

ACCP POSITION STATEMENT

Guidelines for Therapeutic Interchange—2004

American College of Clinical Pharmacy

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This publication is an update of the American College of Clinical Pharmacy (ACCP) Position Statement on “Guidelines for Therapeutic Interchange,”¹ originally published in 1993.

The ACCP supports the practice of therapeutic interchange, in which pharmacists collaborate with physicians and other health care professionals to develop policies and implement programs that improve drug use to provide the best possible patient care at the most affordable cost. The ACCP has established the following guidelines for implementing therapeutic interchange policies and procedures within health care organizations and other appropriate patient care settings:

- Guideline I: Therapeutic interchange is appropriate in institutional and ambulatory settings that have a functioning formulary system and pharmacy and therapeutics committee or equivalent drug use policy-setting bodies.
- Guideline II: Organizations implementing therapeutic interchange programs must accept the obligation to measure their impact on the clinical, economic, and humanistic

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outcomes of care.

- Guideline III: Therapeutic interchange, as defined herein, may be executed by pharmacists when prescribers have been advised of the policy set forth by the pharmacy and therapeutics committee or its equivalent. Notification to each individual prescriber need not occur for each interchange when institutional or organizational policies do not require such. In other cases, prescribers should be notified within a reasonable time frame through written, oral, or electronic communication. Use of technology to aid in managing the therapeutic interchange policy is highly desirable.
- Guideline IV: The pharmacy and therapeutics committee or an equivalent body should ensure that professional staff is educated regarding the policies, procedures, objectives, and rationale for therapeutic interchange. The policies should include provisions for disclosure of therapeutic interchange practices to patients as appropriate to the setting in which therapeutic interchange will occur.
- Guideline V: Therapeutic interchange policies should define a mechanism that permits exceptions to the policy and procedures when necessary and/or appropriate.

Definition

Therapeutic interchange is defined as the dispensing of a drug that is therapeutically equivalent to but chemically different from the

drug originally prescribed by a physician or other authorized prescriber. Although usually of the same pharmacologic class, drugs appropriate for therapeutic interchange may differ in chemistry or pharmacokinetic properties, and may possess different mechanism of action, adverse-reaction, toxicity, and drug interaction profiles. In most cases, the interchanged drugs have close similarity in efficacy and safety profiles.

Overview of Therapeutic Interchange

The role of therapeutic interchange has increased substantially in recent years as a result of two primary influences: the rapid expansion in the number of drugs within the same or comparable therapeutic classes, and the need to control drug and related health care costs while promoting more rational drug therapy. Therapeutic interchange policies and programs grant pharmacists the authority to interchange drugs without prior consent from the prescriber, according to procedures outlined in a specific policy. Prescribers may include physicians, physician assistants, nurse practitioners, and other health care professionals who are authorized to prescribe.

Therapeutic interchange policies and procedures within a health care delivery organization usually are developed and guided by a group responsible for establishing drug use policies, such as the pharmacy and therapeutics committee. This committee is composed of physicians, pharmacists, and other health professionals whose combined and complementary expertise, knowledge, and experience are used to develop policies and procedures to guide the professional staff and administration of an organization on matters related to the therapeutic use of drugs. Among other duties, the committee serves in an advisory capacity to the medical staff and administration in all matters pertaining to the use of drugs, including therapeutic interchange; establishes programs and procedures that help ensure cost-effective drug therapy; establishes or plans suitable educational programs for the professional staff on matters related to drug use; participates in continuous quality improvement activities; and initiates or directs drug use evaluation programs and reviews their results.² A successful and effective therapeutic interchange policy is directly related to the effectiveness of the pharmacy and therapeutics committee in performing its functions, as well as the input of other health

care professionals involved with implementing and maintaining the policy.

The ACCP Guidelines and Rationale for Therapeutic Interchange

As stated, the ACCP supports the concept and practice of therapeutic interchange. The policies should result from a synergistic combination of the expertise and knowledge of pharmacists and physicians whose common goal is to ensure optimum patient care. They should not be interpreted as “bestowing independent prescribing authority on pharmacists.” Although the policies may vary in complexity, most involve the interchange of one drug for another that is deemed to be therapeutically equivalent. They should not be viewed as or become blanket policies allowing pharmacists to choose an alternative drug from an entire class or category of drugs.

This section describes the rationale for each ACCP-supported guideline for implementing therapeutic interchange policies and procedures within health care organizations.

Guideline I

Therapeutic interchange is appropriate in institutional and ambulatory settings that have a functioning formulary system and pharmacy and therapeutics committee or equivalent drug use policy-setting bodies.

Rationale

The success of any therapeutic interchange program is related to the effectiveness of the pharmacy and therapeutics committee or its equivalent body, and the organization's formulary system. An effective committee uses the principles of quality management to govern therapeutic interchange policies and processes of the formulary system. This committee should represent both the pharmacy and medical staffs. It must develop, implement, review, and change policies and procedures to ensure optimum patient care while managing costs. Similarly, it should recommend and assist in educating health professionals regarding policies and approved exceptions to them, assessing organizational effectiveness of the program, and evaluating the patient care outcomes associated with their implementation.²⁻⁴

The pharmacy and therapeutics committee should establish or assign a subcommittee or

department to monitor the effectiveness of therapeutic interchange policies and procedures. Audits or reviews should be conducted according to set policies. Criteria should be developed and used to determine when and why the therapeutic interchange policies may be ineffective (see Guideline II). The issues identified should be addressed and the health professionals notified of resulting changes to policies and procedures.

The specific types of institutional or ambulatory settings for which therapeutic interchange policies are most likely to be effective are those that have drug formularies with a functioning pharmacy and therapeutics committee or its equivalent. This may include, but is not limited to, hospice settings, health maintenance organizations, community hospitals, university hospitals, and ambulatory clinics affiliated with a hospital. Community pharmacists, including home care, and long-term care facility consultant pharmacists also may participate in therapeutic interchange programs in some cases.^{5, 6} If the policies dictate that laboratory or medical record data should be readily available to pharmacists before recommending the use of or dispensing a therapeutic alternative, the setting must provide access to this information. Regardless of the setting, pharmacists and physicians must have a good working relationship and a mutual goal to provide excellent medical care while containing costs.

Therapeutic interchange recently has become a common method used by some health plans, pharmacy benefits management companies, and insurers as part of the effort to control drug expenditures. When therapeutic interchange is adopted by these entities, it is important that a pharmacist who is directly responsible for the care of the patient evaluate the practical impact on the patient that is likely to result. The pharmacist who is directly responsible for the patient's care should act as an advocate for the patient. Patient advocacy by the pharmacist includes, but is not limited to, education of the patient about the potential impact of the interchange, and communication with the prescriber whose orders or prescriptions are affected. Pharmacists should use their expertise to assist both the patient and the prescriber with decisions related to therapeutic interchange.⁷

The institutional setting provides a controlled and continuously supervised health care environment, allowing for oversight and assurance of accurate drug therapy administration. When a

patient is moved from the institutional setting to another institutional or alternative health care setting, the change in the commercial product is more readily apparent to the patient. When a therapeutic interchange occurs, patients will often notice that the specific product or dosage form has changed. Although drugs that have been determined to be therapeutically interchangeable are typically comparable in efficacy, some drug product attributes (e.g., administration frequency or product appearance) may be substantially different and require modified behavior on the part of the patient. Pharmacists should educate patients about any changes that will be apparent to patients as a result of the interchange.

There is less evidence about patient outcomes associated with a change in care facilities, or when a patient transitions from one care setting to another. In general, the principal findings of the limited number of studies performed suggest that patient clinical and humanistic outcomes are neutral and pharmacoeconomic outcomes are positive.⁸⁻¹² The pharmacist responsible for the patient should ensure that a process or procedure is in place related to therapeutic interchange to minimize potential problems for patients when transitioning between care settings. An example of a procedure that improves the patient's experience of uninterrupted and appropriate therapy upon hospital discharge includes documentation of the patient's home drug on the electronic drug administration record.¹³

The lack of accumulated evidence about the impact of therapeutic interchange on patients who transition to new care settings is argument for the importance of ongoing surveillance and reporting.⁹ The United States Food and Drug Administration (FDA) encourages practitioners to report any untoward events thought to be associated with therapeutic interchange to the MedWatch program.

Guideline II

Organizations implementing therapeutic interchange programs must accept the obligation to measure the impact of those initiatives on the clinical, economic, and humanistic outcomes of care.

Rationale

The approval of a therapeutic interchange program is prefaced by acceptance of clinical equivalence of drugs within an interchange

category by an organization's medical staff, pharmacy and therapeutics committee, or other policy-setting body. The evidence supporting equivalence should be derived from clinical trials published in peer-reviewed literature. In some circumstances, organizations may choose to implement therapeutic interchange initiatives with substantially less supportive evidence (e.g., drawing evidence from disparate trials with common design and comparator groups). In either case, the implementation of therapeutic interchange may not result in positive economic, clinical, or humanistic outcomes for patients treated under the policy, and demonstration of true equivalence of outcomes associated with therapeutic interchange is of great importance.

The ideal criteria for establishing clinical equivalence not only must include evidence of equal efficacy (drawing data from randomized clinical trials and answering the question, "Can these drugs produce similar outcomes?"), but also must consider evidence of equal effectiveness (answering the question, "Do these drugs produce similar outcomes?"). Evidence of effectiveness is obtained from patients receiving care under usual patient care conditions, not in the artificial environment of a clinical trial. Furthermore, equivalence of outcome must be shown in a variety of dimensions: clinical, economic, and humanistic.

In economic terms, organizations implementing therapeutic interchange will enjoy lower drug acquisition costs. Therapeutic interchange successfully decreases drug acquisition costs when implemented in a variety of settings. As with all economic evaluations, it is essential that the total cost of care be evaluated to assess the impact of individual interchange initiatives and ensure that the total cost of care is reduced when a less expensive drug is administered in place of a more costly one.

The clinical outcomes of interest will depend on the condition being managed by the drugs being interchanged. Recognizing that outcomes documented in clinical trials often are not achieved under routine clinical practice conditions is essential. Once an interchange is implemented, measurement of treatment success is required. Humanistic outcomes, including quality of life, functional status, and patient satisfaction, also are important and should be included in an evaluation of the success of a therapeutic interchange initiative.

Organizations must be willing to accept the responsibility for conducting postimplementation

outcome evaluations in return for the savings that they enjoy from therapeutic interchange, particularly in the event they implement therapeutic interchange initiatives with imperfect or less than ideal data supporting clinical equivalence. Most organizations have responsibility for conducting drug use evaluations to satisfy Joint Commission on Accreditation of Healthcare Organizations (JCAHO) requirements, and evaluations of postinterchange outcomes can easily be tailored to fit the framework of traditional drug use evaluation.¹⁴ Excellent examples of published outcomes evaluations are available in the peer-reviewed literature and can serve as templates for similar projects in other health systems.^{9, 11, 15}

Guideline III

Therapeutic interchange, as defined herein, may be executed by pharmacists when prescribers have been advised of the policy set forth by the pharmacy and therapeutics committee or its equivalent. Notification to each individual prescriber need not occur for each interchange when institutional or organizational policies do not require such. In other cases, prescribers should be notified within a reasonable time frame through written, oral, or electronic communication. Use of technology to aid in managing the therapeutic interchange policy is highly desirable.

Rationale

Therapeutic interchange policies and procedures should describe in detail the conditions and processes for interchanging drugs. These should include who has authority to enact the interchange, special exceptions to a policy, or procedure and criteria to be evaluated before and after the interchange occurs. Solicitation of approval from individual prescribers is not necessary, providing the interchange is performed according to the policies and procedures set forth by the pharmacy and therapeutics committee or comparable oversight body. However, notification of interchanges to all health care professionals involved in patient care is paramount to the acceptance and management of the policy. Notification may occur in various ways, including written, oral, or electronic orders recorded in the medical record; e-mail communication; direct interface into drug administration records; or incorporation into the prescribing process through the use of computerized physician order entry.

Use of computerized physician order entry provides a distinct opportunity in the management of therapeutic interchange policies. Computerized information systems are powerful tools for structuring, collecting, and managing data. When applied to the setting of drug prescriptions, they have the potential to alter physician prescribing practices substantially.^{15, 16} The greatest advantages to computerized physician order entry lie in the ability of the system to offer only those drugs listed on the institution's or health care system's formulary, or to highlight those preferred drugs approved by the pharmacy and therapeutics committee for therapeutic interchange. Guidelines for drug use, and the rationale for substitution, can be displayed in real time at the critical point of physician initiation. This not only increases adherence to the therapeutic interchange policy, but also allows immediate prescriber notification of the drug to be interchanged.

There are many studies documenting increases in therapeutic interchange policy adherence through the use of computerized physician order entry.¹⁵⁻¹⁹ Statistically significant increases in use of formulary drugs and statistically significant decreases in orders exceeding the maximum recommended dose have been demonstrated.¹⁵ However, there must always be a process by which a prescriber may override a therapeutic interchange recommendation built into the computerized physician order entry system. Computerized physician order entry allows pharmacists to manage a therapeutic interchange policy proactively through the use of computerized warnings, dosage guidance tools, and recommendations of preferred drugs within a class.

Guideline IV

The pharmacy and therapeutics committee or an equivalent body should ensure that professional staff is educated regarding the policies, procedures, objectives, and rationale for therapeutic interchange. The policies should include provisions for disclosure of therapeutic interchange practices to patients as appropriate to the setting in which therapeutic interchange will occur.

Rationale

Proper educational methods should be developed, implemented, reviewed, and revised as necessary to inform the professional staff

regarding the rationale, procedures, and monitoring criteria for therapeutic interchange. These methods may include newsletters, fliers, departmental meetings, meeting minutes, electronic media, and publication of therapeutic interchange policies, such as in an organization's formulary. Physicians should be informed of the policies prospectively, and a list of active policies should be readily available to the professional staff. As part of ongoing education regarding therapeutic interchange, the professional staff should be informed of results from drug use evaluations pertaining to therapeutic interchange. Computerized physician order entry would provide immediate notification of specific therapeutic interchanges and may serve as a constant reminder that such policies exist.^{16, 19}

Patient disclosure and educational materials may be developed in written or audiovisual format as appropriate to introduce the concept of therapeutic interchange, address the potential impact to their care, and promote drug adherence. Managed care plans must prospectively notify or disclose to enrollees information regarding the policies and limitations or restrictions on the benefits package (which should include prescription coverage and policies of therapeutic interchange).²⁰ These therapeutic interchange policies are again reinforced at a more individualized level when prescriptions are filled. Issues of appropriate use, dosage, and adverse effects are routinely part of patient information sheets provided with a prescription. If a drug is therapeutically interchanged for another, however, there remains the need to ensure the patient understands that one drug has replaced another and is not an addition to therapy. Changes in drug regimens can be sources of confusion and may lead to compliance issues,⁵ potential omissions, or duplication of therapy. Ongoing patient education and follow-up by pharmacists and physicians are essential to prevent these problems.^{4, 21}

The pharmacist plays a critical role in therapeutic interchange program management and must be well prepared to communicate effectively with both patients and physicians regarding the concepts of therapeutic interchange.²¹ Knowledge of all relevant policies and procedures for therapeutic interchange is essential. A program to assess pharmacists' understanding of the therapeutic interchange program should be a part of the regular performance evaluation processes of the organization.

Guideline V

Therapeutic interchange policies should define a mechanism that permits exceptions to the policy and procedures when necessary and/or appropriate.

Rationale

Therapeutic interchange may not be applicable to or appropriate for all patients. Allergies or a history of failed therapy or unwanted side effects may warrant that another drug be prescribed. Also, a drug being prescribed for an off-label indication should be allowed if the preferred drug is not appropriate. For example, cimetidine, when prescribed concurrently with a 24-hour creatinine clearance, is used to improve the accuracy of the laboratory test. Other histamine₂ antagonists do not have this pharmacologic effect.¹²

In addition, some chronic disease states may not be amenable to therapeutic interchange. Patients with mental illness, rheumatic disease, and some gastrointestinal disorders may be stabilized or in remission with their current drug regimen. Switching to another drug may have the potential to cause relapse or deterioration in their condition.

Consequently, an acceptable method of exercising exceptions to an organization's therapeutic interchange procedures must be made available to prescribers. The physician should notify the pharmacist either in writing or orally regarding the desire to override the existing policy or procedure. Data on the nature and extent of exceptions to the policy and procedures should be collected and analyzed by the appropriate oversight body.

Some institutions are now adding a statement to their therapeutic interchange policy authorizing changes of the preferred drug in case of a national supply shortage. Changing the preferred drug in times of national shortage should be permissible to alleviate distribution delays and provide continuity of patient care. Implementation of this statement must be restricted to previously authorized drug classes and should not be interpreted as an open invitation that allows pharmacists to interchange any prescribed drug at will.

Additional Background and Discussion

Because interest in therapeutic interchange has become broader, it is important for health care

practitioners to be aware of common practices associated with therapeutic interchange and the factors that influence it. This section describes common practices that are undertaken with a therapeutic interchange program. Typical drug classes that may be considered for therapeutic interchange are highlighted. In addition, the multitude of factors that can affect the success and outcome of therapeutic interchange are reviewed.

Common Practices in Therapeutic Interchange

High-quality, cost-effective formularies are required because of the increasing complexity of pharmacotherapy, the associated increase in the number of therapeutically equivalent drugs that often are considered “me too,” and escalating drug costs. Therapeutic interchange is a widely used option available to accomplish this objective related to formularies while also maintaining optimal patient care.²² Other benefits of therapeutic interchange include minimizing therapeutic duplication, producing positive clinical outcomes, and controlling costs.²³ It also can be used as a vehicle to promote appropriate use of pharmaceuticals, by supporting the highest quality standards of pharmaceutical care to optimize patient wellness and outcomes.

For health care practitioners to develop and support a successful therapeutic interchange program, certain common practices should be associated with the program.^{5, 23–25} The practices to be considered may include, but may not be limited to the following:

- Guidelines should be developed to support decisions in the therapeutic interchange process using an evidence-based approach.
- Clinical pathways and other national standardized guidelines should be used to sustain decision-making processes, and interventions should be performed in accordance with interchange protocols.
- The need for physician support is paramount to the process. Successful programs designed to influence prescribing must involve physicians throughout the process. This involvement may include delineating procedures, communicating to other members of the medical staff, and assisting in implementing and setting up the overall operation of the program.
- Qualified health care personnel are required to monitor prescriber compliance with therapeutic interchange and overall patient

outcomes affected by the interchange program.

- Effective communication with the medical staff and other health care personnel is critical to executing drug interchange strategies. Communication vehicles can include interactive educational programs, pharmacy newsletters, and direct mailings such as “dear doctor” letters.
- Industry involvement is essential to have an impact on the general costs of drugs. Once an institution or health system determines that certain drugs are deemed equivalent within a class, a competitive bidding process can be undertaken with drug manufacturers. By driving market share to a specific drug within the class, manufacturers may be persuaded to offer some price reductions for that product.
- By standardizing a formulary to one or more products within a therapeutic class, the institution can more appropriately manage its inventories. Patient safety can be enhanced by product standardization, allowing for less chance of errors.
- Demonstration of positive clinical outcomes certainly adds support to a therapeutic interchange program. Although the literature is limited in documenting favorable patient outcomes from various drug management techniques, demonstrating that therapeutic interchange did not negatively affect clinical outcomes is important.
- Economic outcomes should be considered with the recognition that health care is a business. Effective fiscal management is vital for long-term economic survival of institutions and health systems. However, these considerations must be balanced with patient care outcomes.
- A therapeutic interchange program should not impede patient access to necessary drugs but, instead, improve patient access to more affordable health care.

Determining which drugs to include in a therapeutic interchange program can vary based on a specific institution's or health system's needs. However, in general, many programs focus on drugs with high risk, high volume, or high costs, or drugs overused in routine conditions.²⁶ Those individuals involved in making decisions about the therapeutic interchange program and which specific drugs to include should minimally include physicians, pharmacists, and pharmacy and therapeutics

committee staff. Other health care professionals including nurses and social workers, as well as risk managers, also may be a part of the decision-making process. Typical classes of drugs for which therapeutic interchange may be undertaken are the following^{5, 22, 26}:

- Analgesics: cyclooxygenase-2-selective inhibitors, nonsteroidal antiinflammatory drugs, opiates, opioids
- Antiinfective drugs: aminoglycosides, antifungals, carbapenems, first-, second-, and third-generation cephalosporins, fluoroquinolones, macrolides, penicillins
- Cardiovascular drugs: angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, β -blockers, calcium channel blockers, direct thrombin inhibitors, glycoprotein IIb-IIIa receptor antagonists, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, low-molecular-weight heparins, nitrates and nitrites, thiazide diuretics, thrombolytics
- Central nervous system drugs: benzodiazepines, neuromuscular blocking drugs, selective serotonin reuptake inhibitors, triptans
- Eye, ear, nose, and throat preparations: antitussives, decongestants, expectorants, low- and nonsedating antihistamines, nasal corticosteroids, ophthalmic β -blockers, respiratory corticosteroids
- Gastrointestinal drugs: antacids, serotonin 5-HT₃ receptor antagonists, histamine₂-receptor antagonists, laxatives and stool softeners, proton-pump inhibitors
- Hormones and synthetic substitutes: insulins, luteinizing hormone-releasing hormone agonists, oral contraceptives, thyroid drugs
- Metabolic drugs: parenteral amino acids, intravenous fat emulsions
- Skin products: antifungal creams and ointments, topical corticosteroids, debriding agents
- Miscellaneous drugs: intravenous immune globulins, iron preparations, potassium supplements, vitamins

Although this list is quite extensive, the 11 drug classes most often used in therapeutic interchange, as reported by a survey conducted in 1999,²² are as follows (listed in descending order of frequency):

- Histamine₂-receptor antagonists
- Proton-pump inhibitors

- Antacids
- Fluoroquinolones
- Potassium supplements
- First-generation cephalosporins
- HMG-CoA reductase inhibitors
- Second-generation cephalosporins
- Insulins
- Third-generation cephalosporins
- Laxatives and stool softeners

Practitioners at individual institutions and health systems should develop a systematic process to determine the specific classes to include in therapeutic interchange programs considering overall value to patient care, clinical and economic outcomes, and practitioner support.

There may be barriers to use of therapeutic interchange or various factors as to why institutions or health systems may not use a therapeutic interchange program. These barriers may include the potential for physician or other health care practitioner nonacceptance, violation of state law, fear of civil liability, lack of staff resources to set up and implement the program, and the cost of initiating therapeutic interchange, which may be greater than the expected benefit.²² However, initiation costs for most new therapeutic interchange initiatives occur only once, whereas the benefits and savings associated with the initiatives continue for years.

Although there are many advantages for institutions or health systems to implement a therapeutic interchange program, there also are associated disadvantages with a program of this nature. One study in community pharmacies showed that for about 10% of suggested therapeutic interchanges, the patient failed to have the prescription filled, even though the mean cost was lower for the interchanged drug.⁵ Although the number of therapeutic interchanges reported in this study was small, the author speculated that it is possible that therapeutic interchange may contribute to noncompliance. Furthermore, it is not known if the patients who failed to fill their prescriptions were being treated for serious conditions such as congestive heart failure or diabetes mellitus, or for an acute, self-limiting condition. For the most part, controlling costs related to drug therapy is a major reason for implementing a therapeutic interchange program. Although interchange programs may decrease costs for institutions and payers, it may create time-related costs for patients and pharmacists.⁵ Patients who have interchanged prescriptions are likely to make

additional trips to an ambulatory pharmacy to have their prescription changed and filled, whereas in the hospital setting, a changed prescription may take more time for health care workers to process. Therapeutic interchange may add time to the dispensing process for pharmacists because of the steps involved to make a change to a prescription and the necessary patient education. Overall, the advantages associated with a therapeutic interchange program appear to outweigh the disadvantages.

Factors That Influence Therapeutic Interchange

Many factors influence the ability of an institution or health system to implement a therapeutic interchange program, and once implemented, contribute to and sustain its success. The following is a list of factors that influence therapeutic interchange practices to some degree. This list may not be exhaustive, but it includes many commonalities seen at various institutions and health systems.

- Health care setting^{3, 4}: therapeutic interchange programs have been used successfully in the hospital setting for many years. In this setting, the process is simple, straightforward, consistent, and ethical because there usually is only one formulary. In general, a single formulary simplifies prescribing decisions as well as the inventory control process. In most ambulatory care settings, the process is not as straightforward or consistent because there usually are multiple formularies, and inventory is not reduced.
- Unit or area in the institution or health system: therapeutic interchange may be more conducive to certain units or areas in the institution due to the types of drugs or drug classes being prescribed for patients on these units. Specific units where the potential for therapeutic interchange is high include specialty care units or step-down units, specialty care clinics, coronary care units, and intensive care units.
- Patient types: the suitability of therapeutic interchange based on drug classes or specific drugs may depend on whether the patient is a neonate, is elderly, has compromised organ function, is pregnant, or is at risk due to comorbid conditions. In addition, health care practitioners involved with therapeutic interchange programs should take into account whether a patient is starting a new

therapy or is switching therapy. Efficacy, effectiveness, safety, and economic data can be used in a straightforward manner with regard to establishing therapeutic equivalent drugs for patients starting a new therapy; however, the situation is more complex when examining these issues for switching well-stabilized patients from one drug to another. Care should be exercised when beginning therapeutic switches for patients who are well stabilized with a drug regimen compared with a patient starting a new regimen.

- Patient preferences: the patient's acceptance of therapeutic interchange and his or her compliance with any change in therapy if warranted affect the outcomes of a therapeutic interchange program. Some patients want the highest quality drugs, always at the lowest cost. Sometimes this can be a barrier, especially for newer drugs and high-technology biologicals. For example, a patient may want to receive a more costly drug from a different class of drugs that has a similar therapeutic effect, but the drug is not a member of the class that is part of the therapeutic interchange program. Although therapeutic interchange requires clinical indistinguishability among drugs in an interchanged class, patients may have a different perception on this. They may equate newer or more expensive drugs with higher quality.
- Drug characteristics²⁷: a variety of issues related to the specific drug classes and drugs within them must be considered when determining suitability for therapeutic interchange. The following are some characteristics to consider:
 - Efficacy—refers to the expected partial or total response or tolerance by a patient to a complete course of therapy under ideal conditions. One must consider the ranges of indications with documented efficacy for each drug in the group.
 - Effectiveness—refers to the expected partial or total response or tolerance by a patient to a complete course of therapy in the usual clinical practice setting.
 - Dosage formulation—refers to convenience of a preparation and administration, frequency of dosing, range of dosage forms, and stability.
 - Safety—includes contraindications, warnings, and adverse effects, as well as lookalike and soundalike products.
- Cost—acquisition cost usually is considered. For intravenous dosage formulations, other ancillary supplies such as minibags and tubing used to administer the drugs may need to be factored into overall costs.
- Changes in reimbursement^{24, 28}: there is a need to monitor business and reimbursement literature as well as health care literature in general to keep abreast of changes in reimbursement. Challenges in reduced reimbursement are evident as a result of the Balanced Budget Act of 1997, and the Outpatient Prospective Payment System created under this act. Payments for services, especially in the outpatient setting, are based on the Ambulatory Payment Classification system, which recently has undergone many changes. Furthermore, there is a need to educate decision makers in general at an institution or health system and those involved at the federal level with setting reimbursement rates about drug costs, by using trend data and benchmarking information. The effects of drug pricing increases usually are attributable to high prices for new drugs and higher prices for older drugs that are being used for new indications. Moreover, higher utilization trends of certain drugs are evident.
- Insurance providers: outpatient drug programs may constantly change their formularies. Patients may change insurance providers and, thus, be exposed to different formularies.
- Pharmacoeconomic variables²⁷: variables other than price, such as costs for laboratory tests, staff, hospitalizations, and recovery times, must be considered when implementing a therapeutic interchange program.
- Ethical practices^{3, 29, 30}: when conceived and managed properly in hospitals, therapeutic interchange provides optimal care in an ethical fashion and in such a way that it is invisible to patients and physicians. Outside the institution, however, the effects of formulary management, including therapeutic interchange, on patients and physicians are less likely to be invisible. For example, financial incentives may be offered to physicians by health plans to provide an incentive to prescribe lower cost drugs.
- Manufacturer issues: the ability of the manufacturer to supply the drug chosen for therapeutic interchange is paramount to the

appropriate functioning of the program. The inability of a manufacturer to supply the selected product could result in switching to a nonformulary alternative in classes where the drugs are deemed equivalent. Manufacturers that supply products with a variety of formulations offer more choice over products with limited formulations. This may ultimately affect which drug is chosen for therapeutic interchange. The willingness of manufacturers to offer contracts that provide pricing advantages through Group Purchasing Organizations or to individual institutions supports competitive friction among drugs within a therapeutic class and ultimately may drive overall costs down.

- Direct-to-consumer advertising: patients may demand that their prescribers provide them with a specific drug that they have heard about through various marketing media. The requested drug may not be the suggested drug to be used within the therapeutic class as a part of a therapeutic interchange program or a drug on an institution's or health system's formulary.
- Regulatory issues or regulatory bodies: the influence of the FDA (off-label vs labeled use of drugs), JCAHO, National Committee for Quality Assurance, and other regulatory bodies can effect therapeutic interchange. In addition, the influence of governmental agencies on Medicare and Medicaid policies can affect drugs that are to be interchanged since reimbursement may be allocated only to a specific drug within a class. The effect of regulatory issues or bodies is more fully described in the Legal and Regulatory Issues section.
- Legislative bodies and policymakers^{3, 29}: legislative restrictions may hinder therapeutic interchange, especially in the outpatient setting. Legislators in many states have faced decisions as to whether and how to regulate therapeutic interchange practices. In many cases, this is a result of critics of therapeutic interchange programs charging that they expose patients to increased risks while resulting in little savings for patients or the employers responsible for paying their insurance premiums. The Legal and Regulatory Issues section provides more in-depth discussion on this topic.
- Appropriate design and implementation of a therapeutic interchange program⁴: initial design of a therapeutic interchange program

must include a plan to monitor patients affected by an interchanged drug. Appropriate follow-up of patients affected by a therapeutic interchange is important to avoid adverse outcomes.

- Clinical practitioners at the institution or health system level^{7, 27, 31}: practitioner buy-in or adaptability to a therapeutic interchange program affects its overall success. An assessment of the impact of the program on staff workload is critical to determining the direction. Adherence to the therapeutic interchange program contributes to its success from a clinical benefit standpoint as well as the ability to control drug expenditures.
- Health care administrators (chief executive, operating, and financial officers): various health care administrators may fully support therapeutic interchange from a clinical and cost-effective perspective. Seeing the benefits in lowering costs of therapy, these administrators may not understand the concept of a therapeutic interchange program and may pressure health care practitioners to include drug classes that are not warranted for interchange.
- Staff resource availability to design, then implement the therapeutic interchange program: the availability of the appropriate types of staff and quantities of staff to pursue a therapeutic interchange program will affect its overall success.

Legal and Regulatory Issues

The legal and regulatory issues concerning therapeutic interchange have evolved, as has the practice. Early concepts regarding the responsibilities of organizations implementing therapeutic interchanges focused primarily on the use of a pharmacy and therapeutics committee, and its formulary, to clearly require collaboration of physicians, pharmacists, and other members of the committee.² Many aspects of drug selection and the legal issues of interchange to be institutional risk management concerns rather than a liability risk have been described.³² In lieu of cases to the contrary, this opinion is still today's legal stance on therapeutic interchange.³³ Since the assertion of therapeutic interchange benefits of risk minimization in 1988, the landscape of liability as it pertains to therapeutic interchange has changed to include new issues such as pharmaceutical care, managed care, and

corporate responsibility.³³

For therapeutic interchange to be a liability risk, an interchange must fulfill the legal criteria of negligence. Negligence is defined as patient injury, a clear breach in duty to protect from potential harm (as it balances with benefit), and the injury caused by the breach in duty (causation).³³ Although patient injury often is obvious, breach in duty and direct causation are difficult to prove in court. If a standard of care, such as a policy and procedure on therapeutic interchange, is in place and adhered to, proof of breach in duty is almost impossible. Similarly, causation requires the act of interchange to be directly responsible for the harm. In most cases of drug-induced toxicity, the link of cause and effect is not absolute, especially when the alternative drug, if not switched, would likely have caused the same possible constellation of problems. It is for all these reasons that no legal cases have been successful in arguing against therapeutic interchange.³³

As originally asserted in the American Society of Health-System Pharmacists (ASHP) formulary management guidelines, the integration of a multidisciplinary pharmacy and therapeutics committee with input into formulary and drug use policy remains integral to a low-risk therapeutic interchange process.² The pharmacy and therapeutics committee sets its institutional standard of practice with respect to the use of drugs. Therapeutic interchange policies are reviewed and approved by the pharmacy and therapeutics committee, and this process provides legal protection for practices that adhere to therapeutic interchange policy and procedure. The formulary represents a blend of clinical and pharmacoeconomic input. As long as the interchange is devised with patient outcomes such as patient risk and benefit in mind, formulary decisions can be determined to be a standard of care. The prescriber liability is reduced when policies are clearly delineated in institutional therapeutic interchange policies. Therapeutic interchange is a result of a compilation of formulary decisions based on clinical studies, consensus guidelines, package labeling, institutional quality information, and any other information the pharmacy and therapeutics committee deems pertinent.

Health care liability risk is shared by health care personnel as well as the health care organizations where they work. Corporate responsibility dictates that the organization providing patient care have the responsibility to

oversee the quality of caregivers, care provided within its walls, safety and maintenance of the facilities, and drug use policy and processes.³³⁻³⁵ Similar to the prescriber's use of primary literature for risk management, the use of a formulary devised by a pharmacy and therapeutics committee represents sound drug use virtues, which protects the organization from liability. In those patient care settings without a formal collaborative process, there is greater risk of breach in duty and unclear standards of care. The collaborative decisions of an organized pharmacy and therapeutics committee provide structure and direction for pharmacists in performing a therapeutic interchange.

Regulatory control of therapeutic interchange has largely been a role of state boards of pharmacy, whose rules and regulations differ from state to state.³³ Obvious liability occurs when any actions are in direct conflict with governmental statute or regulation; otherwise, negligence is difficult to prove and piece together retrospectively. State law delegates the role of drug policy to the inpatient oversight committees for the health care organization (e.g., pharmacy and therapeutics committee).³⁶ Rules and regulations in each state often are similar to prescribing and dispensing standards advocated by professional organizations, such as the American Medical Association (AMA) and ASHP.³⁷ Neither federal law (e.g., Food, Drug, and Cosmetics Act) nor the FDA provide instruction on therapeutic interchange and, thus, have little historical impact on therapeutic interchange. The role of the FDA in risk management is intended for general populations, whereas physicians manage risk for their individual patients. Thus, the FDA has little oversight of physician prescribing.^{38,39} This key difference limits the FDA's role in therapeutic interchange in a specific patient population.

Off-label use of drugs often is of some concern when considering drugs suitable for therapeutic interchange. The likelihood of identical package insert indications for any two or more drugs involved in a therapeutic interchange is extremely unlikely. Because labeling is an FDA assignment of drug use, labeling is not necessarily an up-to-date reflection of clinical drug application from the literature and may not account for more individualized application for each practice setting. The FDA and package labeling are not restrictive of use of the drug,⁴⁰ and use for off-label medical reasons becomes a risk-benefit analysis for each patient. Physician

prescribing of drugs for off-label uses is not in violation of the Food, Drug, and Cosmetic Act,^{40,41} and restriction of this practice may limit physician flexibility in providing optimal and individualized care.⁴² Because therapeutic interchange is still physician prescribing of therapy per institutional standards of care, therapeutic interchange with drugs of differing labeled indications is no different from any other use of drugs for off-label clinical indications.

Regulation of therapeutic interchange is not explicit or standardized by accreditation bodies such as JCAHO. Therapeutic interchange is defined, but no standards are mandated in its 2002 or proposed 2004 standards.⁴³ The standards dealing with selection, procurement, and storage pertain to prudent drug use but are not unique to therapeutic interchange.

Professional Organizations' Viewpoints

This section describes position statements of pharmacy, physician, pharmaceutical industry, and health care organizations developed since the initial ACCP statement on therapeutic interchange published in 1993.¹ Policies of pharmacy associations are universally supportive of therapeutic interchange. The AMA now supports therapeutic interchange under specific conditions. However, not all physician organizations are supportive. Manufacturers' associations have no stated position. Health care organizations—primarily hospitals, integrated health systems, and managed care organizations—have widely adopted therapeutic interchange policies, thus demonstrating their support.

Other Pharmacy Organizations

The ASHP supports therapeutic interchange as one type of policy for administering a formulary system. It defines therapeutic interchange as “the act of dispensing therapeutic alternates in accordance with previously established and approved written guidelines or protocols.”⁴⁴ Therapeutic alternates are defined as “drug products with different chemical structures but which are of the same pharmacological and/or therapeutic class, and usually can be expected to have similar therapeutic effects and adverse reaction profiles when administered to patients in therapeutically equivalent doses.”⁴⁴ Decisions regarding formulary inclusion are “based on scientific and economic considerations that achieve appropriate, safe, and cost-effective drug

therapy,” and include a process for prescribers to use a nonformulary drug “when medically indicated.”⁴⁴

The California and Virginia Societies of Health-System Pharmacists also support therapeutic interchange under collaborative agreements among physicians, pharmacists, and others responsible for health care.^{45,46}

The Academy of Managed Care Pharmacy supports the use of therapeutic interchange programs as part of a comprehensive approach to optimize patient care. These programs should be guided by teams of practitioners who are “experts in the diagnosis and treatment of disease.”⁴⁷

The American Society of Consultant Pharmacists supports therapeutic interchange, defined as “a dynamic process that is administered by an interdisciplinary committee” using established criteria for selection of interchanged drugs.⁴⁸ Authorization of the prescriber and evaluation of each patient before the interchange are required, and patients should be monitored after the interchange.

The American Pharmacists Association continues to support the concept of therapeutic interchange “under arrangements in which pharmacists and authorized prescribers interrelate on behalf of the care of patients.”⁴⁹ In a statement developed in 1987, they support continuing dialogue with other health care organizations with regard to the role of the pharmacist.⁴⁹

The American Association of Colleges of Pharmacy has no policy statement but includes therapeutic interchange in the educational outcomes that are expected of pharmacy students as part of the strategies that are used to manage a formulary system.⁵⁰

The International Pharmaceutical Federation states that “the concept of therapeutic interchange...should be promoted.”⁵¹ Therapeutic interchange is defined as dispensing “a medicinal product containing different active ingredients but which are of the same pharmacological class...in accordance with a protocol previously established...or after individual prior consultation with the prescriber...designed to achieve maximum therapeutic benefit for the patient and to ensure the safest, most effective and economic use of medicinal products.”⁵¹

The National Association of Boards of Pharmacy (NABP) adopted a resolution in 1993 that encourages state boards of pharmacy to provide a legislative basis for therapeutic interchange, which “ensures that the patient

receives the most appropriate drug therapy,” and that NABP should encourage state boards to “work cooperatively with State Drug Use Review Boards to establish protocols based upon the guidelines identified by the Task Force on Therapeutic Interchange that would allow therapeutic interchange by pharmacists in all practice settings.”⁵²

Physician and Other Health Organizations

The AMA has reversed its previous stance¹ and now supports therapeutic interchange, defined as “the authorized exchange of therapeutic alternates in accordance with previously established and approved written guidelines or protocols within a formulary system.”⁵³ Formulary systems are considered acceptable in inpatient hospital and outpatient settings that have an organized medical staff and a functioning pharmacy and therapeutics committee. Specific standards are defined for both the formulary system and the pharmacy and therapeutics committee, including surveillance to monitor compliance with the policy and clinical outcomes, a mechanism for the prescriber to override the system when necessary for patient care, and objective evaluation of usefulness and cost of pharmaceuticals.

The American College of Physicians–American Society of Internal Medicine continues to support therapeutic interchange in hospitals that have a functioning formulary system and pharmacy and therapeutics committee. Their position includes a statement that “immediate prior consent from the authorized prescriber” should be obtained.⁵⁴ If this statement is interpreted literally, it could hinder the effectiveness of an interchange policy because of the pharmacists’ time and the prescribers’ patience that are required to carry out notification, which may cancel out or even exceed any financial benefit expected. In practice, most organizations inform the medical staff about formulary policies as they are developed, and many notify individual prescribers through a progress note, oral notice, or a note on the drug administration record for each act of therapeutic interchange.

The American Psychiatric Association has a brief statement opposing therapeutic interchange without the approval of the treating physician.⁵⁵ The American Heart Association states that it opposes legislation that would permit prescription therapeutic interchange by pharmacists because the pharmacist does not have all the

available clinical information for specific patients.⁵⁶ The National Kidney Foundation states, “No therapeutic drug substitution of a critical dose drug should be allowed without the approval of the prescribing physician or patient.”⁵⁷ The latter statement is in the context of a discussion about generic drug substitution, but the wording and the intent suggest that therapeutic interchange should similarly be restricted. All of these organizations oppose therapeutic interchange without physician approval. However, none of these groups states a position specifically in relation to organized health care.

Pharmaceutical Industry

Neither the Generic Pharmaceutical Association nor the Pharmaceutical Research and Manufacturers of America has a stated position on therapeutic interchange. In the past, they opposed efforts of health care organizations to limit prescribing to certain products.^{58, 59} However, contracts developed by health care organizations and buying groups with manufacturers for products often include clauses that require the organization to limit formulary products to a certain product or group of products to achieve a favorable economic benefit.

Health Care Provider Organizations

The prevalence of therapeutic interchange has increased over the past decade. In 1994, the ASHP survey of hospital pharmacy services found that therapeutic interchange was practiced in 67.4% of hospitals.⁶⁰ In 1996, the number had increased to 74.5%.⁶¹ In 1999, a survey of 463 hospitals of more than 100 beds found that 88% of teaching hospitals, 89% of nonteaching hospitals, and 100% of investor-owned hospitals used therapeutic interchange.²² A survey of Canadian hospitals also found a prevalence rate of 89%.⁶² These findings suggest widespread acceptance of the practice in hospitals, although the extent of the practice varies widely.

Economic pressure has led to similar policies in managed care settings. Inclusion of prescription benefits in health insurance plans has increased, along with the use of tiered systems that encourage the use of preferred drug products. Seeking permission to dispense a different product than that prescribed in community pharmacies as required by patients’ insurance coverage is not well studied. A survey based on a convenience sample in Virginia found

that the rate of suggested interchanges was 4.6/1000 prescriptions. In areas of the country where the presence of health maintenance organizations is greater, the rate may be higher.⁵ In 1999, use of therapeutic interchange had increased to 38% in health maintenance organizations and to 56% of employer-sponsored plans. About 75% of pharmacy benefit managers offered such programs in 1997. However, the current extent of use is not known.⁶³

Hospitals, health systems, and managed care organizations have conducted assessments of therapeutic interchange policies in accordance with recommendations from professional organizations. Hospitals also have begun to assess the impact of a therapeutic interchange on patients' access to drugs and continuity of care once the patient has been discharged.^{6,8,13} These assessments have demonstrated both positive and negative effects on patient care as well as cost savings, both of which are of great interest to health care organizations in a time when they are squeezed between controlling costs and ensuring patient safety.

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