MANUAL FOR THE DEVELOPMENT AND MAINTENANCE OF HOSPITAL DRUG FORMULARIES

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INTRODUCTION

The purpose of this manual is to assist policy makers, hospital administrators, physicians, pharmacists and nurses in developing and implementing drug formulary systems in their health systems and hospitals.

The manual was developed as part of the Russia Rational Pharmaceutical Management (RPM) Project, being carried out by two US non-profit organizations. These organizations are Management Sciences for Health (MSH), and the United States Pharmacopeial Convention, Inc. (USP). Funding for the project is provided by the United States Agency for International Development (USAID).

The technical areas in which RPM provides assistance are:

- Drug Formulary Development and Maintenance
- Drug Procurement
- Drug Use Review
- Rational Drug Use
- Management and Economic Viability of Pharmacies
- Establishing or Expanding Drug Information Services

A brief description of each of these areas follows:

Drug Formulary Development and Maintenance

A critical first step in maximizing the therapeutic benefit of public sector expenditures on drugs is rational selection of drug products. In the US, this process is termed "formulary development." Formularies may be formed for individual facilities, facility types, or at the government level. At the hospital level, this may involve forming a Formulary and Therapeutics Committee responsible for establishing a limited list of drugs approved for procurement and use. Ideally, the list is formed through a careful examination of morbidity, consumption and treatment costs. The list may be further developed into a formulary manual containing basic drug information for use by prescribers, pharmacists and nurses.

Drug Procurement

Drug expenditures make up a significant proportion of most public health budgets, necessitating a management approach that includes prioritizing drugs for procurement, properly calculating quantities, utilizing competitive procurement techniques, selecting and monitoring suppliers, and, if appropriate, use of microcomputers and procurement management software.

Drug Use Review

Drug Use Review (DUR) programs are employed in public and private health systems as an ongoing means to ensure that drugs are used properly. Effective programs address all important therapeutic drug classes, and concentrate on drugs that are frequently used, expensive, used on high risk patients, or have significant side effects. Part of the program may involve establishment of Rational Drug Use Committees to solve identified problems through mechanisms such as establishment of standard treatment guidelines or educational programs.

Rational Drug Use

It is difficult to correct problems related to how drugs are used by prescribers, pharmacists and patients. Most successful rational drug use activities are based on regulatory, managerial and educational actions. Regulatory actions might include de-registration of a drug. Managerial actions might include removing a drug from a formulary list, or restricting use to certain categories of providers. Educational activities can be group or targeted training aimed at providers or patients.

Management and Economic Viability of Pharmacies

As a pharmaceutical sector is progressively liberalized, basic business management skills will become increasingly important to managers in community pharmacies. Managers need the skills to make management decisions in such areas as control of operating costs, staffing levels, procurement strategies, product acquisition costs, and marketing strategies.

Establishing or Expanding Drug Information Services

Provision of current, unbiased, drug information is essential in any health system that wishes to ensure that drugs are prescribed, distributed, and used appropriately. A program to address drug information development may include: formation of a drug information advisory group, performing an assessment of current resources, provision of unbiased information to providers and patients, development of standard treatment guidelines, and establishment of drug information centers.

Definitions

Because this manual introduces new approaches and concepts, it will be useful to provide the reader with definitions of terms and expressions:

Formulary system is a process whereby the medical staff of an institution, working through a Formulary and Therapeutics Committee, evaluates, and selects from the numerous available drug products those that are considered most efficacious, safe, and cost effective. A formulary system is a mechanism to streamline procurement activities, minimize institutional costs and optimize patient care.

The result of the drug selection process is a drug formulary list. The list contains all drugs approved for procurement and use in a given health facility. A drug formulary list is not synonymous with an essential drugs list in that formularies are restrictive, while essential drug lists do not confine the drug usage to only the drugs contained on that list.

Formulary drug lists developed for all health facilities in a health care system become the basis for the development of regional formularies.

Hospitals frequently develop formulary lists into a formulary manual, which is a concise reference book containing basic drug information about each drug on the formulary list.

At the health facility level, formulary development requires establishing an authoritative body, known as the Formulary and Therapeutics Committee, which is responsible for all aspects of the formulary system, including establishing policies and procedures for selection and use of drugs, developing drug information, and designing and conducting ongoing monitoring and evaluation programs that ensure proper use of drugs in the facility.

Why are formulary systems necessary?

At present, as many as 70% of the pharmaceuticals on the world market represent duplicate, "me-too," or non-essential products. Many are minor variations of a prototype drug and offer no therapeutic advantage over other drugs that are already available. Other drugs show high toxicity relative to their therapeutic benefit. In some cases drugs are newly released with insufficient information on efficacy or toxicity. Finally, many new products are for therapeutic indications not relevant to the basic needs of the population. They are nearly always more expensive than existing drugs.

The formulary system is a mechanism by which professional staff can solve these, and a number of other problems known to exist in most pharmaceutical systems:

- limited drug budgets
- increasing numbers of therapeutic alternatives
- improper prescribing and use of medications
- presence of unsafe and non-efficacious drugs
- lack of unbiased drug information
- high costs of handling large numbers of drugs
- drugs of questionable quality on the market

A properly implemented formulary system has the following positive results:

- Eliminating drugs that are unsafe and ineffective can result in decreased morbidity and mortality.
- Reduction in the number of drugs purchased results in either lower overall expenditures, or using the same level of funding to buy greater quantities of safe and effective drugs.
- There may be a decreased length of hospital stays through elimination of unsafe and ineffective drugs.
- Having a finite list of drugs used in the facility provides a focus for the provision of drug information and continuing education programs.

Stages and steps in developing a drug formulary system

This manual presents a chronological approach to the development and maintenance of drug formulary systems in hospitals. With modifications, the approach can be used to develop systems in different types of facilities where drugs are bought, stored and utilized. Likewise, a single formulary can be developed for a group of facilities, or for administrative areas such as districts, or counties.

Stage I. Administrative

Step 1. Introduce the concept and obtain support

Step 2. Establish a Formulary and Therapeutics Committee (FTC)

Step 3. Develop policies and procedures

Stage II. Develop Drug Formulary List

Step 4. Develop or choose therapeutic classification scheme

Step 5. Collect necessary data for analyzing existing drug use patterns

Step 6. Analyze morbidity and drug utilization patterns

Step 7. Conduct drug class reviews

Step 8. Approve the formulary list for use in the health facility

Step 9. Educate hospital personnel about policies and procedures on non-formulary drug use, additions and deletions to the formulary, and generic and therapeutic substitution

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Stage III. Develop Drug Formulary Manual

Step 10. Decide on formulary manual versus formulary list

Step 11. Develop policy and general information section

Step 12. Develop drug information monographs for the formulary manual

Step 13. Develop special information section

Step 14. Develop indexes to facilitate the use of the manual

Step 15. Produce and distribute the manual

Stage IV. The Formulary Maintenance Process

Step 16. Develop and implement Standard Treatment Guidelines (STGs)

Step 17. Design and conduct an ongoing Drug Use Evaluation (DUE) program

Step 18. Design and implement an adverse drug reaction monitoring system

Step 19. Update the formulary list or manual

STAGE I. ADMINISTRATIVE

Step 1. Introduce the Concept and Obtain Support

The desire to implement a formulary system may arise from either operation- or administration-level personnel. Regardless of where this desire arises, successful implementation requires support from both the medical staff and administrators. To obtain necessary support, vital background information is needed, such as:

- yearly drug budget
- drug budget as a percent of hospital budget
- total number of drug products routinely used
- the value of expired drugs during the last year
- names of the top ten drugs arranged by value
- incidence of adverse drug reactions
- number of deaths attributable to drug misadventures
- a list of drugs used in the facility that are banned in the country of manufacture
- examples of drug duplication

This information should be used in meetings and presentations tailored to the audience. Administrators will be more interested in how formulary systems can reduce the hospital drug budget, while clinical information will be of more interest to physicians. Regardless of the audience, presentations should result in familiarization with the benefits of formulary systems, and with the scope of work ahead.

A mandate in a government health plan facilitates formulary system implementation. An appropriate audience for gaining such support includes health administrators at central and local governments, the representatives from health insurance organizations, chief medical specialists, and licensing boards.

At the facility level, physicians must accept the need for restricting drug use, and be willing to change prescribing habits. Those responsible for drug procurement must agree to buy only drugs on the formulary list.

After the hospital administration decides to implement a formulary system the decision should be properly documented and incorporated as hospital policy. This may require changes in the health facility charter, or amendments to labor agreements with health providers.

Step 2. Establish a Formulary and Therapeutics Committee

The main objectives of the Formulary and Therapeutics Committee are the development and implementation of professional policies on drug selection, evaluation, procurement, safe use, and drug information in a given health facility. The committee also assists in the formulation of education programs designed to meet the needs of the professional staff for current and complete knowledge of matters related to drugs and drug practices.

Specific functions of the committee include:

- to develop the criteria for evaluating drugs for inclusion on the hospital formulary
- to serve in an advisory capacity to the medical staff and administration in all matters pertaining to drug use
- to aid in providing optimal drug therapy to all patients through the development of standard treatment guidelines
- to objectively evaluate clinical data regarding new drugs proposed for use in the health facility
- to prevent unnecessary duplication of drugs
- to develop the list of drugs accepted for procurement and use in the hospital
- to recommend and approve additions and deletions from the formulary
- to establish and plan suitable educational programs for professional staff on pertinent matters relating to drugs and their use
- to review reported adverse reactions to drugs administered
- to conduct ongoing drug use evaluation programs
- to design and develop a drug formulary manual and other drug information activities, such as newsletters

The decision to launch a Formulary and Therapeutics Committee is made by the chief physician of the hospital who, together with the first deputy, appoints members of the Committee. Normally, the Formulary and Therapeutics Committee is composed of seven to eleven voting members:

- The Chair - usually the first deputy of Chief Physician
- The Secretary - director of the hospital pharmacy, if such exists, or a pharmacist, or clinical pharmacologist
- Heads of main clinical hospital departments
- Authoritative physicians and specialists

When specific drugs are being considered, the committee may invite other specialists to participate in meetings as needed. These *ad hoc* members do not have voting privileges. A nursing representative should be invited to the meeting as needed. Decisions on inclusion or deletion of drugs are made by vote, according to approved procedures established by the committee.

In order to eliminate bias in drug selection, committee members may not have any business relationships with pharmaceutical distributors or manufacturers.

It is difficult to implement a formulary system in a hospital if physicians lack training in clinical pharmacology. It may be necessary for one or more members of the committee to attend continuing education courses in clinical pharmacology.

Step 3. Develop Policies and Procedures

Developing policies and procedures is imperative to the work ahead. These should be approved by the Chief Physician or Chief Administrator in the organization, so that the Formulary and Therapeutics Committee is empowered to make and implement decisions, and request compliance from the medical staff. Additionally, the policies and procedures serve as a tool to create organization, structure and planning of workload. The policies and procedures should cover the following areas:

- Criteria of formulary drug selection
- Additions to and deletions from the formulary
- Prescribing requirements
- Non-formulary drug use
- Adverse drug reaction monitoring
- Drug usage evaluation
- Investigational drug use
- Sales representatives' guidelines
- Rules governing the Formulary and Therapeutics Committee

The following are examples of hospital Formulary and Therapeutics Committee policies:

A. Drugs will be admitted to the formulary under a nonproprietary (generic) or official name. The combined best judgement of the medical pharmacy staff will decide whether a particular product meets the standards implied by acceptance into the formulary. Approved therapeutic equivalents may be dispensed unless otherwise indicated.

B. When reviewing drugs for formulary decisions the following criteria shall be considered:

- There should be a justified need for the drug.
- There should be no other drug on the hospital formulary list that satisfies the same need.
- Satisfactory clinical trials should be conducted at the facility, or information on such trials conducted elsewhere should be available.
- No drug will be admitted to the formulary if its composition is secret or its therapeutic value has not been established.
- No mixtures of two or more substances will be admitted unless the mixture presents therapeutic advantages over the single substances.
- The cost of the drug should justify its use.
- The drug should be readily available from suppliers.

C. Clinical department heads shall be notified whenever a formulary drug is under consideration for deletion so that they may submit evidence for its retention.

D. The committee may admit specified dosage forms of a drug, and not admit other dosage forms of the same drug.

E. The Formulary and Therapeutics Committee will meet monthly on a regular basis or "on call" by the chair.

F. The secretary of the committee shall notify the committee members about meetings, and carefully take minutes.

Once policies have been established, step by step procedures to implement or enforce policies should be drafted. For example, the procedure for formulary additions and deletions may be:

1. Requests for addition or deletion of a drug to the formulary can only be made by an attending physician. The request is made through completion of a Request for Addition/Deletion Form.

2. The Request for Addition/Deletion Form is sent to the Secretary of the Formulary and Therapeutics Committee, and, if complete, forwarded to the Drug Information Center (or drug information pharmacist, or clinical pharmacologist).

3. The Drug Information Center conducts a literature search and prepares a written evaluation comparing the newly requested drug with current formulary drugs used for the same indications. Criteria for comparison are efficacy, safety and cost.

4. The evaluation should be reviewed by the entire Formulary and Therapeutics Committee.

5. If the new drug is found to be superior to an existing drug on the formulary, or to be unique, it will be added to the formulary.

6. Existing drug(s) on the formulary found to be inferior, and not needed for use for other indications, will be deleted from the formulary.

Policy on use of generic names

One of the most important policy concepts in formulary development is that drugs should be selected and listed in the formulary by generic name.

Each drug on the market has a chemical name (*e.g.*, 6-[D(-)-a amino α-phenyl acetamide]-penicillinic acid) and an international nonproprietary or generic name (*e.g.*, ampicillin). The generic name is a drug's official name, regardless of who manufactures or markets it. A commercial, or brand trade name (*e.g.*, Polycillin®) is often chosen by the manufacturer or distributor to facilitate recognition of the product and to differentiate it from the same drug furnished by other firms.

The use of generic names in formularies should serve to promote purchasing and prescribing by generic name. This practice has the following advantages:

- generic names are more informative than brand names and reflect their affiliation to certain therapeutic or chemical classes;

- generic prescribing facilitates product substitution, whereas prescribing by a brand name often implies filling only the prescribed brand name; and

- generic names facilitate purchasing of products from multiple suppliers, whether as brand name or as generic products. Generically produced drugs are often cheaper than products sold by brand names.

Insistence on the use of a particular brand name drug product by the committee is justified if bioavailability and bioequivalence of drug products from different manufacturers vary so significantly that they can alter the desired therapeutic effect. This mainly applies to cardiac glycosides, anticonvulsants, hormones, antiarrhythmics, anticoagulants and other drugs with a narrow therapeutical index.

When brand names drugs of prolonged action are included in the formulary list, it is critical to clearly specify them. This is another case where use of a particular brand name drug product can be justified.

STAGE II. DEVELOP DRUG FORMULARY LIST

Step 4. Develop or Choose a Therapeutic Classification Scheme

After establishing policies and procedures, the next step for the Formulary and Therapeutics Committee is to develop or choose the drug classification scheme to be used for the formulary list.

Drugs may be classified according to the following principles:

- Therapeutic usage - for example, antianginal drugs, antitumor drugs, antihypertensive drugs, antibiotics, etc.
- Pharmacological effect - for example, calcium channel blockers, diuretics, vasodilators, anticoagulants, etc.
- Chemical structure - for example, cardiac glycosides, alkaloids, steroids, fluorchinolones, cephalosporins, etc.
- Nosological principle - for example, medicines for treatment of bronchial asthma, stenocardia, arterial hypertension, ulcer, etc. This is the most convenient for a clinician.

A unified drug classification adopted by all countries worldwide does not exist. In some countries, such as Great Britain, the National Formulary is organized by disease and organs. American formularies are usually based on therapeutic usage. Holland uses a combined system of classification by anatomic, therapeutic and chemical criteria. For hospitals, it is recommended to use classifications based on therapeutic usage. This is useful for nurses, pharmacists, pharmacy technicians, and non-medical staff involved in drug procurement.

The World Health Organization (WHO) classification scheme is gaining wide international acceptance in formulary systems. This scheme has been adopted by UNICEF and the majority of non-profit international suppliers because adoption of a unified classification scheme facilitates price comparison and distribution.

See Annex One for examples of therapeutic classification schemes.

Step 5. Collect Necessary Data for Analyzing Existing Drug Use Patterns

Before the committee can start evaluating drugs for inclusion into a formulary, the following data need to be collected and analyzed:

A. Morbidity data A hospital drug formulary should be tailored to its own patient population. Therefore, prior to the selection of drugs, data and statistics on prevalent diseases and patient characteristics must be obtained and evaluated. This may take the form of a list of the top 50 diagnoses or top 50 reasons for admission. This list of diagnoses or reasons for admissions needs to be compiled from admission data for an adequate time frame, *e.g.*, one year. The exact information available will depend on statistics kept by the hospital.

B. Drug information available The Formulary and Therapeutics Committee cannot properly select drugs for inclusion into the formulary without reliable and unbiased information. The use of drugs of questionable efficacy can be prevented or reduced by providing unbiased drug information.

Typical examples of biased drug information are drug company brochures, the *Physician's Desk Reference*, and Vidal. Unbiased drug information reference materials are based on studies and clinical trials from different sources, not with the intent to promote a product but to provide the users of the product with relevant data. Examples include *The United States Pharmacopeia Drug Information for Health Professionals*, and *The American Hospital Formulary Service Handbook*.

Hospitals implementing formulary systems must, therefore, evaluate currently available references. If necessary, one or more of the above mentioned unbiased sources of drug information should be obtained.

C. List of all drugs purchased and used by the health facility during the last year The pharmacy or drug procurement department should provide the Formulary and Therapeutics Committee with a list of all drugs that have been purchased during the last fiscal year, calendar year, or previous 12 months. Data from one year is desirable because of seasonal variations in drug use, but a shorter time period can be used if necessary. For the analysis that follows, the following information is needed: drug name, strength, dosage form, cost to facility, and quantity used over a given time period.

Step 6. Analyze Morbidity and Drug Utilization Patterns

Analyze morbidity data

This is a necessary step for the committee to understand if the therapeutic needs of patients are being met, and whether drugs are purchased and used rationally. Accurate morbidity data is required to perform the analyses.

1. Rank order the morbidity data obtained in the previous step (ideally, the top 50 diagnoses) by the number of cases for each disease or condition. This information will be valuable when deciding which group of drugs should be analyzed first.

2. Calculate the percent that each of the top 50 diseases represents in the overall morbidity. Disregard diseases that typically do not require drug therapy. For example, myopia may constitute around 20% of patient visits for nervous and sensory disorders in outpatient settings, but usually requires only a simple eye exam and fitting for eyeglasses.

3. Using the information on drug purchases, choose the drugs (and their costs) that were used to treat the top 50 diseases, and calculate the percent of their value (by disease) to the overall health facility drug budget.

4. Compare the lists compiled in steps 2 and 3 above to get an idea if drug use appears to be rational according to the morbidity in the facility. For example, the morbidity data at a hospital may indicate that infectious and parasitic diseases accounted for 8.0% of outpatient, and 5.4% of inpatient visits, while only 3.14% of purchased drugs (by value) were appropriate therapy for these conditions. Similarly, while "psychological disorders" represented 7.5% of outpatient, and 6.5% of inpatient visits at this hospital, no antipsychotic or antidepressant drugs were among the top drugs purchased (by value), despite the fact that these drugs tend to be expensive.

   These figures suggest that infectious/parasitic diseases and psychological disorders may have been under-treated using pharmacotherapy at this hospital.

Once areas of concern with treatment of disease groups have been identified, it is necessary to identify the specific drugs that represent the greatest portion of the drug budget. This is done through ABC and VEN analyses.

Conduct ABC and VEN analyses

ABC analysis is a method by which drugs are divided according to their annual usage (unit cost times annual consumption), into Class A items (10 - 20% of the items, which account for 70-80% of the funds spent), Class B items (with intermediate usage rates) and Class C items (the vast majority of items with low individual usage, the total of which accounts for less than 25% of the funds spent). ABC analysis can be used to give priority to Class A items in making drug selection and procurement decisions.

VEN analysis is a system of setting priorities for drug selection and purchasing in which drugs are classified according to their health impact: Vital, Essential and Non-essential drugs:

Vital drugs: Drugs that are potentially life-saving (vaccines), or which have significant withdrawal side-effects such that a regular supply is mandatory (*e.g.*, propranolol, steroids)

Essential drugs: Drugs that are effective against less severe, but nevertheless significant forms of illness

Non-essential drugs: Drugs for minor or self-limited illnesses, drugs that are of questionable efficacy, and drugs that have a high cost for a marginal therapeutic advantage

Using both systems provides the Formulary and Therapeutics Committee with important data that will facilitate decision making on which drugs can be eliminated from use, which drugs need to be incorporated into the formulary, and which drugs are being over- or under-utilized.

An example of ABC/VEN analysis is provided as Annex Two.

If desired, a more detailed classification can be done. For example, rather than Vital, Essential or Non-essential designations, the following may be used:

Ethiothrope Therapy - therapy directed at elimination of disease cause
Pathogenic Therapy - therapy directed at elimination or suppression of disease development mechanisms
Symptomatic Therapy - therapy directed at elimination or decrease of certain disease manifestations
Replacement Therapy - is held with the insufficiency of natural biologically active substances
Preventive Therapy - is held for disease prevention

Step 7. Conduct Drug Class Reviews and Create a Draft Formulary List

This step is the most important one in the formulary development process because it is here that the list of drugs to be used in the hospital is created. The drug class review will have impacts that are both therapeutic and economic in nature. Therapeutic aspects include the improvement of patient care through discontinuation of use of drug products that are less safe and/or efficacious. In addition, the results from this step will have an impact on the cost of therapy, and can provide the basis for economic improvements for the hospital budget.

It is, therefore, important to carefully plan and carry-out drug class reviews, and to allow adequate time to conduct them thoroughly. A committee at a large hospital may need to review thousands of drugs, and can expect the process to take up to one year.

At this step in the process, the committee must decide how the formulary list will be developed, by choosing one of these options:

A. The selection process may begin with the assumption that all drugs currently in use in the hospital constitute the hospital formulary list. During the course of the review process, drugs are deleted, and in some cases, new drugs are added. This is the most commonly chosen approach.

B. The formulary may be developed one drug class at a time during the review process. After reviewing the first class of drugs, the formulary contains only the drugs selected for that class. Restricted procurement and prescribing may be immediately implemented only for those drugs. As other classes are reviewed, drugs are added to the formulary.

The information obtained in the ABC/VEN analysis can be used to develop a schedule for drug reviews. For example, if the analysis shows that 30% of the drug budget is used for procurement of antibiotics, the committee may decide to start with this class of drugs. Drug classes that have been known to be problematic in the past should also be given high priority in the process. It may not be possible to create a complete time line for review until the first few reviews have been conducted and the committee can more accurately estimate time requirements. Ultimately, the schedule will be determined by the ability of the committee to prepare reviews, and the number of drugs to be reviewed.

At the time the schedule is created, committee members should be assigned to prepare review presentations of one or more drug classes. If expertise from outside the committee is needed, the chairperson should recruit required specialists. The committee members, or other specified experts, may choose to form a working group to assist in the process. Working groups allow for input from a greater number of physicians. During the review process, it may be reasonable to hold monthly meetings, and review one class of drugs at each meeting.

In general, underlying questions for evaluating a drug for formulary admission are:

- Is there a justifiable need for this drug?
- Is this need met by some other agent already in use?
- Can this need be met in a safer and more efficacious manner by other agents in the formulary?
- Has the drug received adequate clinical evaluation?
- Does the use of the drug justify its expense and associated costs?
- Will this drug be prescribed for outpatients as well, and if so, is reimbursement guaranteed by medical insurances or exempt patient reimbursement procedures?

For each agent a thorough and objective evaluation must be made to ascertain that the agents in each class are being selected rationally. For agents that are the only product in a therapeutic class it should be determined that they are a cost effective form of therapy and appropriate for promoted indications.

Therapeutic aspects of the drug class review

Because the drug class review will have direct clinical impact it is recommended that a short evaluation monograph be prepared. Listed below is information that is typically included in such a monograph:

- Proposed designation according to the therapeutic classification scheme.
- Generic name - The officially approved name, and, if a combination product, all active ingredients by generic name.
- Brand name(s) - This can be important for multi-source products.
- Product source(s) - The name and address of the manufacturer(s) for this product.
- Indication(s) - Ensure that all conditions to be treated are covered by formulary drugs.
- Contraindication(s) - Contraindication(s) can be a basis for non-inclusion.
- Efficacy/Pharmacology - When comparing drugs with similar indications, decisions can be made based on efficacy. It is important to include the mechanism of action and, in the case of anti-infective agents, the microbiologic spectrum of activity.
- Side effect profile - Drugs with small side effect profiles are preferred. It is also important to provide some assessment of the incidence and seriousness of these side effects. If there are significant numbers of people that had to withdraw from clinical trials due to side effects, it should be mentioned here.
- Previous problems experienced with the drug in the hospital - The formulary process can be used to eliminate drugs that have caused adverse drug reactions, or drugs frequently prescribed for non-indicated conditions.
- Administration schedules - There is a trend toward using drugs that are administered fewer times per day. For intravenous drugs, this can reduce administration costs.
- Duration of therapy - Shorter durations of therapy will reduce administration costs and can reduce length of stay.
- Routes of administration - Drugs that can be given orally are less expensive than injectables both in terms of acquisition cost and related administration costs.
- Pharmacokinetic profile - Absorption, route of elimination, ability to cross the blood-brain barrier, etc. are important facts to consider. Specific data such as volume of distribution, percent metabolized in the liver or eliminated unchanged through the kidney, and elimination half-life

should be included. Information about dosing in patients with renal impairment can be included under the elimination subheading.

- Monitoring required - The hospital should have equipment, reagents, etc., needed to monitor formulary drugs. Lack of monitoring equipment in the facility may prevent inclusion on the formulary, however, the risk-benefit of using an efficacious drug without monitoring needs to be considered.

- Drug-drug and drug-food interactions - Drugs with fewer interactions are preferred.

- Availability - The procurement department should report on sources of supply and time required to obtain drugs.

- Similar agents that this drug may replace - List of all agents that are therapeutically similar and that may be eliminated from the formulary if this drug is included.

- Recommendations and critical issues - A recommendation should be made here as to whether or not this drug should be included in the formulary. Specific issues for use can also be addressed here, such as restriction to special services. Examples of possible restrictions follow:

    1. Diagnosis restrictions - Identify indications that constitute acceptable uses for a formulary drug within the health-care setting. The use of toxic or potentially dangerous drugs may be justified when the risk of developing side effects is outweighed by the efficacy in specific diagnoses or medical conditions. For example, a particular colony-stimulating factor might be approved for use only as an adjunct to cancer chemotherapy. Use of the drug for other indications would then fall outside the approved diagnosis criteria.

    2. Prescriber restrictions - Identify prescribers approved to use specific formulary drugs or drug classes. Examples include limiting the use of specific injectable antibiotics to infectious diseases specialists, or restricting use of thrombolytic drugs to cardiologists or emergency room physicians.

    3. Pharmacological restrictions - Identify approved doses, frequencies of administration, durations of therapy, or other aspects that are specific to the use of a formulary drug.

Examples of evaluation monographs: cefuroxime and ceftriaxone.

A. Cefuroxime:

- **Classification**: Second generation cephalosporin.

- **Generic names**: Cefuroxime sodium and cefuroxime axetil.

- **Brand names**: Cefuroxime sodium: Kefurox^{R}, Lilly; Zinacef^{R}, Glaxo.
  Cefuroxime axetil: Ceftin^{R}, Glaxo.

- **Indications**: Lower respiratory tract infections, otitis media, pharyngitis and tonsillitis, genitourinary tract infections, skin and skin structure infections, and bone and joint infections, caused by susceptible organisms.

- **Contraindications**: Hypersensitivity to cephalosporins and penicillins.

- **Precautions**: Modify dosage in patients with renal insufficiency; use with caution in patients with history of gastrointestinal disease, particularly colitis; each gram contains 2.4 mEq sodium.

- **Pharmacology**: Cefuroxime is bactericidal in action. The antibacterial activity results from inhibition of mucopeptide synthesis in the bacterial cell wall. The spectrum of activity includes *staphylococci,* group B *streptococci, H. Influenzae* (type A and B), *E. Coli, Enterobacter, Salmonella, Klebsiella, Proteus mirabilis.*

- **Side effects**: 1% to 10%: Thrombophlebitis, decreased hemoglobin and hematocrit, eosinophilia, transient rise in SGOT (AST)/SGPT (ALT) and alkaline phosphatase. Less than 1%: Dizziness, fever, headache, rash, nausea, vomiting, diarrhea, stomach cramps, GI bleeding, colitis, transient neutropenia and leukopenia, transient increase in liver enzymes, increase in creatinine and/or BUN, pain at the injection site, vaginitis.

- **Administration schedules and dosages**:

Neonates:	10-25 mg/kg/dose every 12 hours
Children:	Oral: Not recommended due to poor absorption
	<2 years: 125 mg twice daily (cefuroxime axetil)
	2-12 years: 250 mg twice daily (cefuroxime axetil)
	IM/IV: Bone/joint infection: 50 mg/kg/dose every 8 hours
	Meningitis: 50-60 mg/kg/dose every 6 hours
	Other: 100 mg/kg/day, divided every 6 hours; max.: 6 gm/24 hours
Adults:	Oral: Not recommended due to poor absorption; 125-500 mg twice daily depending on severity of infection (cefuroxime axetil)
	IM/IV: 750 mg to 1.5 gm every 8 hours; max.: 6 gm per 24 hours

- **Duration of therapy**: Usual course of therapy is 7 to 10 days but should be continued for at least 48-72 hours after patient is afebrile or evidence of eradication of the infection has been obtained.

- **Pharmacokinetics**: Absorption: Following oral administration, the bioavailability of cefuroxime axetil is approximately 27% when fasting, and 52% when given with food. Cefuroxime sodium is not appreciably absorbed. Following IM administration of cefuroxime sodium, peak plasma concentrations of the drug are attained within 15-60 minutes. Distribution: Cefuroxime is widely distributed into body tissues and fluids including the kidneys, heart, gallbladder, liver, prostatic adenoma tissue, uterine and ovarian tissue, aqueous humor, saliva, sputum, bronchial secretions, bone, bile adipose tissue, wound exudates, peritoneal fluid, ascitic fluid, synovial fluid, pericardial fluid and pleural fluid. The apparent volume of distribution of cefuroxime in healthy adults ranges from 9.3 to 15.8 L. Cefuroxime crosses the placenta and is distributed into milk. Elimination: Cefuroxime is cleared renally. The serum half-life of cefuroxime axetil ranges from 1.2 to 1.6 hours. In adults with normal renal function, the serum half-life of cefuroxime sodium following IM/IV administration ranges from 1 to 2 hours. In patients with renal impairment, the serum half-life is prolonged and ranges from 1.6 to 16.1 hours.

- **Drug interactions**: Probenecid increases serum levels of cefuroxime.

B. Ceftriaxone:

- **Classification**: Third generation cephalosporin.

- **Generic names**: Ceftriaxone sodium.

- **Brand names**: Rocephin^{R}, Roche.

- **Indications**: Lower respiratory tract infections, skin and skin structure infections, bone and joint infections, intra-abdominal infections, urinary tract infections, meningitis, septicemia, and gonorrhea caused by susceptible organisms. It has also been used for perioperative prophylaxis.

- **Contraindications**: Hypersensitivity to cephalosporins and penicillins.

- **Precautions**: Ceftriaxone should be used with caution in patients with a history of GI diseases, particularly colitis. Since ceftriaxone can precipitate in the gallbladder, some clinicians recommend that ceftriaxone be used with caution in patients with pre-existing disease of the gallbladder, biliary tract, liver or pancreas.

- **Pharmacology**: Ceftriaxone is bactericidal in action. The antibacterial activity results from inhibition of mucopeptide synthesis in the bacterial cell wall. The spectrum of activity includes *staphylococci,* groups A and B *streptococci, H. Influenzae, Neisseria meningitidis* and *Neisseria gonorrhoeae.*

- **Side effects**: 1% to 10%: Eosinophilia, thrombocytosis, leukopenia, diarrhea, increased serum concentrations of AST (SGOT) and ALT (SGPT). Less than 1%: Increase in alkaline phosphatase, pruritus, fever, chills, jaundice, headache, dizziness, oral candidiasis.

- **Administration schedules and dosages**: IV/IM:
  Neonates: <2000 gm: 50 mg/kg/day every 24 hours
  >2000 gm: 75 mg/kg/day every 24 hours
  Children: 50 - 75 mg/kg/day in 1 or 2 divided doses
  Adults: 1 to 2 gm every 12 to 24 hours, depending on the type and severity of the infection; max.: 4 gm per 24 hours

- **Duration of therapy**: Usual course of therapy is 7 to 10 days but should be continued for at least 48 hours after the patient is asymptomatic or evidence of eradication of the infection has been obtained.

- **Pharmacokinetics**: Absorption: Ceftriaxone is not appreciably absorbed from the GI tract and must be given parenterally. Following IM administration of ceftriaxone, peak plasma concentrations of the drug are attained 1.5 to 4 hours after the dose. Distribution: Following IM or IV administration, ceftriaxone is widely distributed into body tissues and fluids including the gallbladder, lungs, bone, bile, prostate adenoma tissue, uterine tissue, atrial appendage, sputum, tears, and pleural, peritoneal, synovial, ascitic, and blister fluids. The volume of distribution of ceftriaxone is dose dependent and ranges from 5.8 to 13.5 L in healthy adults. Ceftriaxone generally diffuses into CSF following IM or IV administration. CSF concentrations of the drug are higher in patients with inflamed meninges than in those with uninflamed meninges. Ceftriaxone crosses the placenta and is distributed into amniotic fluid. Elimination: Ceftriaxone is cleared renally and in feces via bile. The serum half-life of ceftriaxone is 5 to 9 hours in adults. Ceftriaxone is not removed by hemodialysis or peritoneal dialysis.

- **Drug interactions**: Concomitant administration of probenecid does not seem to affect the pharmacokinetics of ceftriaxone. However, in higher doses of oral probenecid (1 to 2 gm daily), probenecid may partially block biliary secretion of ceftriaxone.

Economic aspects of drug class review

In the past, economic considerations in making formulary decisions dealt mainly with the acquisition cost of a drug. Increasingly, economic analysis has expanded to include costs and/or expenses associated with drugs that are not as obvious. These costs are part of the institution's overall cost related to drug therapy and need to be taken into consideration as well. This expanded horizon of evaluating costs associated with drug treatments has become especially important in this time of shrinking health care budgets and increasing health care costs. The knowledge of a drug therapy's economic impact to health care and ultimately to society has become more and more important. These considerations include the identification, measurement and comparison of all costs and consequences (both positive and negative) of pharmaceutical products. Because drug product acquisition costs are only one cost aspect to consider, medication formulary decisions must consider the full impact of medication use.

Examples of such costs include:

- Drug cost for an entire course of therapy
- Drug administration costs including costs for materials such as IV bags or bottles, solutions, syringes, etc.
- Cost of drugs that have to be co-prescribed, such as premedications, as well as medical supplies needed (examples: the cost of cimetidine as mandatory premedication for Taxol^{R} in the treatment of breast

cancer; or the cost of compression stockings, a mandatory supply during enoxaparin therapy in the preventive treatment of deep venous thrombosis following hip surgery)

- Acquisition and administration costs of drugs that are needed to treat known side effects and complications (example: the cost of hydrocortisone and meperidine to treat rigors following amphotericin B administration)
- Costs related to lab tests, including monitoring equipment and reagents
- Costs related to storage if special storage conditions are required
- Probable effect on length of stay

Although it is very difficult to quantify probable effect on length of stay financially, the economic analysis should minimally include a statement of a proposed drug's probable effect on length of stay.

To the extent possible these costs should be considered when making formulary decisions. Formulary Committees are frequently approached by representatives of the pharmaceutical industry trying to persuade committee members to add a particular product to the formulary. It is appropriate to request sales representatives to outline total costs associated with a particular drug therapy. However, this type of cost analysis can be done by the Formulary Committee itself. A multi-disciplinary make-up of the Formulary Committee will enhance the accuracy of this cost analysis.

The goal of a drug formulary should not be to decrease the drug budget alone, but to decrease the overall costs needed to manage specific diseases. An example of a very basic analysis follows.

Community acquired pneumonia

Treatment options: Cefotaxime 1 gm IV q8h x 7-10 days versus
Ceftriaxone 1 gm IM q24h x 7-10 days [1]

	Unit Cost ($)	Daily Cost ($)	Cost for Course ($)
Cefotaxime 1 gm IV q8h x 7-10 days			
Drug Cost	**12.66**	37.98	265.86 - 379.80
Medical Supply Costs			
syringe/needle	0.65	1.95	13.65 - 19.50
IV set	0.35	1.05	7.35 - 10.50
Total Cost[2]			**286.86 - 409.80**
Ceftriaxone 1 gm IM q24h x 7-10 days			
Drug Cost	**33.64**	33.64	235.48 - 336.40
Medical Supply Costs			
syringe/needle	0.65	0.65	4.55 - 6.50
Total Cost[2]			**240.03 - 342.90**

If a Formulary Committee were to consider only acquisition cost, ceftriaxone appears to be considerably more expensive than cefotaxime ($33.64 - $12.66 = $20.98 more per dose). However, when dosing frequency and the cost of supplies needed to administer the drugs are also considered, ceftriaxone is actually more cost effective to use than cefotaxime ($409.80 - $342.90 = $66.90 less for a ten-day treatment course).

If the cost of the labor required to prepare doses were also considered, greater savings could be shown. However, adding labor costs to the analysis is only valid if the savings can actually be applied, such as through reduction in staff, or reassignment of a staff member from drug preparation to another task.

[1] Please note that neither treatment would be considered treatment of first choice since both cephalosporins provide a broader spectrum coverage than necessary. It is simply the author's intent to demonstrate that a lower acquisition cost sometimes decreases the drug budget but not the overall cost to the institution.

[2] The estimated total costs are not necessarily complete figures, as they include only the acquisition costs for drugs, syringes, needles and IV sets. Costs for nursing time, and other potential supplies, such as alcohol swabs, are not included. Drug costs were quoted from the Red Book, 1995 edition. The acquisition costs for syringes, needles and IV sets were quoted from *The Drug Estimation and Monitoring System*, prepared by MSH.

Step 8. Approve the Formulary List for Use in the Health Facility

After the Formulary and Therapeutics Committee has created the list of drugs to be included on the formulary, a vote is taken to officially approve the list, according to the established procedures. The formulary list is then disseminated to all physicians and pharmacists. The hospital Chief Physician should issue an order of compliance with the formulary drug list. The order may be announced at a general meeting of all hospital health providers, together with the adopted policies of the Formulary and Therapeutics Committee. At this time, the hospital begins to procure only products on the formulary list. Existing stocks of non-formulary drugs may be prescribed and used until the supply is depleted.

Step 9. Educate Hospital Personnel about Policies and Procedures on Non-Formulary Drug Use, Additions and Deletions to the Formulary, and Generic and Therapeutic Substitution

Non-formulary drug use

Normally, only formulary drugs are approved for use in a health facility. However, the therapeutic needs of a small number of patients may not be met by any drug on the hospital formulary. For such cases, the Formulary and Therapeutics Committee establishes procedures for use of non-formulary drugs.

Requests for use of non-formulary drugs are always made for a specific patient, using a Non-Formulary Drug Request Form, designed and approved by committee (see Annex Three for an example). The prescribing physician should complete the form, and forward it to the inpatient pharmacy, or the Formulary and Therapeutics Committee, if there is no organized pharmacy department in the hospital. It may be appropriate for the pharmacist to discuss the use of a formulary drug with a prescribing physician. If the prescribing physician determines that a non-formulary drug is required, the hospital obtains a sufficient quantity of the non-formulary drug for that patient.

The Formulary and Therapeutics Committee should review all non-formulary drug requests on a regular basis. If the committee notes frequent requests for a particular non-formulary drug, and determines that it is superior to a formulary drug, it may vote for its addition, and deletion of the inferior formulary drug.

Requests for formulary addition and deletion

Requests for addition of a drug to, or deletion of a drug from, the formulary are usually made by a staff physician, using a Request for Addition/Deletion Form (see Annex Four for an example).

Unlike non-formulary drug requests, requests for addition are not patient-specific, but rather are requested for general use.

When a physician wants a drug to be added to the formulary, he or she should complete the form and forward it to the Secretary of the Formulary and Therapeutics Committee. A designated specialist on the committee conducts a literature search and prepares a written evaluation comparing the newly requested drug with formulary drugs used for the same indications. Criteria for comparison are cost, efficacy and safety. The committee then reviews the written evaluation. If the new drug is superior to an existing drug or drugs, on the formulary, or fills a gap, it will be added to the formulary. Existing inferior drugs on the formulary, not needed for use for other indications, should be deleted from the formulary.

The committee or the pharmacy department should publish a newsletter about additions in the formulary, including a brief review of the drug.

It is rare for a staff physician to request that a drug be deleted from the formulary. Deletion usually occurs during periodic drug class reviews, or as a result of adverse drug reaction monitoring or Drug Use Evaluation, described later in the manual. If a physician does formally request that a drug be deleted, the committee should determine if deletion will create therapeutic gaps.

Generic and therapeutic substitution

Physicians and pharmacists should have a clear understanding of both generic and therapeutic substitution:

Generic substitution

Generic substitution is defined as the substitution of bioequivalent drug products that contain the same active ingredients and are chemically identical in strength, concentration, dosage form, and route of administration to the drug product prescribed.

For example, substitution of one verapamil product for another is generic substitution, if the quantity of active ingredient, dosage form and strength are identical. Substitution of pork insulin for human insulin is not generic substitution, nor is substitution of a rapid action product for a product with prolonged action.

The Formulary and Therapeutics Committee is responsible for developing guidelines for generic substitution. In US hospitals, the pharmacy department typically makes actual decisions on generic substitution, and there are very few drugs (*e.g.*, phenytoin and digoxin) for which use of generically produced products are not acceptable by the medical staff. In some countries, there may be more drugs for which generic substitution is prohibited by the Formulary and Therapeutics Committee, due to justifiable concern for drug quality.

Therapeutic substitution

Therapeutic substitution is defined as substitution of one drug for another of equal therapeutic value, even though they are not generically equivalent.

An example of therapeutic substitution would be use of *cephradine* for *cephalexin*. In this case the drugs have the same spectrums of action, frequency of use, dosage form, strength, and route of administration. However, a Formulary and Therapeutics Committee may consider drugs of different strengths to be therapeutically equivalent. For example, *cimetidine* 400 mg twice daily is frequently considered to be therapeutically equivalent to *ranitidine* 150 mg twice daily, or *amotidine* 40 mg once daily. It should be noted that there are not officially recognized therapeutic equivalents. Decisions should be made by individual hospitals.

Therapeutic equivalence must be determined by the Formulary and Therapeutics Committee of each individual hospital. Some other examples of drugs frequently considered therapeutically equivalent include:

- *furosemide* 40 mg and *ethacrynic acid* 50 mg
- *prednisolone* 5 mg and *triamcinolone* 4 mg
- *propranolol* 160 mg and *atenolol* 100 mg
- *ampicillin* 250 mg and *amoxicillin* 250 mg

STAGE III. DEVELOP DRUG FORMULARY MANUAL

Step 10. Decide on Formulary Manual versus Formulary List

As mentioned earlier, the Formulary and Therapeutics Committee may choose to produce a simple list of formulary drugs for distribution to physicians, pharmacists, and other involved personnel, or to develop a formulary manual. The committee may decide on a list if the hospital does not have sufficient funds, personnel, or sources of information to develop and produce a manual. In making this decision, the committee should estimate costs of printing, paper, etc. Manuals are typically revised and reprinted every one or two years.

It is important to understand that a formulary manual should not be a full-sized reference book with extensive information, but rather a concise book containing basic drug information. Manuals should be small in size so that they can be carried by physicians while attending to patients. Formulary and Therapeutics Committees face the dilemma of including enough information to aid physicians in making rapid prescribing decisions, but not so much information that the manual is difficult to use.

The remainder of this section of the manual explains how to develop a basic drug formulary manual.

Step 11. Develop Policy and General Information Section

This section is included in a hospital formulary manual to help hospital staff, especially physicians, understand the formulary system and the functions of the Formulary and Therapeutics Committee. The information should enable the reader to understand the roles and responsibilities of various personnel in the formulary process, including how to comply with policies and correctly follow procedures. It should also contain information that promotes rational use of drugs, such as guidelines for correct prescribing of drugs. Example of information that can be included in this section include:

A. Formulary and Therapeutics Committee policies and procedures

B. A description of the Formulary and Therapeutics Committee, its membership and their responsibilities

C. Regulations governing the prescribing, dispensing, and administration of drugs, that may include:
- writing drug orders and prescriptions
- controlled substances considerations
- generic and therapeutic equivalency policies and procedures
- automatic stop orders
- investigational drug policies
- patients' use of their own medications
- policies on "stat" and "emergency" drug orders
- use of emergency carts and kits
- use of floor stock items
- use of drug administration devices
- rules to be followed by drug manufacturer and wholesaler representatives
- standard drug administration times
- adverse drug reaction and medication error reporting

D. Pharmacy operating procedures, such as hours of service, prescription policies, pricing policies, prescription labeling and packaging practices, drug distribution procedures, handling of drug information requests, and other services of the pharmacy (*e.g.*, patient education programs and pharmacy bulletins)

E. Information on using the formulary, including how the formulary monographs are arranged, the information contained in each monograph, and the procedure for looking up a given drug product

F. Reference books on drugs available in hospital library

Step 12. Develop Drug Information Monographs for the Formulary Manual

This section is the heart of the manual, and consists of simple drug monographs for each drug in the formulary. The committee must decide on the sections to be contained in each monograph, and how much information will be included.

Monographs can be arranged in the manual in several ways:

- alphabetically by generic name, with information within the monographs on brand names;
- by therapeutic class; or
- a combination of the two systems with most drugs arranged alphabetically in a "general" section, supplemented by several "special" sections, such as ophthalmic and otic drugs, dermatologicals, and diagnostic agents, etc.

A monograph contains several sections, as decided by the committee. Examples of the most common sections are:

- Generic name
- Common brand names
- Pharmacology
- Active ingredients of combination products
- Pharmacodynamics/Pharmacokinetics
- Indications
- Contraindications
- Precautions (breast-feeding, geriatric, obstetric, etc.)
- Side effects
- Adverse drug reactions
- Drug-drug and drug-food interactions
- Stability
- Dosage forms, strengths
- Usual dose
- Monitoring
- Storage requirements
- Patient information
- Controlled substances class
- Cost information

A sample formulary manual drug monograph for can be found as Annex Five.

Step 13. Develop Special Information Section

If availability of adequate drug information is problematic in the country, the Formulary and Therapeutics Committee can decide to include drug information to supplement monographs.

The material in this section will vary from hospital to hospital, and should contain information not readily available from other sources. Examples of the types of items often found in the special information section are:

A. Tables of equivalent dosages of similar drugs (*e.g.*, corticosteroids)
B. Standard parenteral nutrition formulas
C. Guidelines for calculating pediatric dosages
D. Table of the sodium content of drug products
E. List of sugar-free drug products
F. Contents of emergency kits
G. Lists of dialyzable drugs
H. Pharmacokinetic dosing and monitoring information
I. Examples of blank and completed organizational forms (prescription forms, requests for non-formulary drugs, adverse drug reaction report forms, etc.)
J. Tables of drug interactions, drug effects on diagnostic tests, injectable drug incompatibilities
K. Poison control information, including telephone numbers of poison control centers
L. Dosages, concentrations, and standard dilutions of common emergency drugs
M. Standard vehicles and dilutions for pediatric injections
N. Electrolyte content of large-volume parenterals
O. Costs of drug therapy to treat various diseases
P. Hospital-developed standard treatment guidelines
Q. Equations to estimate creatine clearance
R. Dosing guidelines for drugs with narrow therapeutic indexes (*e.g.*, theophylline, digoxin, and aminoglycosides)

Step 14. Develop Indexes to Facilitate the Use of the Manual

The manual will not be used if desired information is difficult to locate. It is not unusual for one manual to contain several types of indexes:

- Generic - brand name cross index This index is arranged alphabetically, and contains both generic names, and common brand names. It is used when the reader knows a brand or generic name of a product, and wants to locate the monograph. A portion of a generic-brand name cross index might look like this:

  Ophthaine: brand of proparacaine HCl, p. 114
  Ophthetic: brand of proparacaine HCl, p. 114
  Opium tincture, camphorated; synonym for paregoric, p. 103
  Paregoric, p. 103
  Proparacaine HCl, p. 114

- Therapeutic/Pharmacologic index This index lists all formulary items within each therapeutic class. It is useful for ascertaining what therapeutic alternatives are on the formulary for a given class of drug. An example follows:

  11:00 **Antihistamine drugs**
  Clemastine, p. 14
  Chlorpheniramine maleate, p. 14
  Diphenhydramine hydrochloride, p. 14
  Promethazine hydrochloride, p. 62

- Indications index This index lists diseases alphabetically, followed by formulary drugs used to treat the disease. It is useful when a prescriber wants to know what drugs are on the formulary for a given disease or condition:

Allergic Disorders (ophthalmic)
Betamethasone, p. 150
Cromolyn Sodium, p. 194
Dexamethasone, p. 206
Hydrocortisone, p. 289
Prednisolone, p. 407
Promethazine Hydrochloride, p. 416

Hyperlipidemia
Colestipol, p. 191
Gemfibrozil, p. 273
Lovastatin, p. 321
Niacin, p. 366

Step 15. Produce and Distribute the Manual

The physical appearance of a printed formulary manual has an important impact on how extensively it is used. Although elaborate and expensive artwork and materials are unnecessary, the formulary manual should be visually pleasing, easy to read, and professional in appearance. Options for production include a loose-leaf book, or a bound volume resembling a paper-back book.

Loose-leaf manuals are less expensive to produce, and can easily be updated by producing and distributing replacement pages, usually accompanied by instructions for removing and adding pages. Bound volumes have the advantage that they can be produced in pocket size and can easily be carried.

Several techniques can be used to improve the appearance and ease of use of the formulary manual such as:

- Using a different color paper for each section of the formulary
- Using an edge index
- Making the formulary pocket size
- Printing the generic name heading of each drug entry in boldface type or using some other method for making it stand out from the rest of the entry

The manual should be readily available to physicians, pharmacists and nurses, at all times. One approach is to distribute a copy of the manual to all these individuals. Another is to place a limited number of copies of the manual in patient care areas and the pharmacy department. The first approach is costly, but will result in greater use of the formulary. The latter is less expensive, but the manuals are frequently misplaced or stolen.

STAGE IV. THE FORMULARY MAINTENANCE PROCESS

The formulary process does not end with the production and distribution of the formulary manual, and the Formulary and Therapeutics Committee should be considered a permanent decision making body. During the development phase, frequent committee meetings may be necessary, as often as weekly. After that, the chairperson may decide that monthly meetings are sufficient to perform maintenance activities. The number of maintenance activities will vary from hospital to hospital. Usually, these activities would include:

- Development and implementation of standard treatment guidelines
- Implementation of a Drug Use Evaluation program
- Adverse drug reaction monitoring
- Updating the formulary list and manual

Step 16. Develop and Implement Standard Treatment Guidelines

Standard Treatment Guidelines are schemes of management of common diseases and syndromes, developed and approved by leading specialists in order to achieve the maximum therapeutic effect in the most cost-effective way. STGs include recommendations for drug therapy, including drug(s) of choice, directions for use, and possible alternatives. Guidelines should also include non-drug therapy such as surgery, dietary guidelines, and physical therapy, as well as required laboratory monitoring.

STGs can take the form of simple step by step procedures or the algorithm approach.

STGs help ensure that all patients receive the same level of care, and they promote adherence to the formulary**.** While it is beyond the scope of this manual to provide detailed information on the development process, the following should be considered:

- Development of STGs may take place in conjunction with the development of the drug formulary. Obviously, a drug should not be included in an STG if it is not on the hospital formulary.

- STGs may be incorporated in the printed formulary manual.

- Educational programs may be necessary to promote adherence to these guidelines.

Likely steps in the development and implementation process are:

- The committee creates a list of priority diseases for which STGs are feasible and needed.

- Committee members, and other specialists, develop a draft set of STGs.

- Hospital specialist boards review drafts and revise as needed.

- Practitioners review the revised drafts and provide comments.

- Drafts are revised again, based on comments, then approved.

- Approved guidelines are published, and circulated to all relevant health care providers in the hospital.

- Compliance with drug therapy portions of the guidelines is reviewed during the drug use review process.

- Targeted managerial or educational interventions are carried out to promote compliance where problems are found.

In order to illustrate the possible format and content of STGs and algorithms, examples from US university medical centers are included as Annex Six.

Step 17. Design and Conduct an Ongoing Drug Use Evaluation Program

Drug Use Evaluation (DUE) is a continuous review process used primarily as a means to detect irrational, inappropriate, and unnecessarily costly drug therapy. It is performed by the medical staff as a criteria-based, ongoing, planned and systematic process designed to continuously improve the appropriate and effective use of drugs.

The objectives of DUE programs in hospitals are to:

- ensure that drug therapy is rational and meets current standards of treatment;
- enhance responsibility and accountability in the drug use process; and
- maintain control of drug costs.

The basic steps in a DUE program are:

1. Assign responsibility
2. Delineate scope of drug use
3. Identify important drugs to be monitored
4. Identify criteria for use
5. Establish thresholds for evaluation
6. Create a monitoring schedule
7. Collect and analyze data
8. Evaluate drug use when thresholds are reached
9. Take actions to solve problems or improve drug use
10. Assess the effectiveness of actions and document improvement
11. Review and revise the DUE program

Typically, DUE programs are designed to run for a one-year period. At the end of the year, the program is revised, and the cycle beings again.

Procedures for implementation of DUE programs

1. Assign responsibility

The responsibility for compliance with DUE standards rests with the medical staff. The Formulary and Therapeutics Committee is the most logical group of experts to monitor DUE activities since it constitutes a team of medical experts that works closely with the pharmacy department, and its goals include overseeing drug usage within the institution. Some institutions may elect to form a separate DUE Committee to perform these functions. In this case, a close reporting relationship to the Formulary and Therapeutics Committee should be established.

2. Delineate scope of drug use

It is necessary to understand drug use patterns in the hospital in order to plan a DUE program. The ABC analysis report created during Stage Two should be used for this purpose since it contains information on both drug volume and value in decreasing order. The report will be used to help identify the order in which drugs will be monitored.

3. Identify important drugs to be monitored

No hospital has sufficient personnel to monitor every drug on the formulary list. Therefore, selecting drugs for inclusion in DUE is very important. All drugs chosen should meet at least one of these criteria:

- frequently prescribed drugs
- drugs with the greatest inherent risk to patients
- drugs that have presented problems in the past
- expensive drugs

Another way to select drugs for evaluation is for the committee to conduct a survey of physicians, asking them to identify drugs that they frequently prescribe and of which they have the least knowledge.

4. Identify criteria for use

For each drug included in the DUE program, the committee, or designated specialists, must develop criteria for use. Criteria are measurable and objective statements reflecting acceptable ways that drugs are to be used in the facility.

Criteria may be divided into the following categories:

TYPE	USE
Justification for Use	Determine if a drug was prescribed for appropriate indications, or prescribed when contraindicated.
Process	Address appropriate dosing, route of administration, monitoring.
Complications	Determine if side effects are present and treated properly. Can also be used to address drug interactions.
Outcomes	Criteria are used to determine if the outcome of drug therapy was adequate.

One of the best sources of information for developing criteria are hospital-developed Standard Treatment Guidelines. Standard Treatment Guidelines that are developed by official bodies, such as associations of specialists and government authorities, may be also used as information sources for criteria development. In addition, authoritative texts on drug use and therapeutics may be used. Drug company promotional materials should not be used to develop criteria.

A sample DUE for terfenadine is included as Annex Seven.

5. Establish thresholds for evaluation

Following the development of criteria, the committee establishes thresholds for acceptable performance. These thresholds are often arbitrarily set. Thresholds are represented as percentages between 0 and 100%. For example, a threshold of 80% stipulates that 80% of the collected data must show compliance with criteria (in other words, the 80% threshold allows for a 20% noncompliance). The committee may utilize hospital experts in setting the thresholds. It may be advisable to circulate proposed criteria and thresholds to medical staff and solicit input.

It is important to note that correlation should exist between the thresholds established and the risk associated with given criteria. If noncompliance with given criteria would result in serious consequences, a threshold of 100% compliance should be established. For example, the threshold for correct dosing of a drug such as heparin should be 100%, while 80% may be acceptable for dosing of ceftazidime.

6. Create a monitoring schedule

The time frame for the data collection of each drug needs to be set before the actual data collection begins. Usual ranges are from two weeks to three months, depending on how much data is expected to be found. For frequently prescribed drugs, sufficient data for evaluation may be gathered in two weeks. Drugs with low usage will require longer monitoring intervals to gather enough data to be statistically significant. Other factors that may affect a schedule include the personnel available for data collection, level of complexity of criteria, and methods of data retrieval.

Typically, the committee will draft a schedule for monitoring for the upcoming year, and make adjustments as needed.

7. Collect and analyze data

Appropriate DUE data collectors are physicians, nurses or pharmacists. Data collectors should understand the DUE process, and have a working knowledge of the drugs themselves. If physicians are utilized for data collection, it is important that they do not collect data on their own prescribing.

Data collection can be done in three different ways:

a) Retrospective data collection looks at drug use after it has occurred through review of patient medical records. The main advantage of this approach is that data from a long period of time can be evaluated. Disadvantages are that it does not provide an immediate impact on patient care, and the results are affected by accuracy of the medical records.

b) Concurrent data collection looks at drug use as it occurs. This type of evaluation allows for the correction of drug misadventures as they occur and the patient is still in the hospital. For example, a review may target the administration of aspirin in patients on anticoagulant therapy. If data collection detects that aspirin has been wrongfully prescribed to a patient receiving warfarin, the drug regimen can be modified and the patient's situation improved.

c) Prospective data collection looks at medication orders at the time they are written, and if noncompliance with an indicator is detected, the medication is not administered. The greatest advantage of this approach is that errors are prevented from occurring. The main disadvantage is that it can interrupt the work flow of the organization.

8. Evaluate drug use when thresholds are reached

This step and the next one are most relevant when the retrospective approach is used. A designated committee member compiles and summarizes data for evaluation by the entire committee. If data indicates 100% compliance, or the assigned threshold is not exceeded, no action is necessary. If the threshold is exceeded, the committee should review the medical records of those cases that did not meet the criteria. They may find a "violation" to be minor and without any need for corrective action, or they may decide that the drug requires more in-depth studies.

For the concurrent and prospective approaches, an attempt is made to have drug orders changed at the time the non-compliance is detected. In these cases, the results of these interventions should be evaluated.

9. Take actions to solve problems or improve drug use

If data evaluation shows that a drug use problem exists, corrective action must be taken. Possible actions include:

- removing a drug from the formulary
- restricting a drug to specialized services with specifically trained personnel
- developing special order forms for specific drugs
- counseling prescribing physicians
- developing staff education programs
- disseminating information on rational drug use through newsletters, or discussion at meetings

10. Assess the effectiveness of actions and document improvement

Once corrective action has been taken, and system changes have been put in place a mechanism should be implemented that can evaluate if the actions taken resulted in improved drug therapy. This is most easily accomplished by repeating the same DUE as previously performed after six or twelve months.

11. Review and revise the DUE program

At the end of a DUE cycle, usually one year, the committee should evaluate the program to determine:

- appropriateness of drugs chosen for evaluation and thresholds;
- the effectiveness of data collection approaches;
- the appropriateness of actions taken; and
- adequacy of personnel utilized.

The program for the next year should be designed based on this evaluation, and a new ABC analysis report should be produced to facilitate drug selection. Drugs for which no problems were detected can be eliminated from the program.

Step 18. Design and Implement an Adverse Drug Reaction Monitoring System

An adverse drug reaction (ADR) is defined as any undesired or unintended response to medication that requires treatment or alteration of therapy.

By pathogenesis, adverse drug reactions are classified as follows:

- pharmacodynamic (*e.g.*, bronchospasm with beta-blockers administration)
- toxic (*e.g.*, absolute or relative overdosing of amino glycosides)
- allergic reactions
- pseudo-allergic (*e.g.*, reaction to histamine liberators)
- idiosyncratic reactions
- drug-induced diseases (superinfections in antibiotic use)
- withdrawal syndrome or rebound effect (*e.g.*, spontaneous clonidine discontinuation)
- ADR caused by drug interaction

The reactions connected with the development of psycho or physical dependency are singled out as a separate category.

According to the severity of side effects they are subdivided as follows:

- Fatal (*e.g.*, severe anaphylactic shock)
- Severe (*e.g.*, Morgagni-Adams-Stokes syndrome, Lyle syndrome)
- Middle Severity (*e.g.*, discontinuation of the drug and special therapy required)
- Mild (*e.g.*, drug discontinuation is not required, symptoms disappear by themselves with dose reduction)

Adverse drug reactions can be predictable (pharmacodynamic, toxic, secondary), or unpredictable (allergic reaction and idiosyncrasy).

Probability of ADR:

Definite: ADR known to occur with clear-cut temporal association and positive rechallenge or laboratory confirmation.

Probable: ADR known to occur with clear-cut temporal association that could not be caused by other drugs or patient's clinical state and improvement in symptoms of reaction is seen upon withdrawal of the drug.

Possible: ADR known to occur with less clear temporal association that may have an etiology other than the suspected drug.

Doubtful: ADR is judged more likely to be due to another cause.

In the US, a ten-question rating system, called the Naranjo Adverse Drug Reaction Probability Scale, is used to evaluate probability levels of ADR. (See Annex Eight for details.)

The Formulary and Therapeutics Committee is responsible for maintaining an adverse drug reaction reporting program. The goal of this program is to provide ongoing surveillance of adverse drug reactions at the health facility. This surveillance should result in actions designed to eliminate or improve management of adverse reactions:

- changes in the formulary
- implementation of new prescribing procedures
- modification of patient monitoring procedures

The Formulary and Therapeutics Committee is responsible for ensuring that adverse drug reactions are reported, collected data is analyzed and appropriate action to improve drug therapy is taken if needed.

Reporting mechanism for adverse drug reactions

1. Any health professional (physician, pharmacist, nurse) who detects an ADR should notify the attending physician and document the reaction in the patient's case history.

2. The reporting professional should then promptly complete an Adverse Drug Reaction Reporting Form, including assigning a Naranjo probability value, and send it immediately to the inpatient pharmacy or the responsible member of the Formulary and Therapeutics Committee. Reporting forms should be available in all areas of the hospital where drugs are utilized. Sample reporting form are included as Annex Nine.

3. The Formulary and Therapeutics Committee will analyze all cases, summarize, and report the results to health professionals in the hospital.

4. The Formulary and Therapeutics Committee then will initiate changes in drug use and procedures, or design educational programs if necessary. Adverse drug reaction data should be considered when making formulary decisions.

Step 19. Update the Formulary List or Manual

It should be obvious that a formulary list is not static. If monthly committee meetings are held, the list of drugs on the formulary will probably change at every meeting, due to requests for addition and deletion.
It is necessary, therefore, to have a mechanism for informing the hospital staff of all changes in the formulary. One mechanism is through distribution or posting of the minutes of the Formulary and Therapeutics Committee meeting. Another is through the use of a newsletter. Changes may be communicated orally at meetings, but written communication will be more reliable. If a simple list is used in the hospital, rather than a manual, the committee can update the list as changes occur, but even this may prove to be expensive.

Manuals are usually revised and reprinted every one or two years. At the time of revision, the entire contents of the manual should be reviewed and revised to include new policies and procedures, forms, Standard Treatment Guidelines, etc., as well as new drug monographs. If time permits, it is advisable to perform therapeutic drug class reviews with every revision, rather than simply adding and removing monographs based on addition/deletion decisions of the committee. Often, it is found that the practices of duplication, and use of unnecessarily expensive drugs can occur even with a functioning formulary system.

Annex 1

Examples of Therapeutic Classification Schemes

DRUG CLASSIFICATIONS

Principles of Drug Classification

Rapid development of the pharmaceutical industry has led to hundreds of thousands of drugs being used world-wide. This causes many complications for both studying the drugs and for their rational use. That is why it is so essential to develop drug classifications, which will guide a physician through the immense quantity of various pharmaceuticals and to help select an optimal drug treatment for a patient.

It is possible to classify drugs according to the following principles: their therapeutic use (*e.g.*, anti-tumor drugs, anti-anginal agents, antimicrobial agents); pharmacological action (*e.g.*, vasodilators, anticoagulants, diuretics); or their chemical structure (*e.g.*, glycosides, alkaloids, steroids, benzodiazepines).

For the clinical physician it is more convenient to deal with nosologies (*e.g.*, drugs for treatment of bronchial asthma, of stroke, etc.). However, combined classifications provide better foundations for drug selection and rational drug utilization. The American Hospital Formulary Service (AHFS) drug classification is listed below.

AHFS PHARMACOLOGIC-THERAPEUTIC CLASSIFICATIONS

4:00 Antihistamine Drugs

8:00 Anti-Infective Agents
- 8:04 Amebicides
- 8:08 Anthelmintics
- 8:12 Antibiotics
  - 8:12.02 Aminoglycosides
  - 8:12.04 Antifungal Antibiotics
  - 8:12.06 Cephalosporins
  - 8:12.07 Miscellaneous β-Lactam Antibiotics
  - 8:12.08 Chloramphenicol
  - 8:12.12 Macrolides
  - 8:12.16 Penicillins
  - 8:12.24 Tetracyclines
  - 8:12.28 Miscellaneous Antibiotics
- 8:16 Antituberculosis Agents
- 8:18 Antivirals
- 8:20 Antimalarial Agents
- 8:22 Quinolones
- 8:24 Sulfonamides
- 8:26 Sulfones
- 8:28 Antitreponemal Agents*
- 8:32 Antitrichomonal Agents*
- 8:36 Urinary Anti-Infectives
- 8:40 Miscellaneous Anti-Infectives

10:00 Antineoplastic Agents

12:00 Autonomic Drugs
- 12:04 Parasympathomimetic (Cholinergic) Agents
- 12:08 Anticholinergic Agents
  - 12:08.04 Antiparkinsonian Agents
  - 12:08.08 Antimuscarinics/Antispasmodics
- 12:12 Sympathomimetic (Adrenergic) Agents
- 12:16 Sympatholytic (Adrenergic Blocking) Agents
- 12:20 Skeletal Muscle Relaxants
- 12:92 Miscellaneous Autonomic Drugs

16:00 Blood Derivatives

20:00 Blood Formation and Coagulation
- 20:04 Antianemia Drugs
  - 20:04.04 Iron Preparations
  - 20:04.08 Liver and Stomach Preparations*
- 20:12 Coagulants and Anticoagulants
  - 20:12.04 Anticoagulants
  - 20:12.08 Antiheparin Agents
  - 20:12.12 Coagulants*
  - 20:12.16 Hemostatics
- 20:16 Hematopoietic Agents
- 20:24 Hemorrheologic Agents
- 20:40 Thrombolytic Agents

24:00 Cardiovascular Drugs

24.04 Cardiac Drugs
24:06 Antilipemic Agents
24:08 Hypotensive Agents
24:12 Vasodilating Agents
24:16 Sclerosing Agents

28:00 Central Nervous System Agents
28:04 General Anesthetics*
28:08 Analgesics and Antipyretics
- 28:08.04 Nonsteroidal Anti-Inflammatory Agents
- 28:08.08 Opiate Agonists
- 28:08.12 Opiate Partial Agonists
- 28:08.92 Miscellaneous Analgesics and Antipyretics

28:10 Opiate Antagonists
28:12 Anticonvulsants
- 28:12.04 Barbiturates
- 28:12.08 Benzodiazepines
- 28:12.12 Hydantoins
- 28:12.16 Oxazolidinediones*
- 28:12.20 Succinimides
- 28:12.92 Miscellaneous Anticonvulsants

28:16 Psychotherapeutic Agents
- 28:16.04 Antidepressants
- 28:16.08 Antipsychotic Agents
- 28:16.12 Miscellaneous Psychotherapeutic Agents*

28:20 Anorexigenic Agents and Respiratory and Cerebral Stimulants
28:24 Anxiolytics, Sedatives, and Hypnotics
- 28:24.04 Barbiturates
- 28:24.08 Benzodiazepines
- 28:24.92 Miscellaneous Anxiolytics, Sedatives, and Hypnotics

28:28 Antimanic Agents
28:92 Miscellaneous Central Nervous System Agents

32:00 Contraceptives* (e.g., foams, devices)

34:00 Dental Agents*

36:00 Diagnostic Agents
36:04 Adrenocortical Insufficiency
36:08 Amyloidosis*
36:12 Blood Volume*
36:16 Brucellosis*
36:18 Cardiac Function
36:24 Circulation Time*
36:26 Diabetes Mellitus*
36:28 Diphtheria*
36:30 Drug Hypersensitivity
36:32 Fungi
36:34 Gallbladder Function
36:36 Gastric Function
36:38 Intestinal Absorption
36:40 Kidney Function
36:44 Liver Function
36:48 Lymphogranuloma Venereum*
36:52 Mumps
36:56 Myasthenia Gravis
36:60 Thyroid Function
36:61 Pancreatic Function
36:62 Phenylketonuria*
36:64 Pheochromocytoma*
36:66 Pituitary Function
36:68 Roentgenography
36:72 Scarlet Fever*
36:76 Sweating*
36:80 Trichinosis*
36:84 Tuberculosis
36:88 Urine and Feces Contents*
- 36:88.12 Ketones*
- 36:88.20 Occult Blood*
- 36:88.24 pH*
- 36:88.28 Protein*
- 36:88.40 Sugar*

38:00 Disinfectants* (for agents used on objects other than skin)

40:00 Electrolytic, Caloric, and Water Balance
40:04 Acidifying Agents
40:08 Alkalinizing Agents
40:10 Ammonia Detoxicants
40:12 Replacement Preparations
40:16 Sodium-Removing Resins*
40:17 Calcium-Removing Resins
40:18 Potassium-Removing Resins
40:20 Caloric Agents
40:24 Salt and Sugar Substitutes*
40:28 Diuretics
- 40:28.10 Potassium-Sparing Diuretics

40:36 Irrigating Solutions
40:40 Uricosuric Agents

44:00 Enzymes

48:00 Antitussives, Expectorants, and Mucolytic Agents
48:08 Antitussives
48:16 Expectorants
48:24 Mucolytic Agents

52:00 Eye, Ear, Nose, and Throat (EENT) Preparations
52:04 Anti-Infectives
- 52:04.04 Antibiotics
- 52:04.05 Antifungals*
- 52:04.06 Antivirals
- 52:04.08 Sulfonamides
- 52:04.12 Miscellaneous Anti-Infectives

52:08 Anti-Inflammatory Agents
52:10 Carbonic Anhydrase Inhibitors
52:12 Contact Lens Solutions*
52:16 Local Anesthetics
52:20 Miotics
52:24 Mydriatics
52:28 Mouthwashes and Gargles
52:32 Vasoconstrictors
52:36 Miscellaneous EENT Drugs

56:00 Gastrointestinal Drugs
56:04 Antacids and Adsorbents
56:08 Antidiarrhea Agents
56:10 Antiflatulents
56:12 Cathartics and Laxatives
56:14 Cholelitholytic Agents
56:16 Digestants
56:20 Emetics
56:22 Antiemetics
56:24 Lipotropic Agents*
56:40 Miscellaneous GI Drugs

60:00 Gold Compounds

64:00 Heavy Metal Antagonists

68:00 Hormones and Synthetic Substitutes
68:04 Adrenals
68:08 Androgens
68:12 Contraceptives
68:16 Estrogens
68:18 Gonadotropins
68:20 Antidiabetic Agents
- 68:20.08 Insulins
- 68:20.20 Sulfonylureas
- 68:20.92 Miscellaneous Antidiabetic Agents

68:24 Parathyroid
68:28 Pituitary
68:32 Progestins
68:34 Other Corpus Luteum Hormones*
68:36 Thyroid and Antithyroid Agents
- 68:36.04 Thyroid Agents
- 68:36.08 Antithyroid Agents

72:00 Local Anesthetics

76:00 Oxytocics

78:00 Radioactive Agents*

80:00 Serums, Toxoids, and Vaccines
80:04 Serums
80:08 Toxoids
80:12 Vaccines

84:00 Skin and Mucous Membrane Agents
84:04 Anti-Infectives
- 84:04.04 Antibiotics
- 84:04.06 Antivirals
- 84:04.08 Antifungals
- 84:04.12 Scabicides and Pediculicides
- 84:04.16 Miscellaneous Local Anti-Infectives

84:06 Anti-Inflammatory Agents
84:08 Antipruritics and Local Anesthetics
84:12 Astringents*
84:16 Cell Stimulants and Proliferants
84:20 Detergents
84:24 Emollients, Demulcents, and Protectants
- 84:24.04 Basic Lotions and Liniments*
- 84:24.08 Basic Oils and Other Solvents*
- 84:24.12 Basic Ointments and Protectants*
- 84:24.16 Basic Powders and Demulcents*

84:28 Keratolytic Agents
84:32 Keratoplastic Agents
84:36 Miscellaneous Skin and Mucous Membrane Agents
84:50 Depigmenting and Pigmenting Agents
- 84:50.04 Depigmenting Agents
- 84:50.06 Pigmenting Agents

84:80 Sunscreen Agents

86:00 Smooth Muscle Relaxants
86:08 Gastrointestinal Smooth Muscle Relaxants*
86:12 Genitourinary Smooth Muscle Relaxants
86:16 Respiratory Smooth Muscle Relaxants

88:00 Vitamins
88:04 Vitamin A
88:08 Vitamin B Complex
88:12 Vitamin C
88:16 Vitamin D
88:20 Vitamin E
88:24 Vitamin K Activity
88:28 Multivitamin Preparations

92:00 Unclassified Therapeutic Agents

94:00 Devices*

96:00 Pharmaceutical Aids*

* Category is currently not in use in the printed version of *AHFS Drug Information® 97*

List is reprinted from *AHFS Drug Information® 97* by the American Hospital Formulary Service (Ed., Gerald K. McEvoy, Pharm.D.)

Annex 2

ABC/VEN Analysis

Example for Conducting the ABC/VEN Analysis

Step 1. Hospital X uses 21 drugs. The information about each drug (drug name, dosage form, price for a pack, annual utilization, total cost) is entered in the computer using spreadsheet software (any spreadsheet program will do; in this case Excel was used). The information can be entered in any order. Following our data entry the table will appear in the following way:

Drug	Form	Price Per Pack $	Dispensed in 1995	Total Cost $
Ranitidine Hydrochloride 150mg N100	tab	$8.00	500	$4,000.00
Bendazol 0.5% 2ml N10	inj	$0.50	5000	$2,500.00
Cocarboxylase 50 mg 3ml N3	inj	$1.25	1000	$1,250.00
Metoclopramide Hydrochloride 10mg N40	tab	$1.67	1200	$2,004.00
Solcoseril 2ml N25	inj	$20.12	700	$14,084.00
Verapamil Hydrochloride 80mg N100	tab	$5.00	1200	$6,000.00
Nandrolone Decanoate 50mg 1ml	inj	$1.74	800	$1,392.00
Metamizole 50% 1ml N10	inj	$0.30	2000	$600.00
Nitrofurantoin 100mg N10	tab	$0.15	3000	$450.00
Inosine 200mg N100	tab	$20.00	800	$16,000.00
Insulin HM 10ml 40IU/ml	inj	$5.50	2000	$11,000.00
Cefotaxime Sodium 1g	inj	$2.40	2000	$4,800.00
Prednisolone 30mg N3	inj	$1.21	1900	$2,299.00
Digoxin 0.25mg N50	tab	$1.00	600	$600.00
Drotaverine Hydrochloride 0.04 N100	tab	$2.15	5000	$10,750.00
Nystatin 500,000 U N25	tab	$0.73	3000	$2,190.00
Ampicillin 250mg N24	tab	$1.25	1500	$1,875.00
Allylestrenol 5mg N20	tab	$1.63	300	$489.00
Inosine 2% 5ml N10	inj	$1.57	3000	$4,710.00
Chlordiazepoxide 10mg N50	drage	$0.56	800	$448.00
Isradipine 5mg N30	caps	$16.21	600	$9,726.00
				$97,167.00

Step 2. Each drug is placed in one of three categories according to its importance.

Vital — Drugs that are life saving (*e.g.*, vaccines) or those necessary for supporting life (*e.g.*, insulins, steroids, propranolol, etc.).

Essential — Drugs that are effective for treatment of less severe, but still serious, diseases.

Non-essential — Drugs for treatment of mild diseases, drugs of doubtful effectiveness, expensive drugs that are used for symptomatic therapy.

The table now has the following appearance:

Category	Drug	Form	Price Per Pack	Dispensed in 1995	Total Cost
E	Ranitidine Hydrochloride 150mg N100	tab	$8.00	500	$4,000.00
NE	Bendazol 0.5% 2ml N10	inj	$0.50	5000	$2,500.00
NE	Cocarboxylase 50 mg 3ml N3	inj	$1.25	1000	$1,250.00
E	Metoclopramide Hydrochloride 10mg N40	tab	$1.67	1200	$2,004.00
NE	Solcoseril 2ml N25	inj	$20.12	700	$14,084.00
V	Verapamil Hydrochloride 80mg N100	tab	$5.00	1200	$6,000.00
E	Nandrolone Decanoate 50mg 1ml	inj	$1.74	800	$1,392.00
E	Metamizole 50% 1ml N10	inj	$0.30	2000	$600.00
E	Nitrofurantoin 100mg N10	tab	$0.15	3000	$450.00
NE	Inosine 200mg N100	tab	$20.00	800	$16,000.00
V	Insulin HM 10ml 40IU/ml	inj	$5.50	2000	$11,000.00
V	Cefotaxime Sodium 1g	inj	$2.40	2000	$4,800.00
V	Prednisolone 30mg N3	inj	$1.21	1900	$2,299.00
V	Digoxin 0.25mg N50	tab	$1.00	600	$600.00
NE	Drotaverine Hydrochloride 0.04 N100	tab	$2.15	5000	$10,750.00
E	Nystatin 500,000 U N25	tab	$0.73	3000	$2,190.00
V	Ampicillin 250mg N24	tab	$1.25	1500	$1,875.00
E	Allylestrenol 5mg N20	tab	$1.63	300	$489.00
NE	Inosine 2% 5ml N10	inj	$1.57	3000	$4,710.00
E	Chlordiazepoxide 10mg N50	drage	$0.56	800	$448.00
E	Isradipine 5mg N30	caps	$16.21	600	$9,726.00
					$97,167.00

Step 3. With the help of spreadsheet functions reorder the drugs according to the total expenditures for the purchases of each drug (from the most costly purchases to the least ones). Now the table appears in the following way:

Category	Drug	Form	Price Per Pack	Dispensed in 1995	Total Cost
NE	Inosine 200mg N100	tab	$20.00	800	$16,000.00
NE	Solcoseril 2ml N25	inj	$20.12	700	$14,084.00
V	Insulin HM 10ml 40IU/ml	inj	$5.50	2000	$11,000.00
NE	Drotaverine Hydrochloride 0.04 N100	tab	$2.15	5000	$10,750.00
E	Isradipine 5mg N30	caps	$16.21	600	$9,726.00
V	Verapamil Hydrochloride 80mg N100	tab	$5.00	1200	$6,000.00
V	Cefotaxime Sodium 1g	inj	$2.40	2000	$4,800.00
NE	Inosine 2% 5ml N10	inj	$1.57	3000	$4,710.00
E	Ranitidine Hydrochloride 150mg N100	tab	$8.00	500	$4,000.00
NE	Bendazol 0.5% 2ml N10	inj	$0.50	5000	$2,500.00
V	Prednisolone 30mg N3	inj	$1.21	1900	$2,299.00
E	Nystatin 500,000 U N25	tab	$0.73	3000	$2,190.00
E	Metoclopramide Hydrochloride 10mg N40	tab	$1.67	1200	$2,004.00
V	Ampicillin 250mg N24	tab	$1.25	1500	$1,875.00
E	Nandrolone Decanoate 50mg 1ml	inj	$1.74	800	$1,392.00
NE	Cocarboxylase 50mg 3ml N3	inj	$1.25	1000	$1,250.00
E	Metamizole 50% 1ml N10	inj	$0.30	2000	$600.00
V	Digoxin 0.25mg N50	tab	$1.00	600	$600.00
E	Allylestrenol 5mg N20	tab	$1.63	300	$489.00
E	Nitrofurantoin 100mg N10	tab	$0.15	3000	$450.00
E	Chlordiazepoxide 10mg N50	drage	$0.56	800	$448.00
					$97,167.00

Step 4. With the help of spreadsheet functions, calculate the percentage of total expenditures for each drug. The table has the following appearance:

	Drug	Form	Price Per Pack	Dispensed in 1995	Total cost	Total Cost %	Cumulative %
NE	Inosine 200mg N100	tab	$20.00	800	$16,000.00	16.5%	16.5%
NE	Solcoseril 2ml N25	inj	$20.12	700	$14,084.00	14.5%	31.0%
V	Insulin HM 10ml 40IU/ml	inj	$5.50	2000	$11,000.00	11.3%	42.3%
NE	Drotaverine Hydrochloride 0.04 N100	tab	$2.15	5000	$10,750.00	11.1%	53.4%
E	Isradipine 5mg N30	caps	$16.21	600	$9,726.00	10.0%	63.4%
V	Verapamil Hydrochloride 80mg N100	tab	$5.00	1200	$6,000.00	6.2%	69.6%
V	Cefotaxime Sodium 1g	inj	$2.40	2000	$4,800.00	4.9%	74.5%
NE	Inosine 2% 5ml N10	inj	$1.57	3000	$4,710.00	4.8%	79.4%
E	Ranitidine Hydrochloride 150mg N100	tab	$8.00	500	$4,000.00	4.1%	83.5%
NE	Bendazol 0.5% 2ml N10	inj	$0.50	5000	$2,500.00	2.6%	86.0%
V	Prednisolone 30mg N3	inj	$1.21	1900	$2,299.00	2.4%	88.4%
E	Nystatin 500,000 U N25	tab	$0.73	3000	$2,190.00	2.3%	90.7%
E	Metoclopramide Hydrochloride 10mg N40	tab	$1.67	1200	$2,004.00	2.1%	92.7%
V	Ampicillin 250mg N24	tab	$1.25	1500	$1,875.00	1.9%	94.7%
E	Nandrolone Decanoate 50mg 1ml	inj	$1.74	800	$1,392.00	1.4%	96.1%
NE	Cocarboxylase 50mg 3ml N3	inj	$1.25	1000	$1,250.00	1.3%	97.4%
E	Metamizole 50% 1ml N10	inj	$0.30	2000	$600.00	0.6%	98.0%
V	Digoxin 0.25mg N50	tab	$1.00	600	$600.00	0.6%	98.6%
E	Allylestrenol 5mg N20	tab	$1.63	300	$489.00	0.5%	99.1%
E	Nitrofurantoin 100mg N10	tab	$0.15	3000	$450.00	0.5%	99.6%
E	Chlordiazepoxide 10mg N50	drage	$0.56	800	$448.00	0.5%	100.0%
					$97,167.00	100.0%	

Step 5. Analyze the result of ABC/VEN analysis:

The hospital X spent $97,167 for purchases of drugs in 1995. When placing the drugs according to VEN system, six of the 21 drugs were included in the category of vital (V) drugs (insulin, verapamil, cefotaxime, prednisolone, ampicillin, digoxin). Nine drugs were included in the category of essential (E) drugs (isradipine, ranitidine, nystatin, metoclopramide, nandrolone, metamizole, allylestrenol, nitrofurantoin, chlordiazepoxide). The group of non-essential (NE) drugs was represented by six drugs (bendazol, drotaverine, inosine, solcoseril, cocarboxylase).

The ABC analysis was conducted with the purpose of reducing expenditures and increasing effectiveness of drug utilization. This analysis showed that the largest portion of money, 79%, was spent for purchases of eight drugs (Class A-up to 80% of total costs). When analyzing the drugs from this class, it was found that it included both vital drugs (insulin, verapamil, and cefotaxime, with 22.2% of money was spent for these drugs), as well as non-essential drugs, (inosine, solcoseril, and drotaverine, representing 46.9% of total expenditures). Twenty-six percent of the budget was spent on drugs from Classes B and C. These classes also included vital drugs (prednisolone, ampicillin, and digoxin), essential drugs (nystatin, ranitidine, etc.), as well as non-essential drugs (bendazol and cocarboxylase).

The analysis shows the structure of the hospital's expenditures for drug purchases. This analysis allows the hospital to undertake reforms related to the way purchases are conducted, and to use the largest portion of budget for purchases of vital drugs. By limiting the use of such ineffective drugs as solcoseril, inosine and drotaverine, expenditures can be significantly reduced.

This example of ABC analysis shows that such an analysis can become a foundation for selecting the groups of drugs for primary review of a formulary list, as well as for changing purchasing policies.

Annex 3

Example of a Non-Formulary Drug Request Form

(adapted for the purposes of this manual from the University of Arizona, Tucson, Medical Center)

REQUEST FOR A NON-FORMULARY DRUG

Non-formulary drugs may be requested for a specific patient by any faculty or attending physician. Requests must be submitted on a form available from the Pharmacy and Supply department. Completed requests should be forwarded to the Pharmacy and Supply department where immediate steps will be taken to obtain the drug. Delivery of non-formulary drugs may not be prompt since they must be obtained from outside the medical center. In an emergency, a non-formulary drug will be obtained if the physician will call the Pharmacy and Supply department.

The use of all non-formulary drugs will be reviewed by the Pharmacy and Therapeutics Committee at its next meeting.

To be completed by physician:

Name of Drug

Dosage Form Route of Administration

Dosage Schedule

Estimated Duration of Therapy Date and Time Required

Briefly describe use of this drug

Name of patient Hospital number

Date Signature of Faculty or Attending Physician Clinical Service

To be completed by pharmacist:

Date and time drug obtained Amount obtained Cost

Manufacturer and/or brand name

Pharmacist

Annex 4

Example of a New Drug Addition Request Form

(adapted for the purposes of this manual from the University of Arizona, Tucson, Medical Center)

Request for Drug to be Admitted to Formulary

Any faculty or attending physician may initiate a request for a drug to be admitted to the formulary. Requests must be submitted on a form available from the Department of Pharmacy Services. The completed form should be forwarded to the Department of Pharmacy Services, Attn: Secretary, Pharmacy and Therapeutics Committee. The request will be placed on the agenda of the next committee meeting.

To be completed by physician:

1. Name of drug _____

2. Dosage form(s) and strength(s) _____

_____

3. List specific pharmacologic action and therapeutic use that warrants this drug's admission to the formulary

_____

_____

_____

4. This drug is superior to present formulary drugs because _____

_____

_____

5. List specific literature references _____

_____

6. If this drug is admitted to the formulary, the following drug(s) should be deleted _____

_____

7. Have you in the past, or are you currently conducting studies with this drug? _____

8. Are you receiving financial support from this drug's manufacturer? _____

9. Requested by _____ Date _____

_____

10. Pharmacy and Therapeutics Committee Action _____

_____ Date _____

Annex 5

Example of a Drug Monograph for Inclusion in the Formulary Manual (Ampicillin)

(adapted for the purposes of this manual from the University of Arizona, Tucson, Medical Center)

Ampicillin

Use:

Infections caused by susceptible organisms such as Streptococcus, Listeria monocytogenes, E. coli, Proteus mirabilis, H. influenza, Salmonella, Shigella, Neisseria, Nocardia; involving the respiratory tract, otis media, sinus, skin, and urinary tract

Administration:

Ampicillin can be administered IVP over 3-5 minutes at a rate not to exceed 100 mg/minute or IV intermittent infusion over 15-30 minutes; final concentration for IV administration should not exceed 100 mg/ml (IVP) or 30 mg/ml (IV intermittent infusion)

Contraindications:

Known hypersensitivity to ampicillin or penicillin

Precautions:

Dosage adjustment may be necessary with decreased renal function

Adverse Reaction:

>10%: Diarrhea, rash, vomiting, oral candidiasis
1% to 10%: Severe abdominal or stomach cramps and pain
<1%: Penicillin encephalopathy, seizures, lymphocytic leukemia

Drug Interactions:

Amino glycosides (synergism), probenecid, allopurinol

Stability:

Oral suspension is stable for 7 days at room temperature or for 14 days under refrigeration; solutions for IM or direct IV should be used within 1 hour; solutions for IV infusion will be inactivated by dextrose at room temperature; if dextrose-containing solutions are to be used, the resultant solution will only be stable for 2 hours versus 8 hours in the 0.9% sodium chloride injection. D5W has limited stability.

Minimum volume: Concentration should not exceed 30 mg/ml; manufacturer may supply as either the anhydrous or the trihydrate form.

Usual dosage:

Neonates: IM, IV
Postnatal age <7 days:
<2000 g: 25 mg/kg/dose every 12 hours; meningitis: 50 mg/kg dose every 12 hours
>2000 g: 25 mg/kg/ dose every 8 hours; meningitis: 50 mg/kg dose every 8 hours

Postnatal age >7 days:
<2000 g: 25 mg/kg/dose every 8 hours; meningitis: 50 mg/kg dose every 8 hours
>2000 g: 25 mg/kg dose every 6 hours; meningitis: 50 mg/kg dose every 6 hours

Infants and children: IM, IV: 100-200 mg/kg/day in 4-6 divided doses
Meningitis: 200-400 mg/kg/day in 4-6 divided doses; maximum dose: 10 g/day

Children: Oral: 50-100 mg/kg/day divided every 6 hours; maximum dose: 250mg/dose

Adults: Oral: 250-500 mg every 6 hours
IM, IV: ClCr of > 10 ml/minute: 1-2 g every 6 hours
IM, IV: ClCr of < 10 ml/minute: 1-2 g every 8-12 hours

Patient information:

Food may hamper rate and extent of absorption; take on an empty stomach; take full course of therapy (10-14 days).

Information to Nurses:

Ampicillin and gentamicin should not be mixed in same IV tubing; do C&S before starting therapy; observe patient for signs and symptoms of hypersensitivity; have resuscitation equipment, epinephrine, and antihistamine close by in the event of an anaphylactic reaction; give on empty stomach (i.e., one hour prior to, or two hours after meals) to increase total absorption; cannot be mixed in D5W solutions.

Dosage forms:

Capsule, as anhydrous: 250 mg, 500 mg
Capsule, as trihydrate: 250 mg, 500 mg
Injection, as sodium: 125 mg, 250 mg, 500 mg, 1 g, 2 g
Suspension, oral as trihydrate: 125 mg/5ml (100 ml, 200 ml); 250 mg/5ml (100 ml, 200 ml)

Standardized dose:

Oral (mg): 15, 25, 50, 75, 100, 125, 150, 200, 250, 300, 400, 500 (doses > 500 mg will be standardized to the nearest 125 mg)
Injection (mg): 25, 50, 75, 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 275, 500 (doses > 500 mg will be standardized to the nearest 50 mg)

Annex 6

Examples of Standard Treatment Guidelines

(adapted for the purposes of this manual from the Medical Centers at the Universities of California, San Francisco, and Arizona, Tucson, respectively)

A. Guidelines for the use of acid-related gastrointestinal medications

I. Appropriate indications for peptic ulcer disease treatment

A. Prophylaxis of stress-related mucosal damage (stress ulcers) in patients with the following risk factors:

1. Shock
2. Sepsis
3. Acute renal failure
4. Hepatic failure
5. Pulmonary failure with mechanical ventilation >24 hours
6. Multiple trauma
7. Traumatic head injury
8. Coma
9. *S/p* major surgery requiring *npo* status

Treatment:

1. Cimetidine 300mg iv q6-8 hours or 400mg po/ng q12 hours or 900-1200 mg/day as continuous intravenous infusion (37.5 mg/hour)
   or
2. Sucralfate 1 g po/ng q6 hours

Note: Supplemental antacids 30 ml po/ng q1-2 hours may be used to maintain gastric pH >4.

Continue therapy until patient is discharged from intensive care unit, taking adequate enteral nutrition or the risk factors are corrected.

B. Active gastric /duodenal ulcers

Treatment:

1. Cimetidine 400 mg po bid or 800 mg po hs
   or
2. Sucralfate 1 g po qid

Continue therapy for 6 to 8 weeks and re-evaluate. Gastric ulcers must be re-evaluated endoscopically or radiographically to rule-out the possibility of a neoplastic etiology.

C. Maintenance therapy for gastric/duodenal ulcers

Treatment:

1. Cimetidine 400 mg po hs
   or
2. Sucralfate 1 g po bid

Should be reserved for patients at high risk for frequent recurrence or complications (*e.g.*, smokers, NSAID use, documented recurrence, cirrhosis).

D. Zolling-Ellison Syndrome

Treatment:

1. Cimetidine 300 mg po qid (may titrate up to 2.4 g/day)
   or
2. Omeprazole 20 mg po qd (may titrate up to 160 mg/day)

Therapy should be continued for as long as clinically necessary.

II. Inappropriate indications for peptic ulcer disease therapy

A. Treatment of nonspecific gastrointestinal pain.

B. Prophylaxis of ulcers in patients receiving "ulcerogenic" medications (*e.g.*, glucocorticoids, chemotherapeutic agents) in the absence of any other risk factors.

C. Treatment of gastrointestinal symptoms in patients after total gastrectomy.

D. Gastric and duodenal erosions (lesions <5 mm in diameter which have been discovered on endoscopic examination in patients concurrently receiving NSAIDs).

III. Other acid-related gastrointestinal disorders

A. Gastroesophageal reflux disease (GERD)
Treatment:
1. Antacids 30 ml po 1 h and 3 h pc and hs
   or
2. Cimetidine 400-800 mg po bid or 300 mg po qid (may titrate up to 2.4 g/day)
   or
3. Omeprazole 20 mg po qd (may titrate up to 40 mg/day)
   or
4. Cisapride 10 mg po qid (ac and hs)

Continue treatment for 8 weeks and re-evaluate.

B. Helicobacter pylori-associated peptic ulcer disease
1. Indications for treatment:
   a. Duodenal ulcer disease: newly diagnosed duodenal ulcer disease or previous history of duodenal ulcer
   b. Gastric ulcer disease: newly diagnosed gastric ulcer disease or previous history of gastric ulcer disease with NO history of NSAID/aspirin use.
2. Inappropriate indications for treatment:
   a. Non-ulcer dyspepsia
   b. Gastric cancer prevention
   c. Chronic active gastritis
3. Preferred treatment regimens for Helicobacter pylori
   a. Tetracycline 500 mg qid + metronidazole 250 mg qid + Pepto-Bismol® 2 tablets qid
      I. Duration of antimicrobial therapy: 2 weeks
      ii. Concomitant H_2-receptor antagonist therapy if ulcer is present for a total of 6 weeks

b. Omeprazole 20 mg bid + amoxicillin 500 mg qid
   I. Reserve for patients with a history of non-compliance or intolerance to triple therapy
   ii. Duration of antimicrobial therapy: 2 weeks
   iii. If patient is penicillin allergic, substitute clarithromycin 500 mg tid for amoxicillin
   iv. If ulcer is present, continue omeprazole for additional 4 weeks after completion of antimicrobials or change to an H_2-antagonist for 4 weeks duration (to complete 6 weeks of acid suppressive therapy)

4. Therapy for refractory infection (if patient has recurrence of H. pylori after completing previous therapy or has a documented metronidazole-resistant strain)
   a. Amoxicillin 500 mg qid + clarithromycin 500 mg bid + omeprazole 20 mg bid
      I. Duration of therapy: 2 weeks
      ii. If patient is penicillin allergic, delete amoxicillin and use dual regimen with clarithromycin 500 mg tid

IV. Acceptable uses for alternative agents

A. Famotidine

1. Patients receiving concomitant therapy with medications known to have clinically significant drug interactions with cimetidine (phenytoin, warfarin, cyclosporine, theophylline, lidocaine).
2. Transplant patients where cimetidine use may lead to false increases in serum creatinine measurements (due to competition for renal tubular secretion).
3. Patients with documented intolerance to cimetidine (*e.g.*, gynecomastia, impotence, hypersensitivity reaction, etc.). Altered mental status secondary to cimetidine is NOT an acceptable indication for the use of famotidine; patients who experience altered mental status from the use of an H_2-antagonist should be changed to sucralfate, antacids or omeprazole where appropriate.
4. Patients stabilized on prior outpatient regime for an approved indication (applies to oral therapy only).

Dosing of Famotidine:

a. Prophylaxis of stress-related mucosal damage:
   20 mg iv q12 hours or 20 mg po/ng q 12 hours or 40 mg/day as a continuous intravenous infusion (1.7 mg/hour)
b. Active gastric/duodenal ulcers:
   20 mg po bid or 40 mg qhs
c. Maintenance therapy for gastric/duodenal ulcers:
   20 mg po qhs
d. Gastroesophageal reflux disease:
   20 mg po bid (may titrate up to 40 mg po bid)
e. Zollinger-Ellison Syndrome:
   20 mg po bid (may titrate up to 80 mg/day)

B. Omeprazole
   1. Indications for use:
      a. Endoscopically documented gastric or duodenal ulcer refractory to 8 weeks of H_2-antagonist or sucralfate therapy. Exception: used as first line therapy for patient with cirrhosis and acid-related ulcer disease.
      b. Endoscopically documented severe erosive esophagitis (Grade 3 or 4).
      c. Endoscopically documented symptomatic gastroesophageal reflux disease refractory to 8 weeks of H_2-antagonist therapy.
      d. Pathological hypersecretory conditions (*e.g.*, Zollinger-Ellison syndrome)
   2. Dosage/Duration of therapy:
      a. Refractory gastric or duodenal ulcers: 40 mg daily x 4-8 weeks
      b. Severe (Grade 3 or 4) erosive esophagitis: 20 mg daily x 4 - 8 weeks
      c. Refractory reflux esophagitis: 40 mg daily x 4 - 8 weeks
      d. Hypersecretory states: 20-160 mg daily; if total daily dose>80 mg, give in 2 divided doses for indefinite duration based on symptomatic control of disease. Long-term therapy with omeprazole for benign disease (esophagitis, peptic ulcer disease, etc.) should be discouraged until more information regarding the risk of gastric carcinoid formation is accrued.
   3. Administration:
      Omeprazole should not be administered per ng unless absolutely necessary due to uncertain bioavailability when integrity of enteric-coated preparation is altered).

C. Cisapride
   1. Indication for use:
      Symptomatic treatment of nocturnal heartburn due to gastroesophageal reflux disease
   2. Dosage/duration of therapy:
      Therapy should be initiated at 10 mg po bid at least 15 minutes before meals and at bedtime; some patients may require 20 mg po qid to obtain a satisfactory result. Duration of therapy ranges from 4 - 16 weeks.

D. Misoprostol (Non-formulary)
   1. Patients requiring long-term, high-dose NSAID therapy with a history of gastric ulcer or hemorrhage secondary to NSAID therapy.
   2. Patients stabilized on prior outpatient regimen for an approved indication.

E. Ranitidine
   1. Pediatric patients (formulary)
   2. Patients stabilized on a prior outpatient regimen for an approved indication (otherwise non-formulary)

F. Nizatidine (non-formulary)
   Patients stabilized on prior outpatient regimen for an approved indication.

V. Combination therapy

A. Antacids may be used for symptomatic relief in combination with other agents.

B. Combination therapy with H_2-antagonists and sucralfate has not been shown to be superior to monotherapy with either agent in the treatment of peptic ulcer disease.

C. There is no role for combination therapy with omeprazole and H_2-antagonists.

VI. Dosing in renal insufficiency

Cimetidine

CrCl>30 ml/min	300 mg iv q8h	400 mg po bid or 300 mg qhs
CrCl 15-30 ml/min	300 mg iv q12h	300 mg po bid or 600 mg qhs
CrCl<15 ml/min	300 mg iv q24h	400 mg po qd

Famotidine

CrCl>50 ml/min	20 mg iv q12h	20 mg po bid or 40 mg po qhs
CrCl 10-50 ml/min	20 mg iv q24h	20 mg po qd
CrCl<10 ml/min	20 mg iv q48h	20 mg po qod

Hemodialysis: The daily dose should be administered after hemodialysis. Sucralfate and omeprazole do not require dosage adjustment for renal insufficiency.

VII. Pediatric dosing

1. Cimetidine
   Neonates 2.5-5 mg/kg/dose iv/po q6h
   Children 5-10 mg/kg/dose iv/po q6h
2. Ranitidine
   1-2 mg/kg/dose po q12h
   0.5-1.0 mg/kg/dose iv q6h
3. Antacids
   5-15 ml/dose q3-6h po/ng for PUD
4. Sucralfate
   15 ml/kg/dose po/ng q6h (round to nearest 250 mg dose)
5. Omeprazole
   Limited data exist for the dosing and administration of omeprazole in the pediatric patient population. Doses of 20-60 mg po daily have been utilized in patients ranging from 3-17 years without adverse effects.
6. Cisapride
   0.2 mg/kg po tid-qid (ac/hs)

B. Intergroup Antibiotic Management Guidelines

Treatment Guideline

Note: For therapy initiation, please choose any of the products listed in the "Recommended for Initial Therapy" column. When selecting subsequent therapy, please choose products in the "Recommended for Subsequent Therapy" column in the order listed.

Infection*	Recommended for Initial Therapy		Recommended for Subsequent Therapy	
Tonsillitis Pharyngitis	Amoxicillin (Amoxil) Penicillin VK Erythromycin	$ $ $	Cephalexin (Keflex)	
Acute Sinusitis	Amoxicillin (Amoxil) Doxycycline TMP/SMX ERY/SX (Pediazole)	$ $ $ $	Cefaclor (Declor) Loracarbef (Lorabid) Amoxicillin/K Clavulanate (Augmentin)	$$ $$$ $$$$
Otitis Media	Amoxicillin (Amoxil) TMP/SMX (Bactrim) ERY/SX (Pediazole)	$ $ $	Cefaclor (Declor) Loracarbef (Lorabid) Cefixime (Suprax) Amoxicillin/K Clavulanate (Augmentin)	$$ $$$ $$$ $$$$
Bronchitis (negative chest X-ray, no infiltrate)	Amoxicillin (Amoxil) TMP/SMX (Bactrim) Erythromycin	$ $ $	Cefaclor (Declor) Loracarbef (Lorabid) Clarithromycin (Biaxin)	$$ $$$ $$$
Pneumonia (otherwise healthy, community acquired)	Erythromycin TMP/SMX (Bactrim)	$ $	Cefaclor (Declor) Loracarbef (Lorabid) Clarithromycin (Biaxin) Amoxicillin/K Clavulanate (Augmentin)	$$ $$$ $$$ $$$$
Pneumonia (risk factors, more severe presentation)	Erythromycin TMP/SMX (Bactrim) Loracarbef (Lorabid) Clarithromycin (Biaxin)	$ $ $$$ $$$	Cefaclor (Declor) Amoxicillin/K Clavulanate (Augmentin)	$$ $$$$
Urinary tract infections	TMP/SMX (Bactrim) Nitrofurantoin (Macrobid)	$ $$	Cephalexin (Keflex) Ofloxacin (Floxin)	$ $$$
Cellulitis	Dicloxacillin Cephalexin (Keflex)	$ $	Amoxicillin/K Clavulanate (Augmentin)	 $$$$

Recommended treatment guidelines are for informational purposes and are not intended to replace the clinical judgement of the practitioner. The $ indicates relative costs of drugs.

*Consult manufacturers' prescribing information for individual products regarding indicated organisms and dosing information.

Annex 7

Example of Drug Usage Evaluation Criteria (Terfenadine)

(Adapted with permission from the Criteria for Drug Use Evaluation - Volume 1, American Society of Health-System Pharmacists; 1994, Bethesda, MD.

CRITERIA FOR USE OF TERFENADINE

No.	Elements	Standard 100% 0%	No.	Exceptions	No.	Instructions - data retrieval
	Justification of use					
1	Patient with at least one of the following: a) documented seasonal allergic or perennial rhinitis or conjunctivitis in adult intolerant of sedative effects of antihistamines b) documented seasonal allergic or perennial rhinitis or conjunctivitis in child of >3 years old intolerant of sedative effects of antihistamines c) documented histamine-mediated skin disorders unresponsive to standard therapy with cyproheptadine, diphenhydramine, or hydroxyzine AND	X	1A	None	1	History and physical (H&P), physician orders, progress notes
2	Previous, documented unsuccessful trial with at least one of less sedating antihistamines (*e.g.*, brompheniramine, chlorpheniramine, cyproheptadine, triprolidine)	X	2A	Occupation requiring alertness precludes potential for drowsiness	2 2A	H&P, physician orders, progress notes H&P, progress notes
	Critical (Process) Indicators					
3	Appropriate oral dosage prescribed: a) adults: 120 mg/day as single dose or two divided doses b) children: 3-5 years - 15 mg BID 6-12 years - 30 mg BID	X	3A	In obese (>120% ideal body weight) child 6-12 years, 60 mg orally BID prescribed	3 3A	H&P, physician orders, progress notes H&P, physician orders, nursing notes, progress notes
4	Use of other antihistamines discontinued at least 6 hr prior to terfenadine therapy	X	4A	If previous antihistamine is extended-release product, allow 12 hr	4, 4A	H&P, physician orders, medication administration record (MAR), progress notes

No.	Elements	Standard 100% 0%	No.	Exceptions	No.	Instructions - data retrieval
5	Concurrent antihistamine therapy not present	X	5A	Concurrent antihistamine may be given instead of evening terfenadine dose in patient experiencing insomnia or nightmares with terfenadine therapy	5 5A	H&P, physician orders, MAR, progress notes H&P, physician orders, nursing notes, progress notes
	Complications					
6	Gastrointestinal effects: abdominal distress, nausea, vomiting, change in bowel habits, and/or increased appetite	X	6A 6B 6C	Identify other drug and nondrug causes Give terfenadine with meals and/or decrease terfenadine dosage If severe reaction, discontinue terfenadine or switch to alternative therapy	6, 6A, 6B, 6C	Nursing notes, progress notes Physician orders, MAR, nursing noted, progress notes
7	Central nervous system effects: drowsiness, headache, fatigue, dizziness, depression, insomnia, tremor, confusion, and/or nightmares	X	7A 7B 7C	Identify other drug and nondrug causes If mild reaction, give terfenadine as single daily dose or decrease terfenadine dosage If severe reaction, discontinue terfenadine or switch to alternative therapy	7 7A 7B, 7C	Nursing notes, progress notes Nursing notes, progress notes, physician orders Physician orders, MAR, nursing noted, progress notes
8	Anticholinergic effects: dry mouth, nose, and/or throat	X	8A 8B 8C	Identify other drug and nondrug causes If mild reaction, administer sugarless hard candy or fluids If severe reaction, discontinue terfenadine or switch to alternative therapy	8 8A 8B, 8C	Nursing notes, progress notes Nursing notes, progress notes, physician orders Physician orders, MAR, nursing noted, progress notes

No.	Elements	Standard 100% 0%	No.	Exceptions	No.	Instructions - data retrieval
9	Cardiac effects: palpitations, tachycardia, and/or cardiac arrhythmia	X	9A	Identify other drug and nondrug causes	9	Nursing notes, progress notes
			9B	If mild reaction, decrease terfenadine dosage	9A	Nursing progress notes, physician orders
			9C	If patient symptomatic, discontinue terfenadine or switch to alternative therapy; provide symptomatic care and supportive therapy	9B, 9C	Physician orders, MAR, nursing notes, progress notes
10	Musculoskeletal symptoms	X	10A	Identify other drug and nondrug causes	10	Nursing notes, progress notes
			10B	If mild reaction, decrease terfenadine dosage	10A	Nursing notes, progress notes, physician orders
			10C	If severe reaction, discontinue terfenadine or switch to alternative therapy; provide symptomatic care and supportive therapy	10B, 10C	Physician orders, MAR, nursing notes, progress notes
11	Hypersensitivity reaction: anaphylaxis (difficulty breathing, wheezing, laryngeal edema, flushing, or rapid pulse), rash, and/or urticaria	X	11A	Discontinue terfenadine or switch to alternative therapy	11	Nursing notes, progress notes
			11B	Provide supportive therapy, which may include steroids, epinephrine, and diphenhydramine	11A, 11B	Physician orders, MAR, nursing notes, progress notes
	Outcome Measures					
12	Documented adequate relief of allergic symptoms	X	12A	Patient expired	12	Nursing notes, progress notes
			12B	Patient developed respiratory infection	12A-12C	Progress notes
			12C	No subsequent visit or communication with outpatient		

Annex 8

Naranjo Adverse Drug Reaction Probability Scale

The Naranjo Adverse Drug Reaction Probability Scale

The Naranjo Scale represents a 10 question rating system to determine the probability for an adverse drug reaction. It was developed in the 1970s, and is now in use by most hospitals. Literature research has validated the Naranjo Scale as a reproducible method to assign the probability of an adverse drug event. The probability levels are: definite, probable, possible, doubtful.

	Yes	No	Do not know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
4. Did the adverse reaction reappear when the drug was re-administered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drug in any previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
Total score				

Probability that the adverse event was related to drug based on total score:

Definite	>9
Probable	5-8
Possible	1-4
Doubtful	0

Examples:

Amitriptyline:

A 23-year old male had been taking amitriptyline 150 mg daily for 3 months. He developed jaundice, dark urine and pale stools with elevated liver enzymes. Withdrawal of the drug resulted in symptom resolution. He was rechallenged and showed an abrupt increase in liver function tests.

1. Yes = +1
2. Yes = +2
3. Yes = +1
4. Yes = +2
5. Don't know = 0
6. Don't know = 0
7. No = 0
8. Don't know = 0
9. Don't know = 0
10. No = 0

Total score = **6** = **PROBABLE**

Imipenem/cilastatin:

A 65-year old female with an estimated CrCl of 50 ml/min was given imipenem/cilastatin 1 g iv q6h for nosocomial pneumonia. Thirty minutes after her third dose she had generalized tonic/clonic seizures. She has a history of head injury from a car accident two years ago. The drug was discontinued and seizures did not recur.

1. Yes = +1
2. Yes = +2
3. Yes = +1
4. Don't know = 0
5. Yes = -1
6. Don't know = 0
7. Don't know = 0
8. Don't know = 0
9. Don't know = 0
10. No = 0

Total score = **3** = **POSSIBLE**

Annex 9

Examples of Adverse Drug Reaction Reporting Forms

(Adapted for the purposes of this manual from University of Arizona, Tucson (examples A, B and C), and the MedWatch Journal (example D))

Example A

Adverse Drug Reaction
Reporting Card

Patient Name _____

Medical Record No. _____

Room No. _____

Date Of Reaction _____

Type of Reaction Observed _____

_____

_____

Suspected Drug _____

_____

Reporter's Name _____

Title _____

Date _____

Example B

Adverse Drug Reaction

Patient Name _____ Age _____ Sex _____ _____
Medical Record No. _____ Room No. _____ Admit Date _____
Attending Physician _____ Admitting Diagnosis _____
Secondary Diagnoses _____

_____

Drug and/or Other Allergies _____

_____

Type of Reaction/Suspected Drug _____
Date/Time of Onset of Reaction _____
Treatment Initiated for Reaction _____
Date/Time Reaction Abated _____

All Suspected Drugs Taken at Time of Reaction

(Generic Name/Dose/Route/Start Date)

All Drugs Discontinued Within One Week Prior To Reaction

(Generic Name)

Pertinent Abnormal Laboratory Data _____
Prescribing Physician _____
Rechallenge Date/Time/Reaction _____
Reporter's Name and Title _____

Example C

Adverse Drug Reaction

Name _____ Admit Date _____

Drug (generic name)/Dose/Route _____

Attending Physician _____ Date of Reaction _____

Dosing Frequency _____ Duration _____

Indication _____ Use _____

Prescribing Physician _____

Adverse Reaction: 1) _____

2) _____

3) _____

Probability of Adverse Drug Reaction: (circle one) Definite Probable
(Comment) Possible Doubtful

Severity Code:
(Tracer)
0 = No disability
1 = Minor Temporary
2 = Minor Permanent
3 = Major Temporary
4 = Major Permanent
5 = Potential Major Continuing
6 = Death

Mechanism:
Augmented Pharmacological Reaction _____
Idiosyncratic Reaction _____
Irritant Reaction _____
Reporter's Name and Title _____
FDA Report Filed: yes no Date _____

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For VOLUNTARY reporting by health professionals of adverse events and product problems

Page _____ of _____

Form Approved: OMB No. 0910-0291 Expires: 12/31/94
See OMB statement on reverse

FDA Use Only (AHFS)
Triage unit
sequence #

1. Patient identifier	2. Age at time of event:	3. Sex	4. Weight
In confidence	or _____ Date of birth:	☐ female ☐ male	_____ lbs or _____ kgs

B. Adverse event or product problem

1. ☐ **Adverse event** and/or ☐ **Product problem** (e.g., defects/malfunctions)

2. **Outcomes attributed to adverse event** (check all that apply)
☐ death _____
☐ life threatening
☐ hospitalization - initial or prolonged
☐ disability
☐ congenial anomaly
☐ required intervention to prevent permanent impairment/damage
☐ Other: _____

3. **Date of event** (mo/day/yr)

4. **Date of this report** (mo/day/yr)

5. **Describe event or problem**

6. **Relevant tests/laboratory data,** including dates

7. **Other relevant history, including preexisting medical conditions** (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. **Name** (give labeled strength & mfr/labeler, (if known)
#1
#2

2. **Dose, frequency & route used**
#1
#2

3. **Therapy dates** (if unknown, give duration)
From/to (or best estimate)
#1
#2

4. **Diagnosis for use** (indication)
#1
#2

5. **Event abated after use stopped or dose reduced**
#1 ☐yes ☐no ☐doesn't apply
#2 ☐yes ☐no ☐doesn't apply

6. **Lot #** (if known)
#1
#2

7. **Exp. Date** (if known)
#1
#2

8. **Event reappeared after reintroduction**
#1 ☐yes ☐no ☐ doesn't apply
#2 ☐yes ☐no ☐doesn't apply

9. **NDC #** (for product problems only)
- -

10. **Concomitant medical products** and therapy dates (exclude treatment of event)

D. Suspect medical device

1. **Brand name**

2. **Type of device**

3. **Manufacturer name & address**

4. **Operator of device**
☐ health professional
☐ lay user/patient
☐ other:

6.
model # _____
catalog # _____
serial # _____
lot # _____
other #

5. **Expiration date** (mo/day/yr)

7. **If implanted, give date** (mo/day/yr)

8. **If explanted, give date** (mo/day/yr)

9. **Device available for evaluation?** (Do not send to FDA)
☐ yes ☐ no ☐ returned to manufacturer on _____

10. **Concomitant medical products** and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. **Name, address & phone #**

2. **Health professional?**
☐yes ☐no

3. **Occupation**

4. **Also reported to**
☐ manufacturer
☐ user facility
☐ distributor

5. If you do NOT want your identity disclosed to the manufactured, place an "X" in this box. ☐

Mail to: MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787

or FAX to:
1-800-FDA-0178

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.