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LECTURE NOTES
ON

GOOD MANUFACTURING PRACTICES

UNIT –IV

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UNIT IV

PHARMACEUTICAL PRODUCT RECALL

A process for withdrawing or removing a pharmaceutical product from the pharmaceutical distribution chain because of defects in the product, complaints of serious adverse reactions to the product and/ or concerns that the product is or may be counterfeit. The recall might be initiated by the manufacturer, wholesale dealer license holder, or Department of Health.

The procedure is divided into six stages, which are set out below, with a reference to the Section in which detailed information is given.

Classification Recalls

These are classified according to the following system:

Class I recalls occur when products are potentially life-threatening or could cause a serious risk to health.

Examples of Class I Defects –

Wrong Product (label and contents are different products)

- Correct product but wrong strength, with serous medical consequences
- Microbial contamination of sterile injection or ophthalmic product
- Chemical contamination with serious medical consequences
- Mix up of some products („rogues□) with more than one container involved
- Wrong active ingredient in a multi-component product with serious medical consequences

Class II recalls occur when product defects could cause illness or mistreatment, but are not Class I.

Examples of Class II Defects

- Mislabeling e.g. wrong or missing text or figures
- Missing or incorrect information- leaflets or inserts
- Microbial contamination of non-injectable, non-ophthalmic sterile product with medical consequences
- Chemical/ physical contamination (significant impurities, cross contamination, particulates) - Mix up of products in containers (“rogues”)
- Non-compliance with specification (e.g. assay, stability, fill/ weight or dissolution)
- Insecure closure with serious medical consequences (e.g. cytotoxics, child resistant containers, potent products)

Class III recalls occur when product defects may not pose a significant hazard to health, but withdraw may be initiated for other reasons.

Examples of Class III Defects

- Faulty packaging e.g. wrong or missing batch number or expiry date
- Faulty closure

- Contamination- microbial spoilage, dirt or detritus, particulate matter

Class I or Class II recalls are considered to be urgent safety-related recalls.

STRATEGY FOR EFFECTIVE RECALL

Each recall is a unique exercise. There are a number of factors common to all recalls that need to be considered in tailoring an appropriate recall strategy.

These include the nature of the deficiency in the product, the incidence of complaints, public safety, distribution networks, recovery procedures, resources for corrective action and availability of alternative products.

In determining the recall strategy, the Licensee should consider the factors which may affect the duration of the recall action and should inform the Department of Health. The recall should be completed by the date as directed by the Department of Health.

When the required information is available, the appropriate strategy should be proposed by the Licensee to Department of Health. The proposed recall strategy should be agreed by the Department of Health before implementation. The actual implementation of the recall includes use of the basic steps which are summarized in Section B and these will be common to all strategies.

In the recall strategy, the Licensee should mention the followings:

- Indicate the proposed level in the distribution chain to which the recall is extending (see level of recall below), if the recall only extends to the wholesale level, the rationale of not recalling to retail level should be explained;

- In case of consumer level recall, additional information should be mentioned-

Indicate the location of recall spots for consumers, their operation time and duration (at least 7 days);

Indicate the hotlines number(s) for enquiry and the corresponding operating hours; Indicate the proposed refund mechanism at the recall spots, the conditions of refund (applicable to opened products, expired products or parallel-imported products) and methods of refund (by means of money, credit notes or product replacement etc.);

- Indicate the method of notification (e.g. mail, phone, facsimile, email);

- Indicate how the message of recall will be delivered to customers e.g. press release or recall letters etc;

- If the Licensee has a website, it should consider posting the recall notification on it

as an additional method of recall notification;

- Report on what have the customers been instructed to do with the recalled product; - It is necessary for recalling firms to know the name and title of the recall contact person for each of its consignees.

Addressing a recall letter to a recall contact person will expedite the recall process and reduce the potential for the recall letter to get misdirected;

- If product is to be returned, explain the mechanics of the process;

- Explain if the recall will create a market shortage that will impact on the consumer;

- Determine and provide the course of action for out-of-business distributors;

- Provide a proposed disposal plan of the recalled products, whether they would be destroyed, reconditioned or returned to overseas manufacturer; and

- Inform Department of Health before product destruction, the proposed method of destruction would be reviewed and Department of Health may choose to witness the destruction.

Recall Stages

1. Receipt of Pharmaceutical Product Problem Report Notification to the Department of Health- Information on problem of pharmaceutical products.

2. Initiation of a Recall- Information Required for Assessment of Recall -Information on product, problem and distribution is required.

3. Assessment of Recall- The classification, level and strategy of recall are determined depending on the potential hazard of the defective product and the extent of product distribution.

4. Recall- Letters and press release (if required) are dispatched to relevant firms for notifying on the recall.

5. Progress of Recall and Report- Progress reports and final report are submitted to the Drug Office.

6. 6. Evaluation of the Recall The effectiveness of the recall is monitored by the Drug Office.

NOTIFICATION OF A PHARMACEUTICAL PRODUCT PROBLEM

Recall might be initiated as a result of reports or complaints on quality, safety or efficacy on a pharmaceutical product referred to the Licensee from a variety of sources.

The reports or complaints may be referred by manufacturers, wholesalers, retailers and hospital pharmacies, research institutes, medical practitioners, dentists and patients, recall might also be initiated as a result of analysis and testing of samples of pharmaceutical products by the manufacturers and by the Department of Health.

Recall of pharmaceutical products manufactured overseas might be initiated by the local or overseas health authorities, or from information received directly from such authorities. Certain information is essential to permit the assessment of the validity of the report of quality defects, safety or efficacy problem with pharmaceutical products, the potential danger to consumers and the action appropriate to the situation.

INITIATION OF RECALL/ INFORMATION REQUIRED FOR ASSESSMENT OF RECALL

When the Licensee decides to initiate a recall on a pharmaceutical product, it is required to notify the recall a situation with the Recall Notification Form including information outlined below to the Department of Health immediately after the decision to recall is made and the Senior Pharmacist (LC-W), Department of Health is notified on the contact information of Senior Pharmacist (LC-W)).

The Licensee shall not wait to submit this information until ALL applicable information is prepared and assembled prior to notification to the Department of Health. This “early” notification is necessary to allow the Department of Health to review and comment on the written notification and to offer guidance and assistance in the recall process. The information required may include:

Details of the Problem - name, telephone and facsimile number of the person reporting the problem; - date of report; - physical location of the problem; - nature of the problem; -

number of similar report received; - results of tests and other investigations on suspect or other samples.

Details of the Product - name of the product and description including active ingredients, dosage from, strength, registration no, pack size or type; - batch number(s) and expiry date; -

Manufacturer/ distributors and contact telephone, facsimile numbers and email address; - date manufactured, date released –

Quantity of the batch, date and amount manufactured, released - local distribution list; - oversea distribution list of product exported from country; - whether the product is meant to be sterile. Health hazard evaluation and proposed action - type of hazard, and evaluation of health hazard to user; - action proposed by the Licensee; - proposed recall classification and level; and - availability of alternative product.

Level As with classification,

The level (or depth) of a recall is to be assigned by Department of Health. In determining the recall level, the principal factors to be considered are the significance of the hazard (if any), the channels by which the pharmaceutical products have been distributed, and the level to which distribution has taken place. Again, expert opinion may be necessary to determine the significance of the hazard.

There are three levels of recall:
Wholesale,
Retail and
Consumer.

Wholesale level includes: - All parties involved in wholesale distribution and may include wholesalers and retail pharmacies.

Retail level includes: - All public and private hospital pharmacies; - Retail pharmacies; - Clinical investigators and the institutions in which clinical investigations are performed; - Medical, dental and other health care practitioners; - Nursing homes and other related institutions; - Other retail outlets e.g. medicine shops, supermarkets and health food stores; and - Wholesale level.

Consumer level includes: - Patients and other consumers; and - Wholesale and retail levels.

COMMUNICATION TO PUBLIC

Recall letters In case of a recall, the Licensee may prepare letters with a factual statement of the reasons for the recall of the product, together with specific details that will allow the product to be easily identified.

The letter may be sent by mail, facsimile or e-mail to the clients. The recall letter should use company letterhead; include date and name and title of signatory. The text of recall letter may include:

a. Description of the pharmaceutical product: name of the product; registration number; name of manufacturer, pack size; dosage form; batch number(s) and expiry date;

b. Hazard associated with the product: The reason for the recall should be concisely explained. It should be made clear that further distribution or use of the product should cease immediately.

c. Instruction for recall of the product: The method of return, disposal or correction and refund mechanism of the product. There should be a request for a response to confirm receipt and understanding of the action to be taken e.g. pre-addressed cards, telephone replies or a form to complete and return by facsimile or e-mail. The Licensee should clearly identify a hotline for enquiry.

For retail level recall, the Licensee should have confirmation for returning all the stock on hand from the consignees using the Recall Reply Form at Appendix TWO. If safety to the public is involved and distribution is limited, the Licensee may contact the clients of the information listed above by telephone and followed by a recall letter. Press Release Rapid alert to public is usually reserved for hazards classified as Class I, and where appropriate Class II or situation where other means for controlling the hazard appear inadequate.

Rapid alert to public may be issued through appropriate channels which may include press release.

RESPONSIBILITIES OF LICENSEES

Licensee has responsibilities in relation to recall of pharmaceutical products in two general areas: a. in maintaining records and establishing procedures which will assist in facilitating recall should such action become necessary; and b. in taking the prime responsibility for implementing recall in the situation where it is necessary.

Records The Licensee should maintain records for all the pharmaceutical products manufactured or distributed by them in accordance with the followings: For manufacturers - A system should be in operation whereby the complete and up-to-date histories of all batches of products from the starting materials to the finished products are progressively recorded; - The system should allow the determination of utilization and disposal of all starting materials and bulk products.

For distributors - Records of all sales or distribution (including professional samples and export to overseas countries) of pharmaceutical products should be retained or kept readily accessible to permit a complete and rapid recall of any lot or batch of a pharmaceutical product. The complete records pertaining to manufacturing and distribution should be retained for two years after the date of transaction or one year after the expiry date of the batch whichever longer.

Besides, the Licensee should retain records of problem reports received about each product. Problem reports should be evaluated by competent personnel and appropriate action taken. The evaluation of each report and the action taken should be shown in the records. All the above records should be readily available and easy to follow so as to expedite recall whenever necessary. A copy of manufacturing/ import and distribution records should be sent to Department of Health when a recall is implemented.

Recall Procedure

Licensee should prepare procedures for recall action which are consistent with the Guidelines and which are applicable to their own operations.

All senior personnel should be familiar with their responsibilities in connection with the procedure and of the records system for pharmaceutical products. Problem Reporting Where evaluation of a problem report concerning pharmaceutical products indicates that recall may be necessary, the report must be conveyed with the least possible delay to the Department of Health, including pharmaceutical products.

Any batch of a formulated product that has been distributed, or any batch of a starting material that is found not to comply with the approved product specifications or a relevant standard of PICS, must also be reported if it has been used in a distributed products.

Recall Licensee has the prime responsibility for implementing recall action, and for ensuring compliance with the recall procedure at its various stages. However, no recall, regardless of level, should be undertaken without consultation with the Department of Health.

A responsible officer for recall should be appointed to coordinate the recall and his/her name and contact phone number should be notified to Department of Health. In addition, this officer has to report the progress of recall regularly to the Department of Health.

For Class I recall, Licensee should notify its clients within 24 hours upon the decision of recall. The company personnel may be utilized to immediately disseminate information on the recall. This includes telephone advice to quarantine stock pending recall or possible recall followed by recall letters if necessary.

A Recall Reply Form should be sent to all consignees to confirm quantity of stock on hand and have all of them returned. The reply form should be kept for inspection by Department of Health.

All Class I recall should complete within a time as found suitable for the case agreed by Department of Health. For consumer level recall, the Licensee should set up sufficient recall spots for collection of recalled products.

Information of location of the recall spots, their operating hours and duration, conditions of refund as well as method of refund should be noticed to consumers by effective means. Company representatives may be utilized to recover stock which is the subject of recall, providing the provisions are observed in relation to unauthorized possession of certain stock, e.g. dangerous drugs. Licensee may also be required to notify overseas recipients of recall actions that affect them.

Refund Mechanism Licensee should set up a refund mechanism for the recalled products. Post-recall After the timeframe directed by Department of Health to complete the recall, or at other agreed times, the Licensee is to provide the Department of Health with an interim report during recall process for the monitoring of progress within 7 days after initiation of recall.

The interim report should contain the following information: - the number of organizations or persons to whom the defective product has been supplied; - the date and means of notifying them of the recall; - the number of responses received from them; - the names of the non-responders; - the quantity of stock returned; - the quantity of stock has been off shelves pending return to Licensee; - the estimated time frame for the completion of the recall.

A final report (refer Final Report Form at Appendix THREE) contain the following information should be submitted to Department of Health within 14 days after commencing of the recall:

- the circumstances leading to the recall;
- the consequent action taken by the Licensee;
- the extent of distribution of the relevant batch in country and overseas;
- the result of the recall the quantity of stock returned, corrected, outstanding;
- the quantity of stock used by the consignees and;
- the quantity of stock not located;
- date of recall completion;
- - confirmation

where practicable, the retailers have returned all the recalled products to the Licensee and the customers have received the recall letter;

- the method of destruction or disposal of the recalled products; and The licensee should report to Department of Health with relevant explanation and obtain its approval if the final report cannot be submitted within 14 days after completion of the recall, a report on investigation results on the problem and the action proposed to be implemented in future to prevent a recurrence of the problem should be submitted to Department of Health in a timely manner.

These reports establish the effectiveness of the recall and unless satisfactory reports are received, further recall action may have to be considered.

EVALUATION OF THE RECALL

The evaluation consists of a check on the effectiveness of the recall and an investigation of the reason for the recall as well as the remedial action taken to prevent a recurrence of the problem.

Check on the Effectiveness of Recall Action It is the Licensee responsibility to assure that the recall is effective. The Department of Health examines the recall reports and the signed Recall Reply Forms submitted by the Licensee and assesses the effectiveness of the recall action. Recall records may be inspected and in some case the Department of Health may contact a percentage of customers in the distribution list as a means of assuring the Licensee is carrying out its recall responsibilities.

If Department of Health finds the recall to be ineffective, the Licensee will be asked to take appropriate steps, including re-issuing recall letters. Investigation of the Reasons for Recall and Initiation of Remedial Action On completion of a recall, the Licensee is requested to provide a report with investigation on the problem and details of the remedial action proposed to prevent a recurrence of the problem which gave rise to the recall.

Where the nature of the problem and appropriate remedial action are not apparent, investigation and in some cases Good Manufacturing Practice audits may be necessary. Where a recall is initiated following a report submitted by a party from overseas health authorities, the reporter is to be provided with an outline of the results of investigation and a summary of the recall.

REINSTATEMENT OF SUPPLY

The quality of the products shall conform specific requirements before resuming the supply to public.

The Licensee must seek approval from Department of Health for reinstatement of the pharmaceutical product previously “totally recalled”.

Implementation of Remedial Action the Licensee shall identify the root cause of the problem and implement the corrective action accordingly. Furthermore, preventive action shall be imposed to prevent recurrence of the problem in the future.

Submission of Analytical Report After implementing the remedial action and subsequent manufacturing or importing the new batch of the product, the Licensee shall submit analytical report(s) of the new batch tested by external accredited laboratory to Department of Health as a proof of product quality.

The submitted report(s) will be evaluated by the country Government Laboratory via Department of Health. After evaluation, Department of Health would inform the Licensee whether the submitted reports are satisfactory.

Sampling When Department of Health satisfies the submitted reports, sample of the first three batches of the product (being manufactured by the local manufacturer / being imported) will be collected for examination by the country Government Laboratory. The Licensee shall notify Department of Health. The product can be put on the market only upon approval for reinstatement from Department of Health is obtained.

INTRODUCTION TO FINISHED PRODUCT REPROCESSING AND RESALVAGING

"Reprocessing is taking a material (in-spec or out-of-spec) and reintroducing it to an existing (validated)process."

"**Reworking** is taking an out-of-spec product and running it through a non-standard process to bring it back into spec. Concurrent validation is required."

The reworking or recovery of rejected products should be exceptional. It is permitted only if the quality of the final product is not affected, if the specifications are met, and if it is done in accordance with a defined and authorized procedure after evaluation of the risks involved. A record should be kept of the reworking or recovery. A reworked batch should be given a new batch number.

The introduction of all or part of earlier batches, conforming to the required quality, into a batch of the same product at a defined stage of manufacture should be authorized beforehand. This recovery should be carried out in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf life. The recovery should be recorded.

The need for additional testing of any finished product that has been reprocessed reworked or into which a recovered product has been incorporated, should be considered by the quality control department.