

THE APPLICATION OF HACCP AND RISK MANAGEMENT IN THE PHARMACEUTICAL PROCESS

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ABSTRACT

Objective: To apply the Hazard Analysis and Critical Control Points method to the preparation of immunosuppressant drugs. To identify critical control points and to propose control measures and corrective actions to manage these processes.

Study Period & Methods. From November 2011 to January 2012, monitoring of the process performed to assess the risks. Several generic HACCP models were used as a basis for the generation of the model used in this study. The process flow diagram designed in the study shows the process steps to ensure that all aspects of a comprehensive HACCP model were incorporated. The process steps as indicated in the flow diagram are then performed and assessed for risk management. According to the Hazard Analysis and Critical Control Points method, a team is formed. And I worked in the plant with production manager, QA manager & process development manager in order to develop HACCP model, listed all of the critical points and then defined monitoring, control measures and corrective actions for each identified risk.

Results. I described 14 steps in the preparation process and identified 37 critical control points.

Conclusions. The Hazard Analysis and Critical Control Points method is relevant when it is used to target a specific process such as the preparation of immunosuppressant drugs. This method helped us to focus on the production steps, which can have a critical influence on product quality, and led us to improve our process.

Keywords: Hazard Analysis and Critical Control Points method, immunosuppressant drugs, risk management, quality management

INTRODUCTION

Immunosuppressant drugs present toxicity risks for health workers and patients.¹ It is recommended to centralize preparation in the pharmacy to limit the occupational exposure of health workers who come into contact with immunosuppressant drugs. The preparation of immunosuppressant drugs is a complex process, and much non-conformity can occur. Nevertheless, compounding unit is faced with ever-growing production needs and must guarantee high product quality according to good practice guidelines²⁻⁴. Hazards affecting quality can be defined as biological, chemical or physical or as operations that are likely to cause illness or injury to patients or health workers. Various approaches exist to identify risk issues and improve the safety of a process, such as Failure Modes and Effects Analysis, Failure Modes, Effects and Criticality Analysis, Probabilistic Risk Assessment, Hazard and Operability studies or Hazard Analysis and Critical Control Points (HACCP). Among these approaches, I chose to apply a relative new concept known as Hazard Analysis and Critical Control Point (HACCP) method to the preparation of immunosuppressant drugs. The HACCP method is a scientific and systematic approach of identification, assessment and control of safety hazards⁵. The HACCP concept was originally proposed for the food processing industry, but has been successfully applied to medical products. The risk analysis, following the guidelines of the HACCP method and the monitoring of critical steps during the process, was applied to the preparation of immunosuppressant drugs^{6,7}. This analysis led us to establish a preventive monitoring system based on an effective concept for quality assurance. Thus, the central feature of HACCP is the determination of the CCPs at which control can be exercised over one or more factors to eliminate prevent or minimize a hazard to ensure the safety of products. The experience of this HACCP application is described in this study.

METHODOLOGY

Study period

An analytical control of the preparation is performed prior to dispensing. Finally, preparations are delivered and dispatched to the different units. The implementation of the HACCP method began in November 2011. To assess the efficiency of the HACCP method, monitoring is performed from November 2011 to January 2012.

The implementation of the HACCP Plan

Prior to beginning the development of a HACCP plan, I had undertaken a thorough gap analysis of its existing prerequisite programmes and good manufacturing practices (GMPs). As shown in Table 1, five preliminary steps were then taken to facilitate the smooth and quick application of the seven basic HACCP principles.

Table1: The 12-step HACCP programme⁸

Features	Descriptions
Preliminary Steps	1) Assemble HACCP team
	2) Describe product
	3) Identify intended use
	4) Construct flow diagram
	5) Verify flow diagram onsite
Principles of HACCP	1) Conduct Hazard Analysis
	2) Determine CCPs
	3) Establish critical limits for each CCP
	4) Establish monitoring system for each CCP
	5) Establish corrective actions
	6) Establish verification procedures
	7) Establish documentation and record keeping

HACCP analysis

First, I drew up a full description of the product and constructed a flow diagram. It covered all steps of the process to which the HACCP concept was applied. The HACCP team checked and evaluated the whole process according to seven principles: (i) analysis and identification of potential risks (hazard analysis); (ii) identification of critical control points; (iii) definition of limits (target levels and critical limits); (iv) in-process control (critical control points monitoring); (v) the establishment of corrective measures; (vi) the confirmation system (HACCP system verification); (v) the documentation system (procedures and records).

I listed all of the critical points that could occur at each step of the process. Control measures and monitoring of the critical control points were defined, if any existed for the considered hazard. Corrective actions were planned for each critical control point. Then, the HACCP team established quality documents (procedures,

operating instructions, etc.) and record-keeping files related to each critical control point.

Critical control points' determination

When the hazard analysis is complete, I must go over the flow diagram and decide which steps are critical control points (CCPs). A CCP can be a point in the process where a significant hazard can be eliminated or reduced to an acceptable level. A CCP is also a point where loss of control will lead to a significant hazard. It differs from a control point (CP) in that a loss of control at a CP will not lead to a significant hazard. CCPs require a lot of careful development and extra documentation and that is why they should be limited to only those that are truly critical. When determining which steps are critical control points, some companies use what is called the shotgun approach. This is a method that is not based on any true reasoning; rather CCPs are chosen based on the opinions of the team. This may lead to an excessive number of CCPs resulting in problems for the plant. To assess criticality for each control point, a more accurate and feasible method that can reduce the number of CCPs is use of the decision tree. Fig. 1 shows an example of such a decision tree with three questions to answer about each processing step where a hazard is significant. The questions are in "yes or no" format, and will eventually determine whether that step is a CCP. If all questions are answered with yes, a critical control is defined for the hazard.

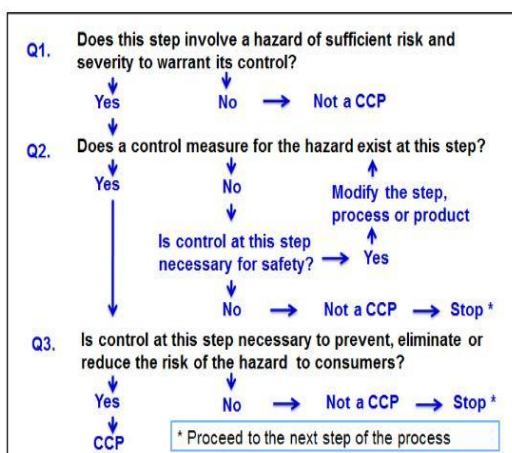


Fig. 1: Decision Tree to Identify Critical Control Points CCP monitoring

Each CCP was systematically collected during the production process. This follow-up was used to assess the HACCP program and to submit specific corrective actions for each critical control point.

RESULTS

Characterization of the process

Hazard Analysis and Critical Control Point (HACCP) is important at different stages of a process. The HACCP system starts from the initial stage of Raw material dispensing through the method of product processing adopted and finally dispatch of the product.

According to the recommendations of the HACCP team, the whole process was characterized by 14 steps: (i) Raw material dispensing (ii) Sifting (iii) Pre-blending & Mixing (iv) Dry-mixing (v) Prep. Of binder solution (vi) Wet granulation (vii) Drying (viii) Dry Sieving (ix) Sifting of post granulation Ingredients (x) Blending (IPQA sampling) (xi) Lubrication of granules (IPQA Sampling) (xii) Compression (xiii) Coating (xiv) Packing. I checked on-site the relevance of the flow chart described in Fig. 2.

Description of the product

The HACCP team defined the product as an individual immunosuppressant drug preparation. Consequently, precautions are required to protect technicians during the handling and preparation process.

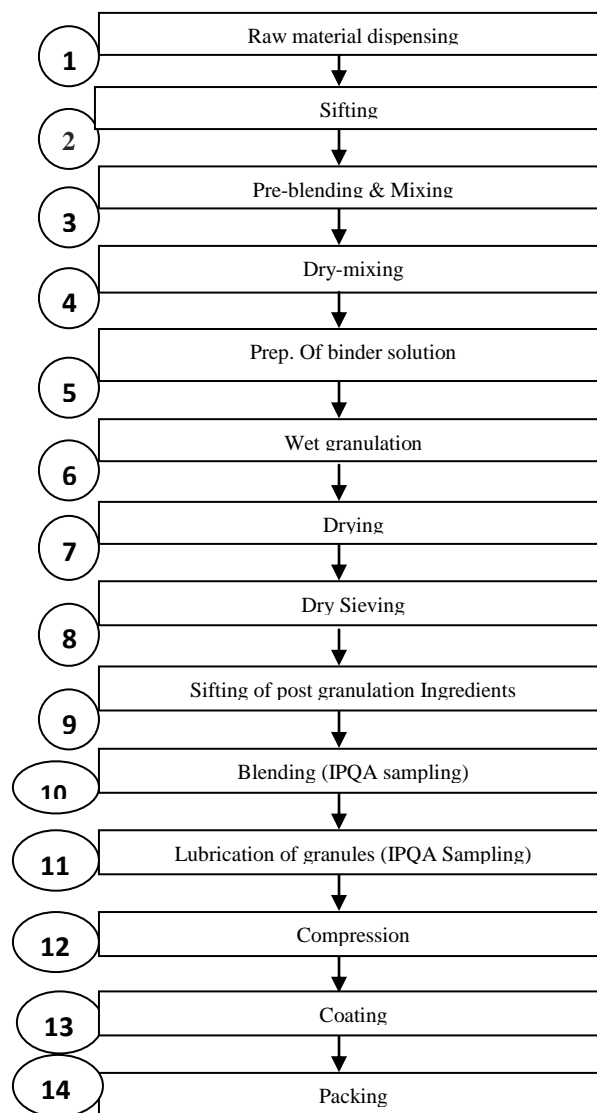


Fig. 2: Flow chart of the immunosuppressant drug preparation process.

Critical control points analysis and corrective actions

Among the 14 steps, we identified 11 critical control points of higher importance (37 overall). The critical control points are detailed in Table 2.

Mechanical disturbances. Vibrations of the support on which the balance stands, temperature differences, pressure fluctuations of the ambient air and even the vibrations in the building cause the disturbances, it is recommended that the balance be set up on a lower floor. If this is not possible, the balance should be used with a specially designed wall console. As a corrective action, a digital filtering feature on the weighing instrument can reduce these disturbances.

Table 2. Critical Control points of higher importance identified.

Processing Step	Critical Control Points
Dispensing	Mechanical disturbances Dispensing the wrong ingredient Dispensing the wrong quantity Dispensing the expired lot Addition of pre-dispensed materials to in-process containers

Sifting of raw materials	Static charges
	Operator error
Dry-Mixing	Damage or fracture on sieve during sifting.
	Cross contamination with products of previous batch during sifting.
Wet Granulation	Exposure of materials to contamination during sifting
	Incorrect dry mixing time and speed of mixing blade
Drying	Quantity of binding solution added & Massing time
	Rotational speed of impeller during massing
	Disheveled gown of operator, insufficient cleaning of equipment
	The loading of the processing bowl
	Incorrect outlet air temperature
	Improper air flow in the inlet-air plenum and velocity of airflow
	Incorrect choice of container and air distributor
	Blockage of filter bag
	Filter bag shaking
	Damage of inlet-air filter, damage of thermometer

Dispensing the wrong ingredient, quantity or the expired lot. There is the possibility that an operator can accidentally dispense the wrong ingredient by misreading the material name on the stock label, dispense an incorrect raw material quantity. The causes of this are varied, but include: an arithmetical mistake, misreading the balance display, an incorrect potency calculation, an incorrect unit of measure conversion or misreading a quantity from the dispensing instructions. Also it is possible for an operator to pick and dispense an expired lot. Computerized raw material dispensing systems make economic sense by cutting errors and improving efficiency. Computerized system uses the barcode on the stock label to identify the material to be dispensed and, if the lot has expired, warns the operator and does not allow the expired lot to be dispensed. A computerized system also recalculates the remaining quantity on change of dispensed container; forces the balance to be zeroed and the container tared before each weighing; performs potency calculations. For this reason, it is not possible to identify and

Processing Step	Critical Control Points
Dry Sieving	Cleanliness and pre-integrity of screen, Improper size reduction
Sifting of post granulation ingredients	Damage or fracture on sieve Cross contamination with products of previous batch. Exposure of materials to contamination
Blending	Blending time and RPM is incorrect and Bin capacity
Final Lubrication of granules & IPQA sampling	Wrong addition of Lubricants
Rapid drop of powder into a Y-branch above tablet press	Improper mixing Powder-blend handling
Compression	Exposure of materials to contamination Metal particles in tablets Wrong tableting parameters
Coating	Degree of rolling and mixing Spray gun clogging
Packing	Mix up of any foreign material or other dosage form during packing Wrong coding of batch details and expiration date

dispense the wrong ingredient and quantity.

Addition of pre-dispensed materials to in-process containers. Another area where errors can occur is in the addition of pre-dispensed or bulk materials to Intermediate Bulk Containers (IBCs), process/mixing vessels or blenders. To control this point, dispensed materials must be labeled properly.

Static , which will cause the particles to fly around. Depending on the polarity of the charged particles involved, this force either repels or attracts, so a weighing result may deviate in either direction. An antistatic device must be used to minimize this. Directly neutralize the surface charges using so-called static eliminators.

Operator error. Mistakes can be the result of operators taking shortcuts in the dispensing process or not following the standard operating procedure (SOP); for instance, different operators sometimes have their own dispensing techniques. Although periodic audits can be used to ensure SOPs are being followed, there is no guarantee that procedures are being followed in the periods between audits.

Damage or fracture on sieve during sifting. If the sieve is damaged, metal can enter in to batch, safety issue. Inspection of sieves to be used in operation before and after operation as per SOP, cleaning has been done as per SOP to control this point.

Cross contamination with products of previous batch during sifting. Contamination can affect the safety, quality, purity. Equipment is duly labeled as 'CLEANED' prior to use. Cleaning validation performed.

Exposure of materials to contamination during sifting. Environmental conditions (Temperature and Humidity) are monitored prior to use as specified in manufacturing instructions. Secondary gowning, protective garments, worker wear gloves, operator training is there to prevent the exposure to contamination.

Incorrect dry mixing time and speed of mixing blade. If operated at high speed particles will become so fine because particles got break by colliding each other and will lead to more compressible particles and produces non-homogeneous blend. The corrective action of this critical point is that batch shall be quarantined.

Quantity of binding solution added & massing time. High levels of the factors operational settings could lead to manufacture of tablets of unacceptable dissolution resulting in enlargement of agglomerates and material becomes so wet and hard. If less amount of binder sol. is added then material will become too soft & friable thus affecting the mechanical properties of the tablets. Thus, it was of primary importance to set their operational ranges at levels that provide quality product within robust manufacturing process.

The optimal quantity of binder solution needed to get a given particle size should be known in order to keep a batch-to-batch variations to a minimum.

Rotational speed of impeller during massing. Impeller and chopper blades operated at high speed cause high-energy collisions between particles. Wet particles bind together and create agglomerates of limited surface area and porosity. The phenomena have direct impact on active substance dissolution rate.

Low impeller speed was not recommended due to potential risk of not sufficient agglomeration and, in consequence, punches sticking. The three factors of the most significant influence on drug dissolution were not set simultaneously at high level anymore. As a result, the structure of agglomerates was not so dense and tablets were of adequate dissolution. Disheveled gown of operator, insufficient cleaning of equipment. Equipment is duly labeled as 'CLEANED' prior to use. Cleaning validation performed. Use long glove and goggle as a corrective action.

The loading of the processing bowl. The transfer of materials to and from a fluid bed processor is an important consideration. Loading can be done either vertically, from an overhead bin because gravity is working to help the process.

Incorrect outlet air temperature. If the outlet temperature rises more rapidly than anticipated, it will indicate an improper fluidization. However, improper fluidization can also be detected by monitoring the outlet air temperature. Process may have to be stopped and manual or mechanical intervention may be required to assist the fluidization.

Improper air flow in the inlet-air plenum and velocity of airflow. If the air is not properly distributed before it reaches the bottom of the container, uneven fluidization can occur. Air flow rate should be controlled properly, should not be too fast or too slow but optimized to have efficient drying. The air flow is controlled by a valve or damper installed just ahead of or after the fan. Designed with two fans, in the inlet and outlet, for a better and more balanced airflow control to achieve the best flexibility.

Incorrect choice of container and air distributor. To properly fluidize and mix the material in the container, the correct choice of shape of instrument body and air distributor must be made. Annular base gives better product and fluidization. The container volume should be chosen such that the bowl is filled to at least 35–40% of its total volume and no more than 90% of its total volume. The correct choice of air distributor is important. Keep the product container and air distributors clean. The container with perforated air distribution plate with mesh includes a motorized stirring system to allow a uniform controlled and balanced mixing with any kind of product.

Blockage of filter bag. If filter bags got blocked, there will be a great pressure developed in filter housing which will lead to explosion. Cleanliness and integrity of filter bags is certified prior to use. Split bags should be installed as a corrective action which allows one portion of the bag to be cleared while the other portion remains in use.

Filter bag shaking. Bag shaking cycle affects particle size distribution of a finished granulation. Also influence granulation performance during tablet compression. Excessively long or short interval produces inferior tablets. Filter Bag Shaking for bag cleaning is pneumatically achieved and programmed by PLC.

By optimizing the shake time & the corresponding interval between bag shakes, it is possible to improve the particle size distribution of a finished granulation. Semiautomatic bag shaking timers are preset and controlled through PLC.

Damage of inlet-air filter, damage of thermometer. To control this point, cleanliness and Integrity of filter has checked visually before start up of operation. Calibration of inlet-air filter and thermometer should be done. Change maintenance period, change calibration period as a corrective action.

Cleanliness and pre-integrity of screen, Improper size reduction. Before use, pre-integrity has checked visually. Training has given in accordance to operating procedure for Sifter cum Multimill. Validation is in place to check the adequacy of blend uniformity analysis.

Damage or fracture on screen. Inspection of screen to be done before and after operation as per SOP. If the screen is damaged, whole of the material pulverized shall be stopped for further processing and material shall be checked thoroughly through metal detector before further processing.

Blending time and RPM is incorrect and Bin capacity. Mixing speed and time are critical variables in this process. Mixing time is critical since under mixing would result in non-uniform distribution of drug and poor flow whereas over mixing will result affect the uniformity of mixing and leads to non-uniform distribution of drug. Also a critical speed approached will diminish blending efficiency considerably.

Timer is calibrated as per schedule. Blender speed may also be a key to mixing efficiency. PLC has been validated as per schedule. Additionally blending timing is monitored as per wall clock or stopwatch. Doer - checker concept is there.

Blending time and RPM is validated and optimized for each respective product, automatically after completion of cycle blender gets stop position. Blend uniformity analysis are checked and established during validation batches.

Wrong addition of Lubricants. Result a non-uniform product. To control this point, lubricants are verified for identification and quantity checked prior to addition.

Improper mixing. To properly evaluate blend performance, Blend analysis is done as per validated approved specification & test procedures.

Powder-blend handling. Powder transfer should not be taken for granted and instead should be considered a critical unit operation for which bins, chutes, and press hoppers are major, design-critical pieces of equipment. Slowing the fill rate can reduce segregation tendencies.

Butterfly valves should be operated in full open position, not throttled to restrict flow. Press hoppers, transfer chutes, and Y-branches must be designed correctly, to avoid stagnant material.

Restricting flow will virtually ensure a funnel flow pattern, which is usually detrimental to uniformity. Minimize transfer steps. With each transfer step and movement of the bin, the tendency for segregation increases.

Metal particles in tablets. Machine affixed as metal detector system to reject tablets with metal debris (ferrous and non ferrous) by performing metal detector challenge test.

Metal detector challenge test is performed by both production & IPQA personal as per SOP before start of batch & observation recorded in Batch manufacturing record.

Wrong tableting parameters. Observations have been recorded in in-process sheets as per SOP by production. Checked by production and IPQA personnel with respective frequencies. In addition frequency of in-process checks are at least twice in a shift/ at starting of a new batch. QC checks the S2 stage sample for the different parameters like assay, identification, dissolution, disintegration time, friability, weight variation, tablet hardness (or tensile strength), tablet thickness, uniformity of dosage units, content uniformity. Doer - checker concept.

Degree of rolling and mixing. Improper design and shape of baffle cause inefficient mixing & thus affects the quick rotation of pan, which minimizes the rate of coating application. And thus prolongs processing time. Mixing of the core bed is important for a uniform application of the coating material as well as for effective drying. With so many different types of mixing baffles available, evaluate them carefully, taking into account their shape and mixing efficiency when analyze the overall coating system. The most basic approach to improve the core bed movement in pans rotating on inclined or horizontal axes was to introduce baffles in the pan.

Spray gun clogging. The spray guns feature an Anti-Bearing-Cap (ABC) system avoiding guns clogging while the machine is working. Should be positioned and adjusted from the outside by using the relevant device. In case of clogging of the nozzle during the process, this structure enables the in-process removal and cleaning of the nozzle. An axially adjustable cleaning needle present in the middle of the nozzle is connected with actuation equipment for cleaning the nozzle during the process.

A 2-media spray nozzle with a flexible cleaning cap, made of silicon or another elastic material, arranged around the nozzle cap. A feed for atomizing the cleaning air is arranged between the nozzle body and the cleaning cap. The atomized cleaning air provides continuous bulge and vibration of the cleaning cap resulting in the removal of product deposition at the nozzle outlet.

Mix up of any foreign material or other dosage form during packing. Equipment and area clearance is done independently by two production personnel and IPQA personnel. Packing operation shall start after IPQA approval as per SOP. Camera system installed

online to detect the defectives (if any). Camera system is challenged during each shift for proper functioning.

Wrong coding of batch details and expiration date. Packing will start after approval of coded components. Batch details shall be checked as per batch production record by production personnel and QA independently. Doer-checker & re-checker concept is there.

DISCUSSION

A risk analysis of the immunosuppressant drugs preparation process has already been conducted using different methods like Failure Modes and Effects Analysis or Failure Modes, Effects and Criticality Analysis. But the present study of risk analysis using the HACCP method to an immunosuppressant preparation process is done for the first time.

The importance of process controls has increased. Controls enhance product quality and traditionally consisted of post-process product testing. In case of non-conformity, this type of testing occurs too late and leads to fresh preparation of the product. This new preparation delays the delivery and is a waste of time for health workers and patients. Finally, destroyed preparations are lost and are economically unacceptable.

The HACCP plan has helped to significantly reduce risks that are passed to the consumer through the company's products. Many critical control points have been highlighted by the HACCP. The CCP decision tree helped to identify the most important critical points and to establish our priorities in terms of risk management. However, the microbial contamination of the dispensing room should be taken into account because of its potential impact on the isolator sterility. This item is a good indicator of the area's hygiene quality. It also gives information about hand hygiene practices of technicians who carry out manufacturing in the positive pressure isolator. Microbial contamination is evaluated twice a month on positive pressure isolator.

To monitor this critical point, target, warning and action levels are defined by the HACCP team using the same template as Swanson et al.⁹ and Ljungqvist et al.¹⁰. During the study period, no microbial contamination is reported.

We can also consider another issue highlighted by the HACCP, such as the monitoring of the drug storeroom temperature. The high temperature range for the warning level was modified to 24–25°C.

Among the 11 critical points of greater importance described, we did not draw up corrective actions or monitoring for some of them. Chemical contamination hazards cannot be monitored for the time being in our department. However, informing technicians of the importance of wearing nitrile gloves at all times inside the compounding room and of the importance of changing their nitrile gloves every 30 min should represent an alternative solution to contain this hazard¹¹. Thereafter, this risk could be avoided definitively. Depending on the drug's stability, we prepared and stored the preparations until the dispensing order was received.

The validation by the QA department also takes place earlier, which improves the detection of errors. Finally, some corrective actions defined in this process may not be applicable for use in other companies. For example, the intermediate storage system in the

compounding room with a unique batch number for each product implies a significant daily production and the systematic control of the products ordered.

The HACCP is a precise method that highlights issues and explains a complex process in detail. This method is helpful for focusing on the production steps, which may have a critical influence on the quality of the product. With the HACCP method, we can concentrate our limited resources on the identified critical points. Finally, the hazard analysis also provides a revision of the documented data such as standard operating procedures, production and check-up protocols.

On the other hand, the HACCP method is extremely demanding on time and human resources. This point represents the major limitation of the method. CCPs were obtained based on the experience of HACCP team members and hindsight of the process. The criticality of the different points may not be relevant and can be open to discussion. The different critical control points were determined on the basis of explicit and CCP decision tree insofar as possible.

In conclusion, the present study demonstrates the interest of the application of the HACCP method in the preparation of immunosuppressant drugs. The efficiency of the HACCP method is relevant when this method is used to target a specific process. Critical points were identified and led to improvement of our process. Following the implementation of the corrective actions, a reassessment of our process is planned in view of the future.

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