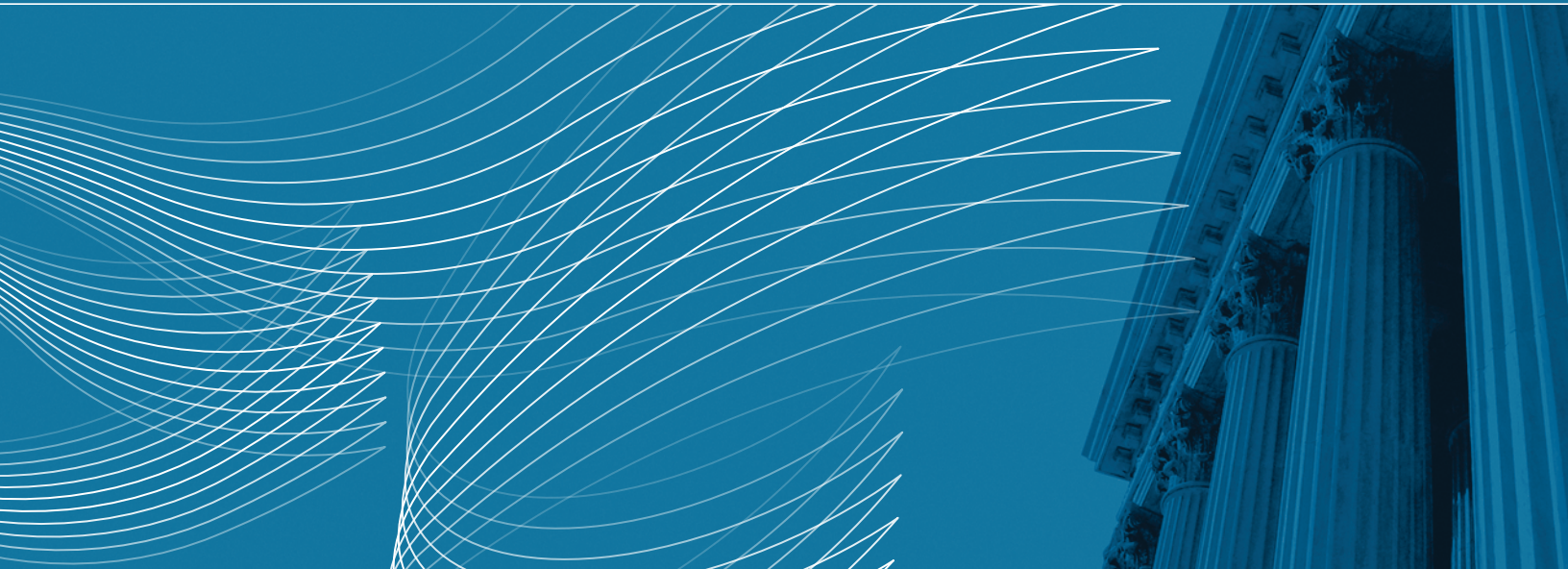


Part D Formularies / Opportunities for Further FDA/CMS Collaboration

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May 2008



This analysis is self-funded by Avalere Health, consistent with our mission to improve the healthcare system through research, education, and strategic advisory services.

Summary

Under the Medicare Modernization Act (MMA), the Centers for Medicare & Medicaid Services (CMS) is charged with administering the Medicare Part D outpatient prescription drug benefit. Its mission is to ensure effective, up-to-date prescription drug coverage and to promote quality care for beneficiaries. The Part D benefit is provided through the private sector, with each private plan offering Medicare beneficiaries a slightly different set of covered prescription drugs in their formularies. CMS is required by law to review plans' proposed formularies to assure that the formularies contain an appropriate mix of drugs. In addition, the MMA requires that any drug offered under Part D must be approved by the Food and Drug Administration (FDA). The FDA is responsible for ensuring the safety and efficacy of drugs, biological products, and medical devices. Over the past several years, CMS has sought to simplify and clarify the process by which plans submit their proposed formularies for review.

To that end, CMS has adopted a strategy to define a standard set of "proxy" codes for the plans to use in describing their proposed formularies. The set of these "proxy codes" is known as the CMS Formulary Reference NDC File (National Drug Code Reference File). Use of the Reference File permits CMS to make "apples-to-apples" comparisons of plans' formulary submissions. The Reference File is not to be used as a benchmark formulary, as CMS is prohibited from establishing a specific list of drugs that must be covered by plans.

CMS significantly reduced the size of the Reference File from 2007 to 2008 (about 1,600 codes, or roughly 23 percent), prompting an inquiry by Avalere Health researchers to explore and understand the changes. We posed the following questions:

- Were unique drugs deleted from the Reference File?
- What prompted CMS to delete drugs from the Reference File?
- What are the implications for various stakeholders in Part D (e.g., beneficiaries, pharmacists, and providers)?

In summary, we find that many of the "proxy" codes eliminated in 2008's Reference File are attached to drugs that lacked FDA approval or are nonprescription drugs and should never have been included in prior years' Part D plan formularies. Other reductions made to the Reference File are attributable to a more efficient collapsing of proxy codes to cut the number of redundant codes. Our research revealed opportunities for enhanced FDA oversight of the marketing of prescription drugs that lack appropriate FDA approval, and that the FDA is presently unable to provide CMS, clinicians, and patients a definitive list of marketed unapproved drugs. The lack of a current and definitive list imposes significant challenges to CMS' mandatory review of private plans' proposed formularies, since the MMA requires that only FDA-approved drugs are eligible for federal Part D subsidies. In addition, the lack of such a definitive list poses a serious challenge to clinicians, pharmacists, patients, and prescription drug plans who currently lack an authoritative reference as to which marketed drugs lack FDA approval.

Further, the annual CMS-driven change to the Reference File may have implications for patients, Part D plans, and pharmacies:

- Beneficiaries taking medications that are deleted from the Reference File—and thus potentially from their private Part D plan’s formulary—may be forced to pay out-of-pocket for the same, now-not-covered drug, or to switch to a different therapy, which could generate clinical implications.
- Plans may choose not to cover drugs deleted from the Reference File, or may choose to offer many of those drugs without recourse to federal subsidies.
- Pharmacists often serve as a major source of Part D information for beneficiaries; pharmacist understanding of the Reference File-driven changes in the drug benefit is essential to patients making informed choices.

Our analysis reveals various challenges faced by the FDA and CMS. The FDA reportedly does not maintain a complete list of products that, despite being marketed to patients and clinicians, have never been approved by the FDA. While compiling such a list of unapproved drugs is challenging, the lack of such a list presents significant clinical, operational, and financial issues to all Part D stakeholders. Complicating the issue is the fact that many of these unapproved products have been prescribed for decades without health professionals knowing of their unapproved status.¹ For a small number of these medications, patients who are stabilized on them depend on them (e.g., pancrelipase). Thus, not all unapproved products can or should be abruptly withdrawn.

While FDA is making progress to remove products with demonstrated safety and efficacy concerns, *several thousand* unapproved marketed drug products remain on the market²—a daunting challenge for the FDA, a problem for Medicare beneficiaries, and an obstacle for health professionals and Medicare Part D plans. Despite the apparent lack of a complete and current FDA-authorized list of unapproved drug products, CMS must meet the statutory requirement to not cover unapproved drugs, and has, to date, held private Part D plans responsible for compliance. These divided accountabilities suggest a need for greater collaboration among CMS, FDA, policymakers, health plans, health professionals, and professional practice associations.

Background: Formulary Reference NDC File

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) added Medicare Part D—a new outpatient prescription drug benefit—to the Medicare program. This new benefit took effect on January 1, 2006. Private plans administer the benefit with oversight and guidance from CMS. Plans offering drug benefits include established managed care organizations (called Medicare Advantage Prescription Drug Plans, or MA-PD plans) and prescription drug only plans (called standalone prescription drugs plans, or PDPs). To participate in Part D, a plan must submit a bid and/or renewal materials to CMS on an annual basis.

¹ FDA. *Drugs Marketed in the United States That Do Not Have Required FDA Approval*. Available at: http://www.fda.gov/cder/drug/unapproved_drugs/default.htm

² FDA. Workshop transcript of *Marketed Unapproved Drugs Workshop*. January 9, 2007

As part of the application and renewal process, a plan must submit to CMS a list of covered drugs, known as a formulary. CMS reviews a plan's formulary to ensure that it includes a sufficient breadth of necessary drugs and that the formulary does not discriminate against certain types of beneficiaries. For calendar year (CY) 2006, the first year of the Part D benefit, CMS required plans to maintain and submit two separate formulary files. Plans submitted one formulary file through the Health Plan Management System for CMS review. Plans submitted a second file that would feed formulary information into the Medicare Prescription Drug Plan Finder, an online tool that allows beneficiaries to explore and select plans. The two formulary files differed considerably and maintaining two separate files created additional burden for plan organizations and for CMS.³

Early feedback from plan organizations prompted CMS to create a new process starting in CY 2007 involving the use of a Formulary Reference NDC File (referred to as Reference File). CMS creates and maintains the Reference File, which "contains a list of drugs that *may* be included on Part D formularies (emphasis added)." Specifically, the file includes a list of single drugs identified by a proxy National Drug Code (NDC), brand name, generic name, dosage form, and strength. The proxy NDC listed in the Reference File serves as a unique identifier for a drug entity—in effect representing *all* other products with the *same* drug, dosage form, and strength.

CMS does not intend for the proxy to endorse the use of a particular manufacturer or product. Rather, the intent of the Reference File is to allow plans to easily indicate which drugs they will cover by using the assigned proxy NDC, and also to allow CMS to easily assess whether a plan covers a sufficient breadth of drugs. CMS designed this process to obviate problems caused in the past when plans used obsolete NDCs as proxy codes in their submitted formularies. CMS releases a new Reference File each year and updates the file periodically by adding new proxy NDCs as new drugs, dosage forms, or strengths become available and by deleting NDCs as drugs become obsolete.

After CMS released individual 2008 Part D plans' formulary information in November 2007, Avalere research noted there were 1,600 *fewer* NDC codes in the Reference File for CY 2008 compared to CY 2007 (the first year of using the Reference File process). The change prompted our analysis of the CY 2007 and CY 2008 Formulary Reference NDC Files. The purpose of this paper is to share what we learned to assist others in understanding the nature of the changes. To further this understanding, the paper assesses the implications of these changes on beneficiaries, pharmacists, Part D plans, and other stakeholders in the Medicare marketplace. We also seek to bring to light possible opportunities for improvement through closer intra-agency collaboration, legislative and/or regulatory changes in health policy, and enhanced Medicare Part D stakeholder education.

³ CMS. *Formulary Reference NDC File Frequently Asked Questions*. Available at: http://www.cms.hhs.gov/PrescriptionDrugCovContra/downloads/FAQCY07FormRefNDCFile_03.01.06.pdf

Methodology

Analysis of Deleted NDCs

After determining that CMS issued a significantly smaller Reference File to plans for 2008 compared to 2007, we sought to compare the files used by plans for their initial formulary submissions for each plan year. CMS does not generally make Reference Files available to the general public, but Avalere obtained files from March 2006 and October 2007 for this comparison. These Reference Files likely reflect those used by plans when submitting bids for the 2007 and 2008 plan years.

We compared the two Reference Files to identify NDCs added to, or removed from, the list. We matched up these NDCs with Generic Product Identifier codes from MediSpan, a drug database, which allowed us to identify cases where CMS had replaced a proxy NDC with a different NDC for the same drug product. We dropped these products from our analysis because they did not reflect *net* changes to the overall number of products in the Reference File. This approach left us with a list of new additional codes identifying products that were *new* to market for 2008, and a significantly larger list of *deleted* codes—about 1,600—for products no longer included on the Reference File.

To better understand the nature of the drugs that were deleted from the Reference File, we assessed the list of dropped products from a clinical and practical perspective. Our initial review revealed common themes and broad categories within the deleted code universe (e.g., unapproved guaifenesin products, over-the-counter [OTC] drugs, cough and cold, pain products), prompting further investigation. We then analyzed the “like groups,” or affinities among these deleted codes, and investigated likely reasons for CMS’ removal by comparing these categories and individual products with: a) definitions of Part D-covered drugs; b) Part D exclusions; c) drugs typically covered under Medicare Part A or B instead of Part D; and d) known regulatory actions (e.g., drugs associated with FDA’s “Drug Efficacy Study Implementation” (DESI) initiative, FDA actions on specific unapproved drugs including carbinoxamine and long-acting guaifenesin). We also identified a number of potential duplicate proxy NDCs by searching the 2008 Reference File for like products.

Our research primarily relied on published literature and web-based resources available from CMS (e.g., Prescription Drug Plan Manual) and the FDA (e.g., the Electronic Orange Book, Drugs@FDA). We also conducted interviews with CMS and FDA staff members, though our views and findings are the sole responsibility of the authors.

Substantial Differences in the 2007 and 2008 Reference Files The Reference File released in March 2006 for plans participating in the 2007 plan year (referred to as the 2007 Reference File) included approximately 7,100 proxy NDCs. The 7,100 proxy NDCs represent roughly 2,200 unique drugs when grouped only by active ingredient(s) and dosage form, and without distinguishing between various indices such as brand/generic status or strength (Figure 1). When we account for brand/generic status as well as active ingredient(s) and dosage form, the 7,100 proxy NDCs represent about 3,000 unique drugs.

FIGURE 1: 2007 and 2008 Formulary Reference NDC Files

	Proxy NDCs in Formulary Reference NDC Files	Total Number of Drugs Represented in Formulary Reference NDC Files	
		Based on Active Ingredient(s), Dosage Form, and Brand/Generic Status*	Based on Active Ingredient(s) and Dosage Form**
2007 Plan Year	(est.) 7,100	2,980	2,238
2008 Plan Year	(est.) 5,500	2,489	1,917
Percentage Change, 2007-2008	(est.) -22.5%	-16.5%	-14.3%

Source: Avalere Health analysis of Formulary Reference NDC Files dated March 24, 2006, and October 5, 2007. We used the March 2006 release as a proxy for the reference file that plans used to develop formularies for the 2007 plan year. The October 2007 release was the first public release to reflect the smaller reference NDC list for 2008.

* Products grouped by active ingredient (or combination of active ingredients) and dosage form (e.g., tablet, injection) with brand name and generic versions counted as separate drug products. All drug products are counted once regardless of the number of strengths (e.g., 20mg, 40mg). For example, we would count all strengths of Zocor[®] tablets together as one drug and all strengths of simvastatin tablets (its generic counterpart) together as a second drug using this methodology.

** Products grouped by active ingredient (or combination of active ingredients) and dosage form, but not by brand/generic status. For example, we count all strengths of Zocor[®] tablets and simvastatin tablets (its generic counterpart) together as one drug using this methodology.

The 2008 Reference File listed approximately 5,500 proxy NDCs, some 1,600 fewer than the 2007 Reference File. The 5,500 proxy NDCs represent about 1,900 drugs when we group products together by active ingredient(s) and dosage form, but without distinction for brand/generic status or strength. When we group drugs by active ingredient(s), dosage form, and brand/generic status (still with no distinction for strength), the 5,500 proxy NDCs correspond to 2,500 unique drugs (Figure 1).

The difference of proxy NDCs in the 2007 and 2008 Reference Files is the net result of the *deletion* of more than 3,000 proxy NDCs and the *addition* of approximately 1,500 proxy NDCs. The next section will describe in greater detail those proxy NDCs deleted from the Reference File, and likely explanations as to why CMS made such changes.

CMS-Deleted Drugs from the Reference File Our analysis found that the drugs deleted from the 2008 Reference File fall into several categories: a) drugs that lack FDA approval; b) cough and cold products that either are over-the-counter and thus excluded by law from Part D, or are not generally recognized as safe and effective (“not GRAS/E”), or that lack FDA approval; c) drugs affected by FDA’s DESI initiative; d) duplicate or redundant codes; e) OTC products (other than cough and cold); and f) discontinued products or products withdrawn from the market. For a small number of drugs, we were unable to determine the basis of CMS’ decision to exclude them from the 2008 Reference File.

FIGURE 2: Most of the Proxy NDCs Removed from the Reference File for 2008 Were for Part D-Excluded Drugs or Duplicate Products

Categories of Deleted Proxy NDCs	Reason(s)	Examples
Unapproved Drugs	Part D pays for FDA-approved products only	Carbinoxamine, long-acting guaifenesin (e.g., Entex LA), salsalate, quinine
Drug Efficacy Study Implementation (DESI) drugs found to be less-than-effective (LTE)	Drugs determined through DESI proceedings to be LTE are not covered under Part D	Entex liquid (expectorant, decongestant for cough/colds), Analpram-HC (hemorrhoidal cream for pain, itching), Cortic otic solution (combination ear drops for pain, infection)
Redundant Proxy NDCs	To streamline the list, multiple generic and brand-name products were eliminated, although at least one proxy remains on the 2008 list	Note: Reference File does not promote specific manufacturers or brands
Nonprescription (OTC) Products	Products available over-the-counter are not covered; Part D=Rx only	Claritin-D 24-hour tablets, miconazole (e.g., Monistat-3) vaginal suppositories/cream, diphenhydramine (Dytuss) elixir
Discontinued/ Withdrawn Products	No longer marketed or available	Aldoril-15; propoxyphene compound; insulin regular (pork)

Source: Avalere Health analysis of Formulary Reference NDC Files dated March 24, 2006, and October 5, 2007.

Non-Part D Drugs Part D drugs are defined in Title XVIII of the Social Security Act and in federal regulation (42 CFR 423.100) (Figure 2). Part D drugs include prescription drug products, drugs that are indicated for the treatment of certain skin conditions but are not considered cosmetic, Vitamin D analogs when used for a medically accepted indication, prescription-only smoking cessation products, prescription Niacin products, and cough and cold medications that have clinical significance other than the symptomatic relief of cough and colds. Drugs excluded from Part D include OTC drugs; agents used for the treatment of anorexia, weight loss, weight gain, sexual/erectile dysfunction; and, agents used to promote fertility or for cosmetic purposes.

FIGURE 3: Part D-Covered Drugs

Part D Drugs	Non-Part D Drugs
<ul style="list-style-type: none"> ▪ Prescription drug products ▪ Part D drugs indicated for the treatment of psoriasis, acne, rosacea, or vitiligo are not considered cosmetic ▪ Vitamin D analogs when used for a medically accepted indication ▪ Prescription-only smoking cessation products ▪ Prescription Niacin products ▪ Cough and cold medications are eligible to meet the definition of a Part D drug in clinically relevant situations other than those of symptomatic relief of cough and colds 	<ul style="list-style-type: none"> ▪ Nonprescription drugs ▪ Agents when used: <ul style="list-style-type: none"> > for anorexia, weight loss, or weight gain > to promote fertility > for cosmetic purposes or hair growth > for the symptomatic relief of cough and colds > for the treatment of sexual or erectile dysfunction ▪ Prescription vitamins and mineral products, except prenatal vitamins and fluoride preparations ▪ Covered outpatient drugs which the manufacturer seeks to require as a condition of sale that associated tests or monitoring services be purchased exclusively from the manufacturer or its designee ▪ Barbiturates ▪ Benzodiazepines

Source: CMS Medicare Part D Manual, Chapter 6.

Accordingly, many cough and cold medications indicated for relief of symptoms and other OTC drugs were eliminated from the 2008 Reference File, and, arguably, should not have been included in prior years' Reference Files. While Part D excludes cough and cold products for symptomatic relief of cough and cold symptoms, there is no exclusion required for approved prescription products used in managing allergy symptoms or cough related to bronchospasm. Other OTC drugs deleted from the Reference File include benzoyl peroxide, typically used to treat acne, and hydrocortisone, typically used to temporarily relieve minor skin irritations or rashes. CMS also excluded cosmetic medications and vitamins from the 2008 Reference File; again, arguably, these should not have been included in prior years. Cosmetic products excluded from the 2008 Reference File include many urea products and products that are used to treat dandruff and to improve skin appearance.

In addition, CMS deleted hundreds of unapproved drugs from the 2008 Reference File. The Social Security Act requires that drugs covered under Part D must be approved as safe and effective by the FDA, unless otherwise specified in statute [Section 1927 (k) 2 (A) (ii) and (iii)]. "Unapproved drugs" are drugs that have not received FDA approval to be legally marketed, such as drugs that were approved prior to 1962 on safety grounds alone or prior to 1938 when FDA approval was first required. Many of the products that fall into this category are medications used for sedation, pain relief, or cough and cold symptoms. Some physicians and pharmacists are unaware that these products are marketed without FDA approval, so they continue to prescribe and dispense them to patients.

In 1962, Congress passed legislation requiring that drugs must be proven safe and effective to be granted approval by the FDA; this requirement was extended to those drugs marketed and approved as safe prior to 1962, requiring they be shown to be effective as well. At that time, the FDA initiated the DESI initiative to evaluate the effectiveness of drugs that had been previously approved based on safety alone between 1938 and 1962. FDA allows these drugs, as well as any drug identical, similar, or related to the drug under study, to be marketed until the administrative proceedings evaluating their effectiveness have been concluded, at which point continued marketing is only permitted if a drug is approved (through the subsequent submission of a NDA [new drug application] or ANDA [abbreviated new drug application]). The vast majority of the DESI proceedings have concluded, but a few are still pending.⁴

In late 2006, CMS issued a memorandum to Part D sponsors to announce that drugs that were found to be "less-than-effective" (LTE) under the DESI program do not qualify for coverage under Medicare Part D.⁵ This is consistent with CMS regulations for state Medicaid programs as well—federal funds will only be used to pay for products proven to be effective. This policy began on February 1, 2007, and an updated list of LTE DESI drugs was released on November 8, 2007. Some of the drugs included in the LTE DESI list were deleted from the 2007 Reference File, indicating that CMS deleted NDCs for LTE DESI drugs from the Reference File to be consistent with the CMS guidance. Agents that have not yet completed review under the DESI program may be included in the Part D benefit.

Discontinued and Duplicate Products CMS deleted drugs that have been discontinued and are no longer available. CMS also deleted repeat listings of NDCs for drugs from the 2008 Reference File in an effort to “clean-up” the file.

Part A or B Drugs Drugs typically covered under Part A or B, the hospital and medical insurance benefits of Medicare, were deleted from the 2008 Reference File, as Part D does not cover such drugs. Most of the deleted drugs are intravenous fluids or medications that are typically administered in inpatient settings or in the physician’s office. Part A or B parenteral products including hepatitis B immune globulin, tetanus immune globulin, and peritoneal dialysis solutions, were deleted from the 2008 Reference File.

Implications

In summary, much of the difference between the CY 2007 and CY 2008 Reference Files is attributable to cleaning up and refining the list—removal of drugs that, arguably, should not have ever been included in the Files—and streamlining the File by minimizing duplication of NDCs for the same product/dosage form/strength. On closer analysis, detailed below, the post-clean up responses by Part D stakeholders suggest potential misperceptions about the role of the Reference Files in Medicare

⁴ CMS. *Medicare Part D Manual Chapter 6*. Available at: http://www.cms.hhs.gov/PrescriptionDrugCovContra/Downloads/PDBMChap6FormularyReqmnts_03.09.07.pdf

⁵ CMS memo to Part D Sponsors. *Clarification of LTE DESI Drugs and Oral Anti-Cancer Agents*. Available at: http://www.cms.hhs.gov/PrescriptionDrugCovContra/downloads/QADESCancer_12.05.06.pdf

Part D formulary development, as well as gaps in the nation's medication information, approval, and marketing systems. Each of these represents an opportunity for enhanced collaboration and improved communication among government agencies and stakeholders.

Perceptions About the Reference File Our research revealed possible confusion about the intended and actual role of the CMS Formulary Reference File. The process and supporting tools for formulary approval may unintentionally propagate an erroneous perception that the CMS Reference File is intended to act as a formulary—a list of covered drugs. This confusion is understandable when considering the Reference File is made up of specific NDCs (albeit as proxy codes), because NDCs are by definition tied to a particular product and manufacturer. In addition, when submitting formularies to CMS for review, plans are required to use only the proxy NDC codes listed in the Reference File. This forces plans to crosswalk their actual proposed covered NDC to the CMS-designated proxy NDC; any other NDCs (even for an equivalent product by a different manufacturer) would be rejected during the CMS review of the plan's formulary due to use of an incorrect proxy code. This rejection would happen even though the underlying products are eligible for Part D, and would be paid during adjudication. Further, the significant reduction in the number of drugs included on the 2008 Reference File superficially appeared to mirror traditional, private-sector formulary reduction (i.e., utilization management) efforts. CMS clarified on inquiry that the Reference File contains only proxy codes and not specific recommended products. However, it is possible that plans, pharmacists, and/or others may have misinterpreted the CMS downsizing decision as conveying an unintended message that the Reference File should guide Part D plans' formulary product selection decisions.

Background materials available on the CMS website state that the listed NDCs are proxy NDCs and in no way endorse a particular manufacturer, although the language used to define the Reference File (i.e., "...Formulary Reference NDC File is a file created and maintained by CMS that *contains a list of drugs that may be included on Part D formularies.*") could be misinterpreted (emphasis added). In our discussions, CMS staff reaffirmed that the Reference File is not intended to serve as a formulary, and that CMS does not promote specific products or favor particular manufacturers. To minimize the use of subjective criteria in determining which code within a class will serve as the "proxy," CMS uses the NDC with the median average wholesale price (AWP) in a category as the "proxy" NDC. While alternative NDCs that do not conform to the proxy convention would be rejected during CMS formulary upload and review, the associated alternative products are fully reimbursable under Part D and would not be rejected during adjudication of a claim down the road. In other words, even if a particular NDC is not on the Reference File, it does not mean that it is not payable under Medicare Part D.

For CY 2009, CMS is again utilizing a Formulary Reference File process with proxy NDCs, but is also introducing a standardized nomenclature, RxNorm, produced by the National Library of Medicine. RxNorm is intended to explore whether this nomenclature system might more effectively identify drug products and possibly serve as an alternative method for formatting future Reference Files.

Implications for Patients For patients, the changes to the Reference File—and the associated deletion of hundreds of medications from Part D-approved plan formularies—have created the potential for direct financial and clinical implications. Specifically, patients using drugs that were excluded in 2008 must either: a) pay out-of-pocket for non-covered drugs; b) cease use of that product; or, c) transition to a comparable covered drug. In some cases, the CMS decision to revise its Reference File to exclude FDA non-approved drugs may have led to decisions by patients or their healthcare providers to discontinue use of these drugs. It is important to consider that some beneficiaries that have been receiving these non-covered drugs may continue to need these medications. CMS allows plans the option to cover drugs not listed on the Reference File through enhanced alternative plans that offer certain Part D-excluded drugs as part of a supplemental benefit or to pay through administrative fees (e.g., nonprescription medications).

Implications for Part D Plans Plans may choose to not cover the drugs that CMS deleted from the Reference File, or choose to offer those drugs allowed (e.g., nonprescription medications) through administrative fees or an enhanced benefit, as noted above. Examination of plans' decisions in this regard are beyond the scope of this paper. Continued clarity with respect to the design and use of the Reference File will be important as plans continue to adjust their clinical review and claim adjudication processes.

Implications for Health Professionals Physicians, pharmacists, and other health providers would benefit from greater awareness of CMS- or FDA-driven changes that might have clinical or financial implications, or that may interfere with patients' ability to access their medications. Better access to authoritative information about unapproved drugs and related issues would also improve clinicians' abilities to prescribe safe and effective medications to their patients. Notably, pharmacists often serve as patients' primary medication information resource, and are often the first points of contact for Medicare beneficiaries when they become aware of changes to their Part D plans. Understanding changes in the drug benefit are important to pharmacists who serve in this frontline patient-provider communications role.

FDA-CMS Collaboration Avalere's analysis brings to light various challenges—and opportunities for collaboration—facing the FDA and CMS. Our research revealed significant and structural limitations in the accessibility of complete information on the status of FDA approval for marketed prescription drugs. As discussed in this report, the FDA does not maintain a single-source list of all marketed products that have never been approved. An estimated 2 percent of all prescription drug products, equating to roughly several thousand individual products, have never been approved by the FDA and are illegally marketed in the United States.⁶

While it may initially seem implausible that the FDA does not maintain a list of unapproved drugs, the challenges to developing such a list are formidable and complex. Specifically, NDCs—the unique 10-digit codes assigned to all marketed drug products—contain only 4-5 digits assigned by the FDA (for labeler/manufacturer code); the product manufacturer assigns the remaining 5-6 digits reflecting the product and package codes (e.g., including active ingredient,

⁶ FDA. Workshop transcript of *Marketed Unapproved Drugs Workshop*. January 9, 2007

dosage form, strength, and package size). Although companies have been required since 1972 to register NDCs with the FDA, the market constantly changes with products coming on and off the market. In addition, FDA drug information resources (e.g., the Orange Book and Drugs@FDA) contain only approved drugs. Complicating the issue is that many of these products have been prescribed for decades and health professionals are often unaware of their unapproved status. For a small number of these medications, there are patients who are stabilized on them and whose well-being is dependent on the continued use and availability of the drugs (e.g., pancrelipase). Not all unapproved products can or should be abruptly withdrawn.

While FDA has significant initiatives under way through the DESI proceedings, Prescription Drug Wrap-Up, and OTC Drug Review activities, as well as its program for adverse event reporting, there still remain many unapproved yet marketed products to be identified. In addition, because action toward manufacturers of unapproved drugs is resource- and time-intensive, FDA appears to be using a prioritized approach—focusing first on those products that pose safety threats to public health, drugs that lack evidence of efficacy, and products that unfairly compete with approved products.

FDA has made significant headway in recent years, targeting products that pose safety concerns or lack efficacy sometimes prompted by major adverse events (including death, as in the case of carbinoxamine and an older high-dose injectable Vitamin E product). In many cases manufacturers have responded to FDA's initiatives with NDAs and ANDAs for long-standing marketed/unapproved products (e.g., levothyroxine, digoxin). The process has yielded helpful information about therapeutic equivalence and bioequivalence of these products. Other products have been withdrawn from the market.

The list of DESI LTE drugs is found on the CMS website, which represents another communication and information challenge. This list includes only the marketed name, not a listing of the active ingredients, significantly hampering efforts to identify all other identical, related, or similar drug products. A somewhat more comprehensive list of DESI LTEs is available through some state Medicaid programs; however, these are not easily found in general searches of the CMS or FDA websites.

FDA includes the issue of unapproved drugs as a priority in its strategic plan, and while the agency is making progress to remove products with demonstrated safety and efficacy concerns, *several thousand* unapproved drug products remain on the market—a daunting challenge for the FDA, a public health concern for beneficiaries, and a clinical and administrative complication for health professionals and Medicare Part D plans. Despite this lack of a complete and current list of unapproved drug products, CMS must continue to meet the statutory requirement not to cover unapproved drugs. This suggests the need for greater collaboration on the part of industry, CMS, FDA, policymakers, health professionals, and professional practice associations.

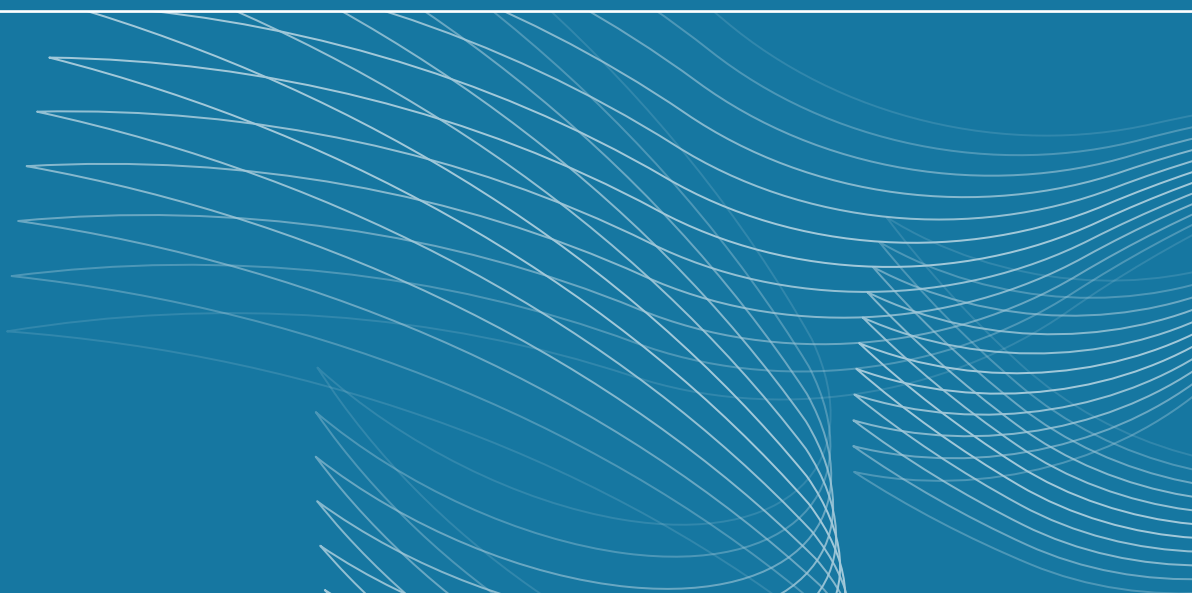
Conclusions

Our analysis of the changes in the Medicare Part D Reference Files reveals a number of gaps in communication and medication information processes within the U.S. healthcare system and among the federal agencies, healthcare providers, patients, and others who work on their behalf. While this inquiry focused on CY 2007 and CY 2008, these issues remain relevant going into CY 2009 and will likely persist until a concerted, collaborative effort is undertaken by those who can effect change in the ways in which unapproved drugs are tracked and addressed in our healthcare system. An Institute of Medicine report released in April 2008 estimates that the number of Americans over the age of 65 will nearly double in the first 30 years of this century.⁷ Addressing problems and issues proactively will prepare Medicare Part D plans, health providers, patients, and federal agencies for success during the rapid growth that will occur between now and 2030.

By statute, CMS cannot pay for unapproved drug products or those determined to be less-than-effective through the DESI proceedings. Nonetheless, several thousand unapproved products remain on the market and patients, plans, pharmacists, and physicians lack an authoritative list of these products. Because many of these products have been used for years, are included in drug information compendia, and patients rely on some of them, many health professionals are unaware of their unapproved status. Although FDA and pharmaceutical manufacturers are engaged in efforts to seek approval or removal of many products, this process will likely take years. It may be appropriate to undertake interim action to help the patients who rely on some of these medications and to protect patients from harm. Pooling efforts within the FDA, CMS, professional organizations, and the health policy community may be the most effective way to find both temporary and sustaining solutions for Medicare beneficiaries, payers, patients, and health professionals.

Finally, our research suggests a need to fill the existing informational gap, consistent with CMS' ongoing efforts to streamline management of the Medicare Part D Prescription Drug Benefit, and to address the issue of marketed unapproved drugs and related drug product information system challenges. Federal agencies and health professionals have expressed a desire and a need to access authoritative and product-specific information and resources to make safe and effective decisions on patients' treatment regimens. The health policy community and professional practice associations could help to address communication, education, and policy needs. A solution-oriented collaboration among FDA, CMS, and other stakeholders committed to improving health and advancing patient care would serve as a strong step toward closing this gap. Such a commitment could bring about positive, breakthrough change to improve medication use among patients who are Medicare beneficiaries and advance the quality of healthcare in our nation.

⁷ Institute of Medicine Committee on the Future Health Care Workforce for Older Americans. *Retooling for an Aging America: Building the Health Care Workforce*. Washington, DC: National Academies Press, April 14, 2008.



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