

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
OFFICE OF DIRECTOR**

ACTION REFERRAL

TO <i>Myers</i>	DATE <i>8-7-08</i>
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DIRECTOR'S USE ONLY		ACTION REQUESTED	
1. LOG NUMBER <i>1000075</i>	<input checked="" type="checkbox"/> Prepare reply for the Director's signature DATE DUE <i>8-15-08</i>	<input type="checkbox"/> Prepare reply for appropriate signature DATE DUE _____	<input type="checkbox"/> FOIA DATE DUE _____
2. DATE SIGNED BY DIRECTOR <i>cc: Ms. Forkner, Depo Host Thursday, Standband</i>	<input type="checkbox"/> Necessary Action		

APPROVALS (Only when prepared for director's signature)	APPROVE	* DISAPPROVE (Note reason for disapproval and return to preparer.)	COMMENT
1. <i>Cleaveland 8/21/08, letter attached.</i>			
2.			
3.			
4.			

JOHN M. "JAKE" KNOTTS, JR.
SENATORIAL DISTRICT NO. 23
LEXINGTON COUNTY



SENATE ADDRESS:
POST OFFICE BOX 142
303 GRESSETTE SENATE OFFICE BUILDING
COLUMBIA, SOUTH CAROLINA 29202
PHONE: (803) 212-6350
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RECEIVED

August 6, 2008

AUG 07 2008

Department of Health & Human Services
OFFICE OF THE DIRECTOR

Ms. Emma Forkner, Executive Director
SC Department of Health and Human Services
Post Office Box 8206
Columbia, SC 29202-8206

Dear Ms. Forkner:

As you may be aware, I have a statewide reputation as being the "Senator of the People" and as such receive an inordinate amount of telephone calls from people all over the state of South Carolina who need help in some matter.

It has become increasingly evident that a large majority of those calls are from people who are on Medicaid and believe that they are not receiving adequate care. I have shared my concerns with Representative Leon Howard, and he also has received more and more calls from constituents who feel they are not receiving quality care.

As we all know, our state leads the nation in hypertension, high cholesterol and diabetes and a large majority of patients suffering from these diseases are Medicaid patients. These particular diseases can be well managed if the correct medications are prescribed and taken as directed. What has become clear to Rep. Howard and me is that the most common complaint we receive from those on Medicaid is that their prescriptions are often being changed to medications that are less and less effective.

I understand that pharmacy services are not a federally mandated program, however I am not aware of any other state that does not provide pharmacy services to their Medicaid recipients. And while we must obviously cut costs whenever and wherever possible, it seems obvious to me that mandating cheaper, less effective drugs is certainly not the right thing to do. Without proper medication, these patients' diseases will only get worse which will lead to further complications that are far more expensive to treat and will only increase the costs to Medicaid. As Benjamin Franklin said, "An ounce of prevention is worth a pound of cure."

*Leg. Affairs
Dir Sign.
cc. Ms. Forkner,
Dept. HHS*

In talking with various professionals in the medical field, including physicians and pharmacists, numerous questions have been raised about the management of our Medicaid Pharmacy Program under DHHS. Rep. Howard and I are both alarmed at many of the things we have heard and have compiled these concerns we believe need to be addressed.

We hope that you do not take these questions as accusations, but as an opportunity for all of us to better understand the South Carolina Medicaid Program and more importantly, to insure that our Medicaid patients are receiving the medical care that everyone deserves.

Thank you for taking the time to answer these questions. We look forward to your response.

Sincerely,



Senator John M. "Jake" Knotts, Jr.
Senate District 23



Representative Leon Howard
House District 76

enclosure

cc: Members of the Medicaid Pharmacy and Therapeutics Committee

Questions concerning the South Carolina Medicaid Pharmacy Program
Senator John M. "Jake" Knotts, Jr.
Representative Leon Howard

1. How much does the state pay First Health Services Corporation (FHSC) to negotiate rebate contracts with manufacturers?
2. What influence does FHSC have in deciding which drugs are selected to be on the preferred list?
3. What influence does Dr. Burton, the Medical Advisor to DHHS, have in selecting which drugs are on the preferred list prior to the Medicaid Pharmacy & Therapeutics Committee presentation meeting?
4. Does the Medical Advisor receive any compensation from the state or FHSC? If so, how much?
5. What influence does the Medicaid Pharmacy and Therapeutics (P&T) Committee have in selecting which drugs are on the preferred list prior to it being presented at the meeting?
6. Do all members of the Medicaid P&T Committee accept Medicaid patients or new Medicaid patients?
7. Would it would be beneficial to have a Community Health Center representative serve on the Medicaid P&T Committee as the majority of Medicaid patients are seen at Community Health Clinics and are federally funded?
8. Would it be beneficial to the state to have separate pediatric, psychiatric and adult Medical Advisors and Medicaid P&T Committees to better serve the diverse needs of each group as they would be experts in their particular area of practice?
9. What is DHHS doing to insure Medicaid patients are being given the best medications to reduce the progression of their disease?
10. What is the method of determining high-risk Medicaid patients?
11. Are high-risk patients given the same benefits as regular Medicaid patients? If not, why?
12. Does DHHS have a specific guideline program for high risk patients? If not, why?

13. Are all doctors qualified to treat high-risk Medicaid patients?
14. Is the selection of preferred/non-preferred medications done on a bidding process? If not, why?
15. Are the supplemental rebates negotiation process done in an open forum? If not, why?
16. What qualifies a drug being selected as preferred? Is it cost or effectiveness?
17. Why is a pharmacist allowed to vote on a preferred/non-preferred medication when it is not in their training to diagnose or treat patients and their outcome?
18. Are all generics equal to brand name drugs?
19. Do pharmacists in retail stores receive bonus money for dispensing generic drugs over prescribed drugs?
20. Do pharmacists in retail stores receive bonus money for changing a patient to a generic drug?
21. Do physicians receive bonus money for prescribing generic drugs?
22. Do physicians receive bonus money for changing a patient to a generic drug?
23. What is the Prior Approval process and what are the advantages and disadvantages?
24. Does the Director of DHHS have the authority to override decisions made by FHSC?
25. If a drug is found to be more effective than a currently preferred drug, how long is the process to have it approved as a preferred drug?
26. Is it true that mental health drugs, psychiatric drugs, HIV drugs, and cancer drugs do not have to give a supplemental rebate?
27. Are pharmacists allowed to change or advise to change prescription drugs for mental health, psychiatric, HIV or cancer drugs?
28. If a patient with a serious disease such as hypertension, high cholesterol or diabetes is prescribed a medication and it is ineffective to the patient, what is the likelihood that their condition will deteriorate and result in hospitalization, amputation, heart attack, stroke or death and at what cost to the state?



State of South Carolina
Department of Health and Human Services

00075
to c/osl

Mark Sanford
Governor

August 21, 2008

Emma Forkner
Director

The Honorable John M. "Jake" Knotts, Jr.
The Honorable Leon Howard
Post Office Box 142
Columbia, South Carolina 29202

Dear Senator Knotts and Representative Howard:

Thank you for your interest in the South Carolina Department of Health and Human Service's Pharmacy and Therapeutics Committee. We were delighted that you took the time to visit with the committee in order to learn about the Preferred Drug List (PDL). I hope you found the meeting informative. We rarely have legislators attend our public meetings and I think your constituents would be pleased to know that you invested a significant amount of your personal time on their behalf.

As you know, the cost of pharmaceuticals has increased dramatically over the past decade. All insurers, including state Medicaid programs, have had to adjust to this financial reality. Our challenge is to find ways to curb costs without adversely affecting patients who rely on these life-saving medications. After hearing about the work of the committee, I hope you will agree that the PDL is a reasonable safeguard that affords clinicians the necessary flexibility to render effective treatment. I believe the members of the committee who volunteer their time and expertise are outstanding professionals who do a great service to both Medicaid beneficiaries and the taxpayers at-large who support the program.

Enclosed you will find the answers to the questions you posed in your letter, including those related to the proviso that exempts certain medications from the normal PDL process. I would welcome the opportunity to further discuss this proviso and explore any changes you believe may be appropriate. Please feel free to contact me directly if you have any additional questions or would like a follow-up meeting.

Sincerely,

Emma Forkner
Emma Forkner
Director

EF:jip
Enclosures



State of South Carolina
Department of Health and Human Services

Mark Sanford
Governor

August 21, 2008

Emma Forkner
Director

The Honorable John M. "Jake" Knotts, Jr.
The Honorable Leon Howard
Post Office Box 142
Columbia, South Carolina 29202

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Sincerely,

A handwritten signature in cursive script, appearing to read "Emma Forkner".

Emma Forkner
Director

EF:jip
Enclosures

Questions concerning the South Carolina Medicaid Pharmacy Program
Senator John M. "Jake" Knotts, Jr.
Representative Leon Howard

1. How much does the state pay First Health Services Corporation (FHSC) to negotiate rebate contracts with manufacturers?

The state has a contract with FHSC to perform a number of services related to the operation of the Medicaid Pharmacy Services Program. Among those services are the Supplemental Rebate Program management, Preferred Drug List (PDL) development, and the Pharmacy and Therapeutics (P&T) Committee support activities. The monthly charge for these services is \$33,242.00.

2. What influence does FHSC have in deciding which drugs are selected to be on the preferred list?

As stated above, FHSC is contracted by the state to develop and maintain a PDL for South Carolina Medicaid. Drug classes which contain multiple drugs that are similar are evaluated for appropriateness for inclusion in the PDL. Once a class has been determined to have potential for inclusion, supplemental rebate bid packages are prepared and sent to manufacturers of all drugs within the class.

South Carolina participates in the National Medicaid Pooling Initiative (NMPI) with 12 other states. As the administrator of the NMPI, FHSC acts on behalf of all participating states to negotiate optimal supplemental rebates for drugs within PDL classes. Contracts are negotiated by FHSC to guarantee a net cost of drugs to the state for a period of three years. All manufacturers are given the opportunity to enhance their rebate on an annual basis. As a participant in the NMPI, South Carolina is able to leverage expanded buying power resulting from the increased number of people covered by the member state.

After completing the bidding process, FHSC completes both financial and clinical analyses and makes recommendations to SCDHHS. FHSC and SCDHHS staffs conduct further clinical analysis to determine the appropriateness of these recommendations for the South Carolina Medicaid population. Included in the SCDHHS team are the executive staff, Medical Director, legal council and the staff pharmacists. During this review, changes to recommendations may be made. It is the result of this review that determines the starting point for discussion at the P&T Committee meeting. Because South Carolina pays a flat rate for services and receives 100% of all rebate money, there is no incentive for FHSC to influence specific drug selections.

3. What influence does Dr. Burton, the Medical Advisor to DHHS, have in selecting which drugs are on the preferred list prior to the Medicaid Pharmacy & Therapeutics Committee presentation meeting?

As the Medical Director for SCDHHS, Dr. Marion Burton plays an important role in the PDL process. He is advised of the potential classes under review and evaluates the clinical appropriateness of the recommendations. In preparation, Dr. Burton consults with other physicians, reviews the current literature, and relies on his professional experience in order to assist in ensuring a clinically sound starting point for P&T Committee discussion.

4. Does the Medical Advisor receive any compensation from the state or FHSC? If so, how much?

Dr. Burton is under contract with SCDHHS, but receives no compensation from FHSC. His compensation from SCDHHS totaled \$75,000 in SFY 2007.

5. What influence does the Medicaid Pharmacy and Therapeutics (P&T) Committee have in selecting which drugs are on the preferred list prior to it being presented at the meeting?

At each P&T Meeting, classes intended for review at the upcoming meeting are provided to the members. Approximately one week prior to the P&T meeting, committee members are emailed therapeutic class reviews (TCRs) for each class of medications that will be discussed. These TCRs contain all information pertinent to the medications in the class, including information on any related studies involving the affected medications. Members are provided access to information supplied by manufacturers regarding their medications under consideration for PDL inclusion. The committee also receives information regarding the recommended preferred vs. non-preferred status of medications. This recommendation is intended to serve as a starting point for discussion among the members.

Members review the provided materials, current literature, consult with peers and utilize their own professional experience to determine the appropriateness of the starting points for discussion. The purpose of the meeting is to provide the committee the opportunity to discuss the merits of medications and the appropriate designation of preferred vs. non-preferred status. Members may retain the status of drugs as presented, shift drugs from preferred to non-preferred, or vice versa. The committee is asked to review these medications from a clinical perspective, and determine if the vast majority of patients may be appropriately treated using drugs classified as preferred.

6. Do all members of the Medicaid P&T Committee accept Medicaid patients or new Medicaid patients?

Yes. All members of the P&T Committee are required to be active providers in the Medicaid program.

7. Would it be beneficial to have a Community Health Center representative serve on the Medicaid P&T Committee as the majority of Medicaid patients are seen at Community Health Clinics and are federally funded?

There are two types of clinics that can be classified as “Community Health Centers,” Federally Qualified Health Clinics (FQHC) and Rural Health Centers (RHC). While these clinics serve an important function, particularly among rural and underserved populations, they represent a relatively small percentage of total Medicaid assistance (.7% and .5% respectively). SCDHHS is in the process of identifying a new member to fill a vacant seat on the P&T Committee, and the agency will certainly consider your recommendation to recruit someone from either a FQHC or a RHC.

8. Would it be beneficial to the state to have separate pediatric, psychiatric and adult Medical Advisors and Medicaid P&T Committees to better serve the diverse needs of each group as they would be experts in their particular area of practice?

Article 8 Section 44-6-1010 specifies the makeup of the P&T Committee. The members must include 11 physicians and four pharmacists licensed to practice in South Carolina. The physicians may include, but are not limited to, doctors who have experience in treating diabetes, cancer, HIV/AIDS, mental illness, and hemophilia and who practice in internal medicine, primary care, and pediatrics. The P&T Committee may request outside “expert” consultation regarding a particular disease or class of medications. When this has occurred, SCDHHS staff has enlisted the assistance of a physician or physicians credentialed in the particular area. This has been done when reviews were performed for medications used in the treatment of Attention Deficit Hyperactivity Disorder (ADHD), glaucoma, growth hormone deficiency and allergies.

9. What is DHHS doing to insure Medicaid patients are being given the best medications to reduce the progression of their disease?

Perhaps the most important step SCDHHS has taken to ensure patients receive the proper medication is the establishment the P&T Committee. The committee works to ensure that a full range of medications is available to physicians without the need for prior approval. As previously outlined, the committee routinely hears testimony and reviews literature concerning the efficacy of particular medications. Since ultimately all federal Food and Drug Administration (FDA) approved medications that meet the Centers for Medicare and Medicaid Services rebate requirements are available under Medicaid, physicians play the most critical role in determining the proper course of treatment for their patients.

10. What is the method of determining high-risk Medicaid patients?

SCDHHS routinely analyzes claims data to determine changes in clinical episodes. This data can be grouped in multiple ways, including a comparison of chronic vs. acute conditions. This analysis allows the agency to identify shifts in the Medicaid population and track which conditions account for the largest expenditures. In addition, the agency's Medical Director regularly reviews the types of Medicaid providers in the delivery system in order to ensure an appropriate mix of specialists are available to recipients.

11. Are high-risk patients given the same benefits as regular Medicaid patients? If not, why?

All regular Medicaid recipients, including those considered high-risk, are entitled under federal law to the same benefits. Medicaid recipients who qualify for special waiver programs, such as the HIV/AIDS program, receive benefits tailored to their disease.

12. Does DHHS have a specific guideline program for high-risk patients? If not, why?

It is the desire of SCDHHS that all patients receive evidence-based clinical care. However, the agency has no authority to mandate specific treatment and believes those decisions are best left to individual physicians. It is important to note that the medical profession requires not only licensing of clinicians, but also requires that they complete periodic continuing education in order to stay credentialed.

13. Are all doctors qualified to treat high-risk Medicaid patients?

SCDHHS does not credential physicians. In order to participate in the Medicaid program, the appropriate licensing body must license a provider. Providers are also required to either complete a provider enrollment agreement form or sign a contract with DHHS depending on what type of services they provide.

14. Is the selection of preferred/non-preferred medications done on a bidding process? If not, why?

The bidding process is one of several steps followed in the determination of the PDL status of medications. Because SCDHHS is committed to providing quality care to its Medicaid beneficiaries, the clinical reviews are the most vital steps in the process. For this reason, committee members are asked to consider clinical merit of the drugs in recommending PDL status.

15. Are the supplemental rebates negotiation process done in an open forum? If not, why?

The supplemental rebate negotiation process is not done in an open forum because these rebates are calculated in conjunction with the federally mandated CMS rebate. This CMS rebate is prohibited from public disclosure under Federal Law at 42 U.S.C. 1396-r8 (b)(3)(D).

16. What qualifies a drug being selected as preferred? Is it cost or effectiveness?

SCDHHS promotes the provision of quality, cost-effective medications to its beneficiaries. Efficacy, safety, and cost are all factors that are considered when determining the PDL status of medications. Potential for abuse or misuse is also a factor. Although clinical effectiveness is the top priority, SCDHHS is required to maintain expenditures within the appropriation allotted the Pharmacy Program. As a result, lower cost, clinically effective alternatives are considered when appropriate.

17. Why is a pharmacist allowed to vote on a preferred/non-preferred medication when it is not in their training to diagnose or treat patients and their outcome?

Pharmacists are trained, educated professionals who have a minimum of six years of college education, with at least four years dedicated specifically to medications and medication therapy. Many pharmacists expand their education by participating in one or two year residencies. Pharmacists are required to pass an examination to determine proficiency in understanding medications and are required to complete fifteen credit hours of continuing education annually in order to renew their license. At least half of the continuing education topics must be directly related to medication therapy. As such, pharmacists are experts in medication management. Many physicians consider the pharmacist an invaluable member of the health care team and utilize their expertise to minimize adverse events and maximize patient outcomes.

While physicians are responsible for diagnoses, a pharmacist is often expected to aid in treatment decisions. Recent articles show how pharmacists can be involved in improving outcomes in hypertension management (for example: *JAMA 2008; 299(24): 2857-67, June 25*). Pharmacists are also involved in special programs that aid in treatment, such as the Ten City Challenge and the Asheville Project, which target diabetes.

18. Are all generics equal to brand name drugs?

Like branded medications, generic products are required to meet strict standards as defined by the FDA. Before the FDA will allow a generic product to be marketed in the United States, the drug must demonstrate that it is therapeutically equivalent to the brand name product. The manufacturer must demonstrate the same batch requirements for identity, strength, purity and quality as the brand product. Attached to this response

is the detail document, *Generic drug variability (Pharmacist's Letter/Prescriber's Letter 2008; 24(7):240704)*. This document describes at length the requirements of generic drugs and manufacturing standards.

19. Do pharmacists in retail stores receive bonus money for dispensing generic drugs over prescribed drugs?

Pharmacists in retail stores may receive bonuses from the management of their respective store, but neither SCDHHS nor FHSC pays bonuses to pharmacists or retail stores.

20. Do pharmacists in retail stores receive bonus money for changing a patient to a generic drug?

Again, neither SCDHHS nor FHSC pay bonuses to pharmacists. As was discussed at the P&T Committee meeting, physicians have the discretion to prescribe only name brand medications if they deem it appropriate.

21. Do physicians receive bonus money for prescribing generic drugs?

Neither SCDHHS nor FHSC pays bonuses to physicians for prescribing generic drugs. We are unaware of any specific bonus arrangements between individual physicians and drug companies.

22. Do physicians receive bonus money for changing a patient to a generic drug?

Neither SCDHHS nor First Health pays bonuses to physicians for substituting name brand drugs for generics.

23. What is the Prior Approval process and what are the advantages and disadvantages?

CMS has very specific requirements regarding Medicaid coverage of pharmaceutical products. It is important to again note that all medications which meet CMS requirements are available to Medicaid beneficiaries. States may require Prior Authorization (PA) in order to control utilization or minimize the potential for abuse or misuse of a medication.

Prior Authorization is a measure utilized by most insurers, including South Carolina Medicaid, to assist in providing cost-effective, clinically sound benefits to program beneficiaries. The PA process enables payers to ensure that high cost or high-risk medications are utilized under nationally recognized guidelines and that utilization is consistent with manufacturers' recommendations. Frequently, as new medications become available, manufacturers advertise directly to consumers as well as prescribers. This type of advertising campaign can lead to a shift to the "newest and latest" technology. New products are often much more expensive than existing therapy. In response to such marketing tactics, patients who are established on therapy with appropriate clinical response and minimal side effects may

be changed to the new medications. This can result in increased costs with no added benefit to the patient. The PA process attempts to control this expenditure growth.

In administering the PA process for Medicaid, FHSC staff, with input from SCDHHS staff and the P&T Committee, develops clinical criteria for any medications requiring PA. Prior authorization requests may be made telephonically or by fax to FHSC's Clinical Call Center. The Clinical Call Center is staffed by certified pharmacy technicians and licensed pharmacists 24 hours a day, 7 days a week. PA requests are processed and responded to within 24 hours of receipt of the initial request. Telephonic requests are resolved prior to ending the call. As an additional option, a web based PA submission tool for prescribers is currently being developed.

As noted above, FHSC is contracted by the state to administer the PA program. As a contractor to the state, FHSC is required to meet or exceed industry standards for call center operation. To ensure that these standards are met, the performance of the call center is monitored on a monthly basis by SCDHHS. The FHSC call center that supports the South Carolina Medicaid program is located in Glen Allen, Virginia. FHSC extends an invitation to Senator Knotts and Representative Howard (or their designees) to tour its facility and experience the operations first-hand.

In summation, advantages of a PA program include the assurance of appropriate utilization of medications while controlling increasing costs. Disadvantages to utilizing this type of program include additional time required for prescribers and a perceived lack of access to certain medications. While an increase in time is a legitimate concern, it may be addressed by adhering to PDL medication when appropriate, thereby reserving use of non-preferred medications for those beneficiaries who fail to respond or have unique clinical situations requiring the use of non-preferred medications.

24. Does the Director of DHHS have the authority to override decisions made by FHSC?

Yes. The Medicaid P&T Committee serves in an advisory capacity to SCDHHS.

25. If a drug is found to be more effective than a currently preferred drug, how long is the process to have it approved as a preferred drug?

Therapeutic classes may be re-reviewed at any time. The following guidelines are observed in determining when to review a class:

- A new product has been introduced in an existing PDL class
- Significant new information has been released regarding a medication in an existing PDL class
- Financial concerns within an existing PDL class
- Introduction of a new class for PDL inclusion

- Request by P&T committee member to open a class

Since the P&T Committee meets on a quarterly basis, it may take up to three months to re-open a class for review, depending on the timing of the new information or request.

SCDHHS seldom places a medication on the PDL without P&T Committee's validation of the safety and effectiveness of the drug. However, if a new drug becomes available that is clearly superior to other available medications, the Director may place it on the PDL prior to review by the committee.

26.

Is it true that mental health drugs, psychiatric drugs, HIV drugs and cancer drugs do not have to give a supplemental rebate?

There is currently in effect in South Carolina law restrictions that prevent Prior Authorization on medications prescribed to treat major depression, schizophrenia or bipolar disorder as defined by the most recent edition of the *Diagnostics and Statistical Manual of the American Psychiatric Association* or following prescribing practice guidelines established by the *American Psychiatric Association*, or HIV/acquired immune deficiency syndrome, or oncology related pharmaceuticals. Due to this proviso, South Carolina Medicaid is unable to limit access to medications in these classes. In order to collect supplemental rebates, medications must be listed as preferred on the PDL supplied to Medicaid providers. Because other states are able to include these medications in their PDLs, contracts do exist for some of these classes. South Carolina Medicaid may list all medications in those classes as preferred and collect rebates. It is important to note that maximization of rebate money depends on manufacturers competing for market share. Also, of particular importance is the fact that a majority of PDL savings may be attributed to market shift. Because the current proviso prohibits PA in these classes of drugs, Medicaid is unable to maximize savings. If access to medications cannot be limited, manufacturers have no incentive to offer rebates to the state.

27.

Are pharmacists allowed to change or advise to change prescriptions drugs for mental health, psychiatric, HIV or cancer drugs?

Pharmacists are not allowed to change any prescription medication without the direct order of practitioner licensed to prescribe medications. Pharmacists are allowed and expected to advise physicians on any medication including those for mental health, HIV, or cancer. Pharmacists frequently consult with physicians regarding selection of medications for a particular patient. Patients who have multiple chronic diseases will see several physicians. Often, these same patients use only one pharmacy to obtain their medications. Because the pharmacist is aware of medications prescribed by all physicians, they are in a position to inform prescribers of potential drug interactions or other concerns related to medication utilization. Also, the FHSC point of sale (POS) system for South Carolina Medicaid, stores medication history for all Medicaid-reimbursed

prescriptions and returns messages to pharmacists regarding drug-drug interactions, drug-disease interactions, and therapeutic duplication, among others. This includes medications from multiple physicians filled at multiple pharmacies. This messaging may be the only link for those patients who use multiple pharmacies as well as multiple physicians. In no case is a pharmacist allowed to change a physician's prescription without the permission of the prescriber.

28.

If a patient with a serious disease such as hypertension, high cholesterol or diabetes is prescribed a medication and it is ineffective to the patient, what is the likelihood that their condition will deteriorate and result in hospitalization, amputation, heart attack, stroke or death and at what cost to the state?

The outcomes of chronic disease are contingent on many factors, including the medication protocol determined by the treating prescriber. A vital component is the adherence and compliance of the patient to the prescribed protocol. The SC Medicaid program is the payer for services and not the prescriber of the treatment regimen. All FDA approved drugs meeting the CMS requirement for OBRA rebate are available, i.e. SC Medicaid has a PDL, but does not have a formulary. If a patient needs specific medication, the physician may need to obtain a PA to justify the need for the drug in lieu of another drug listed on the PDL, but the drug can be obtained.

Obviously, drug therapy is only one component of the costs associated with the co-morbidity of hypertension, high cholesterol, and diabetes. Many other factors such as compliance and lifestyle changes including diet, exercise and weight loss play important roles in the outcome.

Additionally, CMS requires SC Medicaid to maintain a Retrospective Drug Utilization Review (RetroDUR) program for appropriate utilization of drug therapy. The RetroDUR program in South Carolina serves as an educational outreach to alert physicians to potential issues related to medication therapy. Physicians may be alerted when drug therapies are not being utilized according to standards of therapy established by peers.

Generic Drug Variability

Background

There is a misconception among healthcare professionals and consumers that generic drug levels or absorption are allowed to vary as much as 20% from their brand-name counterparts. This stems from the misinterpretation of the requirement that the 90% confidence interval of the mean rate and extent of absorption of a generic drug must be within 80% to 125% of the reference (brand) product to be considered bioequivalent.¹ This article reviews the FDA and Health Canada's definition of therapeutic equivalence and their standards used to approve generic drugs.

The Requirements for Generic Drug Approval

For a generic drug product to gain FDA approval, the manufacturer must submit an Abbreviated New Drug Application (ANDA) to the FDA for review. To be approved for marketing, a generic drug must:²

- be therapeutically equivalent to the innovator (brand) product
- meet the same batch requirements for identity, strength, purity, and quality
- be manufactured under the same strict standards of FDA's good manufacturing practice regulations required for innovator products.

Drug products must demonstrate pharmaceutical equivalence and bioequivalence to be considered therapeutic equivalents. According to the FDA, drug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), are of the same dosage form and route of administration, and are identical in strength or concentration.³ Bioequivalent products are products with comparable bioavailability (rate and extent of absorption) when studied under similar experimental conditions.³

Statistics are used to determine bioequivalence (whether the rate and extent of absorption vary significantly from brand product).

Generic drug applications generally are not required to include preclinical (animal) and clinical (human) data to demonstrate safety and effectiveness. Instead, generic drug applicants must demonstrate that their product is bioequivalent to the innovator drug.

For a generic drug product to gain Health Canada approval, the manufacturers are required to submit an Abbreviated New Drug Submission (ANDS) to the Therapeutic Products Directorate (TPD) demonstrating bioequivalence and they must be pharmaceutical equivalents and be manufactured under the same strict standards of good manufacturing practice.²¹⁻²⁴

Bioequivalence

Confidence interval is a statistically calculated range, which has a known or controlled probability (in this case 90%) to contain the true value. According to the FDA, drugs are considered bioequivalent if the 90% confidence interval of the mean AUC (area under the time vs concentration curve) and the relative mean C_{max} (maximum concentration) of the test product is within 80% to 120% [now 80% to 125% on log transformed data] of the reference product.^{1,3} This criterion was put in place in 1986 after a three-day public hearing where experts were gathered to discuss the FDA's method of determining bioequivalence of generic drugs for immediate release, solid oral dosage forms.¹ This is the same standard used to determine bioequivalence of brand-name drugs if the drug products are reformulated or certain other manufacturing changes are made.¹ To date, no clinical data has been submitted to the FDA that would warrant narrowing of the present confidence interval of 80% to 125 % on any drug or class of drugs. If a tighter statistical interval was used, it is possible

More...

that if a brand-name product is reformulated, the product might not be equivalent to itself.¹⁴

Health Canada also requires generic drugs to demonstrate bioequivalence to the reference drug. Health Canada defines bioequivalence as:⁵

- The 90% confidence interval of the relative mean area under the curve (AUC) of the test to reference product should be within 80% and 125%.
- The relative mean of maximum concentration (C_{max}) of the test to reference product should be between 80% and 125%.

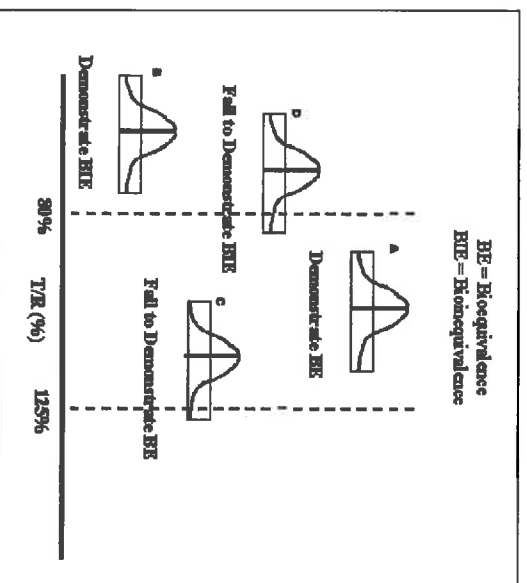
There are exceptions to Health Canada's bioequivalence requirement (e.g., modified-release dosage forms, drugs with complicated or variable pharmacokinetics, drugs with an important time of onset of effect or rate of absorption, high toxicity or a narrow therapeutic range, little or no absorption, a drug measurement methodology insufficiently sensitive or reliable to determine blood concentrations to at least three terminal half-lives, combination products, and biologicals).⁵

For critical dose drugs (drugs with narrow therapeutic index such as cyclosporine, digoxin, flecainide, lithium, phenytoin, sirolimus, tacrolimus, theophylline, warfarin), Health Canada requires the 90% confidence interval of AUC to fall between 90% to 112% and the 90% confidence interval of C_{max} to fall between 80% and 125%. These requirements must be met under fed and fasting conditions. Steady-state studies are not required for critical dose drugs unless warranted by exceptional circumstances. If a steady-state study is required, the 90% confidence interval of the relative mean measure minimum concentration (C_{min}) of the test to reference drug should also be between 80% and 125%. In addition Health Canada recommends that patients, rather than healthy subjects, be used in bioequivalence studies for critical dose drugs.⁶

Since it is not possible to gather information from an entire population, statistics are needed to extrapolate data to the general population. Confidence intervals give us an estimate of amount of error involved in the data collected from a small sample size. They tell us about the precision of the statistical estimates (e.g., means, standard deviations, correlations) that have been

computed.⁷ In a bioequivalence evaluation, a 90% confidence interval means that there is 90% confidence that the "true mean" of AUC and C_{max} of the population lies between the lower and upper bound of the calculated confidence interval.⁸ For a test product to be bioequivalent to the reference product, the calculated confidence interval must be between 80% and 125%.⁸ To evaluate bioequivalence, the FDA and Health Canada use the two one-sided tests procedure, which involves the calculation of a confidence interval for the ratio between the average values of the test and reference product.⁹ The figure below [adapted from the FDA] demonstrates different possible outcomes of bioequivalence testing.⁹

T/R = confidence interval for the ratio between the average values of the test and reference drug.



The figure above shows the different possible outcomes:⁹

- A study with the two-sided 90% confidence interval completely between 80% to 125% demonstrates bioequivalence.
- A study with the two-sided 90% confidence interval completely outside 80% to 125% demonstrates bio-inequivalence.
- A study with the point estimate within 80% to 125% but the two-sided 90% confidence interval outside 80% to 125% fails to demonstrate bioequivalence.
- A study with the point estimate outside 80% to 125% but the two-sided 90% confidence interval overlapping 80% to 125% fails to demonstrate bio-inequivalence.

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Both of the failing cases would require studies with larger sample sizes to draw a definitive conclusion.⁹

Bioequivalence studies are based on a crossover design, where half the subjects receive the test product first and then the reference product, with a washout period in between, and the remaining subjects receive the two products in the reverse order.¹⁰ Typically, bioequivalence studies use at least 12 subjects, but larger numbers may be used especially if absorption or clearance of the drug is highly variable.^{10,11} Multiple blood samples are obtained from each subject to determine the maximum drug concentration (C_{max}), the time to reach C_{max} (T_{max}), and the area under the time vs. concentration curve (AUC). The AUC is a measure of how much drug is absorbed, C_{max} is a function of rate and extent of absorption, and T_{max} is an indicator of the rate of absorption.⁹

Another example below illustrates how confidence interval is used to determine bioequivalence according to the FDA standard:

For example, the ratio of test drug to reference drug AUC (test/reference AUC) for Drug A in six subjects results in the following values:

120%, 120%, 110%, 110%, 90%, 110%

The mean test/reference AUC was 110% with 90% CI of 102 to 117. This means that there is 90% probability that the true mean lies between 102% and 117%. Therefore, the drug passes the bioequivalence test and is considered bioequivalent to the reference drug.

In another example, the test/reference AUC for Drug B in six subjects results in the following values:

110%, 190%, 30%, 130%, 90 %, 110%

The mean test/reference AUC was 110% with 90% CI of 75 to 145. Although the average test/AUC ratio of the drug (110%) is the same as drug A, there is a 90% probability that the true mean lies between 75% and 145%. The confidence intervals are too wide and therefore, Drug B fails to establish bioequivalence with the reference drug.

As illustrated above, the confidence interval range of 80% to 125% does not mean that drug levels can vary up to 20% between referenced (brand) drug and the test (generic) drug. If drug levels vary by more than 10%, the range of possible values within the 90% confidence interval will likely become too broad and the drug

will fail to establish bioequivalence with the reference drug.¹² In fact, in a study using the FDA bioequivalence criteria, the first 224 post-1962 drugs approved over the two year period after the Waxman Hatch amendments were passed, including some narrow therapeutic index drugs, showed a mean bioavailability variation between the generic and brand products of only 3.5%.¹

Generic Substitution Concerns

Although the FDA and Health Canada believe that substitution with a therapeutically equivalent product will produce the same clinical effect and safety profile as the prescribed product, some clinicians have raised concerns about variable drug bioavailability between generic and brand products, especially with narrow therapeutic index drugs (e.g., certain antiepileptic drugs, warfarin, etc).

Opponents of generic substitution for antiepileptic drugs believe substituting with generics can potentially increase healthcare costs and lead to adverse events. There are concerns that the allowed variability in bioavailability between generic and brand product might be too broad for therapeutic index drugs. Opponents in the U.S. also point out that bioavailability studies are carried out in healthy volunteers who are not on concomitant medications, using single doses of the drug. This is different from the clinical situation where the aim is to achieve steady-state conditions for the patient.¹²⁻¹⁵ There is also concern that patients may not get the same generic product in month-to-month refills, which can potentially increase the risk of toxicity or breakthrough seizure.

There are case reports of loss of seizure control or toxicity resulting from changing between brand and generic products or between one generic product and another.¹²⁻¹⁹ However, it is unclear whether the increased incidence of seizure is due to generic substitution of antiepileptic drugs or other factors.

The FDA believes that the bioequivalence criteria of confidence interval falling between 80% and 125% is stringent enough even for narrow therapeutic index drugs. To date, there are no data available to prove otherwise.¹ Furthermore, there is no proof that bioequivalence would be different between healthy and sick subjects. For narrow therapeutic index or critical

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dose drugs, Health Canada requires the 90% confidence interval of mean Cmax to fall between 90% to 112%.⁶

More recently, concerns of substituting time-release generic products have been raised, since the time-release technologies of generic products are often different from their brand-name counterparts. Several anecdotal complaints of adverse effects related to switch from *Toprol XL* and *Wellbutrin XL* to their generic formulations have been posted on the internet.²⁰

Based on their investigation, ConsumerLab.com found that generic metoprolol extended-release products dissolved at a different rate *in vitro*. However, FDA does not look at dissolution rates to determine bioequivalence. Dissolution tests for extended-release drugs are specific for each delivery system and are used only to assure batch-to-batch uniformity within each manufacturer's product line.²⁰

ConsumerLab.com also cited that the drug release rate of generic bupropion was different from the brand *Wellbutrin XL*. The FDA conducted further testing and found that the Tmax was different for generic bupropion and brand *Wellbutrin XL*. However, the differences in Tmax are not clinically significant in this case because the antidepressant effect is dependent upon steady-state drug level.²⁰

In general, the FDA uses Cmax instead of Tmax as the measurement to assess absorption rate. Cmax measures the maximum drug exposure and is a secondary indicator of extent of absorption after AUC. Technically, generics can release drug at a different rate as long as the end peak drug concentration is within testing standards in cases where Tmax is not clinically relevant (e.g., when therapeutic effect depends on steady-state drug concentration). In cases where Tmax is clinically significant (e.g., drugs used to relieve acute headache, etc), the FDA will take Tmax into consideration when evaluating bioequivalency.⁴

Conclusion

To be approved for marketing, a generic drug must demonstrate therapeutic equivalence to its brand-name counterpart, be manufactured under the same strict standards of good manufacturing practice regulations, and meet the same batch requirements for identity, strength, purity, and quality as required for brand products.

There is a common misconception that generic drug levels or bioavailability may vary up to 20% from brand. The misconception generally stems from not understanding the statistics involved in evaluating bioequivalence. In reality, the bioavailability of most generic drugs differs from their brand-name counterparts by less than 4% in the U.S.¹

Although there are anecdotal reports of adverse effects when patients switch from brand-name drugs to their generic counterparts, there is no proof that therapeutically equivalent (i.e., AB-rated in U.S.) drugs would differ in efficacy. Keep in mind that generic products are only tested against the brand product.^{4,21} Therefore, in the U.S., AB-rated generics may not be significantly different from the brand, but there is no testing to prove that they are bioequivalent to one another.

Generic substitution with therapeutic equivalent products generally saves patients a substantial amount of money without adverse effects. In rare cases, adverse effects have been noted when a generic product is used in place of the brand product (e.g., allergies to inactive ingredients, etc). In these cases, an authorized generic or branded generic (the actual brand-name drug product relabeled and marketed under a generic product name), if available, can be considered.

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