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BY E-FILING ON REGULATIONS.GOV

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2013-D-0575
Comment on Section VII. C.: "Evidentiary Criteria for Accelerated Approval" of the FDA "Draft Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics" (hereinafter, "Draft Guidance")

Dear Sir/Madam:

These comments are based on an analysis of FDA's Subpart H approvals from the 1992 promulgation of the Subpart H regulations to the present.

In Section VII. C. of FDA's June 2013 Draft Guidance, the Agency describes several factors that FDA weighs in assessing whether the available evidence is sufficient to allow FDA to conclude that the proposed surrogate is "reasonably likely to predict clinical benefit"[1] and thereby constitute the basis for a Subpart H[2] marketing approval.

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[1] In these comments, when the term "surrogate" is used, it is meant also to encompass what FDA in its Draft Guidance refers to as "a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit." Draft Guidance at p.16, lines 511-513.

[2] In these comments, Subpart H will be the short-hand term used interchangeably with 21 C.F.R. Part 314, Subpart H; 21 C.F.R. Part 601, Subpart E; "Accelerated Approval" and "Fast Track."

Subpart H authority has existed for well over 20 years. FDA created it on its own regulatory ingenuity to address the AIDS epidemic. However, the importance of Subpart H as a regulatory innovation and vehicle for providing patients suffering with serious and often rare diseases where there is inadequate available therapy has recently taken on significant added importance. Two milestone events within approximately the past year illustrate this.

1. In the FDA Safety and Innovation Act (FDASIA) of July 2012, Congress and President Obama revised the statutory provisions of Subpart H[3] to, as FDA in its Draft Guidance states, "facilitate somewhat broader use of accelerated approval to expedite patient access to important treatments for serious conditions[,] . . . provide additional flexibility[,] . . . provide clarification concerning the use of clinical endpoints[,] . . . [and] make clear that FDA has the authority to consider pharmacologic or other evidence . . . in determining whether an endpoint is reasonably likely to predict clinical benefit." Draft Guidance at p. 14, lines 445-453. While these were added in July 2012 by statute, this analysis establishes that here, as is often the case, Congress is merely codifying in statute the practices and policies that FDA had already put into place and acted upon previously. In the text of FDASIA, Congress however directed that FDA expand its use of this authority.

> "FDA should be encouraged to implement more broadly effective processes for the expedited development and review of innovative new medicines intended to address unmet medical needs for serious or life-threatening diseases or conditions, including those for rare diseases or conditions, using a broad range of surrogate or clinical endpoints . . . This may result in fewer, smaller, or shorter clinical trials for the intended patient population or targeted subpopulation without compromising or altering the high standards of the FDA for the approval of drugs. Patients benefit from expedited access to safe and effective innovative therapies to treat unmet medical needs for serious or life-threatening diseases or conditions. For these reasons, the statutory authority in effect on the day before the date of enactment of this Act governing expedited approval of drugs for serious or life-threatening diseases or conditions should be amended in order to enhance the authority of the FDA to consider appropriate scientific data, methods, and tools, and to expedite development and access to novel treatments for patients with a broad range of serious or life-threatening diseases or conditions.

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[3] See Footnote #2.

SENSE OF CONGRESS.—It is the sense of Congress that the Food and Drug Administration should apply the accelerated approval and fast track provisions set forth in section 506 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356), as amended by this section, to help expedite the development and availability to patients of treatments for serious or life-threatening diseases or conditions while maintaining safety and effectiveness standards for such treatments."

2. In September 2012, President Obama became the first President to comprehensively address the complexities of developing new medicines for Americans when he released his report, "Propelling Innovation in Drug Discovery, Development, and Evaluation." In that report, FDA is instructed to expand the use of its Subpart H authority. See President's Council of Advisors on Science and Technology Report to the President on Propelling Innovation in Drug Discovery, Development, and Evaluation. ("Presidential Report") at pp. 59-68. Specifically, this Report recommended that:

- "The FDA should expand the scope of acceptable endpoints used to approve drugs for serious or life-threatening diseases with unmet needs. Under current law, the FDA has considerable discretion in deciding whether a surrogate or intermediate clinical endpoint is 'reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict' clinical benefit. At one extreme, the FDA might be highly risk-averse, requiring near-certainty that the surrogate or intermediate endpoint will translate to clinical benefit. At the other extreme, the Agency might accept endpoints that are simply correlated with disease outcome or plausibly related to disease outcome based on current scientific understanding. Neither extreme would serve the public well. The FDA's interpretation of 'reasonably likely . . . to predict' can have a major impact on the pace of medical innovation and on patient safety . . . Historically, the use of [Subpart H] has been primarily used in a limited number of therapeutic areas—principally, HIV/AIDS, cancer, and inhalation anthrax (87 percent of cases) . . . We believe that the Nation would benefit if the FDA were to expand the use in practice of acceptable indicators to other serious or life-threatening diseases." (Presidential Report at p. 59).

- "Recommendation 3: Expand the Use in Practice of FDA's Existing Authorities for Accelerated Approval and Confirmatory Evidence. The FDA should make fuller use of authorities previously granted by legislation and not yet fully utilized. The FDA should expand the use in practice of its existing authority for Accelerated Approval. FDA should direct its staff, across all divisions, to make full use of the Accelerated Approval track for all drugs meeting the statutory standard of addressing an unmet medical need for a serious or life threatening

illness and demonstrating an effect on a clinical endpoint (other than survival or irreversible morbidity) or on a surrogate endpoint that is reasonably likely to predict clinical benefit." (Presidential Report at p. 61).

Given this renewed recognition of the promise of FDA's Subpart H authority to address those suffering from serious diseases without adequate available therapy, and given FDA's issuance of this Draft Guidance addressing the Agency's Subpart H authority, an analysis of FDA precedents in order to promote a better understanding of the circumstances under which Subpart H may be employed may be both timely and productive. In this way, it is hoped that the regulatory ingenuity of FDA in creating Subpart H and the recent Congressional and Executive exhortation to more fully mobilize this Subpart H power may find expression.[4]

METHODS

First, the FDA Draft Guidance in several places cites to the Subpart H precedents in AIDS and cancer, and there is little regulatory uncertainty as to the evidentiary criteria for a surrogate to be the basis for marketing approval in either of these two therapeutic areas. Therefore, this analysis is of the 19 Subpart H approvals identified by FDA on its website[5] that are for conditions other than AIDS or cancer.

Second, to maximize the usefulness of this analysis as a comment on the Draft Guidance, this analysis of each of these 19 precedents is organized according to the order of factors cited by FDA in Section VII. C., "Evidentiary Criteria for Accelerated Approval" of the Draft Guidance. Organizing this analysis according to the order of the

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[4] One of the two commentators here conducted an analysis of FDA orphan drug precedents that has, to some, proved of some utility (Frank Sasinowski, Quantum of Effectiveness Evidence in FDA's Approval of Orphan Drugs, 46(2) Drug Inf. J. 238-263 (Mar. 2012)); this analysis of Subpart H precedents, it is hoped, may prove to be of like usefulness.

[5] This website is current up to September 2011 and the two commentators have supplemented it to include Subpart H approvals since September 2011. See "CDER Drug and Biologic Accelerated Approvals," available at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevclopedandApproved/DrugandBiologicApprovalReports/UCM278506.pdf.

factors listed in the Draft Guidance has the added benefit of providing a logical structure for this analysis.

- Part 1 of Each Analysis: Regulatory Factors Weighing into FDA Determination - Severity and Rarity of the Condition, Availability of Alternative Treatments, and External Expertise.

Under Section VII. C. 1., "Whether an Endpoint Is 'Reasonably Likely to Predict' Clinical Benefit," FDA acknowledges that "[w]hether a drug effect on a given endpoint is reasonably likely to predict clinical benefit is a matter of judgment" and then, FDA explains that the Agency "considers all relevant evidence and weighs the uncertainty [of the evidence, presumably] against the severity of the disease to be treated and the lack of available therapy. On a case-by-case basis, FDA will make informed judgments using both internal and external expertise." Draft Guidance at p. 18, lines 609-612.

This FDA statement in its Draft Guidance generally tracks what was inserted by FDASIA into the statutory authority for Subpart H. Specifically, FDASIA amended the Federal Food, Drug, and Cosmetic (FDC) Act to provide FDA with the authority to approve a therapy under accelerated approval when FDA determines "that the product has an effect on a surrogate . . . that is reasonably likely to predict clinical benefit . . . taking into account the severity, rarity, or prevalence of the condition and the availability . . . of alternative treatments." FDC Act §506(c)(1)(A) as amended by FDASIA §901 (emphasis added). Comparing the FDASIA text of July 2012 with the Draft Guidance statement from June 2013, there is one conspicuous incongruity, and it has huge implications for the 30 million Americans with rare disorders and their families and friends. Noticeably absent from the Draft Guidance statement is the over year-old statutory requirement that FDA must take into account, in addition to severity of the disease and availability of alternative treatments, whether a condition is rare.[6] Therefore, in the first part of the analysis of each of these 19 Subpart H approvals, consideration is given to each of these factors: the severity of the disease, its rarity, and whether alternative treatments exist. These three factors are, by statute, required to be taken into account by FDA in determining whether to grant Subpart H approval.

[6] To one of the commentators, who has devoted a career, both at FDA and since FDA, to aiding in the development of therapies for our brothers and sisters with rare conditions, it is impossible to overstate the degree of his apoplexy over this oversight in the Draft Guidance.

The first part of each analysis, again tracking the FDA Draft Guidance, also accounts for whether there is any evidence that FDA considered "external expertise" (which most often would have been by seeking the expert input of an FDA Advisory Committee on that therapy). Draft Guidance at p. 18, lines 611-612.

In the aggregate, we refer to this first set of factors in FDA's Draft Guidance as "Regulatory Factors Weighing into the FDA Determination" because each of these four factors is a regulatory decision by FDA: that is, whether the condition is serious, whether it is rare or an "orphan," whether "available therapy" exists, and whether to seek the input of an advisory committee.

- Part 2 of Each Analysis: Understanding of the Disease[7]

In Section VII. C. 1. a., of the Draft Guidance, "Understanding of the disease process," FDA explains the criticality of understanding the disease process as fundamental to achieving the "biological plausibility"[8] of the surrogate. Draft Guidance at pp. 18-19, lines 617-648. Therefore, the second part of the analysis of each precedent is the degree to which the underlying disease is understood.

- Part 3 of Each Analysis: Understanding of the Relationship between Drug Effect and Disease Process

Under Section VII. C. 1. b., "Understanding of the relationship between the drug's effect and the disease process," the Agency notes that "[t]he extent to which a drug's effect on the surrogate endpoint is known to predict an effect on the disease is critical."

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[7] Parts 2-4 not only track the order in the Draft Guidance, but also are tied to the language quoted in FDASIA: "[t]he evidence to support that an endpoint is reasonably likely to predict clinical benefit . . . may include epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence . . . ." FDASIA § 901(a). Specifically, Part 2 relates to "pathophysiological" evidence; Part 3 relates to "epidemiological, . . . pharmacologic, or other evidence;" and Part 4 relates to "therapeutic evidence."

[8] This term is taken from a paper by FDA officials, Drs. Desai, Stockbridge and Temple, Blood Pressure as an Example of a Biomaker that Functions as a Surrogate, 8(1) AAPS J. E146-E152 (2006) ("[B]iological plausibility [is] sometimes intuitive, sometimes supported by animal data or by favorable response in extreme cases (e.g., malignant hypertension).").

Draft Guidance at p. 19, lines 653-654.[9] FDA, in its Draft Guidance, then lists several factors to consider in identifying and assessing a surrogate endpoint, including, "[w]hether there is reliable and consistent epidemiologic evidence supporting the relationship between the endpoint and the intended clinical benefit" and "[w]hether the effect on the [surrogate] endpoint has been shown to predict a clinical benefit with drugs in the same or closely related pharmacological class." Draft Guidance at pp. 19-20, lines 662-675. Therefore, the third part of the analysis of each precedent assesses the evidence for these factors, noting that, for the purposes of this analysis, epidemiological evidence is interpreted more broadly to include all observational studies, including long-term longitudinal studies and "natural history" studies. This part of each analysis essentially assesses the predictive potential of the surrogate.

- Part 4 of Each Analysis: Clinical Evidence for the Surrogate and for the Clinical Benefit

In the Draft Guidance, FDA acknowledges, as noted earlier in this comment, the primacy of clinical evidence of the drug itself, both on the surrogate and on the clinical benefit, but explains, "[h]owever, this guidance does not address clinical evidence requirements because they are not readily generalizable." Draft Guidance at p. 18, lines 614-615. Our analysis has the luxury of not needing to distill general requirements from the many precedents, but can assess the strength of the clinical evidence in each case for each drug's effect, both on that specific surrogate and on that particular clinical benefit. Accordingly, the fourth and final part of the analysis of each precedent is the strength of clinical evidence on the surrogate itself, as well as on the clinical benefit.

Lastly, with respect to the methods employed for these analyses, a word on the weights given to each of the factors in these four parts of each analysis: these weights themselves are a matter of judgment, as are each of the assessments or "scores." Other individuals may prefer either greater or lesser weights for any of these factors, and may even decide that some of these factors should not be included at all or still others be added. Similarly, others – especially the experts in the medical community, Sponsors

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[9] FDA in its Draft Guidance continues (and in so doing helps to explain the relative value of what in this analysis we have divided into Parts 3 and 4): "Sometimes this relationship can be assessed epidemiologically but it is most persuasively established by knowing that a drug that affects the surrogate also affects a clinical outcome." Draft Guidance at p. 19, lines 653-656. In this analysis, we, accordingly, weight more heavily Part 4 (Clinical Evidence) as compared to Part 3 (which is, in part, epidemiology).

and, especially the FDA reviewers and supervisory officials – may disagree with the scores given to any factor or factors for any of these 19 Subpart H precedent approvals. All of these views would be fair, especially when based on a more thorough understanding of the science or evidence, and are understandable.

RESULTS

All available FDA source documents were gathered and analyzed for each of these 19 Subpart H approval precedents in order to "score" each according to the factors laid out in the FDA Draft Guidance according to the weights and scoring of the commentators. Figure 1[10] is a chart summarizing these, and in Appendix 1 there is a narrative text that describes some of the most relevant information pertinent to each of the FDA Draft Guidance factors for each of these Subpart H approvals.

DISCUSSION

Regulatory ingenuity, if not outright genius, led FDA on its own to create the concept of the Subpart H approval in order to address at first, the emerging AIDS epidemic in the 1980s and since then, all other serious conditions for which there is an unmet medical need. The linchpin of the FDA Subpart H system was, and is, the surrogate endpoint that is "reasonably likely to predict clinical benefit" (or intermediate clinical endpoint that is "reasonably likely to predict ultimate clinical benefit.")

There have been many misunderstandings of this Subpart H system. Some have thought that it meant that the quantum or quality of evidence was somehow reduced, and the statutory requirement of "standard evidence of effectiveness" was in some way, in whole or in part, skirted or deferred. While this seems not to be the case in statute, regulation or policy, the other extreme is just as likely not to "serve the public well" (quoting the Presidential Report at p. 59). The other extreme is the view that unless the surrogate is validated, it cannot be relied upon in a Subpart H approval decision. This is sometimes found in reviews that conclude that the Sponsor's evidence failed to satisfy the standard of approval because the trial(s) attempted to prove both the drug's effect on the surrogate as well as on the clinical benefit and the clinical benefit showing was not robust enough to validate the drug's effect on the surrogate.

[10] The drugs in Figure 1 are listed chronologically, from the most recent Subpart H approval, Sirturo, to the earliest, Betaseron.

Between these two extremes, there has existed a gaping hole that has begged to be addressed for nearly three decades and that is – what is the regulatory and evidentiary foundation for FDA's determination that an unvalidated surrogate is capable of supporting a Subpart H approval? Now FDA in its June 2013 Draft Guidance has tackled this and laid out clearly discreet principles and factors.

This analysis (that is, this comment on the Draft Guidance) attempts to apply those principles and factors to the 19 Subpart H approvals (that are not for AIDS or cancer) in order to discern, in that analytical process, the types and patterns of the evidence that FDA has found adequate to be the foundation for these Subpart H precedents.

Let's see what this analysis can tell us, and then, see if those findings can further our understanding, both of Subpart H in general and of when it may be applicable going forward.

- Part 1

Part 1 of the analysis of each precedent assesses the first set of factors that FDA describes on lines 609-612 of the Draft Guidance: severity of disease, lack of available therapy and external expertise (as well as, yes, rarity too). For each precedent, we present the assessment of these factors under the heading of "Part 1" in Figure 1 and in the narratives for each precedent in the Appendix. The consistency of findings across the 19 precedents with respect to these Part 1 factors is highly robust. In its Draft Guidance, FDA explains that it "weighs the uncertainty" of "all relevant evidence" against these Part 1 factors. Trying to predict whether any surrogate will indeed "reasonably predict" clinical benefit will never be an absolute certainty, and so there will likely be at least some residue of uncertainty in each case. This analysis confirms what some may have forecasted, which is that a strong showing in these regulatory Part 1 factors is nearly a prerequisite for qualifying for Subpart H consideration.

- Part 2

Understanding of the disease process is the next key factor listed by FDA in the Draft Guidance (lines 617-648). Part 2 of the analysis of each precedent describes our assessment of this factor for that therapy. For 12 of the 19 precedents, a maximum score of 3 was achieved. This is consistent with FDA's view stated in the Draft Guidance that this can be "an important factor in determining whether an endpoint is reasonably likely to predict clinical benefit." Draft Guidance at lines 631-632.

However, three precedents (Makena for pre-term birth, Luveris for pregnancy, and Remicade for Crohn's Disease) received scores of "1" on a scale of 0 to 3 because in each case the pathophysiology of the underlying disease is complex and not so clearly understood from lesion/dysfunction initiation through causal pathways and factors promoting deterioration in that condition. Nevertheless, a key take-away from this observation is that, although most of the time a clear understanding of the pathophysiology of the disease process will facilitate access to reliance upon a surrogate, the absence of a complete understanding of the disease process or even the existence of a relatively weak understanding of the disease process is not, in and of itself, incompatible with Subpart H.

- Part 3

With respect to the next key factor listed by FDA in its Draft Guidance, Part 3 of the analysis of each precedent reviews how well-understood the relationship is between the drug's effect on the surrogate and on the disease process. For this part of the analysis we searched the FDA reviews for evidence of reliance upon epidemiological associations (see, e.g., Sirturo and Makena), as well as the effect of another drug in the same or pharmacologically similar class of therapy to affect both the surrogate and the disease (see, e.g., Tysabri and Celebrex). Note that in several cases there was only relatively weak support for this relationship between the surrogate and the disease process, such as in the cases of Fabrazyme (in which little had ever been shown between clearance of substrate in particular cell types and renal function), Promacta, Remodulin, Synercid and Biaxin. Again, as in the case of Part 2, a weaker showing in this particular factor was not a bar to Subpart H qualification.

- Part 4

Finally, in its Draft Guidance, FDA noted the critical role of the clinical strength of evidence of the drug both on the surrogate and on benefit as well. While FDA was not able to articulate generalizable principles with respect to the strength of clinical evidence (Draft Guidance at lines 614-615), the power of this analysis is that by looking at the specifics of each of the 19 precedents, we may be able to ascertain that which may otherwise not be discernible. We divided the analysis of clinical evidence into two components: the clinical evidence of the drug on the surrogate and the clinical evidence of the drug on the clinical benefit.

With respect to the clinical evidence of each drug's effect on its surrogate, it is not surprising that 10 of the 19 precedents garnered the highest rating of 4 on a five point scale of 0 to 4. (Note that this factor was given the greatest weight in the overall analysis

because it was viewed by the commentators as the single most important factor.) However, even therapies such as Sulfamylon and Synercid, which had extremely weak strength of clinical evidence on their respective surrogates, were judged by FDA as appropriately qualified for Subpart H, carried mainly on the strength of other factors described for each of these precedents.

The latter half of the assessment of overall clinical evidence was the strength of evidence of clinical benefit. It was not anticipated that this would score high, and generally the Subpart H approval precedents had relatively little clinical evidence of benefit in the clinical data sets that were the basis for each approval. Eleven of the 19 precedents had essentially no substantial positive evidence of clinical benefit, and one of the precedents actually had a fairly strong negative numerical "lean" in clinical outcome evidence, suggesting that the therapy may have a negative impact on long-term clinical benefit.

- Overview

The FDA regulatory factors, which this analysis collected under the heading of Part 1, were remarkably consistently favorable for each of these 19 precedents. As for the relative strength of the FDA factors which this analysis housed under headings of Parts 2, 3 and 4, there were some noteworthy consistencies, especially within Part 2 (understanding of the disease process) and the component of Part 4 on the clinical evidence of the drug's effect on the surrogate. Also, of note, a weak assessment or contribution from Part 2 or Part 3 or even (remarkably to the commentators) the Surrogate Component of Part 4 did not prove to be a barrier to qualifying for Subpart H.

As with the prior analysis of FDA's orphan drug precedents by one of the commentators, this analysis of FDA's Subpart H precedents testifies to FDA's flexibility in applying its standards to therapies under its review. In 2013, both Congress and the President additionally and strongly exhorted FDA to extend and expand its use of Subpart H, especially beyond AIDS and cancer. By interpreting and applying the factors FDA laid out in its Draft Guidance to these precedents, the commentators hope that this analysis will help propel that endeavor.

CLOSING

In summary, this comment is meant to illustrate the various factors cited by FDA in its Draft Guidance, as well as present the strength of clinical evidence in each of the 19 Subpart H approvals. In so doing, this comment sheds light and provides vitality to the factors cited by FDA, in the Agency's Draft Guidance, as well as contributes to an

understanding of the strength of scientific and clinical evidence in FDA's reaching its prior Subpart H approval determinations. We hope that this will enable all to more easily and more frequently embrace Subpart H, this regulatory innovation created by FDA, as some of the veil obscuring the basis for FDA's determination when a surrogate is "reasonably likely to predict clinical benefit" has been, at least partially, now lifted.

Onward!

Sincerely,

Frank J. Sasinowski
Hyman, Phelps & McNamara, P.C.

Alexander J. Varond
Hyman, Phelps & McNamara, P.C.

Enclosures

Figure 1: Subpart H Analysis Keyed to Factors in FDA's Draft Guidance on Expedited Programs

By Frank Sasinowski and Alexander Varond to FDA, August 26, 2013

Drug	**Part 1:** Regulatory Factors Weighing into FDA Determination (Section VII.C.1)[1]				**Part 2:**[2] Understanding of the Disease Process (Section VII.C.1.a)[1]	**Part 3:**[2] Understanding of the Relationship Between the Drug's Effect on Surrogate and the Disease (Section VII.C.1.b)[1]	**Part 4:**[2] Strength of Clinical Evidence (Section VII.C.1)[1]		**Total**
	Statutory Factors			External Expertise (0-1)	Understanding of the Disease (0-3)	Epidemiological, Pharmacologic and "Other Evidence" on the Surrogate or Disease (0-3)	Surrogate Endpoint (0-4)	Clinical Benefit (0-3)	
	Severity (0-2)	Rarity (0-2)	Unmet Need (0-2)						
1. Sirturo	2	2	2	1	2	2	3	-1	13
2. Ferriprox	2	2	2	1	3	2	4	0	16
3. Makena	2	2	1	1	1	3	4	1	15
4. Promacta	2	2	2	0	2	1	4	1	14
5. Exjade	2	2	2	1	3	2	2	0	14
6. Levaquin	2	2	1	1	3	2	4	1	16
7. Tysabri	2	2	2	0	2	3	4	1	16
8. Luveris	2	2	2	1	1	2	2	2	14
9. Fabrazyme	2	2	2	1	3	1	4	0	15
10. Remodulin	2	2	2	1	3	1	3	1	15
11. Cipro	2	2	2	1	3	2	4	1	17
12. Celebrex	2	2	2	1	3	3	4	0	17
13. Synercid	2	1	2	1	3	2	2	0	13
14. Remicade	2	2	2	1	1	1	3	0	12
15. Priftin	2	2	2	1	2	2	2	0	13
16. Sulfamylon	2	2	2	1	3	2	1	0	13
17. ProAmatine	1	2	2	0	3	2	3	0	13
18. Biaxin	2	1	2	1	2	1	2	1	12
19. Betaseron	2	2	2	1	2	2	4	2	17
	Range for Part 1: 5 to 7 (out of 7)				**Range for Part 2: 1 to 3 (out of 3)**	**Range for Part 3: 1 to 3 (out of 3)**	**Range for Part 4: 1 to 6 (out of 7)**		

[1] These citations are to the FDA Draft Guidance

[2] Parts 2, 3, and 4 are also from FDC Act Sec. 506, as amended by FDASIA Sec. 901, specifically, FDASIA uses the following terms for each of these parts:

- **Part 2** relates to "pathophysiological" evidence
- **Part 3** relates to "epidemiological, . . . pharmacologic, or other evidence . . ."
- **Part 4** relates to "therapeutic" evidence

Statistics	Score
Average Score	14.5
Min	12
Max	17
Median	14
SD	1.7

APPENDIX 1

1. SIRTURO (bedaquiline)

This December 28, 2012 approval for treating multi-drug resistant tuberculosis (MDR-TB) was based on a surrogate of time to sputum culture conversion.

Part 1. Regulatory Factors Weighing into FDA Determination

a. Severity of the Condition

"Overall mortality still exceeds 10%, with a range of 8 to 21% for patients enrolled into good treatment programs." (Medical Review, Dec. 26, 2012, p. 22).

b. Rarity of the Condition

FDA granted Sirturo orphan drug designation on January 10, 2005. Furthermore, in FDA's determination that the time to sputum culture conversion is an acceptable surrogate on which to base accelerated approval, it appears that FDA may have taken into account specifically the rarity of MDR-TB in this country in that FDA acknowledged that: "In the United States, the total number of MDR-TB cases has fluctuated from 88 to 132 cases [since] 1993, with 88 cases reported in 2010." (Medical Review at p. 22).

c. Lack of Available Therapy

"Treatment of MDR-TB is more complex (than treating drug-susceptible TB or DS-TB) and prolonged and typically has a favorable outcome rate [of only] 41-70%. Cases of MDR-TB are currently treated with at least five second-line anti-TB drugs for an extended period of time that may last up to two years . . . The challenges of the treatment of MDR-TB include toxicities of the drugs, decreased potency, cost (50-200 times more expensive than DS-TB) and the need for possible hospitalization." (Medical Review at p. 22).

d. Use of External Expertise

FDA did turn for external expertise to the Anti-Infective Drug Advisory Committee, which on June 3, 2009, "voted 18 to 1, recommending that sputum culture conversion . . . could be used as a surrogate . . . [t]herefore, the committee recommended that approval of an antimycobacterial drug could be done under Subpart H regulations (Accelerated Approval) using sputum culture conversion as a surrogate endpoint. Further, traditional endpoints used to evaluate treatment response such as relapse, failure, and mortality should still be used . . . for traditional approval." (Medical Review at p. 28).

Part 2. Understanding of the Disease Process

In this case, the pathophysiology of MDR-TB is well-understood.

Part 3. Understanding of the Relationship Between Sputum Culture Conversion and Relapse, Long-Term Response and Mortality

Epidemiologic evidence exists that supports the relationship between sputum culture conversion and clinical outcome, in particular, mortality. See Shama D. Ahuja et al., "Multidrug Resistant Pulmonary Tuberculosis Treatment Regimens and Patient Outcomes: An Individual Patient Data Meta-analysis of 9,153 Patients," 9(8) PLOS Medicine e1001300 (2012).

Part 4. Clinical Evidence of Sirturo's Effect on Sputum Culture Conversion and on Relapse and Mortality

The FDA Medical Reviewer noted the existence of the epidemiological evidence, but stressed that the clinical evidence provided by the sponsor both on the surrogate and on traditional endpoints of clinical benefit, especially mortality, would be "most persuasive." In this case, the Medical Reviewer listed these traditional endpoints as relapse, long-term response, and mortality. (Medical Review at p. 16).

There were two Phase 2 clinical trials that comprised the clinical evidence for this drug on the surrogate and on clinical benefit, but only one of which was considered to be the single, pivotal trial: Study C208 Stage 2. Study C208 Stage 2 was a randomized, double-blinded, placebo-controlled trial with a 24-week treatment period in which both the drug and "placebo" arms received an optimized background regimen. (Statistical Review, July 26, 2012, p. 6).

a. Sputum Culture Conversion

The primary endpoint, which was the surrogate endpoint, of the time to sputum culture conversion was highly statistically significant (p-value of 0.0005) (N=160 randomized, with 67 and 66 subjects in the drug and placebo arms in the mITT analysis, respectively). Sputum culture conversion at week 24 was a key secondary endpoint (as well as another supportive measure of the surrogate endpoint of sputum culture conversion), and it too was statistically significant (p-value = 0.014) with 78% and 58% of drug and placebo arm subjects, respectively, achieving sputum culture conversion at week 24. (Statistical Review at p. 6). "Lastly culture conversions data after all patients completed 72 weeks in the study showed a statistically significant but diminishing improvement in the time to sputum culture conversion for [Sirturo-]treated patients compared to placebo-treated patients." (Medical Review at p. 44).

b. Relapse and Mortality

Relapse is a "traditional" measure of clinical benefit. The Medical Reviewer notes that in "the mITT population, five subjects (7.6%) in the [drug] group and eight subjects (12.1%) in the placebo group experienced relapse . . . [However,] the subjects in the placebo group appear to take a longer time from culture conversion to relapse than those in the [drug] group." (Medical Review at pp. 59-60). Therefore, the Medical Reviewer conducted an alternative analysis, and in this analysis, "the two treatment arms become more comparable with respect to relapse with 5 relapses on [drug] and 4 on placebo." (Medical Review at p. 60).

Survival is the most objective and clinically meaningful benefit in MDR-TB. In the pivotal study, 9 of 79 in the drug arm died (11.4%) compared to 2 of 81 (2.5%) in the placebo arm. (Medical Review at p. 70). Both placebo subjects died of TB as did 5 of the 9 subjects in the drug group. (Medical Review at p. 70). Signals of QT prolongation and serum transaminase elevation, with one death due to liver injury in the drug arm, were also observed. (Medical Review at pp. 70-71).

In the "summary and conclusions" section of the statistical review, FDA observed: "There was a statistically significant increase in mortality in the [drug] group. Despite the observed treatment benefit in time to culture conversion, it did not lead to a benefit in patient survival. This was a major concern both for efficacy and safety." (Statistical Review at p. 60).

The relationship between the traditional clinical endpoints of relapse and survival and the surrogate endpoint of sputum culture conversion were not robust in this case. In fact, the clinical evidence on survival was actually and strongly in the wrong numerical direction.[1] Notwithstanding this, FDA appears to have, as noted in its Draft Guidance, relied in part on the "external expertise" of the June 2009 Anti-Infective Drug Advisory Committee as well as took "into account" these three factors that were listed in FDASIA: (1) the "severity" of the disease; (2) the "rarity" of the disease; and (3) the "lack of alternative treatments." (See, e.g., Medical Review at top of p. 59).[2]

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[1] This is the reason for the commentators scoring clinical evidence on the actual clinical benefit as -1 on a scale of 0 to 3. The scale was set up under the assumption that, at worst, there would be an absence of any clinical evidence of benefit, or if clinical evidence, then not even any "lean" in favor of the investigational treatment, which then would have been rated as "0."

[2] In addition to Dr. Porcalla's medical review reaching this conclusion, every other review unanimously supported a recommendation for approval. For instance, the statistical review by Dr. Lit Higgins concluded: "The efficacy in terms of a surrogate endpoint, sputum culture conversion, was supported by the pivotal study

2. FERRIPROX (deferiprone)

FDA approved Ferriprox on October 14, 2011 as "an iron chelator . . . for the treatment of patients with transfusional iron overload due to thalassemia syndrome when current chelator therapy is inadequate." Ferriprox was approved on the basis of its showing on an unvalidated surrogate, serum ferritin.

Part 1. Factors Weighing into FDA Determination

a. Severity of the Condition

Persons with certain inherited anemias, especially sickle cell anemia and thalassemia, require frequent red blood cell (RBC) transfusions because they are unable to manufacture hemoglobin. Each unit of packed RBCs contains 200 mg of iron, which is an extreme excess of iron as compared with the dietary intake of 1 mg of iron necessary to maintain normal total body iron stores in healthy individuals. Without a way for the body to excrete excess iron, persons receiving these regular transfusions of RBCs build up massive iron overload which leads to morbidity and often eventually death due to cardiac damage. (Medical Review #1, Sept. 20, 2011, pp. 1-2).

b. Rarity of the Condition

FDA designated Ferriprox as an orphan drug on December 21, 2001.

c. Lack of Available Therapy

At the time of Ferriprox's approval, there were two other approved therapies for iron overload due to transfusions: Desferal (deferoxamine) and Exjade (deferasirox). Ferriprox was given fast track designation in January 2004, before Exjade was approved. Exjade, an orally active iron chelator, was approved in 2005. In January 2004, Desferal was the only available therapy and requires continuous infusion over many hours, every day.

C208 and supportive study C209. There was a significantly elevated mortality risk in the [Sirturo] group. This should be considered in an approval decision and use of this regimen." The reviews of the Cross-Discipline Team Leader, Dr. Navarro (December 21, 2012), the Deputy Division Director, Dr. Laessig (December 27, 2012) and the Office Director, Dr. Cox (December 28, 2012) all recognized the robust finding on the surrogate endpoint of sputum culture conversion and recommended approval despite serious consideration of the clinical safety results, especially the survival results in the pivotal study. This unanimity of support for a Subpart H approval decision within the entirety of the internal FDA expert review team was not always observed in the other 18 Subpart H precedents.

The sponsor first submitted its NDA seeking an indication for "all transfusion-dependent anemias for whom the use of other iron chelators has been considered inappropriate." A complete response letter was issued in November 2009 and a resubmission was made in April 2011 for essentially the same second-line use. However, the data submitted were almost exclusively from thalassemia patients and FDA's October 2011 approval is for "patients with transfusional iron overload due to thalassemia syndromes when direct chelator therapy is inadequate." For this specific use, there is a lack of available therapy.

d. External Expertise

FDA appears to have given consideration to two types of external expertise. First, FDA seems to have given some weight to the "expertise" of clinical practice that uses serum ferritin to monitor the patient's iron status. While serum ferritin is a non-specific endpoint for which FDA noted that "the relationship between the serum ferritin and clinical outcome is not well-established" (Medical Review #2, Sept. 16, 2011, p. 34), FDA nevertheless appears to give serum ferritin some weight because serum ferritin is "a commonly used parameter for following body iron burden in patients undergoing chronic red blood cell transfusions," (Medical Review #1 at p. 12), and because "in clinical practice, measurements of serum ferritin and [liver iron concentration] have been the generally accepted methods of evaluation of the efficacy of therapy in persons with iron overload." (Medical Review #3, November 20, 2009, p. 5).

Second, the Oncology Drugs Advisory Committee recommended Ferriprox for approval on September 14, 2011 by a vote of 10 to 2 for treating patients in whom current chelator therapy is inadequate.

Part 2. Understanding of the Disease Process

In this case, the pathophysiology by which iron overload leads to deposition of iron in tissues and leads to iron-catalyzed peroxidation of membrane lipids, which then leads to morbidity and death due to cardiac damage, is well-known. (Medical Review #1 at p. 1).

Part 3. Understanding of the Relationship Between the Effect on Serum Ferritin and Cardiotoxicity and Death

The mechanism of the drug's action is well-known, that is, binding to iron in a 3:1 complex which is excreted in the urine, and the reduction in iron in these persons is needed to avoid iron overload morbidities. (Medical Review #1 at p. 2). However, serum ferritin is non-specific and "changes in serum ferritin are difficult to interpret because serum ferritin is subject to variations induced by a number of mechanisms that are unrelated to total body iron." (Medical Review #4, Oct. 19, 2009, p. 15). Most of all, "[t]he relationship between the serum ferritin and clinical outcome is not well established." (Medical Review #1 at p. 34).

This part was scored a 2 on a scale of 0 to 3, mainly on the basis of the biologic plausibility that this drug, due to its mechanism, would reduce iron stores, notwithstanding the weakness of serum ferritin itself as a surrogate, due to its lack of specificity as a measure of iron stores. The non-specificity of serum ferritin and the lack of understanding of the relationship between the surrogate and outcomes led to a score of 2 instead of 3.[3]

Part 4. Clinical Evidence of Ferriprox's Effect on Serum Ferritin and on Outcome

It is of value here to note that FDA rejected the original NDA submitted in 2009 for Ferriprox because the "primary efficacy endpoint of the single major controlled trial . . . was the change in cardiac MRI T2* which was said to measure iron content within the heart. FDA stated that this endpoint was a surrogate endpoint and there were no data to support the incremental changes in the values as predictive of clinical benefit." (Medical Review #1 at p. 10) (emphasis added). Moreover, "secondary endpoints [of serum ferritin and liver iron concentration] also were not consistently corroborative of the primary endpoint [MRI T2*] results." (Medical Review #1 at p. 5). Overall, "the study did not find a significant correlation between change in cardiac MRI T2* and measures of cardiac function and there were no differences between treatments in change in liver iron concentration (LIC)." (Medical Review #1 at p. 2). The statistical review observed that "the patients in this study were not followed for clinical outcome and therefore, this study was not designed to obtain internal validation of MRI T2* change as a surrogate for any clinical outcome indicative of reduced cardiac iron."[4] (Statistical Review, March 24, 2009, p. 7).

"Although the data from this study provided statistically significant evidence . . . in MRI T2* . . . this study was not designed to and therefore, does not provide evidence that change in MRI T2* is reasonably likely to predict clinical benefit due to lack of long-term follow-up of these patients." (Statistical Review #2, Nov. 22, 2009, p. 3).

In response to FDA's rejection of the original NDA, the sponsor "conducted an analysis of a subpopulation of patients drawn from its previously conducted studies and defined as being inadequately treated with current chelator therapy." (Medical Review #1 at p. 10). In this analysis, approximately 50% met the primary efficacy endpoint of

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[3] Others may score this differently, perhaps even only a "1" given the non-specificity of serum ferritin and lack of well-established relationship between surrogate and outcomes.

[4] Note that FDA states that this study could provide both evidence of the effect of the drug on an unvalidated surrogate and at the same time, in the same study, evidence of the effect of the drug on clinical outcome, thereby "validating" that surrogate.

having a 20% or greater decline in serum ferritin. Of additional importance, the sponsor-defined "success rate" in this same analysis was 42% for liver iron concentrate (LIC). (Medical Review #1 at pp. 7-8). FDA noted that "change in LIC using liver biopsy has generally been considered to be the standard measure of efficacy in response to iron chelation therapy." (Medical Review #4 at p. 15).

Overall, FDA first rejected the original NDA on grounds that the primary endpoint of the key pivotal study, MRI T2* changes, was not sufficiently correlated with any clinical outcome to warrant being the basis for even an accelerated approval, notwithstanding the disease being severe, rare, and without adequate therapy. However, FDA approved a second resubmission that was based on an analysis of a commonly used measure in clinical practice of patients with transfusion-related iron overload, serum ferritin, which itself was supported internally by a positive finding in the same population on liver iron concentration which is the "standard measure of efficacy in response iron chelator therapy."

FDA's actions on Ferriprox illustrate the fatal flaws in a clinical program attempting to rely upon a surrogate (MRI T2*), the factors to be considered and the clinical evidence that were found by FDA to be of sufficient merit to allow FDA, as a matter of its judgment, to conclude that serum ferritin is reasonably likely to predict clinical benefit, even without any clinical trial results on any cardiac outcomes, such as heart failure or mortality, and notwithstanding an FDA acknowledgement that serum ferritin is a non-specific measure. However, FDA's Subpart H approval here was based clinically on the corroboration of the serum ferritin results by the liver iron concentrate results and bolstered by the known mechanistic action of the drug (i.e., that by its mechanism of action the drug leads to iron excretion in the urine).

Overall, the clinical evidence of the surrogate was scored a full 4 out of a possible 4 due to the strength of evidence on serum ferritin which itself was buttressed by the clinical findings on LIC. However, since there was no clinical evidence on any ultimate clinical outcome, the score for clinical evidence of outcome benefit is zero.

3. MAKENA (hydroxyprogesterone caproate)

FDA's February 3, 2011 approval of Makena to reduce the risk of preterm birth (PTB) was based on a surrogate of reducing preterm birth as defined as those births occurring at less than 37 weeks of gestation. "Preterm birth <37 weeks gestation . . . was a surrogate[5] for pregnancy outcome (neonatal/infant morbidity and mortality)." (Medical Review, Feb. 3, 2011, p. 14).

Part 1. Regulatory Factors Weighing into FDA Determination

a. Severity of the Condition

The risks of miscarriage, stillbirths, and neonatal mortality are associated with delivery prior to full-term gestation, as well as neonatal morbidities and adverse maternal outcomes as well.

b. Rarity of the Condition

Makena was designated as an orphan drug on January 25, 2007.

c. Lack of Available Therapy

"Currently there is no drug product approved in the United States to reduce the risk of preterm birth; however, [the active ingredient in Makena] is compounded by pharmacists and is used widely for this indication in women at high risk." (Medical Review at p. 11). In 1956, FDA had approved an NDA for Delalutin, which had the same active ingredient as Makena, for treating pregnant women for "habitual and recurrent abortion, threatened abortion." (Medical Review at p. 12). In 2000, FDA withdrew the approval of Delalutin at the request of the NDA sponsor because it no longer marketed Delalutin. In a June 25, 2010 Federal Register notice, FDA announced its determination that Delalutin was not withdrawn from marketing for safety or efficacy reasons.

d. Use of External Expertise

With Makena, FDA relied upon two forms of external expertise and FDA reached its "informed judgment" that the surrogate endpoint of preterm birth less than 37 weeks was reasonably likely to predict clinical benefit, that is, pregnancy outcome or neonatal infant and maternal morbidity and mortality. These two forms of external advice are summarized in the Medical Review: (1) 2006 Advisory Committee; and (2) subsequent scientific papers published in the literature.

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[5] While FDA Medical and Statistical Reviews refer to PTB <37 weeks as a "surrogate," preterm birth is a clinical event and, therefore, in the terminology of the Draft Guidance, PTB <37 weeks is an "intermediate clinical endpoint."

i. "The surrogate endpoints of reductions of [preterm birth] at <35 and <32 weeks were thought by the Advisory Committee to predict a reduction in neonatal mortality and morbidity. At the time of the Advisory Committee meeting in 2006, the endpoint PTB at <37 weeks was not believed to be an adequate surrogate for neonatal outcome."[6] (Medical Review at p. 6).

ii. "The Applicant submitted a single phase 3 clinical trial which demonstrated a statistically strong (p<.001) reduction in the incidence of preterm births prior to 37 weeks gestation, the protocol pre-specified primary endpoint. There is recent evidence that 'late preterm births' (births between $34^{0/7}$ and $36^{6/7}$), which comprise 71.3% of all preterm births, are increasing, and suffer greater neonatal and childhood morbidity and mortality than previously thought [5 papers are cited that were published between the time of the 2006 Advisory Committee and the Medical Review]. These data indicate that 'preterm birth prior to 37 weeks' is a surrogate endpoint that is reasonably likely to predict clinical benefit." (Medical Review at p. 5).

Part 2. Understanding of the Disease Process

Here the disease process is complex and has multiple pathophysiologic pathways, and therefore, this mitigates against reliance upon any surrogate. The biological means by which the gestational process progresses to premature delivery is complex and multifaceted. Therefore, the surrogate endpoint of PTB <37 weeks is likely more analogous to the PSA example than the enzyme replacement example in the Draft Guidance (see Draft Guidance at p. 19, lines 634-648) in that PTB <37 weeks is not on the pathophysiological causal pathway and is not the biologic mechanism that causes the neonatal mortality and morbidity, even though, like PSA, it is correlated with increased risk.

Part 3. Understanding of the Relationship Between PTB and Pregnancy Outcomes

a. Epidemiological Evidence

The epidemiological evidence is strong with Makena. The 2006 Advisory Committee assessed the epidemiological evidence supporting the relationship between PTB and pregnancy outcomes and found that this evidence was strong enough to support the endpoints of PTB <32 weeks and PTB <35 weeks as surrogate endpoints but not PTB <37 weeks. However, additional evidence published subsequent to the 2006 Advisory Committee permitted the Medical Officer, Dr. Barbara Wesley, to conclude that PTB <37

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[6] "The Committee stated that a reduction of preterm birth <37 weeks was not an adequate surrogate (Yes: 5; No: 16) but that reductions in preterm birth <35 weeks (Yes: 13; No: 8) and <32 weeks (Yes: 20; No: 1) were adequate surrogates." (Medical Review #2, Jan. 23, 2009, p. 7).

weeks was also a reliable, consistent and acceptable surrogate endpoint.[7] (Medical Review at p. 5).

b. Effect of Drugs in the Same or Closely Related Pharmacologic Class to Affect Pregnancy Outcomes

Since there are no drugs in any pharmacologic class approved for reducing the risk of PTB, there are no analogous therapies here on which to draw support directly for reducing the risk of PTB. However, other progesterones including the active ingredient in Makena have been approved for aiding in assisted reproductive technologies and other conditions supporting the maintenance of pregnancy.

Part 4. Clinical Evidence of the Makena's Effect on PTB <37 Weeks and on Pregnancy Outcomes

a. PTB <37 Weeks

The surrogate of PTB <37 weeks was highly statistically significant ($p<0.001$).

b. Pregnancy Outcomes

"The proportion of babies with at least one event on the [secondary] composite index of neonatal morbidity and mortality was lower in the [Makena] group (11.9%, 35/295 infants) than in the vehicle group (17.2%, 26/151 infants) but the between-group differences was not statistically significant (nominal p-value of 0.1194)." (Medical

[7] It is also likely that the Advisory Committee was opining on PTB <32 weeks, PTB <35 weeks and PTB <37 weeks as validated surrogates which would have qualified Makena for traditional approval, not Subpart H approval. Outside of AIDS and cancer, FDA has not often asked Advisory Committees to opine on whether clinical evidence on a particular endpoint would qualify a therapy for Subpart H approval. For example, note that the August 5, 2013 Cardiorenal Advisory Committee, addressing the approvability of tolvaptan, a vasopressin V2 receptor antagonist, was not asked whether total kidney volume would qualify as an unvalidated surrogate that may support a Subpart H approval if the Advisory Committee found that total kidney volume is "reasonably likely to predict clinical benefit," which, in this case, clinical benefit would likely be end-stage renal disease and/or clinically meaningful outcomes such as significant worsening of renal function or kidney pain. However, there are exceptions outside of AIDS and cancer. For instance, the Oncology Drugs Advisory Committee (ODAC) was asked whether FAP was an adequate "unvalidated" surrogate, that is, to qualify Celebrex (Precedent #12) for Subpart H approval. But even this case was before ODAC, and while FAP is not cancer, the ultimate clinical benefit was prevention of colon cancer, so even this "exception" is not fully outside of AIDS and cancer.

Review #1 at p. 6). "Approximately 6.5% of the women in each treatment group experienced a fetal or neonatal deaths . . . The results . . . show that despite the treatment groups having about the same rate of fetal and neonatal deaths, the losses occur earlier among [Makena] women." (Statistical Review #2, Oct. 19, 2006, p. 20).

This impact on fetal or neonatal deaths was stated another way by the Medical Reviewer: "There was a trend toward an increased risk of miscarriage and stillbirths in the [Makena] treatment arm and a trend toward a decrease in neonatal death, with no overall net survival benefit." (Medical Review #1 at p. 7) (emphasis in original).

Overall, the secondary endpoint of a composite measure of neonatal morbidity/mortality leaned in favor of the Makena group while the separate analysis of neonatal mortality showed essentially no numerical difference and had a nominal p-value of 0.6887 (Medical Review #1 at p. 7). The clinical evidence for the ultimate clinical benefits in the single pivotal trial was not strong.

4. PROMACTA (eltrombopag)

FDA approved Promacta on November 20, 2008 on "short-term platelet count response" as a surrogate marker for longer platelet count responses (platelet counts are recognized as acceptable measures of clinical benefit for patients with ITP [idiopathic thrombocytopenic purpura])." (Medical Review #1, Nov. 4, 2008, p. 3). The two clinical trials of Promacta administered drugs over 6 weeks or less (this is the meaning of "short term" in the Reviewer's statement above). Had the Promacta trials studied and established the drug's effect on platelet counts out to 6 months, this approval would have been a traditional approval and not one under Subpart H.

Part 1. Regulatory Factors Weighing into FDA Determination

a. Severity of the Condition

Chronic ITP is a serious medical condition. (Medical Review #1 at p. 3). The frequency of death from hemorrhage in patients with platelet counts below 30,000/mcl is estimated to be between 1.6 and 3.9% per patient year. (Medical Review #2, Sept. 12, 2008, p. 17).

b. Rarity of the Condition

FDA designated Promacta as an orphan drug on March 4, 2008.

c. Lack of Available Therapy

"[Promacta] approval would provide a meaningful therapeutic benefit to patients over existing treatments because of its minimal risk for immunogenicity (based upon [its] small molecule characteristics). The labeling for romiplostine, the only currently marketed TPO receptor agonist, includes information regarding the risks for immunogenicity. These risks are not applicable to [Promacta]." (Medical Review #1 at p. 3).

d. Use of External Expertise

In the medical and statistical reviews, the commentators found no evidence of any reliance on special government employees (SGEs), an Advisory Committee for Promacta, or specific published literature.

Part 2. Understanding of the Disease Process

"The clinical hallmark of the disease is an increased tendency to bleed." (Medical Review #2 at p. 17). Furthermore, the relationship of platelet count to bleeding is well-established: "Patients with platelet counts between 30,000/mcl and 10,000/mcl are generally considered treatment candidates due to slightly increased risk of spontaneous bleeding or increased risk of bleeding due to trauma." (Medical Review #2 at p. 17).

Part 3. Understanding of the Relationship Between the Drug's Effect on Short-Term Platelet Counts and Increased Risk of Bleeding

There was no epidemiological evidence cited in the FDA review documents to support the surrogate - which is "short term" (that is, six weeks) increase in platelet count - as reasonably likely to predict long-term, chronic increase in platelet count - which is generally established in six month trials or generally on increased risk of bleeding. While there was no evidence to support the use of this surrogate, there was a therapy approved from the same pharmacologic class but based on an endpoint of six-month duration. Earlier in 2008 (the year FDA approved Promacta), FDA had approved romiplostim, a biological product that is a member of the same pharmacologic class - thrompoietin (TPO) receptor agonists - and this approval for the same indication (that is, to treat ITP) was a traditional approval based on two clinical trials, each of six-months duration.

Part 4. Clinical Evidence of Promacta's Shorter-Term (Surrogate) Effect and Long-Term Effect on Platelets and/or Bleeding

Both Promacta pivotal studies showed a robust short-term (surrogate) effect on platelets ($p<0.001$) (Statistical Review, Apr. 29, 2008, pp. 19 and 27).

As for clinical evidence that FDA had at the time of the approval that Promacta's "short-term" (six weeks) impact on platelet counts would predict either clinical benefit of long-term impact on platelet counts or on bleeding, there was mixed evidence.

As supportive evidence that the platelets produced by Promacta behaved in a physiologically "normal" way, the Sponsor had conducted "an exploratory clinical study that demonstrated [that Promacta] prompted platelet count increases in healthy subjects. These drug-stimulated platelets had *in vitro* platelet function characteristics typical of platelets. Hence, this study supported the generally accepted use of platelet counts as an 'accepted' measure of clinical benefit for clinical studies of TPO receptor agonists among patients with chronic ITP." (Medical Review #1 at pp. 2-3).

As Promacta was only administered for six weeks (or less) in the two pivotal trials, there is no clinical evidence as to the impact long-term on platelet counts if Promacta was administered chronically (for which a trial of six-months duration would have been relied upon). Furthermore, of some concern, "discontinuation of [Promacta] at the end of the study resulted in an unacceptable amount of serious hemorrhage." (Medical Review #1 at p. 3). Also, the statistical reviewer observed that within two weeks after the subjects on drug were off treatment, there was a return to placebo levels of platelet counts. (Statistical Review at pp. 27-28).

As for bleeding events, there was a numerical lean in favor of Promacta, but in neither trial was this statistically significant with p-values of 0.121 and 0.088 for the between-group difference on bleeding events in the two pivotal trials. (Statistical Review at pp. 8-9).

5. EXJADE (deferasirox)

The FDA approval of Exjade for treating "chronic iron overload due to blood transfusions" on November 2, 2005 was based on a surrogate endpoint of improvement in liver iron concentration (LIC).

Part 1. Regulatory Factors Weighing into FDA Determination

a. Severity of the Condition

"Chronic iron overload due to requisite blood transfusion is a serious and life-threatening condition." (Medical Review #1, Nov. 2, 2005, p. 2).

b. Rarity of the Condition

Exjade was granted orphan drug designation on November 21, 2002.

c. Lack of Available Therapy

At the time FDA was reviewing the Exjade NDA, the Medical Team Leader, Dr. Dwaine Rieves, stated: "Deferoxamine, the only available therapy for this condition, presents unique compliance and infectious risks due to the need for prolonged administration of the drug. [Exjade] is an orally administered drug that provides a meaningful therapeutic benefit over the existing therapy." (Medical Review #1 at p. 2).

d. External Expertise

FDA sought the advice of the Blood Products Advisory Committee (BPAC) and at its September 29, 2005 meeting, the BPAC found that "the applicant [had] provided substantial evidence of the effectiveness of [Exjade] in the reduction of liver iron concentration, an outcome indicative of a clinical benefit . . . The sponsor's major clinical evidence of [Exjade] effectiveness . . . is based upon alterations in liver iron content, an endpoint the BPAC discussants regarded as a measure of clinical benefit. In this context, the endpoint is not regarded as a surrogate endpoint rather as an endpoint other than survival or irreversible morbidity[8], as cited in the Subpart H regulations." (Medical Review #1 at p. 2).

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[8] An "intermediate clinical endpoint" (rather than a surrogate) is the term used in the Draft Guidelines for this kind of endpoint; however, during the later FDA approval of Ferriprox, the FDA Reviewers refer to both serum ferritin and LIC as "surrogates," and in an earlier medical review of Exjade, FDA refers to LIC in this pivotal trial as a "surrogate" (see Medical Review #2 at p. 38). Therefore, this analysis will refer to LIC as a surrogate and not as an intermediate clinical benefit.

Part 2. Understanding of the Disease Process

See Item 2 under Ferriprox.

Part 3. Understanding of the Relationship Between LIC and Cardiac Outcomes, Including Mortality

"Although accepted by the Division as a clinically meaningful endpoint, the primary endpoint [of LIC] is technically a surrogate endpoint since it does not necessarily address clinically significant morbidity or mortality. The main mortality on β-thallasemia is due to cardiac dysfunction whose etiology in β-thallasemia is probably multifactorial. Nonetheless, most of the literature in β-thallasemia has used LIC as a marker for morbidity for other organ involvement and as a surrogate for mortality. There is some information, however, that LIC does not completely correlate to the extent of cardiac hemosiderosis, the primary cause of mortality. Obviously, repetitive biopsy of the myocardium to measure iron concentration in the heart is not acceptable." (Medical Review #2, Oct. 10, 2005, p. 38).

As for understanding the relationship between drugs in the same pharmacologic class as LIC, the single pivotal trial for Exjade was a noninferiority study design which used as its active comparator, deferoxamine, and therefore, FDA had evidence from a within-study comparison of the only other member of the same or closely related class on the surrogate endpoint of LIC.

Part 4. Clinical Evidence of Exjade's Effect on LIC and/or Cardiac Outcomes Including Mortality

FDA, in its review of this NDA, noted that LIC as "the primary endpoint is acceptable and it was agreed to by the Division in the Special Protocol Assessment. It should be remembered, however, the LIC is a surrogate marker and that the effects of Exjade on morbidity/mortality, which are the truly important clinical endpoints, are not likely to be demonstrated in this short trial." (Medical Review #2 at p. 31).

Rather than bolster LIC results by seeing trends on irreversible morbidity and mortality in this "short" trial, FDA looked to find support from other critical surrogate markers such as serum ferritin.[9]

As for LIC, the protocol had specified that "non-inferiority of [Exjade] to [deferoxamine] was to be established if the two sided 95% confidence interval of the difference in success rate between the two groups was above -15%. The basis for the

[9] The authors must inform the reader that this trial was a year-long trial, and, therefore, by many would not be considered "short;" however, even a year long study is too "short" to see effects on mortality and irreversible morbidity.

choice of this [non-inferiority] margin was unclear in the submission. Notably, FDA had questioned the meaningfulness of this margin during the study's protocol review.[10] (Medical Review #1 at p. 4).

The primary efficacy result was a point estimate difference of -13.5%, with a lower 95% confidence interval of -21.6% (or, in other words, the margin defining success of the trial was not met). About this, FDA concluded: "Given that the original basis of the non-inferiority margin was poorly substantiated, little clinical meaningfulness could be assigned to failure to achieve the primary endpoint. The primary endpoint data did establish that both [Exjade and deferoxamine] lowered LIC over a 12 month period of time, a time period during which subjects would have been expected to have increases in LIC due to continuing blood transfusions. This observation provides evidence of a treatment effect for [Exjade]." (Medical Review #1 at p. 5).

With respect to serum ferritin, FDA concluded that "[s]erum ferritin values declined in a dose-related manner for subjects receiving [Exjade], a pattern similar to that for subjects receiving [deferoxamine]." (Medical Review #1 at p. 5).

[10] Query, though, how FDA nevertheless had accepted the design of this pivotal study under an SPA.

6. LEVAQUIN (levofloxacin)

FDA approved Levaquin for post-exposure prevention of inhalational anthrax on November 11, 2004. Much of what the Agency had learned from its Subpart H approval of Cipro for inhalational anthrax in August 30, 2000 was used to create a draft guidance. "FDA Draft Guidance for Industry: Inhalational Anthrax (Post-Exposure) - Developing Antimicrobial Drugs" ("Anthrax Draft Guidance") (March 2002). FDA then relied on its Anthrax Draft Guidance when it approved Levaquin in 2004. (Statistical Review, Nov. 15, 2007, p. 1).

As for Cipro, there was a two part or "compound" surrogate for this approval in that FDA concluded: (1) that "[m]ortality due to anthrax for animals that received a 30 day regimen of oral Levaquin beginning 24 hrs post exposure was significantly lower (1/10), compared to the placebo group (9/10) [p=0.0011]," and (2) "mean plasma concentrations of Levaquin associated with a statistically significant improvement in survival over placebo in rhesus monkey model of inhalational anthrax are reached or exceeded in adult . . . [human] patients receiving the recommended oral and intravenous dosage regimens." (Levaquin Package Insert).

Part 1. Regulatory Factors Weighing into FDA Determination

a. Severity and Rarity of the Condition

"Mortality for established [inhalational anthrax] even after treatment was 80-100% in the 20th century." (Anthrax Draft Guidance at p. 3). In addition, "inhalational anthrax is extremely rare. There have been only approximately 20 cases in the United States in the past 100 years . . . For these two reasons, the rarity of disease and the extremely high mortality rate, a clinical study is not feasible." (Cipro Statistical Review, Aug. 16, 2000, p. 1).

b. Rarity of the Condition

Although the prevalence of inhalational anthrax is sufficiently low, the Sponsor did not seek orphan drug designation.

c. Lack of Available Therapy

At the time of Levaquin's approval, Cipro was indicated specifically for post-exposure prophylaxis for disease caused by inhaled *B. anthracis*, and, although doxycycline and penicillin G procraine products were not specifically indicated for post-exposure prophylaxis for disease caused by inhaled *B. anthracis*, FDA "had published a notice in the Federal Register (66 Fed. Reg. 55679) that clarified the dosing regiments for [those drugs] in the management of patients with inhalational anthrax." (Anthrax Draft Guidance at p. 5).

d. External Expertise

Although no advisory committee was convened specifically for Levaquin, FDA had sought "input from the Anti-Infective Advisory Committee [and determined that] the use of the rhesus (macaque) monkey disease and treatment model for inhalational anthrax (post-exposure) provides convincing evidence of efficacy for regulatory evidence." (Anthrax Draft Guidance at p. 4).

Part 2. Understanding of the Disease Process

Before the approval of Cipro in 2000, four years before the approval of Levaquin, FDA had stated that "[t]he inhalational form of the disease, which affects the mediastinal lymph nodes, other organs of the reticuloendothelial system and the central nervous system, is considered the most likely clinical entity resulting from the intentional use of an aerosolized preparation of the spores of *B. anthracis*." (Cipro Medical Review, Aug. 31, 2000, p. 2).

Part 3. Understanding of the Relationship between the Monkey Data and Human Mortality; and Part 4. Clinical Evidence

FDA's draft guidance document on the development of treatment for post-inhalational anthrax exposure stated that, "a non-human primate model that models the drug disposition in humans [was] considered an adequate surrogate for human disease and objective endpoints such as mortality, time of death relative to antimicrobial use, pathology, and bacteremia in the macaque." (Statistical Review at p. 1).

Thus, two findings formed the basis of FDA's Subpart H approval of Levaquin for inhalational anthrax:

First, "[s]urvival was significantly better ($p=0.0011$, two-sided Fishers exact test) and time to death was significantly longer ($p<0.0001$, log rank test) [in macaques] in the levofloxacin group compared to the placebo group." (Statistical Review at p. 1). Also, Levaquin had a numerical advantage with 90% (9/10) of the macaques surviving, compared to 80% (8/10) in the ciprofloxacin group, and only 10% (1/10) in the placebo group. (Statistical Review at p. 1).

Second, as for comparative monkey/human exposure levels, the "mean plasma concentrations [and mean steady state AUC_{0-24}] associated with a statistically significant improvement in survival over placebo in the rhesus monkey model of inhalational anthrax are reached or exceeded in adult . . . patients receiving the recommended oral and intravenous dosage regimens." (Levaquin Package Insert).

As for understanding the relationship of drugs in the same or closely related class on the compound surrogate, see above discussion under 1.c. regarding other drugs including Cipro for anthrax.

Monkey survival data was one part of this unusual compound surrogate; see the discussion above. However, there were "complete pharmacokinetic data on the drug in human volunteers . . . and pharmacokinetic data in the rhesus monkey in the efficacy study of inhalational anthrax [is used] to demonstrate that the desired systemic exposure achieved in humans after the anticipated dosage regimen can actually be achieved and is effective in the animal model in preventing inhalational anthrax infection and consequent mortality." (Anthrax Draft Guidance at p. 10).

7. TYSABRI (natalizumab)

FDA approved Tysabri on November 23, 2004 for treating relapsing-remitting multiple sclerosis (RRMS), relying upon the reduction in MS relapse rates at one year as the surrogate endpoint. Applying the terms of the Draft Guidance, this would be an intermediate clinical endpoint that would be reasonably likely to predict the benefit at two years. All previous MS therapies were approved on the basis of two-year relapse rate reduction and "the clinical meaningfulness of a decrease in the relapse rate through only one year is uncertain." (Medical Review, Nov. 23, 2004, p. 6).

Part 1. Regulatory Factors Weighing into FDA Determination

a. Severity of the Condition

Relapsing-remitting multiple sclerosis is a serious, life-threatening condition.

b. Rarity of the Condition

While Tysabri was not designated an orphan drug for RRMS, the statutory threshold for qualifying as an orphan drug was, in part, set in the 1984 amendment to the Orphan Drug Act specifically to include all of multiple sclerosis as an orphan disease, not just the subset of RRMS. This was because, in considering how to amend the original 1983 Orphan Drug Act to make it less difficult to garner orphan drug designation, key Senators caucused with the National Organization for Rare Diseases (NORD) and mutually determined that the maximum number of Americans with a condition which would still qualify as an "orphan" would be 200,000. This number was chosen, specifically, to make sure that MS would be an "orphan" disease, and in 1984 there were just under 200,000 Americans diagnosed with MS. However, soon after FDA approved the first therapy for multiple sclerosis (Betaseron in August 1993, which was also the first non-AIDS Subpart H approval), the number of Americans diagnosed with multiple sclerosis dramatically increased. So, while Tysabri was never designated as an orphan drug for RRMS, the commentators, fully cognizant of the intent of the 1984 orphan drug amendment, view Tysabri as, nevertheless, falling within the "penumbra" of orphan drug status and score Tysabri a "1" on rarity.

c. Lack of Available Therapy

"Accelerated approval requires that the new drug provide evidence of the potential to address an unmet medical need. Many MS patients continue to have exacerbations while taking one of the available first-line MS therapies. None of the currently available therapies have proven efficacy when used as add-on therapy. [One of the two pivotal Tysabri studies] provides evidence that [Tysabri] is effective as add-on therapy for subjects who continue to have relapses while on a first-time therapy (Avonex). Therefore, [Tysabri] has the potential to address an unmet medical need." (Medical Review at p. 6).

d. External Expertise

FDA did not rely on an advisory committee during its initial review of Tysabri. However, Tysabri was withdrawn from the market by the manufacturer in February 2005 after three patients developed progressive multifocal leukoencephalopathy (PML). Subsequently, FDA convened an Advisory Committee to consider the reintroduction of Tysabri in March 2006. Furthermore, FDA had convened and considered the input from several earlier advisory committees on other multiple sclerosis therapies.

Part 2. Understanding of the Disease Process

"Multiple Sclerosis is a chronic, inflammatory, possibly autoimmune, demyelinating disease of the central nervous system." (Medical Review at p. 11). Note that the FDA review status that multiple sclerosis may be "possible autoimmune." Given that Tysabri's mechanism of an action is as an immunomodulator, having a more definitive view of the causative role of autoimmunity in the pathophysiology of this disease would have been more compelling.

Part 3. Understanding of the Relationship Between the One-Year Relapse Rate and Two-Year Relapse Rate

The effect of [Tysabri] on relapse rate in [the pivotal study on Tysabri's use as first-line therapy] was approximately twice the effect observed with current first-line drugs for this indication. Such comparisons of different agents across studies are problematic . . . However, the magnitude of [Tysabri's] effect is sufficient that the effect at one year is reasonably likely to predict a clinical benefit at two years." (Medical Review at p. 102).

As for understanding the relationship of drugs in the same or closely-related pharmacologic class on rate and extent of exacerbations at one year of treatment as predictive of their two year effectiveness, at the time of Tysabri's approval, there were four other approved immunomodulators approved for treatment of MS: Betaseron, Avonex, Rebif and Copaxone. While each of these was approved on the basis of two-year studies of impact on reducing rate and extent of MS exacerbations, their impacts after one year of therapy, while generally more modest than at the end of two years, were predictive of their two year results.

Part 4. Clinical Evidence on One-Year and Two-Year Relapse Rates

"For other MS products, FDA has required two-year data . . . A salutary effect on relapse rate at one year is not a validated surrogate for benefit at two years. However, the apparent treatment effect of [Tysabri] with respect to relapse rate at one year is unprecedented in the MS field, and its magnitude is reasonably likely to predict clinically meaningful effectiveness at two years. If, in fact, the benefit on clinical relapses is shown to be durable through two years, the product may be substantially more efficacious than

currently approved MS therapies. It is possible, however, that the magnitude of [Tysabri's] effect on relapse rate, when assessed through one year, may substantially overestimate [Tysabri's] benefit on relapse rate through two years . . . In particular, the treatment effect appears to wane with the development of [anti-Tysabri] antibodies, which may increase in time." (Medical Review at p. 53) (emphasis added).

8. LUVERIS (lutrepinalfo)

On October 8, 2004, FDA approved Luveris for stimulating follicular development in infertile hypogonadotropic hypogonadal women with profound LH deficiency (LH < 1.2). "The Division Director further concluded that in this orphan population of women with severe LH deficiency (LH <1.2), the surrogate endpoint of follicular development (as defined by the Sponsor) was reasonably likely to predict clinical benefit [with respect to pregnancy] . . . (Medical Review #1, Oct. 6, 2004, p. 2).

Part 1. Regulatory Factors Weighing into FDA Determination

a. Severity of the Condition

The inability to ovulate due to profound luteinizing hormone (LH) deficiency includes, among other serious consequences, the inability to become pregnant. "The Director believes that infertility in the context of hypogonadotropic hypogonadism and profound LH deficiency is a serious condition with very limited options for pregnancy." (Medical Review #2, Oct. 6, 2004, p. 7).

b. Rarity of the Condition

Luveris was granted orphan drug designation by FDA on October 7, 1994.

c. Lack of Available Therapy

"Luveris would be the only LH-alone product . . . on the U.S. market. There are no approved drug products that have the indication of treatment of infertility in women with hypogonadotropic hypogonadism." (Medical Review #3, Sept. 28, 2004, p. 17).

d. External Expertise

The Reproductive Health Advisory Committee considered Luveris on September 30, 2003. "After hearing presentations from experts in Reproductive Endocrinology on the subject of female hypogonadotropic hypogonadism . . . the Committee voted 15 to 0 that the Sponsor's data did not demonstrate efficacy for Luveris in ovulation induction when the primary endpoint was ovulation rate. The Committee voted 8 to 7 that the Sponsor's data demonstrated efficacy for Luveris in ovulation induction when the primary endpoint was follicular development. Finally, the Committee voted 11 to 3 . . . that the Sponsor's data demonstrated efficacy for Luveris for follicular development when the primary endpoint was follicular development." (Medical Review #1 at p. 2) (emphasis in original).

Part 2. Understanding of the Disease Process

FDA's medical review suggests that the disease process is complex and multifactorial: "the role of LH in hypogonadal female infertility patients is clouded by the spectrum of clinical disorders that cause hypogonadotropic hypogonadism with the

differing patterns of gonadotropin secretion may further confound clinical outcome results." (Medical Review #3 at p. 19).

Part 3. Understanding of the Relationship Between Follicular Development and Fertility

"The Division believed that although both follicular development and ovulation are surrogates for pregnancy (the clinically meaningful outcome), ovulation is more temporally proximate to pregnancy and therefore more appropriate as a surrogate." (Medical Review #2 at p. 5). Nevertheless, follicular development is on the causal pathway, as is ovulation. However, there was no epidemiological evidence cited in the FDA review documents linking follicular development to pregnancy.

As for understanding the relationship of drugs in the same or closely-related pharmacologic class on follicular development: "Recognition of the therapeutic potential of gonadotropins began in the 1950's with the extraction and purification of human menopausal gonadotropins (both follicle stimulating hormone and luteinizing hormone) from both human pituitaries and urine sources. Successful clinical pregnancies resulting from the use of these human-derived gonadotropins were first reported in the 1960's. In the 1990's cells that are capable of producing biologically-active LH in culture produced LH. This recombinant derived LH is from in vitro cultured cells." (Medical Review #3 at p. 17).

Part 4. Clinical Evidence of Luveris on Follicular Development and Fertility

"The primary efficacy parameter for both Studies 6905 and 6253 was follicular development as defined by three co-primary endpoints (follicle size as measured by ultrasound, pre-ovulatory serum estradiol levels and mid-luteal progesterone levels). The Sponsor's analysis demonstrated that in Study 6253, 75 IU of Luveris was numerically better than 25 IU of Luveris or placebo for follicular development in women with LH <1.2 IU/L." (Medical Review #1 at p. 3). "The Division's analysis of Study 6905 demonstrated . . . the placebo was as efficacious as 75 IU of Luveris. Therefore, in the opinion of the Division, Luveris was not demonstrated to be effective." (Medical Review #1 at p. 3).

Therefore, the Sponsor planned and conducted a third study, Study 21008, with follicular development as the Sponsor's prespecified primary endpoint, despite the Division's recommendations that ovulation rate be the primary endpoint. The Sponsor's "evaluable patient analysis of Study 21008 demonstrated that 67% of patients receiving 75 IU of Luveris achieved follicular development compared to 20% of patients receiving placebo." (Medical Review #1 at p. 4). "The Director [Dr. Shames] concluded that the results from Studies 21008 and 6253 provide substantial evidence that Luveris 75 IU, when administered concomitantly with FSH, induces follicular development in this population of infertile women. These studies, however, do not demonstrate a positive effect on clinical pregnancy, etc. Study 21415 evaluated titrable FSH dosing with the

dose of Luveris fixed at 75 IU and demonstrated a 36% clinical pregnancy rate after one cycle. While reassuring, this finding is not definitive because there was no placebo comparator group in Study 21415, and the finding has not been replicated in a second trial." (Medical Review #1 at p. 7). Study 21415 also reported follicular development rates of 63% "in all cycles combined." (Medical Review #3 at pp. 29-30). Therefore, in Study 21415, there was within-study clinical evidence both on follicular development, the surrogate, as well as on pregnancy, the ultimate clinical outcome.

9. FABRAZYME (agalsidose beta)

FDA approved Fabrazyme on April 23, 2003 to treat Fabry's disease. This approval was based on a surrogate endpoint of near-elimination of all accumulation of enzyme in renal capillary endothelium, one type of vascular endothelium.

Part 1. Regulatory Factors Weighing into FDA Determination

a. Severity of Condition and Lack of Available Therapy

"[W]ith age, the principal manifestations of concern in Fabry's disease are in the kidney, heart, and brain. Renal disease is manifested by proteinuria, hypertension, and progressive azotemia; the principal cause of death in Fabry's disease in the past was renal failure . . . The median age of death for homozygous males is 50 years." (Medical Review #1, Apr. 21, 2003, p. 4).

b. Rarity of the Condition

Fabrazyme was designated an orphan drug on January 19, 1988.

c. Lack of Available Therapy

"There is no specific treatment for Fabry's disease." (Medical Review #1 at p. 4).

d. Use of External Expertise

"Vessels (capillaries in this case) that are essentially near-normal in appearance that may well lead to an altered development of vascular occlusion, and thus to an alteration in expression of the clinical impairments of the disease. The [January 2003] Advisory Committee has also supported this assessment of the potential impact of near-absence of capillary accumulation, as well as concurring that the evidence submitted by [the Sponsor has] demonstrated this effect on capillary endothelium." (Medical Review #2, Apr. 23, 2003, p. 3).

Part 2. Understanding of the Disease Process

"The underlying basis of Fabry disease is well understood; it is an X-linked enzyme deficiency leading to a lipid storage disorder. Lipid storage occurs in a wide variety of cell types, and consequently there are a wide variety of signs and symptoms from different organ systems . . . However, [there] is widespread belief that a number of the organ injury manifestations are related to vascular injury. It is believed that while this may not be the sole pathologic process, progressive substrate accumulation within vascular walls will ultimately lead to local vessel occlusion, with organ impairment as a consequence." (Medical Review #2 at p. 3).

Part 3. Understanding of the Relationship Between Near-Elimination of Substrate in the Renal Capillary Endothelium and the Outcomes of Fabry's Disease Including Renal Failure and Mortality

"Vascular injury does appear to be an important mechanism of promoting the progressive organism impairment, and substrate accumulation within vascular walls is the basis for this. The exact (quantitative) relationship between the amount of substrate accumulation and the degree or rate of vascular ischemia is unknown and not addressed in any information presented by [the Sponsor]. It is unknown if reducing substrate accumulation by half might show vascular injury by half, or if there is a threshold effect, wherein some specific amount of accumulation will invariably lead to vascular occlusion and thus no change in the clinical expression of the disease. However, by focusing upon a near-elimination of all accumulation within a specific cell type [the Sponsor's] data appear to overcome these concerns." (Medical Review #2 at p. 3).

"Following FDA requests to [the Sponsor], additional data were submitted which demonstrated that while not all cell types show a marked decrease in substrate accumulation (e.g., renal podocytes, with a limited degree of reduction in substrate accumulation) there are a variety of cell types with moderate and several that show marked reduction in substrate accumulation." (Medical Review #2 at p. 1).

As for understanding the relationship of drugs in the same or closely related pharmacologic class on near-elimination of substrate in specific cell types and Fabry's disease, there were no other drugs approved at that time, and there was only one other drug with controlled clinical studies in Fabry's disease, Replagal.

Part 4. Clinical Evidence on Substrate Reduction in Certain Cell Types and Fabry's Disease Outcomes

a. Substrate Reduction

The primary endpoint in the 58 patient, placebo-controlled randomized trial was clearance (that is, elimination) of kidney intestinal capillary endothelium GL-3 inclusions (or substrate). While none of the 29 placebo subjects achieved a score of "zero" GL-3 inclusions over the 5 month duration of the trial, 20 of the 29 Fabrazyme subjects "cleared" all substrate ($p<0.001$) (Medical Review #1 at p. 30).

b. Clinical Outcomes

"The clinical trials failed to show clinical benefit on a wide range of tests of neurologic, renal, and cardiac function. This finding weakens confidence in the clinical importance of the reduction of kidney interstitial capillary endothelial cell GL-3 [enzyme substrate] that constituted the primary endpoint of the pivotal trial." (Medical Review #1 at p. 74).

In the pivotal study, there was only one secondary endpoint that assessed a clinical outcome, and that was pain. In the five ways in which pain was assessed, the placebo group outperformed the treated group in 4 of the 5 measures of pain. (Medical Review #1 at pp. 35-36). There were tertiary endpoints that assessed clinical outcomes and in eight of these, there were no numerical between-group differences, and in one measure of neuropathy, the placebo group fared somewhat better and in two measures (symptom-free days and episode-free days), the Fabrazyme group fared somewhat better. Of interest, renal function was assessed by Inulin-GFR and by serum cystatin-C, and on both of these measures of renal function, there were essentially no numerical differences between placebo and Fabrazyme groups. Among "other" endpoints, there were ophthalmic assessments, and "the ophthalmological findings, like the tertiary endpoints, did not show a clinical change effected by the product." (Medical Review #1 at pp. 39-42).

10. REMODULIN (trepostinil)

The May 21, 2002 approval of Remodulin for treating pulmonary hypertension (now referred to as pulmonary arterial hypertension or PAH) was based on an intermediate clinical endpoint of 6-minute walk (6MW) test, a measure of exercise capacity that is a clinical endpoint, but not the ultimate clinical outcome of this serious disease.

Part 1. Regulatory Factors Weighing into FDA Determination

a. Severity of the Condition

PAH is a serious, life-threatening condition.

b. Rarity of the Condition

FDA designated Remodulin for PAH an orphan drug on June 4, 1997.

c. Lack of Available Therapy

The only other therapy approved before Remodulin was Flolan, whose labeling states that "8 of 40 patients receiving standard therapy alone died, whereas none of the 41 patients receiving Flolan died (p=0.003)." (Medical Review, Mar. 28, 2001, p. 55). This same Medical Review states also that Flolan's "use is difficult and inconvenient. The infusion of Flolan requires the insertion of an indwelling central catheter with the . . . subsequent risk of catheter infection . . . Any inadvertent interruption of the infusion is potentially life-threatening." (Medical Review at p. 55).

d. External Expertise

The Cardiovascular and Renal Drugs Advisory Committee, on August 9, 2001, voted 6 to 3 in favor of approving Remodulin.

Part 2. Understanding of the Disease

The pathophysiology of PAH is well-understood.

Part 3. Understanding of Relationship Between 6MW Results and Clinical Worsening of PAH

Exercise capacity as measured by the 6MW test was judged by FDA as reasonably likely to predict clinical benefit, which was determined to be clinical worsening of PAH symptoms. Confirmation of FDA's decision to rely upon the 6MW test results as predictive of clinical benefit was later seen in that this same measure, 6MW, was the basis for the approval of several subsequent PAH therapies, especially after this Sponsor's successful completion of its Phase 4 confirmatory trial established Remodulin's effect on preventing clinical worsening ($p<0.001$). The Sponsor's Phase 4

trial results on clinical worsening demonstrated the positive predictive value of the 6MW test results with Remodulin.

Part 4. Clinical Evidence on 6MW and on Clinical Worsening or Mortality

The primary endpoint of the pivotal trials was "change in [6 minute] walking distance from baseline at the end of week 12 . . . The database was to be considered demonstrating a benefit for [Remodulin] if either both studies where by themselves significant at the $p<0.049$ or if one study was significant ($P<0.049$) and the pooled studies had a p-value of less than 0.01 . . . Neither of the studies demonstrated a p-value of <0.049 ($p=0.06$ for both studies), although the pooled studies demonstrated an overall p-value of <0.01 ($p = 0.006$ for the pooled studies)." (Medical Review at p. 10). In the pivotal [Remodulin] studies, the drug demonstrated no mortality benefit. (Medical Review at p. 14).

11. CIPRO (ciprofloxacin hydrochloride)

On August 30, 2000, FDA approved a supplemental NDA for Cipro for prophylaxis after exposure to inhalational anthrax. There was a two-part or "compound" surrogate for this approval in that FDA concluded: (1) that Cipro reduced "the rate of death due to anthrax over control in the macaque monkey model," (Statistical Review, Aug. 16, 2000, p. 3), and (2) "that [Cipro] serum concentrations achievable in human populations reach or exceed those associated with improved survival in animals exposed to aerosol challenge with spores of *B. anthracis* [in that] serum concentrations in both human and animal populations consistently exceed the MIC_{90} of the causative organism."[11] (Medical Review, August 31, 2000,[12] p. 34).

Part 1. Regulatory Factors Weighing into FDA Determination

a. Severity of the Condition

"The mortality rate of inhalational anthrax is as high as 80-100% . . ." (Statistical Review, August 16, 2000, p. 1).

b. Rarity of Condition

"[I]nhalational anthrax is extremely rare. There have been only approximately 20 cases in the United States in the past 100 years . . . For these two reasons, the rarity of disease and the extremely high mortality rate, a clinical study is not feasible." (Statistical Review at p. 1). Although the prevalence of inhalation of anthrax is sufficiently low, the sponsor did not seek orphan drug designation.

c. Lack of Available Therapy

"There are drugs with currently approved labeling by FDA for disease associated with *B. anthracis.* Labels for penicillin, tetracycline, doxycycline, and minocycline products list *B. anthracis* among the organisms susceptible to these agents. None of these agents is indicated specifically for post-exposure prophylaxis for disease caused by inhaled *B. anthracis.*" (Medical Review at p. 2).

d. External Expertise

The Anti-Infective Drug Products Advisory Committee on July 28, 2000 unanimously voted "yes" to the question: "Do the data presented support the safety and

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[11] Obviously, there was no requirement for a Phase 4 confirmatory study, and the commentators hope there is never any open-label uncontrolled anecdotal evidence obtained.

[12] The Medical Review was completed, signed and dated the day after the approval.

efficacy of [Cipro] for post-exposure prophylaxis of inhalational anthrax?" (Medical Review at p. 33).

Part 2. Understanding of the Disease Process

"The inhalational form of the disease, which affects the mediastinal lymph nodes, other organs of the reticuloendothelial system and the central nervous system, is considered the most likely clinical entity resulting from the intentional use of an aerosolized preparation of the spores of *B. anthracis*." (Medical Review at p. 2).

Part 3. Understanding of the Relationship Between the Monkey Studies and Human Mortality; and Part 4. Clinical Evidence

First, "the p-value comparing the death rate of [Cipro] to that of control is highly significant (p=0.0011) showing that the treatment with [Cipro] significantly reduces the rate of death due to anthrax over control in the macaque monkey model." (Statistical Review at p. 3).

Second, as for comparative monkey/human exposure levels, the data "demonstrates that [Cipro] peak and trough serum concentrations achieved in the Rhesus monkey are reached or exceeded in human populations receiving the doses recommended for the post-exposure inhalational anthrax. Peak and trough concentrations reported in both monkey and human populations are shown to consistently exceed 0.06 mcg/ml, the value of the MIC_{90} for *B. anthracis*." (Medical Review at p. 10).

As for understanding the relationship of drugs in the same or closely related class on the compound surrogate, see above discussion under 1.c. regarding other drugs approved for anthrax, but note that none had evidence that assessed their utility specifically against post-exposure inhalational anthrax.

Monkey survival data was one part of this unusual compared surrogate; see the discussion above. Moreover, the Medical Reviewer stated: "There have been no prospective studies performed that link clinical outcome to drug exposure for infection with *B. anthracis*. However, in general, when there is a demonstrated relationship between plasma concentrations of drug and response, pharmacokinetic data may be used as one way to relate dose and possible outcome." (Medical Review at p. 14).

12. CELEBREX (celecoxib)

FDA's December 23, 1999 approval of a supplemental NDA for Celebrex to reduce the risk of colorectal cancer in patients with familial adenomatous polyposis (FAP) was based on a surrogate endpoint which was reduction in colorectal polyps.

Part 1. Regulatory Factors Weighing into FDA Determination

a. Severity of the Condition

"The average life expectancy for patients with untreated FAP has been estimated to be 42 years." (Medical Review, Dec. 22, 1999, p. 25).

b. Rarity of the Condition

"The frequency of the FAP gene has been estimated on the basis of disease prevalence to be 1 in 5,000 to 1 in 7,500." (Medical Review at p. 22). Although the prevalence of FAP is sufficiently low, the Sponsor did not seek orphan drug designation.

c. Lack of Available Therapy

"Surgical therapy is the only acceptable option for patients with FAP after colonic polyps have been detected." (Medical Review at p. 26).

d. Use of External Expertise

Here are the recommendations of the Oncologic Drugs Advisory Committee that met on December 14, 1999:

i. Do you believe that a reduction in colorectal polyps count in FAP patients in focal areas of some magnitude is "reasonably likely" to predict benefit?

Yes: 13 No: 0 Abstain: 2

ii. Do you believe that the observed reduction (about 25% at 6 months) is likely to predict benefit in FAP patients?

Yes: 12 No: 0 Abstain: 3

iii. Do you recommend approval of Celebrex under the accelerated approval rule for treatment of FAP?

Yes: 14 No: 0 Abstain: 1

(Medical Review at pp. 76-77).

Part 2. Understanding of the Disease Process on Polyp Counts on Colon Cancer

"FAP is characterized by the presence of hundreds to thousands of colorectal adenomatous polyps and the inevitable development of colon cancer . . . The disease results from germ line mutations of the APC gene . . . The APC gene is thus believed to be a tumor suppressor gene." (Medical Review at pp. 22-23). "A significant body of evidence suggests that cellular expression of COX-2 is prominent in several types of tumors, including colon . . . as well as pre-cancerous changes such as Barrett's esophagus, the adenomatous polyp and actinic keratosis." (Medical Review at p. 15).

Part 3. Understanding of the Relationship Between Reducing Polyp Counts and Colon Cancer

"Celebrex was evaluated in two models of colon cancer. The Min mouse model represents a genetic model of human FAP . . . Adenomas and adenocarcinomas of the colon can be chemically induced in rats by administration of azoxymethane." Celebrex was shown to prevent or inhibit colorectal tumor development in both of these animal models. (Medical Review at pp. 16-17).

As for understanding the relationship of drugs in the same or a closely-related class on FAP polyp counts, "studies have shown that Sulindac, one of the non-selective NSAIDs, induces apoptosis . . . Recent study of COX-2 inhibitors showed that inhibition of COX-2 produced sequential increases in arachidonic acid and ceramide, the latter a potent stimulant of apoptosis. Furthermore, *in vitro* evidence exists that angiogenesis is regulated by COX-2 expression in colon cancer cells. Therefore, another mechanism by which tumor growth may be inhibited by COX-2 inhibitor is through blockade of angiogenesis and tumor vascularization." (Medical Review at pp. 15-16).

Part 4. Clinical Evidence on Polyp Counts and on Colon Cancer

"A single, randomized, double-blind, placebo-controlled study has been submitted. A total of 83 patients received treatment with either placebo, Celebrex 100mg BID, or Celebrex 400mg BID for 6 months (with a 1:2:2 randomization) . . . The mean reduction in colorectal polyps count was 28% on the Celebrex 400mg BID arm, 15% on the Celebrex 100mg BID arm and 5% on placebo. Only treatment with Celebrex 400mg BID was associated with a statistically superior mean reduction in polyp counts, with p=0.003." (Medical Review at pp. 1-2). In a six-month study there were, as expected, no cases of colon cancer in any arm of the trial.

13. SYNERCID (dalfopristin/quinupristin)

The FDA approval of Synercid on September 21, 1999 was for treating patients with vancomycin-resistant *Enterococcus faecium* (VREF) and was based on a surrogate showing of clearance of the VREF bacteremia.

Part 1. Regulatory Factors Weighing into FDA Determination

a. Severity of the Condition

"The mortality rates in both [pivotal] studies [were] approximately 50%." (Statistical Review, Mar. 5, 1998, p. 17).

b. Rarity of the Condition

The Sponsor has no intention of developing Synercid for this use, but a "rise in the United States in both the number of nosocomial infections due to *E. faecium* and in the proportion of strains of this pathogen found to be vancomycin-resistant, led to increasing requests for the emergency use of Synercid." (Medical Review, Aug. 21, 1998, p. 2). Synercid appears not to have been granted orphan drug designation. Given the Sponsor's reluctance to submit an NDA for this use, the Sponsor likely never had applied for designation, even though the condition was rare.

c. Lack of Available Therapy

Those patients who enrolled in the two pivotal trials were only those "infected with VREF who did not have any other therapeutic option." (Statistical Review at p. 2).

d. External Expertise

On February 19, 1998, the Anti-Infective Drugs Advisory Committee voted 9 to 1 in favor of approval of Synercid for VREF.

Part 2. Understanding of the Disease Process

The understanding of the pathophysiology of infections with vancomycin-resistant strains of *Enterococcus faecium* is well-known.

Part 3. Understanding of the Relationship Between Clearance of the VREF Bacteremia and Mortality (and Other IDSA/FDA Guideline Clinically Meaningful Endpoints)

"The VREF literature is clear that VREF bacteremia . . . should be treated and that clearance of VREF from the bloodstream can be seen as beneficial to the patient . . . There is consensus that bacteremia should be treated. Thus, while clearance of bacteremia is not a clinical benefit by itself, it can be seen as likely to predict clinical benefit. Thus, it is proposed that the clearance of VREF bacteremia be viewed as a

surrogate endpoint likely to predict clinical resolution of infection." (Medical Review at p. 32).

Part 4. Clinical Evidence on VREF Bacteremia Clearance and Mortality

FDA concluded that the four emergency use VREF studies did not provide evidence of an improvement in mortality or resolution of infection due to a host of issues. None of these four studies had a concurrent control and, while FDA had advised that the lack of concurrent control would be acceptable because it would be unethical to include a placebo arm, FDA had stipulated that the studies either: (1) had to show a "dramatic improvement in overall mortality as compared to a historical perspective" (Medical Review at p. 30) and these studies did not (these four studies had mortality rates of 48.8%, 49.5%, 53.8% and 54.0% compared to the VREF literature reporting "all-cause" mortality rates in the range of 30% to 70%) (Medical Review at p. 18); or (2) had to have a historical control and this was not established (Medical Review at pp. 18-19).

While two of the four studies, according to the FDA Medical Reviewer, established clearance of VREF bacteremia, only 18% of the patients in these emergency use studies were "evaluable" due primarily to missing data, and there was a low response rate as well. (Medical Review at pp. 19-20, 29-32). In addition, "in the unevaluable patients who died on therapy but with negative blood cultures, there is 'apparent' clearance of the organism." (Medical Review at p. 32).

14. REMICADE (infliximab)

The August 24, 1998 FDA approval of Remicade to treat patients with Crohn's disease was based on an intermediate clinical endpoint of a clinical response defined as a reduction in the Crohn's Disease Activity Index (CDAI) of at least 70 points at the 4-week evaluation.

Part 1. Regulatory Factors Weighing into FDA Determination

a. Severity of the Condition

"The prognosis for Crohn's disease is generally unfavorable . . . The mortality rate increases with the duration of disease and most likely ranges from 5% to 10%. Most deaths occur from peritonitis and sepsis." (Medical Review, July 10, 1998, p. 4).

b. Rarity of the Condition

"In . . . the United States, the prevalence is estimated at 20 to 40 per 100,000." (Medical Review at p. 3). Remicade was designated as an orphan drug on November 14, 1985.

c. Lack of Available Therapy

The FDA Medical Review surveys all the therapies being used and at the time, no robustly effective therapies were available. "Because its cause is unknown, medical management of the disease is largely empirical and is designed to reduce inflammation." (Medical Review at p. 5).

d. External Expertise

On May 28, 1998, the Anti-Infective and Gastrointestinal Drug Advisory Committees voted unanimously in favor of approval for both: treatment of patients with moderate-severe inflammatory disease refractory to conventional therapy, and treatment of patients with fistulizing Crohn's disease for the reduction in the number of draining enterocutaneous fistula(s).

Part 2. Understanding of the Disease Process

"Crohn's disease most likely represents a heterogeneous group of disorders. After much effort that has focused on the identification of a specific pathogenic cause, it is being recognized that disease manifestations could result from a combination of any, or all of, a number of factors." (Medical Review at p. 2).

Part 3. Understanding of the Predictive Potential of a 70 Point Change in CDAI at Week 4 on Crohn's Disease

"Pathologic review of biopsy . . . often can aid in . . . measurement of extent and severity of disease. Pathologically, Crohn's disease is described as a transmural disease with focal or microscopic skip areas of inflammation in the lamina propria. The degree of inflammation in the most heavily involved area often is an accurate assessment of the severity of disease . . . Disease activity indices are used to objectively measure the activity of disease for judgment of response in clinical trials. The [CDAI] was developed . . . [in] 1979 . . . to objectively assess response to therapy . . . Although imperfect and cumbersome, e.g., requirement of recording of symptoms for 7 days and for hematocrits, the CDAI remains the most commonly [used] index." (Medical Review at p. 4).

As for understanding the relationship between drugs in the same pharmacologic class, Remicade is a chimeric monoclonal antibody to Tumor Necrosis Factor (TNF). As such, Remicade was the first of this kind in a new class of immunomodulatory drugs. Other immunomodulatory drugs, including azathioprine, mercaptopurene, cyclosporine, and methotrexate were accepted for use for long-term treatment of some Crohn's patients. "The mechanism of action of these drugs may involve inhibition of lymphocyte function, primarily that of T cells." (Medical Review at p. 5). As such, they have a different mechanism of action than Remicade.

Part 4. Clinical Evidence on CDAI and on Long-Term Clinical Benefit

Study T16, a placebo-controlled, dose-ranging (n=108) study, "was designed as a Phase 2 trial to determine an effective dose in the acute treatment of patients with active Crohn's disease not responding to immunosuppressant therapy and to explore maintenance therapy with a single dose in patients who responded initially. This clinical trial became the pivotal trial for licensure of [Remicade] for this indication." (Medical Review at p. 10). "65.1% of the [Remicade] treated patients achieved a clinical response ($\geq$ 70-point reduction from baseline in the CDAI) at the week 4 evaluation compared to 16.7% of the placebo patients ($p<0.001$) . . . There was no apparent relationship between [Remicade dose] [5mg/kg, 10mg/kg, 20mg/kg] and the proportion of patients responding; the highest clinical response was observed in the 5mg/kg dose group (81.5%; $p<0.001$ vs placebo)." (Medical Review at p. 19).

In the Medical Review's Summary Conclusions on the Review of the Safety and Efficacy Data, the Medical Reviewer stated that "[t]he Sponsor has presented phase 2 clinical data results to support licensing of a potent, novel immunomodulating agent for the management of patients with Crohn's disease, a chronic debilitating disease . . . The number of patients with moderate to severe disease who have received the proposed dose of 5mg/kg . . . is very low (n=28) and no patients have received chronic retreatment with 5mg/kg every 8 weeks as proposed in the original submission. The effects of a single dose [last] approximately 12-16 weeks, compatible with the half-life of the compound.

For patients with fistula, although the majority of patients experienced stoppage of drainage in two weeks, there are no data on internal healing of the fistula canal. Once [Remicade] was stopped the effect of therapy was lost. In summary, there are inadequate data to support the long-term benefit of [Remicade] in patients with either fistulizing or moderate/severe disease." (Medical Review at p. 81).

From the conclusions of the Medical and Statistical Reviews, there appear to have been some concerns among FDA Reviewers as to the appropriateness of the short-term (CDAI improvement after 4 weeks) surrogate endpoint as being adequate to predict long-term benefit in a chronic disease. The conclusion of the Statistician on Study T16 in moderate to severe Crohn's disease patients was redacted from the publicly available version of the Statistician's Review. However, there was a second Phase 2 study in patients with Crohn's disease with fistula, Study T20, which is referred to in the conclusions of the Medical Review. From the information in the Statistician's Review of Study T16 that was made publicly available, it would seem that the Statistician's conclusions with respect to Study T20 may have closely paralleled those for Study T16. With respect to Study T20, here are the Statistician's conclusions: "Although the differences in response rates between the placebo group and the [Remicade]-treated groups were statistically significant, questions remain about the durability of response. Patients received doses at weeks 2, 4, and 6, but this dosing strategy should be thought of as one-time dosing. After 6 months of follow-up, the drug effect had disappeared and the proportion of responding patients in the placebo arm was similar to the proportions in the treatment arms. The data suggest, therefore, that although this agent has an initial beneficial effect on Crohn's disease, a single set of doses is unlikely to provide durable benefit in this chronic disease. There are no data to assess chronic use of [Remicade] for this indication. There is no information regarding the formation of neutralizing antibodies (HACA) with repeated dosing and how this may affect the efficacy of this product. There is also no safety data to allay concerns of a possible increase in malignancies or serious infections. The Agency should carefully weigh the observed early benefits seen with this product against the paucity of information regarding the safety and efficacy of repeated use for this chronic indication." (Statistical Review, Aug. 5, 1998, p. 13).

15. PRIFTIN (rifapentine)

On June 22, 1998, FDA approved Priftin for treating pulmonary tuberculosis (TB) and this approval was based on a surrogate of a 6-month relapse rate as contrasted with the standard 2-year relapse rate information for a traditional approval.

Part 1. Regulatory Factors Weighing into FDA Determination

a. Severity of the Condition

"[TB] is the leading infectious cause of morbidity and mortality worldwide." (Medical Review, June 19, 1998, p. 5).

b. Rarity of the Condition

"In 1990, there were 25,701 new cases of TB reported in the [U.S.]" (Medical Review at p. 5). Priftin was designated as an orphan drug on June 9, 1995.

c. Lack of Available Therapy

"During development of rifapentine for TB, the applicant was encouraged to submit 6 month follow-up data from one study, under the accelerated approval regulations (21 CFR 314 Subpart H). There is a need for new anti-tuberculosis medications, and for medications which will potentially increase the adherence to dosing thereby decreasing the potential for the development of resistant organisms. It was anticipated that rifapentine would be such an agent. Six-month relapse data would serve as a surrogate for two-year relapse data predictive of long term clinical benefit." (Medical Review at p. 8). FDA had previously approved rifampin for use in treating TB.

d. Use of External Expertise

At the Anti-Viral Advisory Committee Hearing on May 5, 1998, "the committee voted to recommend approval of [Priftin] for the treatment of pulmonary tuberculosis, with only one dissenting vote." (Medical Review at p. 61).

Part 2. Understanding of the Issues

In this case, the pathophysiology of TB is well-understood.

Part 3. Understanding of the Predictive Potential of a Six-Month Relapse Rate on Two-Year Relapse Rate and on Mortality

The Medical Review stated that: "It is expected that the majority of relapses will occur by 6 months of follow-up, however, the 'gold standard' is 2-year relapse rate." (Medical Review at p. 19). However, the pattern of relapses for [Priftin] does not appear to reflect the same showing of relapses in the latter half of six-month follow-up that was seen for rifampin in the pivotal study. See discussion of results under Section 4.

Part 4. Clinical Evidence on Six-Month and Two-Year Relapse Rates

The single pivotal trial was an open-label, randomized, two-arm parallel, rifampin-controlled trial with 570 patients in the modified ITT analysis. "The primary efficacy endpoint for this accelerated approval review was treatment outcome at the end of 12 months (6 months of active treatment + 6 months of follow-up). This was a binary variable with success defined as achieving a negative sputum culture during active treatment and sustaining it to the end of [6] months of follow-up." (Statistical Review, July 27, 1998, p. 3).

"There is essential equivalence for [negative sputum culture] rates at the end of [the 6-month active treatment] between the rifampin [83% negative sputum cultures] and [Priftin] [88%] arms." (Medical Review at p. 39). However, "[t]here is a statistically significant difference between the treatment arms for relapse . . . The risk is 5% for rifampin . . . and 11% for [Priftin]." (Medical Review at p. 40). The Statistical and Medical Reviews agree that while 10 of the 11 relapses on rifampin occurred within the first 6 months of follow-up, 7 relapses occurred in the [Priftin] arm at time points between 6 and 12 months of follow-up. (Note: While the endpoint was at 6 months of follow-up, almost all subjects had had 12 months of follow-up, so FDA analyzed the 12 months of follow-up data as well and noted that the Priftin arm continued to experience sizable numbers of relapses beyond the first 6 months of follow-up, which was much different than the pattern of relapses observed for rifampin).

Despite the above discrepancy between the rifampin and Priftin arms in relapse rate beyond 6 months, the FDA reviewers seemed (as well as the Advisory Committee members) to believe that this may reflect lack of optimized dosing of Priftin, rather than a lack of confidence in the prognostic surrogate of 6-month relapse rate predicting 2-year relapse rate, and eventually, survival. However, at the time of approval there appear to be no clinical evidence of Priftin on 2-year relapse rate or on mortality.

16. SULFAMYLON (mafenide acetate)

FDA approved Sulfamylon on June 5, 1998, "to control bacterial infection when used under moist dressings over meshed autografts on excised burn wounds." The approval was based on an intermediate clinical endpoint of evidence derived from patients who were burned over up to 20% of their total body surface area (TBSA) with a Phase 4 commitment to conduct a confirmatory trial in patients with 20% to 60% TBSA thermal injuries.

Part 1. Regulatory Factors Weighing into FDA Determination

a. Severity of the Condition

The Medical Review commenting on the results of the single pivotal trial (done exclusively in children) observed the following: "It is remarkable that so many of these severely burned children survived to leave the hospital . . . It is not unexpected that survival rates fall as TBSA burned increases." (Medical Review, Sept. 23, 1997, p. 17). Large [TBSA] burns are serious and life-threatening." (Medical Review at p. 49).

b. Rarity of the Condition

The number of persons in the country in need of such care is small, thankfully, very small. FDA designated Sulfamylon as an orphan drug for this use for two different sponsors at separate times: on August 29, 1985 and on July 18, 1990. (Medical Review at p. 3).

c. Lack of Available Therapy

"There is no existing approved treatment for these burn patients who require excision and meshed autografts." (Medical Review at p. 50).

d. External Expertise

"Sulfamylon [was] discussed by the FDA Anti-Infective Drug Products Advisory Committee [on July 24, 1996]. The Committee concluded that since topical antimicrobial solutions had evolved to a standard of care [(SOC)] over the last 20 years, a placebo-controlled study would be unethical." (Medical Review at p. 3).

Part 2. Understanding of the Disease Process

"There is adequate evidence available in the literature to establish that wounds, including burn wounds, may be expected to progress satisfactorily if the microbial load present is reduced to less than 10^5 organisms per gram of tissue . . . it may be said that if a topical antimicrobial is successful in maintaining low bacterial levels on a newly placed skin graft until the graft is adequately vascularized, the antimicrobial has contributed to take of the graft." (Medical Review at p. 42).

Part 3. Understanding of the Relationship Between the Treatment Failures in Those with <20% TBSA Burned and Treatment Failures in Those with >20% TBSA Burned

"The applicants have been reluctant to use a vehicle control on the grounds that failure to treat a burn patient with a [TBSA] burn of larger than 10-20% would be unethical." (Medical Review at p. 4). This was supported by the deliberations of the Advisory Committee. Therefore, while the single pivotal trial enrolled all patients with burns, regardless of how extensively the body was burned, there was "no protocol-specified assignment of patients to treatment with [either Sulfamylon or standard of care (SOC)]. This was a medical decision, made by the attending physician . . . The reviewers separated the results into patient groups by TBSA burned. All patients who had burns covering more than 40% TBSA were treated with [Sulfamylon] . . . It is impossible to assess the effect of [Sulfamylon] in this group. In the 20-40% TBSA burn group, there were a few patients who received [SOC] but . . . the contribution of [Sulfamylon] is difficult to quantify. However, there [were] sufficient [SOC] patients in the 0-20% TBSA burn group to permit comparison of the two treatment regimens." (Medical Review at p. 48).

As for understanding the relationship between drugs in the same pharmacologic class as Sulfamylon, "Sulfamylon for 5% Topical Solution" is the drug product that was the subject of this NDA. However, "Sulfamylon cream is currently approved for use in the treatment of second and third degree burns and the proposed indication for the Sulfamylon 5% solution is related. (Medical Review at p. 49). "Because of the pain caused by the cream, burn physicians began to make a 5% solution using mafenide acetate power in the mid-1970s . . . and the 5% solution has become the standard of use in some burn units for maintaining skin grafts in the period between graft placement and graft take." (Medical Review at p. 4).

Part 4. Clinical Evidence on Those with <20% and Those with >20% TBSA Burned

The single pivotal efficacy study was an unblinded, retrospective, non-randomized, parallel group study with an active control of Standard of Care (SOC) and was conducted at a single site and with a single investigator: Dr. Glenn Warden at Shriner's Burn Institute in Cincinnati, Ohio.

In this study, among the 229 procedures in persons with less than 20% TBSA burned, there were 19 (19%) who were "treatment failures" in those treated with Sulfamylon compared to 33 (26%) who failed on SOC. However, those treated with Sulfamylon had more serious burns, that is, third-degree burns (6.5% vs. 3.3% SOC), a higher percentage of the body surface area burned (10.6% vs. 7.0% SOC), and fewer with only less serious burns, that is, those with second-degree burns only (4.4% vs. 17.3% SOC).

"In her review, the reviewing Statistician, Dr. Yulan Li, reached the following conclusion: Based on the Cincinnati study, the applicant has demonstrated that the use of [Sulfamylon] is associated with the decreasing of treatment failure in the subgroup of patients with 0-20% TBSA burns after separately adjusting for etiology and degree of burn. However, it is unknown whether . . . treatment failure reflects the benefit of [Sulfamylon] due to non-random treatment assignment and investigator knowledge of treatment at the time treatment failure was assessed." (Medical Review at p. 6).

While there appears to be no disagreement in any FDA review as to the intermediate clinical endpoint of effect in those with less than 20% TBSA burned as "reasonably likely to predict benefit" in those with burns over more than 20% TBSA; there were concerns expressed, especially by the Statistician, as to the strength of the efficacy evidence for the findings in those with less than 20% TBSA burned.[13]

[13] While scored as a "1," the strength of clinical evidence on the surrogate here with Sulfamylon could reasonably be scored as either "1" or "zero," and the same may be said of the strength of clinical evidence for the surrogate in Synercid, Precedent #13.

17. PROAMATINE (midodrine hydrochloride)

FDA approved Proamatine for treating "symptomatic orthostatic hypotension" on September 6, 1996 on the basis of "increases in 1-minute standing systolic blood pressure, a surrogate marker likely to correspond to a clinical benefit" (as stated in FDA-approved labeling).[14]

Part 1. Regulatory Factors Weighing into FDA Determination

a. Severity of the Condition and Lack of Alternative Therapy

Although the review documents for Proamatine are not publicly available on FDA's website, the Agency's Subpart H approval of Proamatine has to mean that FDA assessed the condition as rather serious and lacking available therapy.

b. Rarity of the Condition

Proamatine was designated as an orphan drug on June 21, 1985.

c. External Expertise

There is no evidence from documents currently available, including approved labeling and trade press, whether FDA sought the advice of an Advisory Committee. Therefore, we scored this as a "zero."

Part 2. Understanding of the Disease

For FDA to have approved Proamatine on the basis of a change in 1-minute systolic blood pressure suggests that FDA must have considered that there was a sound understanding of the pathophysiology of the disease.

Part 3. Understanding of the Relationship Between Change in 1-Minute Systolic Blood Pressure and the Ability to Perform Life Activities

Since there are no other drugs in any class approved for this condition, FDA could not have relied upon their effects on this disease. However, many drugs are approved on changes in blood pressure as a validated surrogate based upon both robust epidemiology and multiple interventions affecting serious cardiovascular outcomes such as MACE, and FDA may have relied upon this strong association for support of the power of a change in 1-minute systolic blood pressure in this disease to predict clinical benefit in this disease.

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[14] All of the formation in this analysis is drawn from the FDA approved labeling, as no Medical or Statistical Reviews from FDA were publicly available.

Part 4. Clinical Evidence on 1-Minute Systolic Blood Pressure and Clinical Outcome

"Midodrine has been studied in 3 principal controlled trials, one of 3-weeks duration and two of 1-to-2 days duration. All studies were randomized, double-blind and parallel-design trials in patients with orthostatic hypertension of any etiology and supine-to-standing fall of systolic blood pressure of at least 15 mmHg accompanied by at least moderate dizziness/lightheadedness . . . In the 3-week study in 170 patients . . . , the midodrine-treated patients . . . had significantly higher (by about 20 mmHg) 1-minute standing systolic pressure 1 hour after dosing . . . for all 3 weeks. After week 1, midodrine-treated patients had small improvements in dizziness/lightheadedness/unsteadiness scores and global evaluations, but these effects were made difficult to interpret by a high early drop-out rate (about 25% vs. 5% on placebo). Supine and sitting blood pressure rose 16/8 and 20/10 mmHg, respectively, on average. In the 2-day study, after open-label midodrine, known midodrine responders received midodrine 10 mg or placebo at 0, 3, and 6 hours. One-minute standing systolic blood pressures were increased 1 hour after each dose by about 15 mmHg and 3 hours after each dose by about 12 mmHg; 3-minute standing pressures were increased also at 1, but not 3, hours after dosing. There were increases in standing time seen intermittently 1 hour after dosing, but not at 3 hours. In the 1-day, dose-response trial, single does of 0, 2.5, 10, and 20 mg of midodrine were given to 25 patients. The 10- and 20-mg doses produced an increase in standing 1-minute systolic pressure of about 30 mmHg at 1 hour; the increase was sustained in part for 2 hours after 10 mg and 4 hours after 20 mg. Supine systolic pressure was =200 mmHg in 22% of patients on 10 mg and 45% of patients on 20 mg; elevated pressures often lasted 6 hours or more." (Midodrine Package Insert).

18. BIAXIN (clarithromycin)

FDA approved Biaxin on December 23, 1993 for treating disseminated mycobacterial infections due to mycobacterium avium complex (MAC) on the basis of a showing of Biaxin's effect on the surrogate of decreases in MAC bacteria.

Part 1. Regulatory Factors Weighing into FDA Determination

a. Severity of the Disease, Rarity, and Lack of Alternative Therapy

The pivotal studies were conducted in persons with CDC-defined AIDS and CD_4 counts <100 cells/μL, and median survival time in the one trial that was randomized and blinded was 249 days and 215 days for the two dose groups reported in the approved labeling.[15]

While Biaxin was not designated as an orphan drug for this use, this condition was not prevalent and the absence of orphan drug status is likely due to the FDA approval of Biaxin for many other prevalent diseases (such that orphan drug exclusivity would have had substantially diminished, if any, value).

b. External Expertise

On May 11, 1993, the Antiviral Drugs Advisory Committee provided insight on the approvability of Biaxin for treatment of MAC.[16]

Part 2. Understanding of the Disease

The pathophysiology of MAC in immune-compromised AIDS patients was likely understood relatively well for the extent of time that the condition had been known.

Part 3. Understanding of the Relationship Between Reducing MAC Bacteremia and Clinical Outcomes

The general axiomatic principles of infectious disease likely guided and illuminated FDA's interpretation of the prognostic value of reducing MAC bacteremia on achieving negative cultures and clinical benefit. Other antibiotic regimens had shown some value as well.

Part 4. Clinical Evidence on Reducing MAC Bacteremia and Clinical Outcomes Including Mortality

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[15] There were no FDA medical or statistical reviews publicly available and nearly all information is from the FDA approved labeling.

[16] Based on public documents currently available, it is unclear what the outcome of this Advisory Committee was.

Of the 3 studies conducted from May 1991 to March 1992, Study 500 was the only one to be blinded and randomized (dose comparison trial of 3 different doses of Biaxin). Study 500 showed a reduction in MAC bacteremia with the lowest dose having the smallest decrease in colony-forming units (CFUs). There was seemingly no survival benefit, as the FDA-approved labeling reported that: "The median survival times for these [Biaxin] dosages were similar to recent historical controls with MAC when treated with combination therapies." However, there was some evidence of improvement in other signs and symptoms of MAC infection including night sweats, fever, and weight loss.

19. BETASERON (interferon beta-1b)

FDA approved Betaseron as the first therapy to treat multiple sclerosis (MS) on July 23, 1993 on the basis of a showing on both rate and extent of exacerbations and on improvement in MRI-measured lesion area.

Part 1. Regulatory Factors Weighing into FDA Determination

a. Severity, Rarity, and Lack of Available Therapy

MS is a serious disease for which, prior to Betaseron, there was no FDA approved treatment. Betaseron was designated as an orphan drug on November 17, 1988.

b. External Expertise

The FDA Peripheral and Central Nervous System Advisory Committee on March 19, 1993 voted 7-2 to recommend approval of Betaseron.

Part 2. Understanding of the Disease

The pathophysiology of multiple sclerosis was known to a fair degree at the time of the conduct of the pivotal trial which permitted the Sponsor, in collaboration with the lead FDA CBER official, Dr. Woodcock, and her office, to have general agreement on co-primary endpoints of clinical utility related to exacerbations, as well as somatic measures of the putatively key causal biologic marker, MRI lesion volume.

Part 3. Understanding of the Relationship Between MRI Lesion Volume and Multiple Sclerosis

"It was also clear that the Committee as a whole placed great weight on the MRI findings in their deliberations. Specifically, although the clinical benefit, as measured by the proportion of exacerbation-free patients and exacerbation frequency, was considered real and of value clinically, the Committee considered the size of the treatment effect to be relatively small.

However, it was obvious that great emphasis was placed on the MRI findings. Specifically, the Committee appeared convinced by the firm's presentation that the drug had an important effect on the underlying pathology as measured by total lesion area as seen on MRI. The statistically significant decrease in the total lesion area in the high dose group as compared to placebo patients over the course of the study that the sponsor claimed was demonstrated was interpreted by the Committee, in my view, as powerful support for the conclusion that the drug was having an important effect on the underlying disease process. While the Committee stopped short of declaring that the data **proved** the drug had an effect on the progression of the disease, I believe it is fair to characterize their view with a quote, made at the meeting, by Dr. McFarland, who said at one point, that, while the sponsor had not proved that the drug had an effect on the course of the

disease, 'I would be amazed if it didn't change the course of disease.' A number of Committee members explicitly referred to Dr. McFarland's comments in this regard when explaining their votes." (Memo of Dr. Katz, May 28, 1993, pp. 356-357) (emphasis in original).

"That is, it appears clear that the Committee felt that the MRI results not only were consistent with the clinical benefit observed (i.e., the changes seen corresponded to the exacerbation rate data at a given point in time), but that they could be relied upon to accurately 'predict' patients' future courses. In other words, the MRI data were considered, for all intents and purposes, as a surrogate marker for disease." (Memo of Dr. Katz at p. 359)

"If the lesions detected on MRI are taken to be a better index of the 'activity' of the pathologic process than are clinical manifestations of MS, (a not unreasonable possibility given the knowledge that lesions detected on MRI may be unaccompanied by clinical signs/symptoms when they occur in so-called 'silent' regions of the CNS) and if the rate of clinical progression of MS (in the sense of increasing physical disability) is a positive function of the activity of that pathologic process, it follows logically that any drug suppressing this 'activity' 'must'[17] have some beneficial effect on the progression of MS (as manifest by increasing physical disability). Although the clinical evidence collected[18] in Study TB01-35(6/8)86 does not provide convincing affirmative support for

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[17] "Must" appears in quotations as a reminder of prior occasions in the history of therapeutics where perfectly logical extrapolations based on beliefs about the pathophysiology of a disease and the postulated mechanism of a drug's action have led experts to reach totally incorrect conclusions about the promise of a particular drug (e.g., CAST: the suppression of ventricular ectopy 'must' save lives.) [Footnote is part of quotation.]

[18] In their report of the study, the sponsor asserts that the correlation between EDSS disability scores and MRI lesion areas detected at both baseline (r=0.169) and at the end of year two (r=0.2) establishes that MRI 'burden' predicts disability (EDSS score). Although these statements are correct in a statistical sense, the correlation does not tell us what we really seek to learn: whether a treatment reducing the extent of MRI area increase over time will reduce the extent of clinical worsening, as judged by EDSS, over the same interval or in a future one. [Footnote is part of quotation.]

this hypothesis, that does not necessarily undercut its appeal or its psychological impact on those asked to render an opinion about the 'therapeutic potential' of Betaseron.

During the PCNS meeting, the sponsor's representatives, several members of the Committee and, in particular, Dr. Henry McFarland, who was attending the meeting as the Agency's expert consultant on neuro-imaging and MS, espoused the hypothesis just described. Although virtually all proponents of this hypothesis acknowledged that the link between MRI lesion frequency/intensity/area and subsequent outcome (progression in level of physical disability) in MS was not proven, almost all affirmed that they would be very surprised if the link was not eventually demonstrated. Thus, for many experts, the number and area of lesions detected on MRI are tantamount to a 'surrogate' endpoint that predicts disease progression in MS." (Memo of Dr. Leber, May 28, 1993, pp. 340-341) (emphasis in original).

"In the Betaseron data there is a second kind of replication, the MRI results, which are more or less persuasive, depending on one's beliefs. At a minimum, as Dr. Leber says, these data are an independent measurement that supports the clinical finding, a kind of 'within-study' replication. At best, they are evidence of an effect far more important than the modest effect on exacerbations. We certainly are not qualified to choose between these interpretations, but our advisors seem to believe the latter, even though all would agree that, strictly, the correlation of improved clinical outcome and improved MRI has not been made.

It would be possible, we believe, to grant approval under the accelerated approval regulations, which allow this procedure where a surrogate or clinical, but <u>non-ultimate endpoint</u> is the basis for approval. (Memo of Dr. Temple to Dr. Woodcock, June 3, 1993, pp. 329-330) (emphasis in original)

Part 4. Clinical Evidence on MRI Lesion Volume and on Reduction in Exacerbations of MS

"The trial was designated as a randomized, double-blind, and placebo-controlled study to evaluate the safety and efficacy of Betaseron in the treatment of patients with relapsing-remitting MS . . . The protocols proposed that the primary efficacy evaluations will be based on reduction in frequency of exacerbations per subject and proportion of exacerbation-free subjects." (Statistical Review, March 1, 1993, p.1).

"The proportions of exacerbation-free subjects in the three arms of the study are given in Table 1. If we consider all reported exacerbations, 18 of the 112 placebo patients (16.1%) and 36 of the 115 45 mIU Betaseron patients (31.3%) were exacerbation-free. This difference was significant at p=0.008." (Statistical Review at p. 3).

"The second primary endpoint, prospectively specified in the protocol, was the frequency of exacerbation per subject . . . If we consider the outcomes in all six

categories of exacerbations (i.e., 0, 1, 2, 3, 4, and 5+) then the probability of better response on Betaseron therapy is 63%. It is significantly different (p=0.0004) from 50%." (Statistical Review at pp. 5-6).

As for the MRI lesion volume results, depending upon the analysis used by the FDA reviewer, Dr. Jay Siegel, the p-value for the comparison between Betaseron and placebo arms ranges from a p-value of 0.03 to a p-value of 0.001. (Memo of Dr. Siegel, June 24, 1993, p. 1)