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By Fax: 301-827-6870
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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Re: Docket No 2006N-0061
(Charging for investigational drugs)
RIN 0910-AF13

Dear Sir or Madam:

On behalf of Pfizer Inc., we submit the following comments on FDA's proposed rule to broaden the permissibility of charging for drugs used in clinical trials.

Pfizer is a leading pharmaceutical company with over 200 clinical trial programs underway. The Company's research enterprise involves over 13,000 employees, hundreds of academic and industry partners, and represents a commitment of over $7 billion a year. We routinely make our drugs for life-threatening and serious conditions available to qualified patients through compassionate use and expanded access programs (usually after phase II efficacy data is available). Among other programs, we currently have a $48 million, 6,000 patient, expanded access program under review at FDA.

Pfizer shares the Agency's commitment to facilitating access to potentially life saving drugs in development and FDA's efforts to update its now 20-year-old investigational new drug (IND) regulations. FDA's record of working with sponsors to make promising new drugs and investigational therapies available to patients through clinical trials and expanded access programs is strong. However, the rules regarding expanded access and

the circumstances in which patients may be charged for drugs used in clinical studies are complicated and not always well understood.[1]

Discussion

FDA's investigational new drug (IND) requirements should not prohibit investigators, sponsors, sponsor-investigators, or healthcare providers (or their institutions) from charging patients or payors for the cost of *approved* drugs that are purchased for use in an FDA approved clinical trial. Clarification of FDA's existing rules in this area is important and welcome.

The Agency's proposal to elaborate on the provisions of 21 CFR § 312.7 regarding charging patients for *unapproved* drugs has the potential of impeding access to clinical trials and is likely to have a number of adverse consequences. FDA should take into consideration the fact that the costs of experimental medicines are rarely eligible for coverage by insurers and that the proposed policy could have the effect of encouraging a shift of part of the costs of such trials to patients. Even for patients who can afford to pay, there are ethical considerations associated with charging for unproven medicines.[2] Sponsors who choose to charge patients for access to an unapproved drug are likely to increase the time needed to complete enrollment for the trial, which will result in a delay in getting the drug to market as well, thereby impacting the availability of the medicine that could help other patients.

Fundamentally, deciding what costs should be charged to patients to enroll in a clinical trial or an expanded access program is not a good use of FDA resources (and tax payor funds) and is outside the Agency's statutory mission of ensuring the safety and efficacy of drugs and clinical trials.

Charging For Approved Drugs Used In A Trial

Proposed 21 CFR § 312.8(b)(2)-(3) (71 Fed. Reg. 75180-81) describe the conditions under which sponsors may charge for an approved drug obtained from another entity that will be used in a clinical trial. Charging for such medicines clearly does not constitute the "*commercialization*" of an unapproved drug and is consistent with FDA's statutory authorities, as well as the public interest in furthering research about new medicines. The

[1] FDA advises that it receives about 22.6 requests per year to charge patients for investigational drugs. 71 Fed. Reg. 75175. FDA's notice does not specify whether most of these requests are for approved drugs being used in a post-marketing trial or for experimental drugs. The notice also does not indicate how many requests are denied and if denied, why they were denied. The Agency also claims that the cost of making an investigational drug available to a limited number of patients is "not usually extraordinarily expensive". *Id*. at 75177. We are unclear as to what FDA considers extraordinarily expensive and have some concern about FDA's role in making such decisions.

[2] See generally, J. Groupman, "The Right to a Trial: Should dying patients have access to experimental drugs?" The New Yorker (December 18, 2006), posted at http://www.newyorker.com/printables/fact/061218fa_fact. GAO "Report on New Drug Development" (November 2006) at p. 8, posted at http://www.gao.gov/new.items/d0749.pdf.

use of commercially available drug supplies is also consistent with the government's interest in improving access to clinical trials by providing reimbursement. *See* Presidential Memorandum of June 7, 2000 directing HCFA (now CMS) to "explicitly authorize payment for routine patient care costs...and costs due to medical complications associated with participation in clinical trials."[3]

Approved drugs are commonly used in clinical trials, as comparators and in combination therapy, as well as in investigations of new conditions of use for the drug -- particularly where the drug is already recognized as a standard of care treatment. Typically, Sponsors and Sponsor-Investigators have no choice but to use the approved drug to meet ethical and legal requirements relating to maximizing the benefit-risk ratio of the intervention. Pfizer supports clarifying FDA's rules, 21 CFR § 312.7, regarding charging the use of commercial supplies and specifically, the use by investigators of an *approved* drug, for which patients may be charged.

Ethically, the cost of such drugs can be passed on to subjects in a trial because they are likely to have received the identical, approved drug (and to have been charged for it), as part of their routine medical care. In addition, such costs are not a barrier to treatment since insurers (including Medicare Plans) generally pay the cost of standard of care therapies, especially in the case of a life-threatening or serious diseases and conditions.

A second reason that supports charging for approved drugs used in a clinical trial is the fact that the investigational new drug (IND) regulations are only intended to prohibit the commercialization of unapproved drugs. By definition, an approved drug can be introduced into commerce and used by physicians and physician-investigators in accordance with medical standards of care. Such an FDA-approved medicine that is used in a clinical trial as a positive control (*i.e.*, as a performance benchmark against which the investigational drug is compared) is not, itself, investigational. Similarly, an FDA-approved drug that is used concomitantly with an investigational drug is not itself an investigational drug and should not be treated as such. In that case, the unapproved drug is the investigational agent. A subject in such a study would not be charged for the unapproved drug, but only the cost of the background, comparator, or standard of care treatment (involving one or more FDA approved drugs).

Pharmaceutical companies seldom charge patients for the cost of an approved drug that may be used in a trial. Where such costs are charged, it is usually the investigator who purchase, administer, and charge for the drug, in accordance with the Study Protocol. We believe that FDA needs to clarify how its rules about charging apply to these other groups involved in clinical trials– investigators, hospitals, and other providers. FDA should clarify, in its proposed rule, that investigators are allowed to charge patients for the cost of an approved drug used in an FDA regulated trial (an approved drug purchased for use

[3] http://clinton4.nara.gov/WH/Work/060700.html; *see also* http://www.cancertrialshelp.org/patientAdvocates/policies/000607.jsp (statement of June 7, 2000 by the Cancer Leadership Council).

in a well-designed clinical trial, for which an investigational new drug application is required).[4]

The proposed rule, if finalized, should also recognize that the amount that may be charged for an approved drug used in a clinical trial may be different than the "direct costs" (that FDA defines for investigational drugs, Proposed Rule § 312.8(d)). That difference arises because the acquisition cost is often somewhat different than the amount approved by payors for reimbursement.[5]

For all of the reasons described above and because the approved drug has already met the threshold for an FDA approval, there is no reason for FDA to prohibit sponsors from including the use of commercially available drugs in protocols submitted to FDA or for the FDA to prohibit investigators from charging for standard of care drugs that they purchase and administer in a clinical trial.

Charging For Unapproved Drugs Used In A Trial

FDA's proposal to amend 21 C.F.R. § 312.7 (2006) and to promulgate a new § 312.8 to clarify and expand on the conditions for charging for unapproved drugs would reduce the ambiguity of the current regulations, but is unlikely to improve access to clinical trials. The proposed rule seems to have the potential to adversely impact drug development, access to clinical trials, and FDA resources. Pfizer does not believe, as a general matter, that patients would benefit from the proposed regulatory changes regarding charging for unapproved drugs. Charging for such unreimbursed, experimental medicines has the potential to discourage physicians from recommending appropriate trials to their patients, prolong clinical trial recruitment, and discourage enrollment by lower income patient groups.[6] Finally, FDA's authorities to regulate safety and efficacy of clinical trials does

[4] Proposed § 312.8(b)(4) indicates that the authorization to charge for an approved drug will usually last for the duration of the trial, unless FDA specifies a shorter period. Our interpretation of how that provision will work is that FDA's approval of the IND (after 30 days) will constitute authorization to charge for an approved drug, purchased for use in the trial -- so long as the protocol states that the sponsor or investigators may charge for use of the approved drug.

Again, FDA should understand that it is very rare for a sponsor to charge for the use of an active control or comparator. Rather, protocols sometimes allow investigators to administer commercially acquired active controls or comparators (where the drug is considered to be standard of care) and they or their institutions will charge for such drugs. Alternatively, to facilitate enrollment, sponsors may reimburse investigators for the out of pocket costs of acquiring an expensive comparator (i.e., an approved drug) that is not recognized as standard of care.

[5] See e.g. 2007 "Reimbursement Schedule for Medicare Part B Drugs," posted at http://www.cms.hhs.gov/McrPartBDrugAvgSalesPrice/01a_2007aspfiles.asp ("where applicable, the payment amounts are 106 percent of the Average Sales Price (ASP)").

[6] It is worth noting that Congress, NIH, and FDA have long been committed to expanding the diversity of clinical trial populations. *See* E. Toigo et al, "Participation of Racial/Ethnic Groups in Clinical Trials and Race-Related Labeling: A Review of New Molecular Entities Approved 1995-1999", Journal of the National Medicine Association (December 2001 Supplement) posted at http://www.fda.gov/cder/reports/race_ethnicity/race_ethnicity_report.htm Nonetheless, low income,

not authorize it to regulate what and how much can be charged for an experimental medicine.

Turning first to FDA authority, Congress has vested FDA with authority to regulate the introduction of drugs into commerce and to require that an approved application be in effect. 21 USC § 355. FDA has no authority to regulate the price for which a medicine, approved or unapproved, is sold. Simply put, the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 301 et seq., ("FDCA") does not authorize government regulation of pricing or cost-recovery pricing. In the inspections context, the statute even affirmatively precludes FDA from reviewing data on costs and prices in its inspections. FDCA § 704(a), 21 U.S.C. § 374(a) ("No inspection ... shall extend to financial data, sales data . . . [or] pricing data . . . ."). Therefore, it is difficult to extrapolate any authority for FDA to regulate cost-recovery pricing for experimental drugs. The relevant provisions, 21 USC 371 and 355(I), authorize rules that allow for the efficient enforcement of the Act (regarding approval, adulteration, misbranding and so on) and for exempting investigational drugs from the requirements relating to approved drugs. Price regulation is not part of the Federal Food, Drug, and Cosmetic Act.

FDA should amend its proposed rule for practical reasons as well. The proposed rule would require numerous determinations that are well outside of FDA's expertise and would require economic and accounting resources. The proposed administrative determinations would include deciding: (i) whether the cost of an investigational drug is "extraordinary," proposed § 312.8(b)(1)(iii); (ii) whether, in addition, "the clinical trial could not be conducted without charging," *id.*; and (iii) whether the price proposed by the Sponsor would "recover only the direct costs of making the investigational drug available," proposed § 312.8(d)(1). To support its determinations regarding such charges, FDA would need to require and review factual analyses about the Sponsor's costs, comparative costs of other treatments, and arguments about what costs are "ordinary" versus those that might be "extraordinary".

With respect to the required determinations, FDA would have to decide whether the cost of an investigational drug is "extraordinary" would necessitate the development of an understanding of what costs at different points in development are "ordinary." This would require that FDA collect data about manufacturing and supply costs for different types of molecules and then make comparisons to determine what "ordinary" costs are. FDA would then need to make accounting and economic assessments about the range of "ordinary" costs for different molecules and different therapies. For example, companies are developing vaccines for preventing diseases such as cancer and AIDs, and for treating diseases for which there is no effective treatment. Deciding what the "ordinary" cost would be and whether a different cost for an experimental drug would be "extraordinary" would be complicated, to say the least.

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elderly, racial/ethnic minorities, and those who live in rural areas are often under-represented in clinical trials. *See e.g.* "Report of the Intercultural Cancer Council" (April 2006) posted at http://iccnetwork.org/cancerfacts/cfs11.htm.

Second, deciding whether a clinical study "could not be conducted without charging" necessitates a determination of a Sponsor's finances and intentions. FDA would need a way to assess the financing of the trial, the potential return on investment of any intellectual property at stake, the Sponsor's cash flow and its access to capital markets. FDA would need to determine the Sponsor's willingness to conduct the trial without charging and if not, whether others might sponsor the trial. The agency would need accounting personnel and economists to develop methodologies for making defendable assessments and for applying those methodologies to IND filings.

Third, FDA's accountants would have to scrutinize each Sponsor's asserted "direct costs" to ensure fairness and consistency in its handling of the policy. While the rule has a basic definition of "direct" and "indirect" costs, in application, identifying direct costs is likely to be complicated. One need only look at the federal income tax apparatus and how the definitions of income, expenses, amortization, and transfer pricing work, to gain an appreciation for some of the difficulties that are likely to arise in trying to distinguish between so-called direct and indirect costs.

Fourth, determining whether "charging is interfering with the development of a drug for marketing approval," as proposed for § 312.8(a) (4), would necessitate analyses by FDA of patterns of enrollment in clinical trials, the causes of insufficiencies in enrollment, and what amounts of delay are unacceptable. Put simply, charging for an expensive drug will delay enrollment in most cases. The amount of delay that FDA would consider to be "interference" is unknown and will be difficult to define.

The findings and assessments that would be required under proposed 21 CFR §§ 312.8(a)(4), 312.8(b)(1) and (d)(1) are not within FDA's mission, authority, or expertise. The resources needed to implement a price control scheme in a fair, non-capricious, and non-arbitrary manner would be significant and may not serve the public interest. Given these considerations, FDA should address the existing authorization in 21 C.F.R. § 312.7 and whether to prohibit charging for unapproved drugs used in clinical trials. At a minimum, FDA should not take responsibility for reviewing and approving the amount to be charged for investigational drugs.

Charging For Unapproved Drugs Made
Available Through Expanded Access Programs

In the proposed rule, FDA also proposes to allow Sponsors to charge for investigational drugs made available to certain patients with life-threatening or otherwise serious conditions. FDA proposes that such charges be predicated on sufficient enrollment and progress in clinical trials, and be restricted to certain "direct costs" and "the costs of monitoring the expanded access IND or protocol, complying with IND reporting requirements, and other administrative costs directly associated with the expanded access." Proposed § 312.8(d)(2). The Agency states that such charges would not be excessive and would be justified by an increase in the availability of investigational drugs, 71 Fed. Reg. 75175; however, there is little evidence for these claims. The costs are likely to be very high in some cases and relatively low in other cases.

We expect that sponsors will continue to be reluctant to charge for a product for which the safety and efficacy is unproven, for which there is no reimbursement to help patients pay such costs, and where the allowable charges are limited to the "direct costs" of manufacturing and distributing the product. As described in the preceding section, FDA's proposal would divert Agency resources and improperly vest responsibility with the FDA for reviewing and approving the calculation of manufacturing and administrative costs. It also may impact the public interest if it results in the exclusion of qualified individuals who are unable to afford the cost of the program (especially given that insurance programs may not cover the cost of early stage, unapproved medicines).

If FDA concludes that its rules must allow companies to charge for unapproved drugs made available through expanded access programs, we recommend that FDA allow sponsors to charge a reasonable administrative fee rather than basing such charges on a FDA reviewed calculation of "direct costs". This could be based on the cost of other drugs in the class or based on the cost of treating the condition with other therapies, for example. This would have the benefit of simplifying the administrative process and would better encourage sponsorship of expanded access programs. One approach that we believe should be considered is that FDA allow sponsors to charge an administrative fee, set by the Sponsor after consultation with relevant patient groups. FDA might set a ceiling for these administrative fees on an annual basis.

Conclusion

For the foregoing reasons, FDA should amend current § 312.7(d) and revise proposed § 312.8 to clarify that sponsors, investigators, and providers may charge for approved drugs administered to patients in clinical trials. The Agency should also address the existing authorization in 21 C.F.R. § 312.7 and whether the public interest supports allowing "cost-recovery" for various costs associated with the use of unapproved drugs being tested in clinical trials. Finally, FDA should also amend its rules for expanded access programs to provide that any drug charge should not exceed a modest administrative fee, set by the Sponsor in consultation with patient groups, rather than by the FDA.

We appreciate the opportunity to comment on FDA's proposed rule and hope that you will contact us if you have any questions or wish to discuss our experience as a sponsor of hundreds of clinical trials and expanded access programs.

Sincerely,

Marc Wilenzick