablets were dispatched to the US Market.

3. Other examples of the former were found for other products as follows:



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(b) (4)

B. A confirmed OOS, AM1/OOS/148/17, was found for (b) (4) mg tablets, Batch # (b) (4) (b) (4) tablets) and Batch # (b) (4) (b) (4) tablets) stability sample at 1M storage condition 40°C/75%RH for Related Substances. These batches were manufactured in April 2017 and put on stability, Time zero (T₀), on 19 June 2017. 1 month (1M) testing began on 16 November 2017 (3 months after T₀ and 7 months after manufacturing) and was not completed in the Laboratory Information Management System (LIMS) as of 26 March 2018. In addition, this batch is currently under investigation in your LIMS System. This batch was distributed on (b) (4) to the US Market.

1. Long term stability testing at 3 month (3M) Storage condition 25°C/60%RH for Batch # (b) (4) and Batch # (b) (4) were completed late for (b) (4) mg tablets. These batches were manufactured in April 2017 and put on stability T₀, 19 June 2017. 3 months (3M) testing was started on 06 November 2017 (3 months after T₀ and 7 months after manufacturing). Results of testing were not reviewed and approved until 21 March 2018. Also stability testing at 3M storage condition (b) (4) °C/75%RH for Batch # (b) (4), was completed late. 3M testing was started on 06 November 2017 (3 months after T₀ and 7 months after manufacturing). Results of testing were not reviewed and approved until 21 March 2018.

C. We observed inconsistent gaps in timeframes when samples were received into your Central Quality Control (CQC) and the dates when a stability (b) (4) occurred. During our assessment of the stability program, we found Stability Samples of Exhibit Batches and Manufactured Batches are documented as T₀, the date samples are (b) (4). Below are some examples:

Date of Receipt of Sample by Central	Product Name	Batch Number	Batch Release Date (T ₀)	Market Intended for
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Quality Control (CQC)				
March 09, 2017	(b) (4)		March 21, 2018	Commercial US
January 04, 2018		March 05, 2018	Exhibit US	
December 11, 2017		Date for T ₀ not Documented	Exhibit US	
December 11, 2017		Date for T ₀ not Documented	Exhibit US	
December 11, 2017		Date for T ₀ not Documented	Exhibit US	
February 13, 2018		Date for T ₀ not Documented	Commercial US	
March 01, 2018		March 14, 2018	Commercial US	
January 22, 2018		February 1, 2018	Commercial US	

D. In addition, on 24 March 2018, your firm's QC Manager reviewed and approved 130 samples (twice as many) pending in LIMS for stability samples, in-process samples, and finished product samples during his daily participation of this FDA inspection. Your QC Manager reported he

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spends approximately (b) (4) per (b) (4) (b) (4) per analysis packet; totaling approximately (b) (4) completed analytical reviews per (b) (4).

OBSERVATION 3

Laboratory controls do not include the establishment of scientifically sound and appropriate specifications, sampling plans and test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality and purity.

THIS IS A REPEAT OBSERVATION

Specifically,

- A. Integration parameters are not established to ensure impurity peaks are detected. Your Quality Unit failed to conduct an investigation where unknown peaks were observed due to inhibiting integration. Unknown peaks were observed in the following chromatographs where integration was inhibited. For example, but are not limited to:

During the (b) (4) test for (b) (4) by GC (ID: QC/260) sample set (b) (4), on 18 February 2017, we noted your firm inhibited integration in portions of the chromatograms where impurities may be present. Processing Method (b) (4); Method ID: 19672) was used to process the sample for (b) (4), Batch # (b) (4), as below:

Function	Start Time (min)	Stop time (min)
Inhibit Integration	(b) (4)	(b) (4)
Inhibit Integration		
Inhibit Integration		

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Inhibit Integration	(b) (4)	
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Your QC Head agreed that known or unknown impurities will not be identified even if they are present if integration of the peaks is inhibited for a particular time frame. Your firm manufactured (b) (4) batches of (b) (4) (b) (4) mg Capsules ((b) (4) count bottles) using (b) (4) USP, Batch # (b) (4); totaling the distribution of (b) (4) bottles to the US market. No Investigations were initiated.

B. Your firm produced (b) (4) batches of (b) (4) products and (b) (4) batches of (b) (4) in 2017. However, your firm conducts air samples (b) (4) to ensure cross-contamination of these products do not occur in the (b) (4) Block ((b) (4) products). This sampling plan frequency is not representative for the amount of (b) (4) and (b) (4) products manufactured at your firm.

OBSERVATION 4

The responsibilities and procedures applicable to the quality control unit are not fully followed.

THIS IS A REPEAT OBSERVATION

Specifically,

A. According to the spreadsheet used by your firm's Quality Assurance Department to track and trend (b) (4) data, your Quality Unit failed to follow your established written procedure for handling of Out of Specifications (OOS) and Out of Trends (OOT) results within the specified timeframe in 2017. For example, but not limited to the following:

1. One hundred eleven OOSs:

Analysis Conducted	# of OOS not completed
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	within specified timeframe
Assay	27
Blend uniformity	2
Physical Description	2
Dissolution	20
Organic Impurity	13
Particle size	3
Related substance	34
TOC	2
Water content	6
Total # of OOS \geq (b) (4)	111

2. Twenty-three OOTs:

Analysis Conducted	# of OOT not completed within specified timeframe
Assay	8
Dissolution	12
UOD	3
Total # of OOT \geq (b) (4)	23

B. Your firm failed to log samples in the Central Laboratory per your written procedure, "AC/QA/012, Sampling of In-Process, Semi-Finished and Finished Product, Effective Date: 28/11/17". We observed samples in the Sample Storage area lacking the following required information on a Sample Analysis Sheet, Product Name, Batch No., Manufacturing Date, Expiration Date, Stage, Test, Sampled by, and Date of sampling.

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OBSERVATION 5

The written stability testing program is not followed.

THIS IS A REPEAT OBSERVATION

Specifically,

A. Your firm failed to initiate and approve a change control authorizing the discontinuation of stability condition (b)(4) °C/75%RH. In the absence of an approved change control, testing for this condition was halted resulting in a back log of (b)(4) samples since January 2017. However, according to your firm's stability protocols, these conditions are to be tested from (b)(4). The following products were distributed to the US Market, including but are not limited to:

- (b)(4) Tablets USP (b)(4) mg
- (b)(4) Tablets USP (b)(4) mg
- (b)(4) Capsules USP (b)(4) mg

B. On 23 March 2018, we observed, 45 comingled boxes of pending and analyzed stability samples, stored in the "RH Room" without temperature control or monitoring. There is no log book or tracking of these samples and their location. For example, (b)(4) Capsules USP (b)(4) mg, Batch # (b)(4), was found in the "RH Room" pending for 25°C/60%RH for 3M. The batch was manufactured in February 2017. Testing was initiated on 27 October 2017 and is listed in LIMS as "Under Test".

OBSERVATION 6

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Laboratory records do not include complete data derived from all tests, examinations and assay necessary to assure compliance with established specifications and standards. Electronic records are used, but they do not meet requirements to ensure that they are trustworthy, reliable and generally equivalent to paper records.

*****THIS IS A REPEAT OBSERVATION*****

Specifically, your firm failed to assure the accuracy and reliability for data recorded which are derived or entered using non-validated and unprotected excel spreadsheet that are not managed and controlled to ensure unauthorized changes do not occur per your firm's written procedures. No Deviations were recorded and no investigations were initiated.

- A. During the inspection, we observed two (2) different QC lab analyst demonstrate the ability to change calculation functions in the excel spreadsheet used for finished product testing for the following:
1. On 22 March 2018, we observed your QC Analyst use an uncontrolled excel spreadsheet to calculate the Average, Standard Deviation, and %RSD values for (b)(4) Tablets, Batch # (b)(4), for (b)(4) product release testing. The use of this spreadsheet is not mentioned in any written procedure when conducting (b)(4) Product Release Testing. In addition, this excel spreadsheet is not saved or printed. Therefore, the QC Reviewer is unable to verify these calculations are correct and the correct formula was used.
 2. On 23 March 2018, we observed the QC Reviewer use an uncontrolled excel spreadsheet to verify the potency of (b)(4) working standard during the Analytical Worksheet review for (b)(4) Tablets, Batch # (b)(4). The use of this spreadsheet is not mentioned in any written procedure when conducting Analytical Report reviews.
- B. On 19 March 2018, we observed your QC Manager's use an excel spreadsheet to track quality

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functions, such as stability samples. This document is not maintained through document control and there is no protection from data manipulation, overwriting, erasing of data, or audit trails.

C. On 19 March 2018, during the inspection, we observed two (2) (b)(4) employees use an uncontrolled spreadsheet to calculate due dates used during the manufacturing and packaging of drug products.

1. For example, but not limited to, the (b)(4) stage is to be completed within (b)(4) initiating the compressed tablet stage. However, the dates used to calculate these timeframes have not been validated. In addition, this spreadsheet was not password protected.

OBSERVATION 7

Established laboratory control mechanisms are not documented at the time of performance.

Specifically,

- A. During our inspection of the QC laboratory on 19 March 2018, we observed your QC Analyst entering data electronically into an excel spreadsheet, in the absence of raw data. This same data was also entered into the 9M Stability Study Logbook for (b)(4) Tablets (b)(4) mg, Batch # (b)(4), manufactured April 2017 (2 months late).
- B. On 23 March 2018, we observed a QC Executive reviewing an OOS/OOT investigation for (b)(4) (b)(4) mg Tablets, Batch # (b)(4), where the stability and scoring study were OOT. The employee had a pen for signing for the review, but no checklist, paper, or workstation for recording errors. In the event of an error the employee reported, they would notify the Section Head and Analyst, but not document it.
- C. On 23 March 2018, we observed an Analytical Worksheet for Raw Materials for (b)(4), Batch # (b)(4), did not contain any data for the UV conducted on 13 March 2018. The QC Analyst that conducted this analysis stated he did not document these

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recordings on the Analytical Worksheet because his data packet was removed by other Analysts without his knowledge.

D. On 22 March 2018, we observed a manufacturing employee entering tablets weights non-contemporaneously during the manufacturing of (b) (4) Tablets USP (b) (4) mg, Batch # (b) (4) in the (b) (4) Block building.

OBSERVATION 8

The in-process control procedures were deficient in that it did not include an examination of tablet and capsule weight variation.

Specifically, your firm failed to implement checks for tablets, such as: tablet weight, before, during, and after packaging for weight, etc. for rejection during manufacturing to prevent product mix-ups. The lack of this parameter caused product mix-ups where a (b) (4) mg tablet of (b) (4) was found by a customer in a (b) (4) mg bottle of tablets for (b) (4) mg, (b) (4) ct., Batch # (b) (4). Furthermore, your investigation failed to evaluate patient impact, as, the report does not address risk to the patient that needed the higher dose, but may have received a much lower dose than needed.

OBSERVATION 9

All processing lines and major equipment used during the production of a batch of drug product is not properly identified at all times to indicate the phase of processing of the batch. Electronic signatures based on are used, but they do not meet the requirements of 21 CFR Part 11.

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A. Your firm uses Programmable Logic Controllers (PLC) equipment during the manufacturing of drug products, which require a password and username to operate. Your firm uses the following manufacturing PLC equipment that are not password protected:

Location	Number of Equipment with PLC without Password Protection
(b) (4) (b) (4) -Block	322
(b) (4) (b) (4) -Block	6
(b) (4) (b) (4) -Block	95
Grand Total	423

B. In addition, on 22 March 2018, we observed a manufacturing employee operating the (b) (4), Equipment ID AB/TM/23, in (b) (4) -Block. This equipment has PLC capabilities with alarms. However, your firm does not assess alarms to verify if the alarms affected manufacturing for the following equipment:

Location	Number of Equipment with that does not utilize alarms
(b) (4) (b) (4) -Block	63
(b) (4) (b) (4) -Block	19
(b) (4) (b) (4) -Block	14
Grand Total	96

OBSERVATION 10

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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 3/19/2018-3/27/2018*
	FEI NUMBER 3006370524

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Dr. Adil D. Billimoria, President-Quality & Compliance

FIRM NAME Alkem Laboratories Ltd	STREET ADDRESS 167 Mahatma Gandhi Udyog Nagar Road
CITY, STATE, ZIP CODE, COUNTRY Daman, Daman And Diu, 396210 India	TYPE ESTABLISHMENT INSPECTED Drug Manufacturer

Equipment and utensils are not at appropriate intervals to prevent that would alter the safety, identity, strength, quality or purity of the drug product.

Specifically, your QC Analyst failed to appropriately clean glassware used in assay testing for (b) (4), Batch # (b) (4) and Batch # (b) (4). On 24 March 2018, we observed your QC Analyst use the same (b) (4) on these two batches of (b) (4), without cleaning. According to your Assistant General Manager QC, glassware is to be cleaned (b) (4) batch in accordance to your firm's written procedure, AC/QC/139, "Cleaning of Laboratory Glassware". In addition, your firm has not conducted a cleaning validation for your laboratory equipment, which is non-dedicated.

OBSERVATION 11

(b) (4) drug products were not tested for the presence of (b) (4), when a reasonable possibility existed that a (b) (4) drug product has been exposed to a cross-contamination with (b) (4).

Specifically, on 21 March 2018, we observed unsealed bottles and loose capsules of (b) (4) in the Sample Storage Room in non-dedicated areas the General Laboratory on the (b) (4) floor where other (b) (4) products are also stored. Your firm's QC Manager explained the bottles of (b) (4) are opened in order to obtain a physical description. However, this analysis is conducted in an uncontrolled environment in the Central QC Laboratory, where high traffic volume occurs for sample analysis of all (b) (4) products.

The unsealed (b) (4) we observed in the Sample Storage Room include, but are not limited to the following:

Drug Name	Batch Number
(b) (4) Capsules USP (b) (4) mg	(b) (4)

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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 3/19/2018-3/27/2018*
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FIRM NAME Alkem Laboratories Ltd	STREET ADDRESS 167 Mahatma Gandhi Udyog Nagar Road
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CITY, STATE, ZIP CODE, COUNTRY Daman, Daman And Diu, 396210 India	TYPE ESTABLISHMENT INSPECTED Drug Manufacturer
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(b) (4)	Capsules	(b) (4) mg	(b) (4)
(b) (4)	Capsules	(b) (4) mg	(b) (4)
(b) (4)	Suspension USP	(b) (4) mg / (b) (4) mL	(b) (4)
(b) (4)	Suspension USP	(b) (4) mg / (b) (4) mL	(b) (4)
(b) (4)	Capsules USP	(b) (4) mg	(b) (4)
(b) (4)	Capsules USP	(b) (4) mg	(b) (4)
(b) (4)	Suspension USP	(b) (4) mg / (b) (4) mL	(b) (4)
(b) (4)	Suspension	(b) (4) mg / (b) (4) mL	(b) (4)

OBSERVATION 12

Buildings used in the manufacture, processing, packing or holding of drug products are not maintained in a clean and sanitary condition and free of infestation by rodents, birds insects, and other vermin.

Specifically,

- A. On 22 March 2018, your firm did not identify and investigate fungal growth on the walls of the (b) (4) area as identified in work order dated 28 August 2016. From 01 July 2016 – 27 September 2016, according to General Manger of Quality Assurance, (b) (4) batches of drug products were manufactured using raw materials (e.g. API, excipients).

We observed document titled “Compliance Charter-2016 Block (b) (4)” on a computer station in the manufacturing area. That document states “Walls of (b) (4) area became Spotted, dirty and observed with fungal growth.”

- B. In addition, your firm failed to establish, implement, and monitor a Pest Control program and procedures inside Quality Control areas, such as, the stability laboratory, where samples are kept, and the Central and (b) (4) laboratories where all samples are stored and analyzed. Flying

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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 3/19/2018-3/27/2018*
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CITY, STATE, ZIP CODE, COUNTRY Daman, Daman And Diu, 396210 India	TYPE ESTABLISHMENT INSPECTED Drug Manufacturer

insects, including, but not limited to, mosquitos and gnats, were found too numerous to count in the aforementioned areas.

OBSERVATION 13

Employees engaged in the manufacture and processing of a drug product lack the training and experience required to perform their assigned functions.

Specifically, your firm uses an electronic training management system, Nichelon5, to document the training of your employees, which was accessed on 27 March 2018. Your system documents an employee that was observed using an uncontrolled, non-validated spreadsheet to calculate % RSD, did not attend Training on Good Documentation Practice (GDP) and Good Laboratory Practices (GLP) conducted by your firm on 17 January 2018. According to your firm's written procedure, CQA\0031, "Training Management System", cGMP refresher training is to be completed (b) (4); missed trainings are to be completed within (b) (4).

***DATES OF INSPECTION**

3/19/2018(Mon), 3/20/2018(Tue), 3/21/2018(Wed), 3/22/2018(Thu), 3/23/2018(Fri), 3/24/2018(Sat), 3/26/2018(Mon), 3/27/2018(Tue)

X Kellia N Hicks
Investigator
Signed By: Kellia N. Hicks -S
Date Signed: 03-27-2018 17:18:55

X Dipesh K Shah
Office of International Programs Employee
Signed By: 1300184065
Date Signed: 03-27-2018 17:20:47

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