Department of Defense
Pharmacoeconomic Center

2421 Dickman Rd., Bldg. 1001, Rm. 310
Fort Sam Houston, TX 78234-5081

MCCS-GPE **7 May 2002**

MEMORANDUM FOR: Executive Director, TRICARE Management Activity (TMA)

SUBJECT: Minutes of the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Executive Council Meeting

1. The DoD P&T Executive Council met from 0800 to 1600 hours on 7 May 2002 and from 0800 to 0815 hours on 8 May 2002 at the Officers Club, Fort Sam Houston, TX.

2. MEMBERS PRESENT

CDR Terrance Egland, MC	DoD P& T Committee Co-chair
COL Daniel D. Remund, MS	DoD P& T Committee Co-chair
LTC (P) Joel Schmidt, MC	Army
MAJ Brett Kelly, MS	Army
COL John R. Downs, MC	Air Force
COL Mark Nadeau, MC (Representing COL Bill Sykora, MC)	Air Force
LtCol George Jones, BSC	Air Force
CAPT (select) Matt Nutaitis, MC	Navy
CDR Kevin Cook, MSC	Navy
CAPT Robert Rist	Coast Guard
Dick Rooney	Department of Veterans Affairs
MAJ Mickey Bellemin, BSC	Defense Supply Center Philadelphia
LTC Mike Kieffer, MS	Joint Readiness Clinical Advisory Board

MEMBERS ABSENT

COL Rosa Stith, MC	Army

OTHERS PRESENT

COL William Davies, MS	DoD Pharmacy Program Director, TMA
Howard Altschwager	Deputy General Counsel, TMA
CAPT Betsy Nolan, MSC	Navy Pharmacy Specialty Leader
COL Mike Heath, MS	Army Pharmacy Consultant; Chair, DoD Pharmacy Board of Directors
CAPT Joe Torkildson, MC	DoD Pharmacoeconomic Center
LtCol Ed Zastawny, BSC	DoD Pharmacoeconomic Center
CDR Denise Graham, MSC	DoD Pharmacoeconomic Center
LTC Don De Groff, MS	DoD Pharmacoeconomic Center
LTC (P) Doreen Lounsbery, MC	DoD Pharmacoeconomic Center
LCDR Ted Briski, MSC	DoD Pharmacoeconomic Center
SFC Agustin Serrano	DoD Pharmacoeconomic Center
HM1 Lisa Drumm	DoD Pharmacoeconomic Center
Shana Trice	DoD Pharmacoeconomic Center
Dave Bretzke	DoD Pharmacoeconomic Center
Eugene Moore	DoD Pharmacoeconomic Center
Angela Allerman	DoD Pharmacoeconomic Center
Paul Vasquez	Defense Supply Center Philadelphia
CAPT Howard Hays, MD	USPHS/Indian Health Service
CAPT Samuel Hope	USPHS/Indian Health Service
CAPT Robert Pittman	USPHS/Indian Health Service
LCDR Thomas Berry	USPHS/Indian Health Service

3. REVIEW MINUTES OF LAST MEETING

The minutes from the last meeting were accepted as written.

4. INTERIM DECISIONS/ADMINISTRATIVE ISSUES

Four members of the Indian Health Service (IHS) National Formulary Work Group attended the DoD P&T Executive Council meeting. The IHS is evaluating the feasibility of establishing a national formulary.

5. LEVONORGESTREL 0.75 MG (PLAN B)

At the February 2002 DoD Pharmacy & Therapeutics (P&T) Executive Council meeting, the Council recommended the addition of levonorgestrel 0.75 mg (Plan B) to the Basic Core Formulary (BCF), subject to the review and approval of the Director, TRICARE Management Activity (TMA) and/or the Assistant Secretary of Defense for Health Affairs (ASD (HA)). On 28 March 2002, the Executive Director of TMA signed an Action Memo approving the recommendation. On 3 April 2002 the co-chair of the DoD P&T Committee informed the Council members and service pharmacy consultants of the decision, and re-informed the Council on 7 May 2002. On 8 May 2002 the Executive Council was reconvened briefly to announce that the Council co-chairs had been informed that the ASD (HA) also wanted to review the Council's recommendation and that the Executive Director of TMA had rescinded his earlier approval. Therefore, Plan B has NOT been approved for addition to the BCF at this time, and the ASD (HA) is reviewing the Council's recommendation.

MTFs are required to include all BCF drugs on their local formularies. As a result of Plan B's removal from the BCF, each MTF's P&T committee must now re-evaluate whether this product is within the scope of practice at the MTF and whether the MTF wants to continue to have Plan B on its formulary.

6. NATIONAL PHARMACEUTICAL CONTRACTS AND BLANKET PURCHASE AGREEMENTS (BPAs)

Contract awards, renewals, and terminations

- Contracts for oral contraceptives, etodolac, fexofenadine, hydrochlorothiazide, insulin needle/syringes, isosorbide mononitrate, capsaicin cream, and ticlopidine were renewed.
- New contracts were awarded for ibuprofen tablets and fluoxetine capsules.
- DoD contracts for lisinopril and hepatitis A are up for renewal.
- The following joint DoD/VA contracts are up for renewal: ointment base, carbidopa/levodopa SA; glyburide tablets, amantadine capsules, fluocinonide cream/ointment, terazosin tablets/capsules, sotalol tablets, bupropion tablets, acyclovir tablets/capsules, hydroxyurea capsules, pentoxifylline tablets, rifampin capsules, and sucralfate tablets.
- The following joint DoD/VA contracts are up for resolicitation: salsalate tablets, prednisone tablets, and cimetidine tablets.
- The following joint DoD/VA contracts are in various stages of solicitation: benztropine mesylate tablets, minoxidil tablets, carbidopa/levodopa IR tablets, famotidine, chlorpromazine tablets, thiothixene, penicillin VK tablets, dicloxacillin capsules, cephalexin capsules, amoxicillin capsules, and trihexyphenidyl.

7. REEVALUATION OF THE BASIC CORE FORMULARY (BCF)

A. BCF Objective – As outlined in HA Policy 98-034, the objective of the BCF is to ensure the uniform availability of cost-effective pharmaceuticals at MTF pharmacies in order to meet the majority of patients' primary care needs. An analysis of prescriptions dispensed by MTF pharmacies between 1 Oct 01 and 15 Mar 02 revealed that 62% were for BCF items if prescriptions for OTCs were included, and 71% if OTC items were excluded. These data suggest that the BCF objective is being accomplished to a substantial degree.

Some people propose that a large number of drugs should be added to the BCF in order to retain and recapture prescription workload from retail pharmacies where the drugs cost more. This proposal assumes that the addition of a drug to the BCF will actually cause patients to get their prescriptions filled at an MTF rather than a retail pharmacy. Many factors influence patient behavior, so it is difficult to predict the impact that BCF status will actually have on the retention/recapture of prescription workload.

The Council faces a dilemma: Should inclusion on the BCF be reserved for only the more cost-effective drugs in an attempt to encourage the use of agents that offer the best overall value? Or should the Council simply ignore the BCF objective and add a bunch of drugs to the BCF (regardless of their cost-effectiveness) in the hope that it will help retain

and recapture workload from retail pharmacies? The Council did not reach a consensus on this issue.

B. *OTC Coverage on the BCF* – TRICARE policy provides limited coverage of OTC drugs at retail pharmacies and the NMOP. Chapter 7, Section 7.1 of the TRICARE Policy Manual states that: "Insulin and related supplies may be cost-shared for diabetic patients, regardless of whether or not a prescription is required under state law"; and "Vitamins may be cost-shared only when used as a specific treatment of a medical condition." Non-covered benefits include: "Drugs, including compounded preparations, that are available over the counter."

   Although TRICARE policy does not govern the availability of OTC products at MTF pharmacies, the Council has historically refrained from adding OTC products to the BCF. The BCF currently includes only 11 OTC items. The recently published Uniform Formulary Proposed Rule states, "The Basic Core Formulary (BCF) is a subset of the Uniform Formulary and is a mandatory component of all MTF pharmacy formularies". If the BCF is to be a subset of the Uniform Formulary, the inclusion of OTCs on the BCF will be limited by TRICARE policy.

   From 1 Oct 01 to 15 Mar 02, MTFs dispensed 3.7 million prescriptions for OTC drugs, which accounted for 16.3% of total prescriptions dispensed during that time period. The eleven OTC items on the BCF accounted for only 500,000 of the 3.7 million prescriptions for OTC drugs, so MTFs clearly provide many more OTC drugs than those included on the BCF.

   In light of the Uniform Formulary Proposed Rule, the Council unanimously voted not to add any additional OTC products to the BCF beyond those identified in the TRICARE Policy Manual. However, the Council encourages MTFs to continue providing OTC medications when they represent cost-effective alternatives to legend drugs. The Council will explore mechanisms other than the BCF to promote uniform availability of cost-effective OTC medication at MTFs.

C. *Comparison of the BCF to VA's National Formulary* - The term "formulary" most properly refers not only to a list of drugs on the formulary of a health care institution or system, but also to related information concerning the use of drugs and to the drug use policies of that institution or system as a whole. The BCF and the VA National Formulary (NF) have fundamental differences that reflect underlying differences in the MHS and VA drug delivery systems, despite similar underlying concepts—both are intended to make cost-effective drug therapies uniformly available across large health care systems. Formulary status on the BCF and/or the NF is increasingly being used to leverage lower prices for commonly used pharmaceuticals in classes where several therapeutically equivalent alternatives exist.

   One of the fundamental differences between DoD and the VA that affects formulary structure is the fact that VA facilities generally do not fill prescriptions from outside providers. The VA also lacks a full-service mail order point of service analogous to the NMOP (the VA Consolidated Mail Outpatient Pharmacy (CMOP) is used to expedite the processing of refills) and VA beneficiaries do not have the option of taking their prescriptions to retail network pharmacies. In addition to point of service and

administrative differences, there are well-known patient population differences between the two systems that may affect drug formularies.

DoD and the VA differ even when considering only MTFs and VA facilities, most notably in the degree to which local formulary decision-making is retained by individual facilities. In the VA, the NF is supplemented by 22 regional (VISN) formularies, but local formularies are forbidden and local formulary decision-making is restricted to antimicrobials (to accommodate local resistance patterns). The BCF is supplemented by both regional (in some cases) and local formularies; individual facilities typically have independent P&T committees that retain broad autonomy over local formularies and drug use policy.

The NF drug list contains 1214 items (individual listings) in 28 categories, while the BCF contains 176 items in 24 categories. These counts were based on using the VA classification system and the formularies as listed on the VA PBM and DoD PEC websites as of May 02, after adjusting both lists to use common terminology. The VA drug classification system was chosen for this comparison because it provides consistent categories for all items on both the NF and the BCF, including medical supply items.

Three major categories where the two formularies differ substantially are injectable medications, medical supply items, and OTC medications. The NF contains a large number of medications that have not been traditionally represented on the BCF, including 344 injectable medications, most of which are typically only used on an inpatient basis (compared to 7 on the BCF); 131 medical supply items, including syringes, dressings, IV supplies, catheters, etc. (compared to 2 on the BCF); and 185 OTC medications (vs. 11 on the BCF).

Even if injectable medications, medical supply items, and OTC medications are excluded, the NF still contains more line items than the BCF (570 vs.156). The difference can be broken down into three primary contributing factors:

1) The NF contains some categories, such as antimicrobials, central nervous system medications (including antidepressants and antipsychotics), and antineoplastics, which appear to contain virtually all commonly used drugs in those categories. This may be due to resistance concerns (as would be the case with antimicrobials) or to lack of therapeutic interchangeability of drugs in these categories. Some of these drugs may be subject to criteria for use.
2) The NF covers some types of drugs traditionally not well represented on the BCF because they are considered to be specialty drugs (e.g., antineoplastics, antivirals, diagnostic agents, topical anesthetics).
3) The NF tends to list more alternatives than the BCF even in commonly used drug classes listed on both formulary lists. For example, the NF lists 5 oral glucocorticoids while the BCF lists 2, and the NF lists 8 nonsteroidal anti-inflammatory drugs while the BCF lists 3.

8. DRUG USE AND EXPENDITURE REVIEW

The Council was unable to assess the FY 02 budget execution by MTF pharmacies because:

- Prime vendor data are missing for so many MTFs that expenditures cannot be accurately estimated.
- CHCS pharmacy cost reports are not uniformly available from MTF pharmacies.
- MTF pharmacy expenditures reported by the TMA resource management differ significantly from the pharmacy expenditures reported by the resource managers for the three services.

9. PENDING CONTRACT INITIATIVES

A. Status of Contracting Initiative for Leutinizing Hormone Releasing Hormone (LHRH) Agonists – The DoD and the VA have agreed in principle on pursuing a contract for a Leutinizing Hormone Releasing Hormone (LHRH) agonist. The solicitation will be for a 1 and 3 month product from the same manufacturer for the treatment of prostate cancer; other formulations and strengths will not be included. The solicitation is currently being written, but has not yet been released.

B. Status of Contracting Initiative for Nasal Corticosteroids – The DoD and VA issued a joint solicitation to select a single source for flunisolide nasal inhalers. This solicitation does not stipulate that the contracted drug will be on the BCF. The DoD and VA are also working on a joint solicitation for a once-daily nasal corticosteroid inhaler that will place the contracted product on the BCF.

C. Status of Contracting Initiative for Triptans – The DoD and VA are working on a joint solicitation that will comply with the Council's previous stipulation that any contracting initiative must either allow or require MTFs to have at least two triptans on their formularies.

10. DRUG CLASS EVALUATIONS TO DETERMINE CLINICALLY ACCEPTABLE CONTRACTING/FORMULARY STRATEGIES

: COL Remund briefed the Council on the PEC's attempt to outline the process that the Council has been using to identify clinically acceptable contracting/formulary strategies for drug classes. The Council followed the process described in Appendix A to evaluate the following drug classes.

A. Statins – The current DoD statin contract will expire in February 2003. A joint solicitation with the VA for a follow-on contract is currently being considered. A high potency statin (simvastatin or atorvastatin) must be included on the BCF in order for patients to attain the LDL-cholesterol goals established by the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guideline. A low potency statin could also be included on the BCF if it would enhance the cost effectiveness of cholesterol-lowering therapy in the Military Health System. The following analysis focuses on the high potency statins.

Therapeutic Interchangeability: Although atorvastatin can achieve larger reductions in LDL-cholesterol than simvastatin, less than 10% of patients require the magnitude of LDL-cholesterol reduction that can only be achieved by atorvastatin. Some studies indicate that atorvastatin may not raise HDL cholesterol levels as much as simvastatin, but the Council doubted that any difference in the effect on HDL levels would significantly affect the therapeutic interchangeability of these drugs for most patients. Long-term clinical trials prove that simvastatin reduces cardiovascular morbidity and mortality. Similar evidence is not available for atorvastatin. There are no data that demonstrate significant differences in safety or tolerability between atorvastatin and simvastatin. The Council concluded that simvastatin and atorvastatin have a high degree of therapeutic interchangeability.

Clinical Coverage: Simvastatin and atorvastatin each have the capacity to satisfy the LDL-cholesterol reduction needs of at least 90% of the DoD population. Some patients may have a clinical need to use pravastatin because of its lower potential for drug interactions, but these patients comprise less than 5% of statin patients. Providers expressed a preference for having more than one statin on the BCF, but they did not provide a clinical justification for a second statin on the BCF. The Council concluded that either atorvastatin or simvastatin would provide adequate clinical coverage.

Provider Acceptance: Provider acceptance of simvastatin is clearly supported by the fact that simvastatin currently accounts for about 95% of all statin prescription fills at MTF pharmacies. Providers also expressed a willingness to use atorvastatin. Providers voiced strong opposition to any contract that would require patients to be switched from one statin to another statin. Opposition to switching patients is understandable because (1) approximately 150,000 patients had to switch statins after the DoD statin contracts were awarded in August 1999 and (2) approximately 100,000 patients had to switch statins after cerivastatin was withdrawn from the market in August 2001.

The Council voted unanimously to support any contracting/formulary strategy (to include a closed class contract) that places at least one high potency statin on the BCF and does not require patients to be switched from one agent to another. The Council also supports the inclusion of a low-potency statin on the BCF if it is projected to enhance the cost-efficiency of statin therapy.

B. *Angiotensin Receptor Blockers (ARBs)* –Seven ARBs are available: losartan (Cozaar, FDA-approved in Apr 95), valsartan (Diovan, Dec 96), irbesartan (Avapro, Sep 97), candesartan (Atacand, Jun 98), telmisartan (Micardis, Oct 98), eprosartan (Teveten, Oct 99), and olmesartan (Benicar, Apr 02). All the ARBs are FDA-approved for hypertension.

ARBs offer a slight clinical advantage (lower incidence of cough and angioedema) compared to angiotensin-converting enzyme inhibitors (ACEIs) in the treatment of hypertension, but ARBs cost much more than ACEIs. The JNC-VI Guideline advises that ARBs should be reserved for hypertensive patients who are unable to tolerate ACEIs. ARBs are also used "off-label" for congestive heart failure (CHF) and prevention of renal disease progression in diabetics. Despite a recent ADA recommendation that an ARB should be used as first line therapy in type 2 diabetes with hypertension and

microalbuminuria or clinical albuminuria, many providers still think that ARBs should be reserved for second line therapy when patients experience adverse effects on an ACEI.

Despite their "second line" place in therapy, ARB purchases by MTFs increased about 56% from $9 million in FY 00 to $14 million in FY 01. A significant price reduction might be achieved through a contracting initiative that places one or more ARBs on the BCF.

Therapeutic Interchangeability

- *Hypertension*: The Council considered the information contained in a joint VA/DoD clinical review of the ARBs (published on the PEC website). The Council concluded that ARBs have a high degree of therapeutic interchangeability in the treatment of hypertension.
- *CHF*: The FDA has characterized valsartan as "approvable" for CHF in patients not receiving an ACEI or as a substitute for an ACEI (despite the FDA advisory committee recommendation against approval). The ELITE I study showed increased survival for CHF patients on losartan compared to an ACEI, but the larger ELITE II study showed no significant difference in all-cause mortality for patients on losartan compared to an ACEI. The RESOLVD trial was discontinued because candesartan was associated with an increase in hospitalizations and death compared to CHF patients treated with enalapril. A large CHF trial comparing candesartan to an ACEI (the CHARM trial) is underway. Data are not available for the other ARBs in the treatment of CHF. The Council decided that the data are insufficient to conclude that the ARBs are therapeutically interchangeable for CHF.
- *Prevention of renal disease progression in diabetics*: A FDA advisory committee concluded that the IDNT and IRMA-2 trials were suggestive of efficacy, but the data were insufficient to support approval of irbesartan for prevention of renal disease progression in patients with type 2 diabetes. An FDA advisory committee recommended approval of losartan for the prevention of renal disease progression in diabetics based on the RENAAL trial. Data are not available for the other ARBs for this indication. The Council decided that the data are insufficient to conclude that the ARBs are therapeutically interchangeable for prevention of renal disease progression in diabetics.

Clinical Coverage: There is no evidence that if a hypertensive patient fails therapy with one ARB, a better response would occur with another ARB. Any of the ARBs would probably provide adequate clinical coverage when used for hypertension, but there are no data to support a conclusion that one or more of the ARBs is sufficiently safe, tolerable, and effective to satisfy the clinical needs of at least 90% of the patients when used for CHF or prevention of renal disease progression in diabetics.

Provider Acceptance: Losartan, valsartan, and irbesartan account for about 90% of prescription fills for ARBs at MTF pharmacies, and providers expressed a preference for these three ARBs. Nephrologists and endocrinologists prefer irbesartan and losartan. Cardiologists prefer valsartan. These three have been on the market longer than the other ARBs, so providers have more confidence in their safety profiles. Providers were uniformly opposed to switching patients from one ARB to another.

The Council unanimously voted to add at least one ARB to the BCF in an open class, with guidelines for appropriate use. The Council also stipulated that any contract for an ARB should not require patients to be switched from one ARB to another ARB.

C. *Thiazolidinediones (TZDs, "glitazones")* – While the TZDs offer a relatively modest reduction in HbA1C compared to other antidiabetics, diabetic patients frequently require combination therapy with two or more agents. Even small reductions in HbA1C correlate with a decreased risk of microvascular complications. There has now been sufficient clinical experience with TZDs to lessen the concern regarding hepatoxicity. The VA is currently considering adding a TZD to its National Formulary. A DoD and VA joint procurement strategy for TZDs might achieve a substantial price reduction.

Therapeutic Interchangeability: There are no large, randomized, controlled head-to-head trials comparing rosiglitazone (Avandia) and pioglitazone (Actos). However, comparison of clinical trial data suggests that they reduce HbA1C by the same degree when equivalent doses are used (pioglitazone 45 mg qd = rosiglitazone 4 mg bid, or pioglitazone 30 mg qd = rosiglitazone 8 mg qd). Both drugs are approved for monotherapy and for use in combination with metformin or a sulfonylurea. Pioglitazone is approved for use with insulin, and the FDA has classified rosiglitazone as "approvable" for use with insulin. There are case reports of heart failure occurring with both drugs when used in combination with insulin. There is insufficient evidence to conclude that the drugs differ in their propensity to cause or exacerbate heart failure.

Comparison of data from clinical trials suggests that pioglitazone has a more favorable effect on LDL-cholesterol and triglycerides than rosiglitazone. However, due to the significant intra-person and inter-person variability in lipid levels, the variability in methods used to measure lipid levels, and potential differences in study subjects across the trials, it is difficult to draw a definitive conclusion about any true differences in lipid effects. The clinical significance of the potential differences in lipid effects is also unknown. Table 1 shows the range of changes in mean lipid levels from clinical trials for rosiglitazone and pioglitazone.

Table 1: Range of Mean Lipid Changes from TZD Clinical Trials

	Rosiglitazone[a]	Pioglitazone[b]
LDL	↑ 5.3 – 22%	↑ 2.8 – 7.7%
HDL	↑ 8.4 – 18%	↑ 9.1– 15.8%
Triglycerides	↑9 – 19.6%	↓ 9.6 – 15.9%

[a] Rosiglitazone LDL results from 7 studies, HDL results from 5 studies, and triglyceride results from 2 studies.
[b] Pioglitazone results from 5 studies.

Rosiglitazone and pioglitazone appear similar to placebo in their propensity to cause elevation in liver transaminases. There are no data to suggest that they differ significantly in their potential to cause hepatotoxicity, edema or weight gain.

Clinical Coverage: Based on their FDA-approved indications, either of these drugs can be expected to have the desired clinical effect in over 90% of patients.

Provider Acceptance: Providers would generally accept either agent, but some indicate a preference for pioglitazone due to its more favorable lipid profile. PDTS prescription data

show that pioglitazone has consistently increased its share of prescription fills for TZDs across all three outpatient pharmacy points of service over the past year.

Council members had difficulty reaching consensus on whether this class is suitable for a closed class contract. Objections to a closed class contract centered on the potential lack of therapeutic interchangeability between pioglitazone and rosiglitazone in regard to their effects on LDL-cholesterol and triglycerides. Some Council members also expressed concern that the potential for discovery of new clinical information about these drugs makes a closed class contract risky for this drug class. After two motions failed, the Council approved a third motion to add one TZD to the BCF via a procurement initiative that leaves the TZD class open and does not require patients to be switched from one TZD to another.

11. DRUG/DRUG CLASS EVALUATIONS TO DETERMINE BCF ADDITION

A. *COX-2 Selective Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)* – The major advantage of COX-2 selective NSAIDs ("COX-2 inhibitors") compared to non-specific NSAIDs is a reduced incidence of complicated upper gastrointestinal (GI) events (GI bleed, perforation, and obstruction) and symptomatic but uncomplicated ulcers. Evidence that COX-2 inhibitors actually provide this benefit is primarily derived from two large trials: the Vioxx Gastrointestinal Outcomes Research Study (VIGOR) and the Celecoxib Long-term Arthritis Safety Study (CLASS).

VIGOR demonstrated a statistically significant reduction in the annualized incidence of complicated upper GI events in patients receiving rofecoxib (0.6%) vs. naproxen (1.4%), which equates to a number-needed-to-treat (NNT) of 125. In other words, 125 patients would need to be treated with rofecoxib rather than naproxen for one year to prevent one complicated upper GI event. CLASS (celecoxib vs. ibuprofen and diclofenac) failed to demonstrate a statistically significant reduction in complicated upper GI events for its overall patient population, but a statistically significant reduction in complicated upper GI events did occur in the subgroup of patients not receiving aspirin. A statistically significant reduction also occurred for the broader endpoint of complicated upper GI events plus symptomatic but uncomplicated ulcers regardless of aspirin use.

If the reduction in complicated upper GI events in VIGOR is generalized to all COX-2 inhibitors and the daily cost of COX-2 inhibitor and nonspecific NSAID therapy is estimated to be $1.50 and $0.15, respectively, treating 125 patients for one year with COX-2 inhibitors rather than nonspecific NSAIDs would prevent one complicated GI event at an incremental drug cost of about $61,600. This does not take into account the effect of reductions in the incidence of symptomatic but uncomplicated ulcers and possibly in the incidence of GI symptoms and the use of medications to treat GI symptoms (e.g., H2-blockers and PPIs).

Because the risk of NSAID-associated GI events is known to differ among patient populations (based on factors such as age, use of other medications that increase GI risk, use of prophylactic medications, and history of peptic ulcer disease and/or prior GI events), the NNT from the VIGOR trial and the associated cost to prevent one GI event cannot be generalized to all patients. The NNT and the associated costs would be much higher in a patient population without known risk factors (e.g., young patients, many of

whom would receive relatively short-term treatment with NSAIDs) than in the patient population studied in VIGOR (older RA patients requiring chronic NSAID therapy).

Estimates of the background risk of GI events in a general patient population are not readily available. However, if the baseline annualized risk of NSAID-associated GI events in such a patient population is assumed to be about 0.5%, and the relative reduction in events with COX-2 inhibitors vs. nonspecific NSAIDs is assumed to be similar to the reduction in VIGOR (about 50%), the NNT would be 400. Using the same daily medication costs described above, 400 patients would have to be treated for one year with COX-2 inhibitors rather than nonspecific NSAIDs to prevent one complicated GI event, at an incremental drug cost of $197,000.

COX-2 inhibitors appear to be somewhat better tolerated with regard to dyspepsia and other GI symptoms than the non-specific NSAIDs to which they have been compared. COX-2 inhibitors appear similar to non-specific NSAIDs in regard to other adverse effects (e.g., renal adverse effects and propensity to cause edema and blood pressure elevation). COX-2 inhibitors do not affect platelet aggregation.

The VIGOR trial demonstrated a statistically significant increased risk in serious cardiovascular (CV) thrombotic events (primarily acute myocardial infarctions) in patients treated with rofecoxib compared to patients treated with naproxen (1.1% vs. 0.5%). The cause of this finding, its potential applicability to other COX-2 inhibitors, and its real meaning in day-to-day clinical practice are subject to considerable debate. Subsequent analyses of pooled data comparing rofecoxib to NSAIDs other than naproxen or to placebo have not shown an increased in CV risk for rofecoxib.

COX-2 inhibitors do NOT appear to be any more effective than non-specific NSAIDs in the treatment of osteoarthritis, rheumatoid arthritis, acute pain, or dysmenorrhea.

After reviewing the clinical data, the Council reiterated its conclusion that even if COX-2 inhibitors are used only in patients at increased risk for NSAID-associated GI events, the DoD would incur a large increase in drug costs for a rather small decrease in GI events. If COX-2 inhibitors are used in patients with a “normal” risk for GI events, the DoD would incur huge incremental costs for miniscule incremental benefits. The Council acknowledged that the COX-2 inhibitors are being considered for addition to the BCF because of the potential financial impact of shifting prescriptions from the retail network to MTFs—not because of the clinical value they offer in comparison to their cost.

To estimate the potential for increased use of COX-2 inhibitors if a COX-2 inhibitor were added to the BCF, the PEC compared COX-2 inhibitor prescription fill rates (as a percent of all Rx fills) at MTFs that have one or more COX-2 inhibitors on formulary to MTFs that do not have a COX-2 inhibitor on formulary. Assuming that the prescription fill rates at sites that do not currently have a COX-2 inhibitor on formulary would increase to the same rate as sites that do, the total number of COX-2 Rx fills at MTFs would increase by 180,000 per year (32.8%) if a COX-2 inhibitor were added to the BCF. This increase would inevitably include use of COX-2s in both patients likely to benefit (i.e., long-term use in patients with risk factors for GI complications) and patients unlikely to benefit (short-term use in patients without risk factors) from using COX-2 inhibitors.

At the last meeting, the Council asked DSCP to issue a request for Blanket Purchase Agreement (BPA) price quotes to the pharmaceutical companies that market COX-2 inhibitors for the purpose of adding a COX-2 inhibitor to the BCF in an open class. The request for BPA price quotes also asked companies to submit their plans for assisting MTFs in targeting the use of COX-2 inhibitors to the patients at greatest risk for GI events. The VA decided not to participate in this BPA request for quotes.

The Council evaluated the projected weighted average daily cost per patient that would result from the price quotes offered for each COX-2 inhibitor. The Council also used a mathematical model to estimate the potential financial impact of adding each COX-2 inhibitor to the BCF. The model took into account likely increases in use and projected shifts in utilization amongst the three points of service. After evaluating a variety of scenarios, the Council concluded that it was in the best interest of the government not to accept any of the BPA price quotes, so a COX-2 inhibitor was not added to the BCF.

B. *Raloxifene (Evista)* – Raloxifene was evaluated for potential addition to the BCF based on high retail network use. PDTS data from July through December 2001 showed 37,200 prescriptions for 13,000 unique patients in the retail network, with an annual cost to DoD of $5 million.

Raloxifene is the first of a new class of agents known as selective estrogen receptor modifiers (SERMs). A derivative of tamoxifen, raloxifene has a mixed agonist-antagonist effect on estrogen receptors throughout the body. It is indicated for the prevention and treatment of osteoporosis in postmenopausal women. Alendronate, also approved for the treatment of osteoporosis, is currently on the BCF.

The most common side effects of raloxifene are hot flashes and leg cramps. Patients treated with raloxifene were at higher risk of venous thromboembolism (NNH 143) than the placebo group. The increased risk is similar to the risk of venous thromboembolism seen with hormone replacement therapy (HRT). In the MORE trial, raloxifene reduced the risk for new vertebral fractures by 50% in women without previous fractures (NNT 46) and by 30% in those with previous fractures (NNT16). Both reductions were statistically significant. Raloxifene also increased BMD of the femoral neck and spine by 2-3%. The drug cost to prevent one vertebral fracture in 3 years is $42,000 compared to a cost of $27,000 for alendronate to prevent one vertebral fracture in 3 years.

Raloxifene's nonskeletal effects include reductions in LDL cholesterol (11%) and total cholesterol (7%), without changes in HDL cholesterol. Raloxifene reduced the risk of invasive breast cancer by 76% in the MORE trial. Studies are underway to investigate the cardiovascular benefits of raloxifene and to compare it to tamoxifen in the prevention of breast cancer.

Providers and pharmacists were surveyed regarding their use and potential use of raloxifene. Eighty-five responses were obtained. All responses favored the addition of raloxifene to the BCF. Raloxifene 60 mg is currently on the formulary of approximately 20% of MTFs.

The Council voted to add raloxifene to the BCF.

C. *Calcium (calcium and calcium + vitamin D)* – Given the Council's previous decision not to add any OTC medications to the BCF beyond those identified in the TRICARE Policy Manual, the Council did not consider the proposal to add calcium and calcium + vitamin D to the BCF. The Council acknowledged that clinical data fully support the use of calcium in patients with osteoporosis and especially in patients treated for osteoporosis with prescription medications. The Council encourages all MTFs to make available and promote adequate calcium supplementation in patients for the prevention and treatment of osteoporosis.

D. *Guaifenesin/pseudoephedrine sustained release tablet (generic Entex-PSE)* – Entex-LA eq. (guaifenesin & phenylpropanolamine long-acting) was removed from the BCF at the Nov 00 P&T Committee meeting because of safety concerns expressed by the FDA regarding phenylpropanolamine. The Committee had intended to select an alternative agent for the BCF after manufacturers reformulated their products, but an alternative agent was not selected. The PEC recently identified that guaifenesin (GFN) and pseudoephedrine (PSE) long-acting, the logical replacement for Entex-LA eq., was the second most prescribed non-BCF drug. Many different brands and formulations exist (e.g., Entex-PSE, Duratuss, Deconsal-II), but MTFs overwhelmingly use the GFN 600mg/PSE 120mg formulation. Three manufacturers currently offer prices of less than $0.07 per tablet for this product. The Council unanimously voted to add GFN 600 mg/PSE 120 mg long acting to the BCF.

12. CLARIFICATION OF BCF LISTING

Carbinoxamine/pseudoephedrine (Rondec) Drops — Lt Col Zastawny presented a clarification of the BCF listing of carbinoxamine/pseudoephedrine drops. A recent formulation change for the branded product (Rondec®) decreased the concentrations of the ingredients from 2mg carbinoxamine and 25mg of pseudoephedrine per mL to 1mg carbinoxamine and 15 mg of pseudoephedrine per mL. Changes were also made in the recommended dosing schedule included with the product. The new 1mg/15mg per mL formulation appears to be the only formulation currently being produced by the brand and generic manufacturers. The change in recommended dosing raises concern about the potential for dosing errors resulting in excessive dosing of pseudoephedrine in pediatric patients if the two dosage forms were used interchangeably.

The Council agreed to (1) specify the newer carbinoxamine 1mg and pseudoephedrine 15mg per mL formulation on the BCF, 2) remove the Rondec® brand name reference from carbinoxamine/pseudoephedrine drops listing on the BCF, and 3) provide a link from the BCF listing to a drug and dosing information page.

13. MTF REQUESTS FOR BCF CHANGES

A. *Request to remove propranolol LA from the BCF* – A request to delete propranolol long-acting (LA) from the BCF cited lack of generic availability and low utilization. The PEC confirmed the shrinking availability of generic forms of propranolol LA. Approximately 4000 patients use propranolol LA. The number of unique users has remained relatively constant over the past three years. The Council voted to delete propranolol LA from the BCF because of decreasing generic availability and availability of preferable alternatives on the BCF (e.g., metoprolol, atenolol).

B. *Request to add Combivent (18 mcg ipratropium/103 mcg albuterol) MDI to the BCF –* An Air Force pulmonologist provided the following rationale for the request:

- Seven studies have shown that the addition of an anticholinergic with a beta agonist can achieve enhance bronchodilation.
- Patients with COPD (stage II and III) are required to take both medications. Combivent is included as the standard of care in the VHA/DoD, ATS, and new GOLD guidelines for the management of COPD.
- Compliance with a MDI increases when only one device or inhaler is used and guarantees the patient receives both medications for maximal effect.

Safety and tolerability of the combination product are similar to the same dosages of the products administered by separate inhalers. Combination therapy with ipratropium and albuterol has been shown to produce superior bronchodilation without additional side effects compared to monotherapy with albuterol or ipratropium. In stage II and III COPD, a combination of ipratropium plus a beta-agonist is associated with lower rate of exacerbations and lower total health-care costs than compared to albuterol or ipratropium monotherapy. Efficacy of Combivent is similar to the same dosages of the ipratropium and albuterol administered by separate inhalers.

The PEC requested provider (physician and pharmacist) input on this issue and received 33 responses: 26 favoring, 5 against, and 2 inconclusive regarding addition of Combivent to the BCF. Providers made several key points:

- This medication is used in patients with COPD, who frequently are noncompliant and smoke. They need the ipratropium to assist with lung function, but they don't necessarily feel the effect like they do with albuterol.
- Each inhaler requires 2 inhaled puffs 3-5 minutes apart, and to do both albuterol and ipratropium at a time would take up to 20 minutes, which most patients are not willing to do. Combivent only takes 3-5 minutes, and they won't get the two confused.
- The addition of Combivent to the BCF may improve patient satisfaction and compliance.
- Although we see a fair amount of civilian prescriptions, it is not on our MTF formulary. If it is cheaper for us to fill than the Tricare network, than I guess that would be a positive.
- There is a potential to reduce waste and pharmacy labeling costs from the use of two products.

Prime vendor data show that nonavailability of the contracted brand of albuterol MDI causes MTFs to actually pay more than the contract price for albuterol MDIs. FSS and contract pricing as of April 02 for Combivent and the individual products compared to the MTF average price paid (Nov 01- Jan 02) are presented in the following table:

Item Description	Doses/container	FSS Price As of April 02	MTF Ave Price (PV data Nov 01 – Jan 02)
Albuterol MDI	200	$ 1.65 (Contract price as of Nov 01)	$ 3.26
Ipratropium MDI	200	$ 19.59	$ 18.82
Combivent MDI	200	$ 22.47	$ 21.59

The cost of Combivent is compared to the cost of the individual products using both lowest available FSS price and MTF average price in the following table:

	Combivent cost/day 2 puffs four times daily	Cost/day of equivalent dose of individual products	Additional cost per day for Combivent
FSS Price	$ 0.90	$ 0.85	$ 0.05
MTF Ave Price	$ 0.86	$ 0.88	($ 0.02)

Combivent is on approximately 53% of MTF formularies. It ranks #25 in total MTF prescription fills of legend drugs that are not currently on the BCF. Combivent also falls in the top 100 prescriptions filled in the retail network.

Addition of Combivent to the BCF could improve patient satisfaction and compliance. There is also a potential reduction in waste. There is a potential for cost savings to the government since the average MTF price for Combivent is $0.02/day less expensive than the cost/day of equivalent dose of individual products. The Council voted to add ipratropium/albuterol (Combivent) to the BCF.

C. *Request to remove Fosamax 5 and 10 mg from the BCF* – The PEC received a request to remove the 5 mg and 10 mg strengths of alendronate, citing low usage of the daily dosage forms of these agents since the weekly forms became available. In general, the BCF listing of a drug includes all formulations and dosage strengths. The Council found no compelling reason to change the listing for alendronate, and voted unanimously to retain alendronate 5 mg and 10 mg on the BCF. Individual MTFs must make the drug available, in all strengths, when needed. Decisions about stocking levels may be made at the MTF level based on usage at that facility.

14. ADJOURNMENT

The meeting adjourned at 1600 hours on 7 May 2002. The next meeting will be held at the Uniformed Services University of the Health Sciences, Bethesda, Maryland at 0800 on 7 August 2002. All agenda items should be submitted to the co-chairs no later than 8 July 2002.

<signed>	<signed>
DANIEL D. REMUND	TERRANCE EGLAND
COL, MS, USA	CDR, MC, USN
Co-chair	Co-chair

Appendix A: Drug Class Evaluations to Determine Clinically Acceptable Contracting/Formulary Strategies

1. The DoD P&T Executive Council evaluates the relative safety, tolerability, efficacy, price/cost and other pertinent issues ("STEPO" evaluation) to assess three factors that affect the acceptability of various contracting/formulary strategies:

   a. *Therapeutic interchangeability*: Therapeutic interchangeability is the extent to which drugs have similar clinical attributes, are used for the same indications, are used for the same patient populations, and can be expected to achieve similar clinical outcomes. Closed class contracts that require patients to be switched to the contracted drug require the highest degree of therapeutic interchangeability.

   b. *Coverage of clinical needs*: The drug(s) selected for a closed class contract must be sufficiently safe, tolerable, and effective to satisfy the clinical needs of at least 90% of the patients for whom the drug will be prescribed. Too many patients and providers will be forced to use the non-formulary/special order process if fewer than 90% of the patients can be successfully treated with the contract drug.

   c. *Provider acceptance*: Provider acceptance is the extent to which DoD providers are willing to use the contracted drugs and refrain from using the non-contracted drugs. There are two components to this condition. The first relates to provider behavior when first starting a patient on one of the agents in the class. For some drug classes providers will not accept a requirement to prescribe a particular agent even though it has been determined to be therapeutically equivalent to other members of the class. This is often true of newly approved drugs, but may apply to other members of the class as well. A lack of long-term safety data is a common cause for this concern. The second component relates to whether prescribers are willing to switch patients currently being treated with one drug in a class to the contract winner following contract award. Willingness to switch is tied to the perceived likelihood that the contracted drug will effectively substitute for the patient's current therapy and the amount of effort it takes to make the switch.

2. The DoD P&T Executive Council then decides which (one or more) of the contracting/formulary strategies described below are clinically acceptable and specifies any "clinical imperatives" that must accompany a given strategy. The VA/DoD Pharmaceutical Contracting Workgroup decides which specific contracting strategy to use from among the strategies that are acceptable to the DoD P&T Executive Council. Potential contracting/formulary strategies include the selection of one or more drugs for:

   a. A closed class contract that puts the contracted drug(s) on the BCF and requires patients to be switched to the contract drug(s).

   b. A closed class contract that puts the contracted drug(s) on the BCF, but does not require existing patients to be switched to the contracted drug(s).

   c. A closed class contract that does not put the contracted drugs(s) on the BCF, but requires existing patients to be switched to the contract drug(s).

   d. A closed class contract that does not put the contracted drugs(s) on the BCF and does not require existing patients to be switched to the contract drugs.

   e. A contract that puts the contracted drug(s) on the BCF but leaves the class open.

   f. The BCF based on an evaluation of the responses to a Blanket Purchase Agreement (BPA) request for price quotes

   g. The BCF based on a BPA(s) offered by one or more companies

   h. The BCF based on existing BPA(s)

   i. The BCF based on existing FSS prices