Breckenridge Pharmaceutical, Inc.

December 17, 2003

Docket Management Branch (HFA- 305)
Food And Drug Administration
5630 Fishers Lane Room 1061
Rockville, MD 20852

Dear Sir or Madam:

This letter is to provide Breckenridge Pharmaceutical's comments on the draft FDA Compliance Policy Guide on Unapproved Drug Products[1], published on October 17, 2003.

Breckenridge understands that the draft guidance has two goals:

"(1) Clarify for FDA personnel and the regulated industry how we intend to exercise our enforcement discretion regarding unapproved drugs and

(2) Emphasize that illegally marketed drugs must obtain FDA approval." [lines 50-52]

We will direct our comments to the following additional excerpts from the draft guidance, which we believe reflect FDA's enforcement rationale and the Agency's concept of providing "...an incentive to firms to be the first to obtain approval to market a previously unapproved drug":

(a) "In general, in recent years, FDA has employed a risk-based enforcement approach with respect to marketed unapproved drugs that includes efforts to identify illegally marketed drugs, prioritization of those drugs according to potential public health concerns or other impacts on the public health, and subsequent regulatory follow-up." [lines 70-73]

(b) "FDA intends to evaluate on a case-by-case basis whether justification exists to exercise enforcement discretion to allow continued marketing for some period of time after FDA determines that a product is being marketed illegally." [lines 142-144]

(c) "Sometimes, a company may obtain approval of an NDA for a product that other companies are marketing without approval.[2] We want to encourage this type of voluntary compliance with the new drug requirements because it benefits the public health by increasing the assurance that marketed drug products are safe and effective — it also reduces the resources FDA must expend on enforcement." [lines 157- 160]

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[1] FDA "Draft Guidance... distributed for comment purposes only"", titled "Guidance - Marketed Unapproved Drugs – Compliance Policy Guide", issued October 15, 2003; posted October 17, 2003; FDA Office of Training & Communications, Drug Information Branch HFD-210, CDER; available at the website http://www.fda.gov/cder/guidance/5704dft.pdf.

[2] FDA footnote in original: " [8] These may be products that are the same as the approved product or a somewhat different product such as a different strength."

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(d) "Thus, because they present a direct challenge to the drug approval system, FDA is more likely to take enforcement action against remaining unapproved drugs in this kind of situation. However, we will take into account the circumstances once the product is approved in determining how to exercise our enforcement discretion with regard to the unapproved products. In exercising enforcement discretion, we intend to balance the need to provide incentives for voluntary compliance against the implications of enforcement actions on the marketplace and on consumers who are accustomed to using the marketed products." [lines 160- 166]

(e) "When a company obtains approval to market a product that other companies are marketing without approval, FDA normally intends to allow a grace period of roughly 1 year from the date of approval of the product before it will initiate enforcement action (e.g., seizure or injunction) against marketed unapproved products of the same type. However, the grace period provided is expected to vary from this baseline based upon ...factors" [lines 168- 172]

(f) "The length of any grace period and the nature of any enforcement action taken by the FDA will be decided on a case-by-case basis." [lines 182- 183]

(g) "The shorter the grace period, the more likely it is that the first company to obtain an approval will have a period of de facto market exclusivity before other products obtain approval. [lines 192- 193]... If the FDA provides for a shorter grace period, the period of effective exclusivity could be longer. The FDA hopes that this period of market exclusivity will provide an incentive to firms to be the first to obtain approval to market a previously unapproved drug."[3] [lines 197- 199]

Significant Issues and Burdens in the Proposed Draft CPG

Our principal concern is that Breckenridge, as providers of quality Rx drug products to the American public, as well as our trade customers, the prescribers of our products and their patients, have an on-going interest in the market for both FDA-approved and unapproved products, which is entirely consistent with public health. We believe the availability of hundreds, if not thousands, of cost-effective, high quality Rx drugs would be unfairly and unnecessarily impacted to the detriment of public health under the policies of the draft CPG.

The draft CPG, as written, places arbitrary and unpredictable risks and burdens on suppliers, prescribers and consumers, which fail to be balanced with suitable incentives. By the FDA's own estimate "...in the United States today, perhaps as many as several thousand drug products are marketed illegally without required FDA approval.[4]"

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[3] FDA footnote in original: " [9] The agency understands that, under the Act, holders of NDAs must list patents claiming the approved drug product and that newly approved drug products may, in certain circumstances, be eligible for marketing exclusivity. Listed patents and marketing exclusivity may delay the approval of competitor products. If FDA believes that an NDA holder is manipulating these statutory protections to inappropriately delay competition, the agency will provide relevant information on the matter to the Federal Trade Commission. In the past, FDA has provided information to the FTC regarding patent infringement lawsuits related to pending abbreviated new drug applications, citizen petitions, and scientific challenges to the approval of competitor drug products."

[4] FDA footnote in original: " [2] This rough estimate is made up of several hundred drugs in various strengths, combinations, and dosage forms from multiple distributors and repackagers. For example, the FDA recently took action against single-ingredient, extended-release guaifenesin drug products. For this one drug, there were

Market sales from IMS Health shows the DESI-type product market has been growing at a rate of about 4% for the last two years. The total market for these products is in excess of $1 billion. This is a major market segment that cannot be replaced easily by a dramatically reduced number of suppliers, nor can a significant increase in product costs be borne by the public without economic hardship. Moreover, the increasing linkage of government prescription drug reimbursement programs to FDA approvals will have further negative impact on the ability of senior citizens and others with restricted means to afford vital prescription therapies. This also will affect the states negatively with the loss of HCFA / CMS Rebates paid on these products. Many states are not in a fiscal position to absorb these losses.

The inescapable reality of the American Rx drug marketplace is that the unapproved products exist because:

(i) They are well accepted by their prescribers and consumers as safe and effective drug therapies, and

(ii) They represent, in the great majority of cases, both high quality and significant cost savings relative to FDA-approved alternative therapies.

In short, the marketplace benefit/risk assessment appears to differ markedly from the FDA's traditional benefit/risk assessment on this issue. It is in everyone's best interest to substantially reduce this divergence in the perceptions of the regulators, the industry and the public.

Breckenridge understands and supports that there are compelling benefits to all Americans in having a healthy FDA drug approval process by which safe, clinically effective and cost-effective Rx drugs are regulated. For us, as for many other small to mid-sized health care firms, the main issue is not the federal approval process *per se* – it is the arbitrary and unpredictable risks posed by policies as are presented in the subject draft CPG.

Moreover, many unapproved products have no consensus standards either within FDA or in the marketplace as to what would be acceptable relative to bioavailability, bioequivalence, analytical chemistry or clinical efficacy, and therefore would not qualify for ANDA suitability. The added burden of sponsoring new scientific research or clinical studies to develop such standards, in accordance with an NDA submission under section 505(b) of the FD&C Act, is often beyond the capability of many small to mid-sized firms in the multi-source segment of the industry.

The arbitrary nature of this aspect of the draft CPG policy therefore discriminates strongly against suppliers of products that, in many cases, have been confidently prescribed and consumed for decades despite the lack of a "new drug" approval. Firms that operate on a reduced-cost basis, because they are not major international R&D entities, often have difficulty justifying "voluntary compliance" in the absence of a well-defined existing market opportunity. In contrast to original research firms, smaller entities are not in a financial

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approximately 20 manufacturers and approximately 50 repackagers and private label distributors, many of whom sold multiple single-ingredient, extended-release guaifenesin products."

position to literally create new therapies or markets. Therefore, where costs, risks and time frames for achieving approvals are almost impossible to predict, it should come as no surprise that such entities do not always equate "voluntary compliance" with business success.

Arbitrary, Unpredictable Timeframes for Approvability and FDA Enforcement Constitute a Disincentive to Industry

The Agency has proposed that any competitor to a product that achieves "first NDA approval" for a previously unapproved drug would generally be subject to a grace period of "roughly" one year. The "grace period" to follow each "first approval" of a product type, according to the draft CPG, therefore remains arbitrary and unpredictable, rendering the "compliance incentive" ineffective.

Sporadic, Unpredictable Marketplace Transition

First, the interests of public health would be best served if the FDA policy aimed at an orderly transition for the majority of existing suppliers to approved status. The proposed grace period of "roughly" one year - or, as FDA has also suggested, possibly an even shorter grace period, to be determined solely at the Agency's discretion - has the contrary effect of discouraging the great majority of suppliers from attempting to achieve approval. The CPG acknowledges that FDA approval is likely to approximate at least 2 years from the date of the "first approval" for a given product type. This is cited by the Agency as providing "a period of de facto market exclusivity before other products obtain approval". [CPG line 93]

This de facto exclusivity is likely to amount to 1 year or more, in inverse proportion to the length of the "grace period" laid down by FDA. This non-quantifiable, highly variable "incentive" is insufficient to motivate most suppliers of previously unapproved products to submit for approval. Therefore, the draft CPG does not support the objective of an orderly transition, but rather aims to substantially reduce competition to a small number of products in a sporadic, unpredictable manner.

Predictable, Undesirable Cost Impacts

Second, we believe the potentially high variability of the proposed 1-year grace period policy sets up several counter-productive market cost dynamics. FDA has acknowledged that many unapproved Rx products with significant national annual prescription volumes have multiple manufacturers, as well as many additional secondary distributors in the "repacker" category. The net impact of increased costs of compliance with FDA review and approval requirements for all these suppliers – or even a significant part of them – is potentially huge, and will inevitably be reflected in significantly higher drug prices.

A case in point which we believe to be very representative of the draft CPG's potential inflationary impact on costs to the consumer was seen with the Mucinex™ Tablets product, an NDA product manufactured and sold by Adams Laboratories. Mucinex is an extended-release guaifenesin expectorant formulation that was commonly dispensed as an unapproved multisource DESI-type product. Prior to receiving NDA approval of Mucinex, a similar tablet cost less than 12 cents/tablet. With the approval of Mucinex and FDA enforcement

action against competing products, the Mucinex price escalated dramatically to approximately 75 cents per tablet.

While the economic effect of the Mucinex approval is undoubtedly beneficial for its marketer, this is a product with an active ingredient long accepted in the OTC and Rx marketplace as safe and effective. In contrast, many of the remaining Rx products in the multisource marketplace will face more challenging technical and clinical hurdles to achieving approval. Accordingly, the increased cost impact on consumers for achieving FDA approval of the many remaining unapproved Rx products would be commensurate and undesirable.

Multiple Approvals Difficult for Small Market Products

Third, the Agency asserts, in its public press release "Questions and Answers on the Unapproved Drug Compliance Policy Guide" issued on October 17, 2003, that the historical case of Levothyroxine Tablets shows that multiple competing suppliers can successfully obtain approval of a previously unapproved drug. We submit that this "model" is not representative of the great majority of Rx products that would be subject to the draft CPG, were it to be implemented as written. As the Agency admits, the case of Levothyroxine was a "medical necessity" drug, with a very large established market (over 15 million patients annually). We believe that it was FDA's 4-year deferral of enforcement, affording a reasonable transition time, coupled with the unusually large "top 100" market opportunity, which enabled 8 different suppliers to achieve approval as competitors in the case of Levothyroxine, rather than the effectiveness of the approval system *per se*. These factors will not apply to the vast majority of unapproved drugs currently in the market and proposed to be subject to this CPG policy in the future.

The draft CPG, if enforced as written, would likely have the effect of vastly diminishing the number of quality suppliers, while substantially and unnecessarily increasing the operating costs for those few suppliers remaining – resulting in substantially higher costs for reimbursement programs and patients.

In effect, the Agency in this draft CPG proposes arrogating to itself the sole discretion to determine, case-by-case, what will be the approval procedure for each drug type, as well as whether the "grace period" allowed subsequent to each future "first approval drug" will be 6 months, 12 months, 48 months or any other period that it deems appropriate, based on at least six (6) different, highly variable "factors" listed in the CPG.

This scenario does not afford a rational basis for the multi-source segment of the Rx industry to make informed decisions as to which products are reasonable investments relative to the higher burdens, risks and costs of seeking FDA approvals. In summary, the potential burdens for suppliers and consumers will be predictably high, whereas the benefits cannot be quantified due to unpredictable approval requirements and time frames, further complicated by the arbitrary "grace period" mechanism contemplated by FDA.

Recommended Alternatives to the Unapproved Products Draft Compliance Policy Guide

As stated above, the interests of public health would be served if the FDA policy aimed at an orderly transition for the majority of the suppliers to approved status. This would best be achieved by the Agency setting forth, by a clear and unambiguous mechanism, the priorities for different categories of Rx drug products to come into compliance, on an industry-wide basis.

Fixed Categories, Fixed Enforcement Deadlines

FDA has asserted that it favors a risk based enforcement policy. As in the field of safety management, product types could be prioritized by high adverse event potential, together with market prevalence or exposure. Hundreds of Rx suppliers routinely purchase highly accurate market surveys of national Rx drug prescription rates and sales volumes, and these are readily available to FDA, together with the enormous database of drug safety reports submitted to FDA from the regulated industry and health care professionals.

In fact, any reasonable, rational system for establishing product type or therapeutic category definitions and enforcement priorities would be preferable to a labyrinthine set of variable factors defined and assessed only internally within CDER, as described in the draft Unapproved Products CPG. Equity requires that the criteria be clearly determined and open to public scrutiny and comment. This program could be done as part of a national monograph system for "provisional status Rx drugs", or could simply be implemented by Federal Register Notices, leaving each sponsor free to propose their own approval standards to FDA reviewers. In the areas of Cough/Cold and Vitamin/Mineral products, an Rx product monograph system would be particularly useful.

Improve and Utilize Existing FDA Reporting Systems and New Fees to Support Enforcement

Existing systems, such as the FDA Drug Registration and Listing System, could be improved, streamlined, and used as a basis of a mandatory submission program to identify all unapproved products, by product class or therapeutic category. Having defined enforcement priorities for each class or category in a reasonable, rational manner by established criteria, the Agency could establish a fixed compliance timeframe for each class/category.

In place of the approach taken with the first "DESI" program, which attempted to prospectively assess all known NDA drugs and IRS products, the logistical and financial burden of coming forward with an "approvable" data set meriting FDA approval could be left with each drug sponsor.

The FDA would need added resources to support pre-submission consultations and submission reviews for unapproved products in each class/category. These could be obtained by imposing an "unapproved / marketed product" drug listing fee within a relative short period after FDA public notice defining each product class or category. Given the large volume of unapproved/ marketed products, the fee structure could be moderate and yet generate significant resources supporting FDA review and enforcement activities.

Congressional support for an amendment to the PDUFA legislation, to support a more orderly system for transition of currently unapproved Rx drugs to approved status is entirely rational. It would likely be supported by the industry, health care professionals and the public, as superior to the current expectation for unmitigated instability in the unapproved product Rx marketplace.

The implementation of "unapproved /marketed product" listing fees and the fixing of an enforcement deadline by which each sponsor must achieve FDA approval in each product class or type, would vastly facilitate the orderly transition of the "unapproved /marketed" Rx drug marketplace.

Determine a Uniform, Reasonable Time Frame for Achieving Monograph, NDA or ANDA Approval

A reasonable time frame for initiating enforcement against unapproved products after the FDA publication date identifying each category or product type would be three (3) years. This would be adequate to enable firms with unapproved /marketed products to decide whether or not they wished to make the investments necessary to achieve approvals, and to implement the approval process. The 3-year period would be a minimum need to enable sponsors to deal with complex issues of establishing chemistry and clinical standards suitable for submission with many of these products, which, as mentioned earlier, lack the regulatory history to be suitable for ANDAs or a Monograph for a therapeutic class, and would be approvable only via a 505(b) NDA of some type.

Market-Based Compliance Incentives and Equitable Treatment

As to the matter of "voluntary compliance incentive", we believe there is ample financial incentive in the marketplace to become an approved supplier, if the alternative is unequivocal enforcement action. In such an unambiguous system, there is no need for FDA to control the timing of the enforcement program product by product. Case-by-case enforcement determinations for each of the hundreds or thousands of remaining unapproved products will force FDA to become embroiled in "de facto exclusivity" determinations with their inevitable inequities and legal challenges, inordinately consuming both time and FDA resources.

Summary

A variable set of approval time frames, enforcement priorities and "grace periods" for unapproved /marketed Rx products, described in the draft Unapproved Products CPG is an ineffective system. Some version of this FDA-discretionary system has already been in effect since the 1983 *Prescription Drug Wrap-Up* program, and it has left hundreds or thousands of unapproved products in a still-unresolved legal status after more than 20 years.

The burdens, costs and major uncertainties of the draft CPG system as proposed are evident, but there is insufficient incentive for the great majority of suppliers to attempt to achieve approval, since there are at least three major factors that each unapproved product marketer will not be in a position to prospectively determine:

1. How long a "de facto exclusivity" period would a "first approval" sponsor gain, over which we may recoup our substantially higher costs?

2. What will be the "grace period" allowed to achieve our product's approval subsequent to someone else achieving a "first approval" for the same product type? and
3. Will the FDA grant 3-year exclusivity to the "first approved" product, precluding our return to the market in a reasonable time frame, even if we do submit for approval?

Given these major uncertainties, we believe a large number of unapproved/ marketed product sponsors will opt to "take their chances", reasoning that they will earn more profits betting on FDA's shortage of resources to act against them, than they would by coming forward to initiate an FDA approval process. This is not conducive to meeting the Agency's mandate to protect public health and regulate the Rx marketplace, and is counter productive.

A positive alternative is to define clear product types or therapeutic categories, and to then establish across-the-board compliance deadlines for FDA approval in each category. The burden to come forward to achieve approval would be on the industry, rather than on the FDA, as it was in the first DESI program. This could be implemented through an Rx Monograph System, or by amending the current NDA/ANDA system, or both.

The time frame for achieving approval should be at least 3 years after FDA public notice for each product type/category. New user fees would be appropriate to support this new program, and would likely win industry and popular support, enabling an amendment of PDUFA rules. This would allow rational, well-reasoned drug quality, safety and efficacy standards to be proposed and accepted during the FDA approval process.

Such a positive approach, rather than challenging competing firms to risk winning or losing attempted "first approvals" in highly unpredictable circumstances, would result in an orderly transition of the American pharmaceutical marketplace to FDA approvals.

We respectfully request your attention and response.

Sincerely,

On behalf of
BRECKENRIDGE PHARMACEUTICAL INC.

Robert A. Falconer
Regulatory and Technical Consultant