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

| DISTRICT ADDRESS AND PHONE NUMBER | DATE(S) OF INSPECTION |
|---|---|
| ORA OPQO HQ, Room #2032<br>12420 Parklawn Drive, Rockville, MD 20857<br>ORAPHARMInternational483responses@fda.hhs.gov<br><br>Industry Information: www.fda.gov/oc/industry | 09/19/2019-09/27/2019*<br>FEI NUMBER<br>3007373532 |

| NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED | |
|---|---|
| Mr. Madan Mohan Reddy, Director | |
| FIRM NAME<br>Aurobindo Pharma Limited | STREET ADDRESS<br>Unit VII, Formulation Plant, Plot S-1, Survey 411, 425, 434-435, 458, TSIIC, Green Industrial Park |
| CITY, STATE, ZIP CODE, COUNTRY<br>Polepally, Mahaboob Nagar, Telangana, 509302, India | TYPE ESTABLISHMENT INSPECTED<br>Finished Product 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 a failure to thoroughly review any unexplained discrepancy and the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.**

Specifically, your firm's investigations were found to be deficient in that the Out of Specification (OOS) results have been invalidated for various tests without identifying scientifically sound and justifiable root causes. Human errors and instruments error have been attributed as major potential root causes and passing retest results have been reported. Our review of your OOS Investigations during the period beginning January 2017 until September 2019 revealed the following for U.S. marketed products:

| Category | Total OOS | Total Invalided | % Invalidated* |
|---|---|---|---|
| Raw Material | 112 | 102 | 91% |
| In-Process | 85 | 65 | 76% |
| Hold Time Study | 16 | 15 | 94% |
| Process Validation | 42 | 18 | 43% |
| Finished Product Testing | 172 | 112 | 65% |
| Finished Product Stability | 72** | 72 | 100% |

*rounded, **excludes exhibit batches

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Examples include, but are not limited to, the following investigations:

**(A)** OOS Investigation FUSTOOS190024 for (b) (4) Tablets (b) (4) mg batches (b) (4) was initiated on 04/29/2019 to investigate Assay failures during the 3M stability testing (25°C/ 60%RH). The investigation suspected incorrect sonication time as the probable root cause. Based on this assumption, 5 hypothesis studies were initiated using (b) (4) mins sonication without intermittent shaking, and the last hypothesis study for (b) (4) mins sonication with intermittent shaking (i.e. as per STP instructions). The initial failing results and hypothesis results are as follows:

| Batch No. | Assay (%) [Specification: (b) (4) to (b) (4) %] |
|---|---|
| (b) (4) | (b) (4) |
| **Hypothesis Study** | |
| Hypotheis-1A, (b) (4) mins | (b) (4) |
| Hypothesis-1B, mins | |
| Hypotheis-1C, mins | |
| Hypothesis-1D, mins | |
| Hypothesis-2, (b) (4) mins (per STP) | |

We were unable to determine if the hypothesis studies were actually conducted. Specifically, our review indicated that all associated analytical worksheets for the purported hypothesis studies have the same sonication time of (b) (4) minutes. The analytical worksheets were reviewed and approved by the QC and QA personnel. We were unable to ascertain how the low Assay values were obtained for hypothesis studies

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1A and 1B when associated records show that they were sonicated for (b) (4) minutes. The results from the hypothesis studies were utilized to conclude that the initial failing Assay results were due to inadequate sonication of samples. All four impacted batches covered in this investigation are currently in the U.S. market.

**(B)** OOS Investigation FU7STOOS190023 for (b) (4) USP (b) (4) mg (b) (4) (b) (4) mg (b) (4) mg (b) (4) was initiated on 04/25/2019 to investigate the OOS results (b) (4) %, (b) (4) %, (b) (4) % for the (b) (4) *Related Compound* (b) (4) against a specification limit of NMT (b) (4) % w/w) found during Related Substance testing at the 9-month time point (25ºC/ 60%RH, batch # (b) (4) ). The investigation concluded human error caused by the use of a contaminated beaker with (b) (4) During the extended laboratory investigation, two hypothesis studies were conducted; experiment 1 using an intentionally contaminated beaker with (b) (4) , and experiment 2 as per STP requirement. Experiment 1 yielded (b) (4) % for the (b) (4) *Related Compound* (b) (4) whereas, experiment 2 yielded (b) (4) % for the same impurity. However, no pH measurement of the original sample solution was considered to confirm the presence of (b) (4) in the sample. The firm also referenced the product's forced degradation study which was conducted using (b) (4) that yielded a value of (b) (4) % for the same impurity. It is unclear how the firm utilized the (b) (4) degradation study performed with (b) (4) (b) (4) to draw an equivalent conclusion with an unknown concentration of (b) (4) (b) (4) during the hypothesis study.

**(C)** OOS Investigation FU7STOOS190044 for (b) (4) Tablets (b) (4) mg, batch #s (b) (4) was initiated on 07/29/2019 to investigate the OOS results found during the 3-month stability testing (25ºC/ 60%RH). The OOS results were obtained during the Organic Impurity testing (by HPLC). Specifically, (b) (4) yielded OOS results of (b) (4) % (w/w) and (b) (4) % (w/w) against a specification limit of NMT (b) (4) % (w/w) for the (b) (4) impurity. The subsequent investigation concluded that the root cause is due to analyst error (i.e. sample sonication at the incorrect temperature of 40ºC vs. the STP sonication

temperature requirement of 5±3°C). The hypothesis studies that were conducted to substantiate the root cause merely suggested that the impurity increases by (b) (4) % (w/w) for the (b) (4) impurity when sample is sonicated at 40°C. The investigation failed to conclusively prove that the sonication at 40°C is the root cause of significantly higher levels (i.e. (b) (4) % and (b) (4) %) obtained during the initial testing. The initial results were invalidated and passing re-test results were reported as the valid result of record. Batches (b) (4) are both commercially distributed in the U.S. market with an expiry date of 01/31/2021.

Product Complaint Investigations:

**(D)** Several of your complaint investigations of broken tablets or capsules since 2017 conclude that the origin of the defect was obtained after the product left your manufacturing facility. However, upon the review of the complaint investigation and the packaging batch records pertaining to the complaints, it was observed that all the product rejects were re-inspected and repackaged after visual inspection. Broken or defective units (tablets/capsules) are part of the rejection criteria on the packaging lines. For example:

1. Complaint APL-7-2018-PC-1-54327337 was received on 10/16/2018 because the customer found several bottles containing broken capsules of (b) (4) Capsules USP (b) (4) mg, batch # (b) (4) Complaint investigation APL-FU7-2018-USA-PCM-00375 was opened by the firm on 17/10/2018. The packaging batch record for this lot has documented that approximately (b) (4) capsules were rejected during initial primary packaging. After visual inspection of the rejected capsules it was found that all (b) (4) capsules were good capsules and were repackaged (no broken capsules were noted). The details of this visual inspection were not documented such as how it was performed.

2. Complaint PC2019-0672 was received on 07/22/2019 because the customer found 27 broken tablets throughout (b) (4) bottles of (b) (4) Tablets USP (b) (4) mg, batch # (b) (4)

Complaint investigation APL-FU7-2019-USA-PCM-00728 was opened by the firm on 07/24/2019. The packaging batch record for this lot has documented that approximately (b) (4) tablets were rejected during initial primary packaging. After visual inspection of the rejected tablets it was found that all (b) (4) tablets were good tablets and were repackaged (no broken tablets were noted). The details of this visual inspection were not documented such as how it was performed.

3. Complaint PC2018-0010 was received on 01/16/2018 because the customer found 42 broken tablets throughout (b) (4) bottles of (b) (4) Tablets USP (b) (4) mg, batch #(b) (4) Complaint Investigation CU02018-U07 was opened by the firm on 01/17/2018. The packaging batch record for this lot has documented that approximately (b) (4) tablets were rejected during initial primary packaging. After visual inspection of the rejected tablets it was found that all (b) (4) tablets were good tablets and were repackaged (no broken tablets were noted). The details of this visual inspection were not documented such as how it was performed.

4. Complaint PC2018-0326 was received on 08/13/2018 because the customer found one bottle with 32 broken tablets of (b) (4) Tablets USP (b) (4) mg, batch # (b) (4) Complaint investigation APL-FU7-2018-USA-PCM-00257 was opened by the firm on 16/08/2018. The packaging batch record for this lot has documented that approximately (b) (4) tablets were rejected during initial primary packaging. After visual inspection of the rejected tablets it was found that all (b) (4) tablets were good tablets and were repackaged (no broken tablets were noted). The details of this visual inspection were not documented such as how it was performed.

5. Complaint PC2018-0338 was received on 08/16/2018 because the customer found a broken tablet of (b) (4) Tablets USP (b) (4) mg, batch (b) (4) Complaint investigation APL-FU7-2019-USA-PCM-00261 was opened by the firm on

08/17/2018. The packaging batch record for this lot has documented that approximately (b) (4) tablets were rejected during initial primary packaging. After visual inspection of the rejected tablets it was found that all (b) (4) tablets were good tablets and were repackaged (no broken tablets were noted). The details of this visual inspection were not documented such as how it was performed.

**(E)** Product complaint Number APL-FU7-2019-USA-00068 for (b) (4) Tablets USP (b) (4) batch (b) (4) was initiated following a complaint received on 01/23/2019. The complaint reported from this U.S. distributed batch was for an unknown discolored (i.e. greyish) material embedded in the tablet. The investigation concluded that the greyish foreign material could be due to '*processing of hard remnants settled at the bottom of*' the (b) (4) equipment utilized during batch manufacturing. Additionally, UV spectrum of the purported complaint sample (b) (4) mg) was generated and compared with a (b) (4) standard solution (b) (4) mg) using an Assay method. Deficiencies with the investigation include, but are not limited to:

- Failure to investigate the root cause of greyish discoloration. The finished product is a (b) (4) (b) (4) tablet.
- Failure to describe in the UV analysis work sheet if the sample prepared representing the complaint sample of (b) (4) mg included the greyish unknown material from the returned complaint sample. This is not specifically described in the work sheet. Additionally, the UV spectrum only indicates the presence of (b) (4) in the purported complaint sample that was analyzed. However, there is no evidence provided to conclusively substantiate that the greyish material is free of other potential degradants. No other physiochemical analysis was considered to positively identify the structure/composition of the greyish foreign material.
- The retain samples from this batch were visually checked as part of the complaint investigation. The samples were not checked to verify if any embedded material is inside the retain tablets.

**(F)** A product complaint report APL-FU7-2019-USA-PCM-00774 reported from the U.S market was

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found in the QA documentation room on inspection day 1 (09/19/2019). This document was signed by the author on 09/14/2019 indicating all associated tasks during the complaint investigation (including control sample evaluation) was completed on or before 09/14/2019. However, review of your control sample retrieval history in LIMS and other associated documentation indicate the control samples were not evaluated until 2 days after the report was authored (i.e., on 09/16/19). The document's author did not provide any explanation for the discrepancy in control sample evaluation dates in the report and LIMS.

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**OBSERVATION 2**

**There are no written procedures for production and process controls designed to assure that the drug products have identity, strength, quality, and purity they purport or are represented to possess.**

Specifically,

**(A)** We observed the presence and use of executed batch manufacturing records that were not identified in the records presented during the inspection. When requested for the complete list of executed batches for (b) (4) Capsules (b) (4) mg and (b) (4) mg (b) (4) your firm provided a list of (b) (4) full batches (each involving (b) (4) stages) of which 3 of them were submission batches. The Vice President of Quality stated that no additional batches were made other than the batches included on the list. However, review of the firm's record management system (Data Storage and Retrieval System) audit trail showed that additional batch records have been issued and executed. For example, the following issued batch records were not included in the provided list but shown in the audit trail:

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| Batch No. | Process Stage | Issued Date* | Status* |
|---|---|---|---|
| (b) (4) | | | |

According to the firm's electronic records, approximately (b) (4) additional batch records for this product have been issued but not executed. The (b) (4) application for (b) (4) Capsules (b) (4) mg and (b) (4) mg (b) (4) is currently under review by the FDA.

**(B)** Review of the re-issuance of records maintained by the Quality Assurance department indicated more than 100 logged events of batch record (or related documents) issuance in an uncontrolled Excel Sheet. The reasons for re-issuance identified in the file was either 'server is down', 'half pages downloaded', 'due to printer error', etc. However, several records have remained unaccounted for and the firm was unable to provide any record of reconciliation during the inspection. In addition, the destruction records maintained by the QA department do not include any printed/unexecuted batch records. Examples of unaccounted documents include batch records, protocols, etc. For example;

- Batch record (b) (4) (b) (4) Capsules, USP (b) mg)
- Batch record (b) (4) ((b) (4) Tablets, USP (b) (4) mg)
- Batch record BRSA18053-A (b) (4) Capsules, USP (b) (4) mg (b) (4) mg)

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**OBSERVATION 3**

**Control procedures are not established which of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.**

Specifically,

**(A)** Your approach to commercial process validation (PV) is deficient. Several examples were found where either the first attempted commercial validation batches have failed, or commercial batches following the validation campaigns have intermittently failed. Since 2017, approximately (b) (4) products have failed the initial commercial PV attempt. This include approximately 41 PV batches that were rejected purportedly with a root cause, and 3 PV batches rejected without any assignable root cause. Your approach to process performance qualification lacks adequate process understanding and demonstrable control. A few examples of U.S. marketed products where either the initial process validation batches failed or during subsequent post-validation commercial campaigns that failed are:

1. (b) (4) Tablets USP (b) (4) mg (first 3 commercial batches failed)
2. Tablets USP (b) (4) mg (4 PV batches failed)
3. Tablets USP mg (2 post validation commercial batches failed)
4. (b) (4) Capsules USP (1 post validation (b) (4) batch failed)

**(B)** The sample quantities used to establish (b) (4) hold time are not representative of the bulk (b) (4) batch sizes. For example, the sample quantity used to establish hold time for several (b) (4) products is approximately (b) (4) grams irrespective of the batch size. This approach was utilized by the firm in establishing bulk hold time for approximately (b) (4) products intended for the U.S. market.

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## OBSERVATION 4

**Laboratory records do not include complete data derived from all tests, examinations and assay necessary to assure compliance with established specifications and standards.**

Specifically,

Review of the electronic audit trails from the Tiamo software application that operates Auto titrators / Karl-Fischer titrators indicated repeated events of 'Determination stopped', 'Determination reprocessed', 'Determination interrupted' and 'Determination error' during the progress of test runs. For example, during the test runs, the following incidents were observed between April 2018 and September 2019:

| Instrument ID | Number of Times Stopped | Number of Times Error Message | Number of Times Interruption | Number of Times Reprocessed |
|---|---|---|---|---|
| KFAZ0001 | 3 | 0 | 2 | 3 |
| KFAZ0003 | 4 | 8 | 3 | 6 |
| KFAZ0004 | 7 | 6 | 1 | 3 |
| KFAZ0006 | 3 | 5 | 6 | 5 |
| KFAZ0007 | 7 | 0 | 10 | 15 |
| KFAZ0008 | 7 | 21 | 2 | 2 |
| POAZ0001 | 7 | 4 | 3 | 3 |

The 'Determination error' message included event such as *Communication lost with device*. However, your quality unit did not periodically review these audit trails and assess what may have caused these events. You also failed to investigate what those interruptions are and why the analysts may have stopped during a run. Some of the products that were running during this purported communication loss include, but are not limited to, (b) (4) USP, (b) (4) USP, (b) (4) USP, (b) (4) USP, (b) (4) Capsules, (b) (4) Capsules, (b) (4) Capsules,

(b) (4) Capsules, etc. The following table summarizes the approximate number of OOS investigations pertaining to Karl-Fischer auto titrators since January 2017:

| | Valid OOS | Invalid OOS |
|---|---|---|
| Stability | 4 | 8 |
| Others (RM, In-Process, FP) | 7 | 47 |

**OBSERVATION 5**

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

Specifically,

**(A)** Several lists of documents requested were either provided as incomplete, inaccurate, and or explained with potentially misleading statements throughout the inspection. For example, on 09/24/2019 (day 4 of the inspection), two (2) representatives from the Corporate Quality group stated independently that there are no Aberrant Results Investigations associated with In-Process testing of product lots manufactured at Unit VII. The same quality personnel stated that they are also responsible for review of Aberrant Results investigations. However, the list of Aberrant Results investigations provided on day 1 included approximately 11 investigations for in-process results directly contradicting the statements provided. The corporate quality personnel who answered our questions were later found not to have undergone training on the Aberrant Results investigation SOP.

**(B)** An original Aberrant Investigation Report Form (No. ABR/QC/030/19, date of initiation: 04/08/2019) for (b) (4) Tablets, USP (b) batch # (b) (4) and (b) (4) Tablets USP (b) mg/ (b) (4) mg batch #s (b) (4) was found in the QA documentation room. The 10-page document with attachments had the original signatures of the author (signed 04/21/2019) and reviewer

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(signed 04/22/2019) with no signature of the final QA approver. Your DGM-QA stated that the document was intended for destruction. However, no explanation was provided when the index list of 2019 Aberrant Investigation Reports had ABR/QC/030/19 listed as a "***closed***" investigation. This aberrant investigation report was initiated to investigate the *below LOQ* results obtained and reported for the (b) (4) content in the batches listed above.

**(C)** An original Aberrant Investigation Report Form (No. ABR/QC/058/19) for (b) (4) (b) (4) Tablets USP (b) (4) mg (batch (b) (4) ) was found in the QA documentation room. This 24-page document details the manufacturing investigation conducted to determine the root cause of total impurities result of (b) (4) % against a specification limit of NMT (b) (4) %. The report had signatures of the author (dated 06/28/2019) and reviewer/department head (dated 06/28/2019) with missing signatures of the QA in-Charge and Head QA/Corporate Quality Head. Your DGM-QA did not provide a clear explanation for the status of the report and why it had remained unsigned while the 2019 Aberrant Investigation Reports index (provided during the investigation) had ABR/QC/058/19 assigned to another unrelated product lot.

**(D)** Several product samples in (b) (4) bottles with labels that indicated "Samples for Analysis" and other unknown product samples in Ziplock bags containing no identifiable information were found in the QA documentation room. Your DGM-QA stated that the samples pertain to complaint samples however, no accompanying documentation was available to substantiate the claim. In addition, the samples with the labels "Samples for Analysis" as per the DGM-QA were allegedly pulled based on Inter Office Communication(s). No documentation was available for our review to substantiate the origin or the intended purpose of the product samples that were found in the QA documentation room.

**(E)** Too numerous to count executed batch records were found stored in an In-Process QA (Packing) room in the (b) (4) block on day 1 of the inspection. The batch records were stored under a section labelled "Waiting for COA". The GM-Production explained that batch records awaiting release of FP COAs are stored in the area. However, several batch records with accompanying COAs were found in the area and

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several had missing final approval by Quality Assurance on the batch records. In addition, finished product lots with unapproved batch records (by QA) were found in a released status in the Oracle based ERP system. For example, the following U.S marketed batches had a released status in the ERP system:

| Product | Batch Number | Release Status in Batch Record as of 9/19/19 | ERP Release Date/Time | Batch Shipment Date |
|---|---|---|---|---|
| (b) (4) | | Incomplete | 30-AUG-2019 10:38:14 | 11-SEP-2019 |
| | | Incomplete | 31-AUG-2019 10:32: 23 | 06-SEP-2019 |
| | | Incomplete | 05-SEP-2019 13:07:35 | 13-SEP-2019 |

**(F)** Your computer system administrator for multiple laboratory equipment was discovered to have a reporting structure directly within the quality assurance department. The system administrator stated during the inspection that he is involved in the review of electronic audit trails from multiple laboratory systems. This reporting structure provides no confidence in maintaining the integrity of electronic data without potential conflict of interest.

**(G)** On 09/19/2019, we discovered the use of uncontrolled documents in the QC laboratory. This included a large bound log book that included entries of OOS investigations. This log book is not part of any QC-related SOPs and not officially issued by the Quality unit.

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**OBSERVATION 6**

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

Specifically,

| SEE REVERSE OF THIS PAGE | EMPLOYEE(S) SIGNATURE | DATE ISSUED |
|---|---|---|
| | Tamil Arasu, Investigator TA<br>Jogy George, Investigator JG<br>Emmanuel J. Ramos, Investigator | 09/27/2019 |

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

| DISTRICT ADDRESS AND PHONE NUMBER | DATE(S) OF INSPECTION |
|---|---|
| ORA OPQO HQ, Room #2032<br>12420 Parklawn Drive, Rockville, MD 20857<br>ORAPHARMInternational483responses@fda.hhs.gov<br><br>Industry Information: www.fda.gov/oc/industry | 09/19/2019-09/27/2019*<br>FEI NUMBER<br>3007373532 |

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Mr. Madan Mohan Reddy, Director

| FIRM NAME | STREET ADDRESS |
|---|---|
| Aurobindo Pharma Limited | Unit VII, Formulation Plant, Plot S-1, Survey 411, 425, 434-435, 458, TSIIC, Green Industrial Park |
| CITY, STATE, ZIP CODE, COUNTRY<br>Polepally, Mahaboob Nagar, Telangana, 509302, India | TYPE ESTABLISHMENT INSPECTED<br>Finished Product Manufacturer |

On September 19, 2019, a cleaned (b) (4) (Equip No. (b) (4) A0001, located in (b) (4) Area, (b) (4) was found with visible unknown residue inside the (b) (4) in a location that was approximately (b) (4) behind the (b) (4). The location was found inaccessible when requested to take a swab sample and conduct an analysis to identify the source of powder residue. The (b) (4) was documented on the log book as C-cleaned and verified by production personnel. The C-cleaning is procedurally required during product changeovers. An unclean (b) (4) (b) (4) in a (b) (4) has the potential to contaminate products that are loaded on to the machine during routine operation.

## OBSERVATION 7

**Written production and process controls procedures are not followed in the execution of production and process control functions.**

Specifically,

Procedure FU7-PR-PK-GEN-011, Handling of Rejects in Packing, states that all rejected material must be collected and stored in a properly labelled red crate. However, during inspection of your packaging operation of U.S. bound product (b) (4) Capsules (b) (4) mg batch # (b) (4), the inline rejected material was noted as being collected in blue crates without proper identification of the material status.

## *DATES OF INSPECTION

9/19/2019(Thu), 9/20/2019(Fri), 9/23/2019(Mon), 9/24/2019(Tue), 9/25/2019(Wed), 9/26/2019(Thu) and 9/27/2019(Fri)

| SEE REVERSE OF THIS PAGE | EMPLOYEE(S) SIGNATURE | DATE ISSUED |
|---|---|---|
| | Tamil Arasu, Investigator<br>Jogy George, Investigator<br>Emmanuel J. Ramos, Investigator | 09/27/2019 |