SHREE H. N. SHUKLA INSTITUTE OF PHARMACEUTICAL EDUCATION AND RESEARCH

B.PHARM

(SEMESTER –VII)

SUBJECT NAME: QUALITY ASSURANCE

SUBJECT CODE: BP706TT

UNIT 04 (a): COMPLAINTS

Content

Complaints: Complaints and evaluation of complaints, Handling of return goods, recalling and waste disposal.

Complaints and evaluation of complaints

"Complaint is defined as statement that is something wrong or not good enough, which shows customer dissatisfaction about the company and the product".

Need for Complaint Handling System:

- It gives the company an opportunity to improve the quality of the product
- It is helpful to maintain cGMP.
- It maintains committed relationship between the customer and company.
- It is the regulatory obligation.
- Aid in implementing solutions to these quality problems
- Reduce costs and improve production schedules
- Reduce employee confusion
- Improve the safety and performance of devices.
- Identify poor performance in the overall quality system, particularly faulty design of devices, and faulty manufacturing processes
- Verify confidence in, and improve the performance of the quality system
- Reduce medical device reporting
- Improve customer relations by reducing the frequency of problems, complaints, and recalls; and,
- Assure compliance with device regulations and consensus standards.

Types of Complaint

Quality complaints: Originate at consumer level and concern with physical, chemical and biological properties or condition of labeling and /or packaging of the product.

Adverse reaction complaints: Due to allergic reactions of any other untoward reaction or fatal reaction or near fatal reaction.

Other medically related complaints: Include complaints such as lack of efficacy or clinical response.

Steps Involved in Handling of Complaints

The proposed handling system is in compliance with the GMP Guidelines of EU, USA and Brazil and is presented in four steps:

1. Receiving complaints.
2. Technical investigation.
3. Corrective actions/feedback to Customers.
4. Monthly reports/trend analysis.

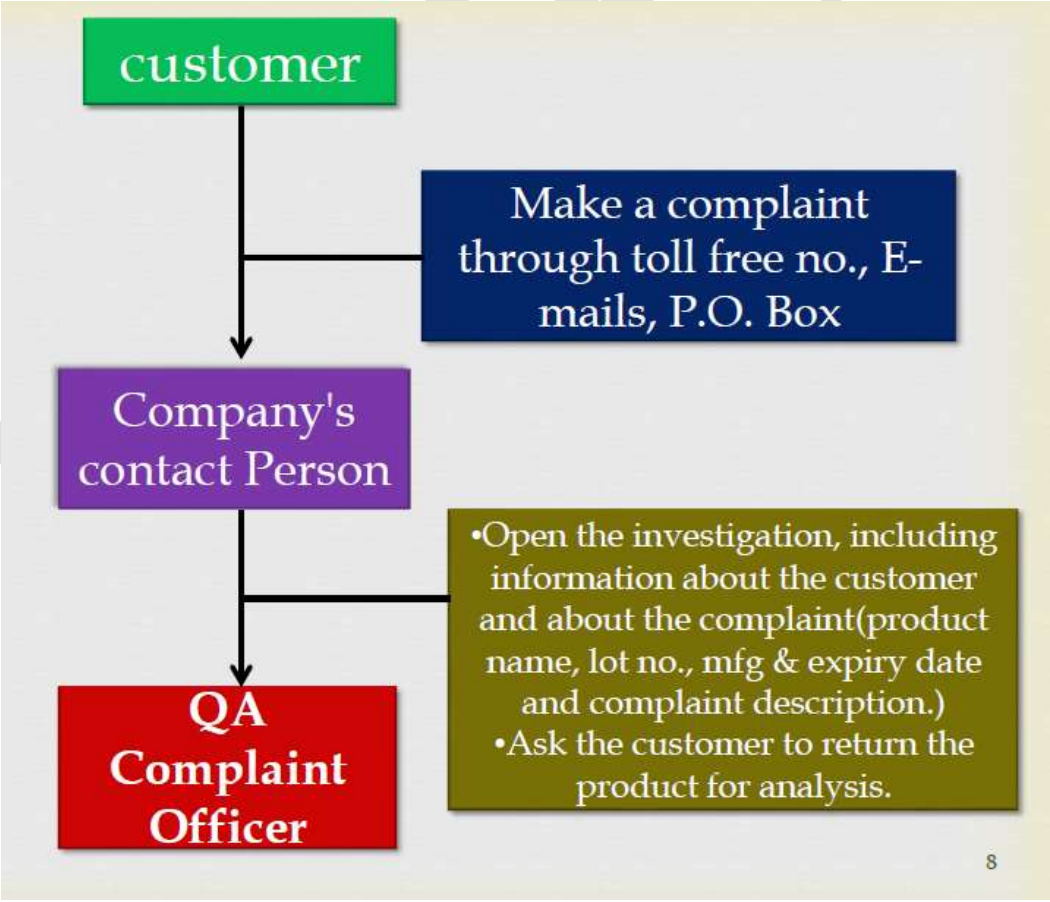
Step 1: **Receiving Complaints**

It is important to have open channels with customers in order to receive their suggestions, doubts and complaints. Generally, these channels are toll-free numbers, e-mails, chat-rooms and P.O. boxes.

The most flexible channels are toll-free numbers and chat-rooms.

Whatever the channel, it is necessary to have a person in charge of receiving the complaints and in putting them into an appropriate investigation form that shall be addressed to the Quality Assurance (QA) unit for investigation.

A written record should be maintained for all complaints received. The quality complaints should be forwarded to the quality control department of the manufacturing unit. Reports of adverse reaction should be handled by a committee of experts in the field.



Step 2: Technical Investigation

Upon receipt of the investigation form, the QA unit is able to start the investigation, which can be divided in two phases:

- Documentation based investigation.
- Laboratory analysis.

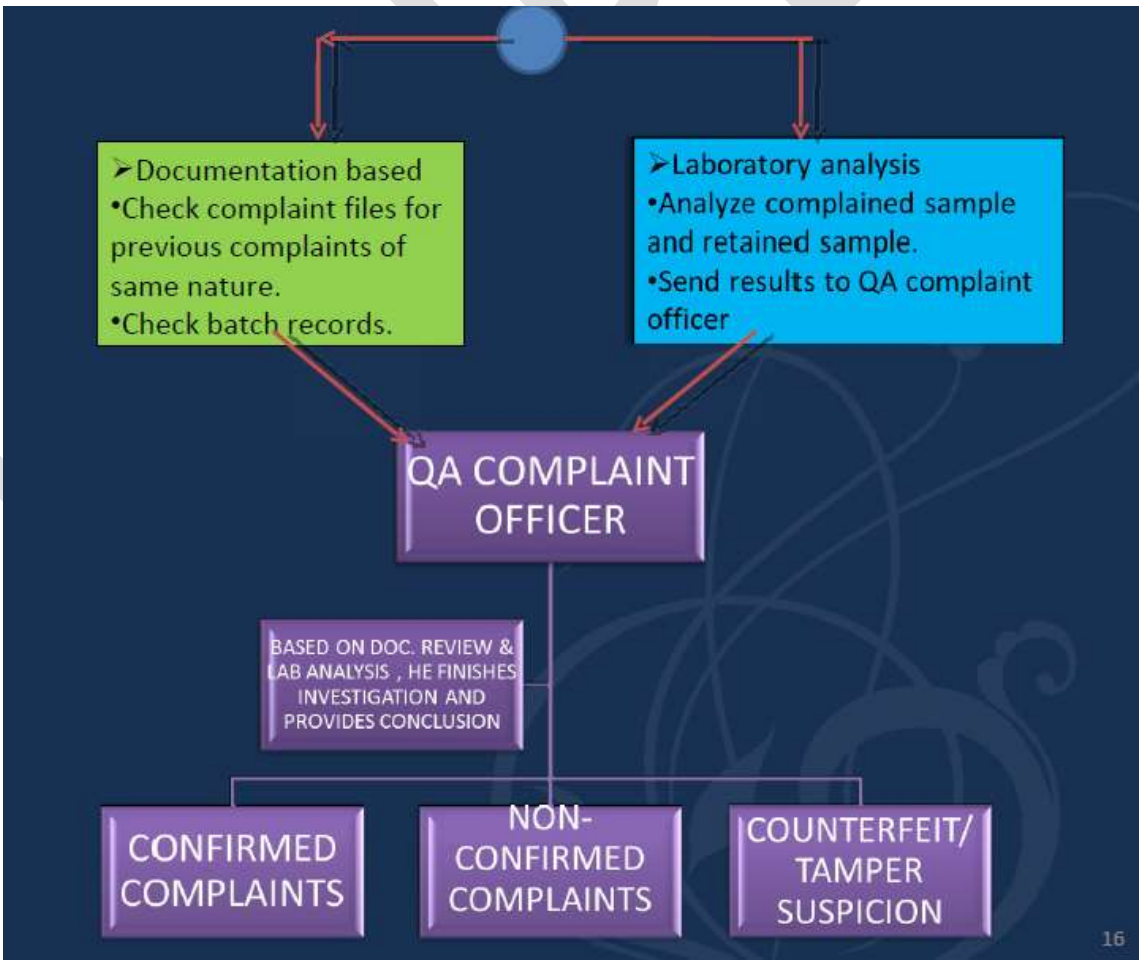
1) Documentation-based investigation:

The primary documentation to be reviewed consists of:

- ✓ Complaint files: This is constituted to check how many other complaints of the same nature had occurred to a specific lot and how they were handled.
- ✓ Batch records must be verified in order to see if there were any non-conformance during the production.

2) Laboratory analysis phase

Requesting QC laboratory to analyse both samples (complaint & retained). If the customer did not send the complaint sample for analysis, the lab. Investigation will be carried out production only with the retained.



After receiving the analytical results, there are three possible conclusions, as follows:

1. **Confirmed complaint** - When both complaint and retained samples showed out-of-specification (OOS) results or when only the complaint sample showed OOS results, it is clearly a single unexplained failing product.

   Example:
   A single unexplained failure may be when one tablet is missing in the intact blister strip in the complaint sample, but no deviation was found in the retained samples or during the in-process controls and final QC analysis recorded in the batch record.

2. **Non-confirmed complaint-** When both complaint and retained samples showed results in compliance with specifications or when only the complaint sample showed OOS results.

   OOS results in a complaint sample can be attributed to misuse or mishandling, when the drug product was not kept under appropriate conditions of temperature, humidity and light so that the identity, strength, quality and purity of the drug product could be affected.

   Example:
   Tablets of the complaint sample show a change in their appearance that is characteristic of a light, humidity or high temperature exposure.

3. **Counterfeit / tamper suspicion** - When the retained sample is within the specification but the complaint sample is clearly OOS with no reason for that, such as a counterfeit or tampered drug product.

   Example:
   An example of counterfeit is when packaging material is different from the original; an example of tampering is when the color of the drug product is completely different from the original or when any foreign substance was added to the product.

- ✓ The Complaint Officer must also check if the complaint represents a serious and unexpected adverse drug experience.
- ✓ The Complaint Officer and the QA Manager must sign off the investigation form once the investigation is completed.
- ✓ 30 days is a reasonable time to conclude an investigation.
- ✓ Complaint files should be retained for at least 1 year after the expiry date of the lot.

Step 3: Corrective Actions and Feedback to Customers
When investigation is complete, conclusion on the cause and action should be reported to the management. If it has been found out that complaint is the result of defective production then a copy of completed report should be sent to the production department to take corrective actions.

- **For all confirmed complaints,** corrective actions must be implemented. These actions can range from a simple and quick training to some employees to a formal Corrective Action and Preventive Action (CAPA) handling.

The criteria for choosing appropriate action depend on the nature of the complaint, and the complaint incidence.

If a CAPA is opened, a multidisciplinary team consisting of representatives of QA, QC, Regulatory Affairs and Production Management must be established.

As feedback to the customer, the company must write a response letter to the complainant to explain the investigation approach taken, the results obtained and any implications, in case the quality problem was confirmed.

The customer should be sent a free replacement product together with the response letter, since the customer returned the product (the 'complaint sample') to the company for analysis and a quality problem was found.

- Concerning non-confirmed complaints originating from misuse or inadequate handling of the drug product, even if there is no need for internal corrective actions, corrective measures should be implemented to provide orientation to the customer.

The customer should receive a written response together with scientific information on the correct use and handling.

Step 4: Monthly Reports and Trend Analysis-

Monthly reports should be elaborated in order to evaluate the amount and the nature of the complaints received and to perform a trend analysis of these complaints.

The monthly reports must answer the following questions:

- How many complaints did the company receive in the period?
- How many were confirmed?
- How many were non-confirmed or were counterfeit/tamper suspicion?

Graphic methods of displaying data are important adjuncts to data analysis and presentation.

The report must be readily available mainly during GMP inspections.

Complaint Record

It is responsibility of the In-charge, Quality control to see that each complaint is recorded, evaluated and reported to the management. Records of complaints should include the following information:

(i) Content of complaint

These should include:

- Name, dosage form, package form, batch no.;
- Date and the place of occurrence of complaint;

- Cause of complaint;
- Name and address of complaint in detail

(ii) Results of investigations

These should include:

- Result of investigation regarding market place, circulation condition and condition in which the defect was observed;
- Results of investigation of retained reference sample;
- Results of investigation of analysis and testing records, production and storage records;
- Results of investigation should be referenced to the BPR of the product

(iii) Evaluation

(iv) Follow up measures

Follow up measures include:

- Reply to the complainant,
- Remedial action so that complaint of this type do not recur and or drug recall;
- Competent authorities should be informed of any serious defect or problem.

Customer Complaint Record Book

Report no.	Date received	Product name	Received by	Product lot no.	Date investigation started	Date investigation ended

Handling of return goods, recalling

Recalling

Recall is an action taken to withdraw/remove the drugs from distribution or use including corrective action for which deficiencies are reported in quality, efficacy or safety.

Recalls also include drugs prohibited under the Provisions of Drugs & Cosmetics Act and also those products for which product licenses are suspended/cancelled.

Products which are already distributed or sold, may require at times to be recalled from market for various reasons.

Reasons for recalling:

- Substandard quality detected after the product was distributed i.e. damage of goods during transit. Such recalled products should be clearly identified and stored separately in a secure area until a decision is taken on their force.

- FDA authorities may order a recall for substandard quality of the finished product or for any other justified reasons.

- Manufacturer himself may find problems with the product such as:
  - substandard quality
  - problems related to the stability of the product
  - based on the market complaint received from a customer or physician

- Accidental damage of the consignment may also happen during transportation. In such case product quality may not be questionable, but packages may get damaged and cannot be sold or distributed as such in the market, and hence required to be recalled.

Types of Recall

A. Compulsory Product Recall

Industries do not take the responsibility of recalling the product voluntarily.
Commission conducts a "Compulsory Product Recall"

B. Voluntary Product Recall

Industries voluntarily recall the products in consultation with ICCC.
Encouraged by the commission where suppliers recall a product as soon as a defect is found that makes a product hazardous or unsafe for use or consumption.

Classification of Recall

1. CLASS I RECALL

Class I is a situation in which there is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death.

- Examples of Class I Recalls
  - Pathogens in ready-to-eat food: Salmonella, Listeria monocytogenes, E. coli, Clostridium
  - High levels of sulfites
  - High levels of heavy metals
  - Choking hazards for susceptible populations

2. CLASS II RECALLS

Class II is a situation in which use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote.

- Examples of Class II Recalls
  Foreign objects that pose a physical hazard
  Pathogens: Shigella, hepatitis A, Cyclospora, Cryptosporidium

3. CLASS III RECALLS

Class III is a situation in which use of, or exposure to, a violative product is not likely to cause adverse health consequences.

- Example of Class III Recalls
  An example might be bottles of aspirin that contains 90 tablets instead of the 100 stated on the label.

Level of Recalls

WHOLESALE PRODUCT RECALL (Distributor)
wholesale, distribution Centre's and importers

RETAIL PRODUCT RECALL (Dealer)
supermarkets, stores, hospitals, restaurants and major retail outlets

INDIVIDUAL CONSUMER RECALL
individual consumer

Product Recall Procedure

The following steps may be taken while executing the drug recall. These steps may be included in the written procedure for the drug recall:

- Determine the degree of recalling. There are three degrees of recall;

  Degree I – Product with high health risk requiring freezing of stock within 24 hours
  Degree II – Product with minor health risk or substandard requiring freezing of stock within 72 hours,
  Degree III – Product with other reasons for recall

- Disseminate recall instructions using telephone, telegram, postage, mass media, radio TV, depending upon the seriousness of the defect.

- Freeze the internal stock of the product

- Establish the record and report of the recalled product
- Organize the return of the recalled product

Information/data given below will be usefull to perform the recall of the drug product:

- Reason for recall
- Details of what is covered by recall and what is not covered, for example, individual batch or dosage form;
- The nature of risk, if some patients are at risk, advise as to how they should be managed;
- The cause of defects, if known;
- Organization of return of the defective product;
- Address, telephone number of persons to be contacted at national, provincial levels;
- Addresses, Telex and telephone numbers of radio, TV, press agencies;
- Addresses, telephone, telex number of distributors, wholesalers and hospitals etc.

A person should be designated to execute and coordinate drug product recalls. Sufficient staff should be given to him to handle all aspects of recall. This person should normally be independent of sales and marketing department. Quality control In-charge or a subordinate to him may be designated for product recall.

There should be written procedures for drug product recalls. These procedures should be reviewed and up-dated.

All competent authorities of all those countries to which the suspected product has been distributed, should be informed of any intension to recall the product. Distribution records should be readily available to the person who has been designated to execute and coordinate the recalls.

Progress of recall process should be recorded time to time and subsequently a final report should be issued including reconciliation between the quantities in hard, distributed and recovered. Recalled product should be stored in secured segregated area till its fate is decided.

Returned Drug Product

Pharmaceutical companies may receive returned goods because of many reasons through the marketing and distribution channel. There should be a clear and effective guidelines to be followed for the handling of pharmaceuticals.

The reasons of return goods from market

1) Through instructions of drug control or regulatory authorities
2) Return goods from distribution channel e.g.
    a. Expired products
    b. Products with damaged containers,
    c. Problems related to closures in packaging,
    d. Product unidentifiable due to improper printing of labels, (name or batch number)
3) Returned products by any voluntary action
4) Any problems associated with product reported by customers

Handling of return goods

Procedure for handling of return goods

1) Receiving unit should receive and record amount and identification of returned drug products.
2) After recording receipt, the receiving unit should hand over the returned drug products to the incharge of warehouse.
3) Incharge of warehouse then place returned goods in quarantine area so that stocks of such products do not get mixed up with trade stocks.
4) Quality control unit should be informed of the returned drug products which shall examine them and give opinion whether these should be held for possible recovery or should be destroyed.

On the basis of quality control testing, returned drug products may be classified into three types:

i. Drug products that still comply with all acceptable standards according to investigation by quality control unit.
ii. Drug products which can be reprocessed to comply with appropriate specifications;
iii. Product failing specifications or unacceptable products.

5) If recovery is possible, it should be brought to the knowledge of higher management which after considering all the consequences shall give decision whether recovery should be made or not.

6) Where it is decided to destroy the returned drug products, such products should be destroyed under the supervision of quality control personnel. Destruction should be carried out in such a way that it does not cause pollution of environment and products do not get into the hands of unauthorized persons. While disposing off drugs, provisions of Bio-medical waste Rules, 1998 may also be referred, if drug are biological products.

7) Records of disposition of returned drug products should be maintained. These records include records of reprocessing, repackaging and or destruction. Particulars that should be recorded in these records include:

   - Name of the product
   - Batch/lot number
   - Labelled potency
   - Dosage form
   - Quantity
   - Date of receipt
   - Origin of returned product
   - Storage conditions
   - Transportation

8) A written recommendation should be issued by quality control unit whether to salvage the returned drug product or destroy it. Where returned drug product has been recommended to the destroyed, a certificate of destruction should be issued after destruction and should be signed

by incharge warehouse and in-charge, quality control. This certificate should form a part of batch documentation.

Waste disposal

WHO provides guidelines on waste disposal in pharmaceutical industry.

These guidelines can be used by all relevant health authorities, competent to authorize the use or disposal of drugs. In many countries drug disposal will also involve environmental and waste management authorities, and experts at ministerial, regional and local level.

Treatment of pharmaceutical waste is very important because improper disposal may also have an adverse effect on land values, create public nuisances, otherwise; the failure or inability to salvage and reuse such materials economically results in the unnecessary waste and depletion of natural resources.

PHARMACEUTICAL WASTE COMPOSITION

- Organic chemical residues from manufacturing processes
- Helogenated/non-helogenated sludges and solids
- Sludge & tars
- Heavy metals
- Test animal remains

DISPOSAL METHODS

1. Return to donor or manufacturer
2. Landfill
3. Waste immobilization: encapsulation
4. Waste immobilization: inertization
5. Sewer
6. Burning in open containers
7. Medium temperature incineration
8. Novel high temperature incineration
9. Chemical decomposition

1. Return to donor or manufacturer

Those that arrive past or unreasonably near their expiry date it may be possible to return them to the donor for disposal.

Cross-frontier transfer of pharmaceutical waste

There are currently no international conventions regulating transfer of pharmaceutical products across frontiers. However, expired or spoiled pharmaceuticals are considered as hazardous waste and as such, if transferred across frontiers, become regulated and subject to the Basel Convention on the Trans frontier Shipment of Hazardous Wastes.

This involves prescribed procedures to obtain permission to cross international borders along the transit route prior to actual transport.

2. Landfill

To landfill means to place waste directly into a land disposal site without prior treatment or preparation. Landfill is the oldest and the most widely practiced method of disposing of solid waste. Three types are recognized.

A. Open uncontrolled non-engineered dump

Untreated waste discharged into an uncontrolled, non-engineered open dump does not protect the local environment and should not be used. Discarding of untreated waste pharmaceuticals into such a site is not recommended except as a last resort.

They should preferably be discharged after immobilization by encapsulation or inertization. As a last resort, where it is not possible to immobilize the waste pharmaceuticals, then the untreated wastes must be covered rapidly with large quantities of municipal waste to prevent scavenging.

B. Engineered landfill

Such a landfill has some features to protect from loss of chemicals into the aquifer. Direct deposit of pharmaceuticals is second best to discharging immobilized pharmaceutical waste into such a landfill.

C. Highly engineered sanitary landfill

Properly constructed and operated landfill sites offer a relatively safe disposal route for municipal solid wastes, including waste pharmaceuticals. The top priority is protection of the aquifer. An appropriate landfill consists of an evacuated pit isolated from watercourses and above the water table.

Each day's solid waste is compacted and covered with soil to maintain sanitary conditions.

3. Waste immobilization: encapsulation

Encapsulation involves immobilizing the pharmaceuticals in a solid block within a plastic or steel drum. Drums should be cleaned prior to use and should not have contained explosive or hazardous materials previously.

They are filled to 75% capacity with solid and semi-solid pharmaceuticals, and the remaining space is filled by pouring in a medium such as cement or cement/lime mixture, plastic foam or bituminous sand. For ease and speed of filling, the drum lids should be cut open and bent back.

Once the drums are filled to 75% capacity, the mixture of lime, cement and water in the proportions 15:15:5 (by weight) is added and the drum filled to capacity. A larger quantity of water may be required sometimes to attain a satisfactory liquid consistency.

Steel drum lids should then be bent back and sealed, ideally by seam or spot welding. The sealed drums should be placed at the base of a landfill and covered with fresh municipal solid waste.

4. Waste immobilization: inertization

Inertization is a variant of encapsulation and involves removing the packaging materials, paper, cardboard and plastic, from the pharmaceuticals. Pills need to be removed from their blister packs.

The pharmaceuticals are then ground and a mix of water, cement and lime added to form a homogenous paste. The main requirements are a grinder or road roller to crush the pharmaceuticals, a concrete mixer, and supplies of cement, lime and water.

5. Sewer

Some liquid pharmaceuticals, e.g. syrups and intravenous (IV) fluids, can be diluted with water and flushed into the sewers in small quantities over a period of time without serious public health or environmental affect.

Fast flowing watercourses may likewise be used to flush small quantities of well-diluted liquid pharmaceuticals or antiseptics. The assistance of a hydrogeologist or sanitary engineer may be required in situations where sewers are in disrepair or have been war damaged.

6. Burning in open containers

Pharmaceuticals should not be destroyed by burning at low temperature in open containers, as toxic pollutants may be released into the air. Paper and cardboard packaging, if they are not to be recycled, may be burnt.

Polyvinyl chloride (PVC) plastic however must not be burnt. While burning pharmaceutical waste is not advocated as a method of disposal, it is recognized that it is not infrequently used. It is strongly recommended that only very small quantities of waste pharmaceuticals be disposed of in this way.

7. Medium temperature incineration

In emergency situations the responsible authorities may consider it acceptable to treat expired solid form pharmaceuticals using a two-chamber incinerator that operates at the minimum temperature of 850°C, with a combustion retention time of at least two seconds in the second chamber.

Many older municipal solid waste incinerators are medium temperature incinerators and the use of these facilities is encouraged as an interim measure, rather than less safe options, such as inadequate discharge to a landfill.

In this case, it is recommended that the pharmaceutical waste is diluted with large quantities of municipal waste (approximately 1:1000). Such incinerators are not designed to incinerate halogenated compounds safely. The very low halogen content in most pharmaceuticals is likely to result in negligible halogen content in the combustion gases.

8. Novel high temperature incineration

Industries which use high temperature technology, such as cement kilns, coal fired thermal power stations or foundries usually have furnaces that operate at temperatures well in excess of 850°C, have long combustion retention times.

During burning the cement raw materials reach temperatures of 1450°C while the combustion gases reach temperatures up to 2000°C.

9. Chemical decomposition

If an appropriate incinerator is not available, the option of chemical decomposition can be used in accordance with the manufacturer's recommendations, followed by landfill.

For disposal of a small quantity of antineoplastic drugs this method may be practical. However for large quantities, for example, more than 50 kg of antineoplastics, chemical decomposition is not practical, as even small consignments need to be treated through repeated application of this method.

Summary of disposal methods in and after emergencies

DISPOSAL METHODS	TYPES OF PHARMACEUTICAL COMMENTS	COMMENTS
Return to donor or manufacturer, transfrontier transfer for disposal	All bulk waste pharmaceuticals, particularly antineoplastics.	Usually not practical - transfrontier procedures may be time consuming.
High temperature incineration with temperatures greatly in excess of 1200°C	Solids, semisolids, powders, antineoplastics, controlled substances.	Expensive.
Medium temperature incineration with two-chamber incinerator with minimum temperature of 850°C. Cement kiln incineration	In the absence of high temperature incinerators, solids, semi-solids, powders. Controlled substances.	Antineoplastics best incinerated at high temperature.
Immobilization		
Waste encapsulation	Solids, semi-solids, powders, liquids, antineoplastics, controlled substances.	
Inertization	Solids, semi-solids, powders, antineoplastics, controlled substances.	
Landfill		
Highly engineered sanitary landfill	Limited quantities of untreated solids, semi-solids and powders. Disposal of waste pharmaceuticals	

	after immobilization preferable. PVC plastics.	
Engineered landfill	Waste solids, semi-solids and powders, preferably after immobilization. PVC plastics.	
Open uncontrolled nonengineered dump	As last resort untreated solids, semisolids, powders - **must** be covered immediately with municipal waste. **Immobilization** of solids, semi-solids, powders **is preferable**.	Not for untreated controlled substances.
Sewer	Diluted liquids, syrups, intravenous fluids, small quantities of diluted disinfectants (supervised).	Antineoplastics, and undiluted disinfectants and antiseptics not recommended.
Fast-flowing watercourse	Diluted liquids, syrups, intravenous fluids; small quantities of diluted disinfectants (supervised).	Antineoplastics, and undiluted disinfectants and antiseptics not recommended.
Burning in open containers	As last resort, packaging, paper, cardboard.	Not acceptable for PVC plastics or pharmaceuticals.
Chemical decomposition	Not recommended unless special chemical expertise and materials available.	Not practical for quantities over 50 kg.

Summary of pharmaceutical categories and disposal methods in and after emergencies

CATEGORY	DISPOSAL METHODS	COMMENTS
Solids	Landfill	No more than 1% of the daily municipal waste should be disposed of daily in an untreated form (non-immobilized) to a landfill.
Semi-solids	Waste encapsulation	
Powders	Waste inertization	
	Medium and high temperature incineration (cement kiln incinerator)	
Liquids	Sewer	Antineoplastics not to sewer.
	High temperature incineration (cement kiln incinerator)	
Ampoules	Crush ampoules and flush diluted fluid to	Antineoplastics not to sewer.

	Sewer	
Anti-infective drugs	Waste encapsulation	Liquid antibiotics may be diluted with water, left to stand for several weeks and discharged to a sewer.
	Waste inertization	
	Medium and high temperature incineration (cement kiln incinerator)	
Antineoplastics	Return to donor or manufacturer	Not to landfill unless encapsulated.
	Waste encapsulation	Not to sewer.
	Waste inertization	No medium temperature incineration.
	Medium and high temperature incineration (cement kiln incinerator) (chemical decomposition)	
Controlled drugs	Waste encapsulation	Not to landfill unless encapsulated.
	Waste inertization	
	Medium and high temperature incineration (cement kiln incinerator)	
Aerosol canisters	Landfill Waste encapsulation	Not to be burnt: may explode.
Disinfectants	Use To sewer or fast-flowing watercourse: small quantities of diluted disinfectants (max. 50 litres per day under supervision)	No undiluted disinfectants to sewers or water courses. Maximum 50 litres per day diluted to sewer or fast-flowing watercourse. No disinfectants at all to slow moving or stagnant watercourses.
PVC plastic, glass	Landfill	Not for burning in open containers.
Paper, cardboard	Recycle, burn, landfill	