

Paul G. King's
Formal Comments On Docket Number: 98N-0339

Thursday, 3 September 1998

Documents Management Branch [HFA-305]
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

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Copy 1

RE: Docket No. 98N-0339

FORMAL COMMENTS ON:

Docket Number : 98N-0339

**Comments On : Food and Drug Administration Modernization Act of 1997
(FDAMA)**

**Pursuant to a "request for comments" promulgated under Section
406(b) of FDAMA In:**

Federal Register, 63(142), 39877-39879, Friday, 24 July 1998

REFERENCED SECTION OF FDAMA

SEC. 406. FOOD AND DRUG ADMINISTRATION MISSION AND ANNUAL REPORT.

- (a) Mission.— Section 903 (21 U.S.C. 393) is amended —
- (1) by redesignating subsections (b) and (c) as subsections (d) and (e), respectively; and
 - (2) by inserting after subsection (a) the following:

"(b) Mission.— The Administration shall —

 - (1) promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner;
 - (2) with respect to such products, protect the public health by ensuring that —
 - (A) foods are safe, wholesome, sanitary, and properly labeled;
 - (B) human and veterinary drugs are safe and effective;
 - (C) there is reasonable assurance of the safety and effectiveness of devices intended for human use;
 - (D) cosmetics are safe and properly labeled; and
 - (E) public health and safety are protected from electronic product radiation;
 - (3) participate through appropriate processes with representatives of other countries to — reduce the burden of regulation, harmonize regulatory requirements, and achieve appropriate reciprocal arrangements; and
 - (4) as determined to be appropriate by the Secretary, carry out paragraphs (1) through (3) in consultation with experts in science, medicine, and public health, and in cooperation with consumers, users, manufacturers, importers, packers, distributors, and retailers of regulated products."

98N-0339

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(b) Annual Report. — Section 903 (21 U.S.C. 393), as amended by subsection (a), is further amended by adding at the end the following:

- " (f) Agency Plan for Statutory Compliance.—
- (1) In general.— Not later than 1 year after the date of enactment of the Food and Drug Administration Modernization Act of 1997, the Secretary, after consultation with appropriate scientific and academic experts, health care professionals, representatives of patient and consumer advocacy groups, and the regulated industry, shall develop and publish in the Federal Register a plan bringing the Secretary into compliance with each of the obligations of the Secretary under this Act. The Secretary shall review the plan biannually and shall revise the plan as necessary, in consultation with such persons.
 - (2) Objectives of agency plan.— The plan required by paragraph (1) shall establish objectives and mechanisms to achieve such objectives, including objectives related to —
 - (A) maximizing the availability and clarity of information about the process for review of applications and submissions (including petitions, notifications, and any other similar forms of request) made under this Act;
 - (B) maximizing the availability and clarity of information for consumers and patients concerning new products;
 - (C) implementing inspection and postmarket monitoring provisions of this Act;
 - (D) ensuring access to the scientific and technical expertise needed by the Secretary to meet obligations described in paragraph (1);
 - (E) establishing mechanisms, by July 1, 1999, for meeting the time periods specified in this Act for the review of all applications and submissions described in subparagraph (A) and submitted after the date of enactment of the Food and Drug Administration Modernization Act of 1997; and
 - (F) eliminating backlogs in the review of applications and submissions described in subparagraph (A), by January 1, 2000.
- (g) Annual Report.— The Secretary shall annually prepare and publish in the Federal Register and solicit public comment on a report that —
- (1) provides detailed statistical information on the performance of the Secretary under the plan described in subsection (f);
 - (2) compares such performance of the Secretary with the objectives of the plan and with the statutory obligations of the Secretary; and
 - (3) identifies any regulatory policy that has a significant negative impact on compliance with any objective of the plan or any statutory obligation and sets forth any proposed revision to any such regulatory policy."

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“OBJECTIVES” ON WHICH COMMENT IS BEING SOLICITED

1. “Maximizing the –
 - 1.1 availability of –
and
 - 1.2 clarity of –
 - 1.3 information about the agency –
 - 1.3.1 application –
and
 - 1.3.2 submission review –
 - 1.3.3 processes;
2. maximizing the –
 - 2.1 availability of –
and
 - 2.2 clarity of –
 - 2.3 information –
 - 2.3.1 for –
 - 2.3.1.1 consumers –
and
 - 2.3.1.2 patients –
 - 2.3.2 concerning new products;
3. implementing –
 - 3.1 inspection –
and
 - 3.2 postmarket monitoring provisions of the act;
4. assuring access to the –
 - 4.1 scientific –
and
 - 4.2 technical –
 - 4.3 expertise –
 - 4.5 needed to carry out FDA’s obligations;
5. establishing mechanisms,
 - 5.1 by July 1, 1999,
 - 5.2 for meeting specified time periods for the review of –
 - 5.2.1 applications
and
 - 5.2.2 submissions;

and
6. eliminating backlogs in the review of –
 - 6.1 applications
and
 - 6.2 submissions.”

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To Whomever It May Concern:

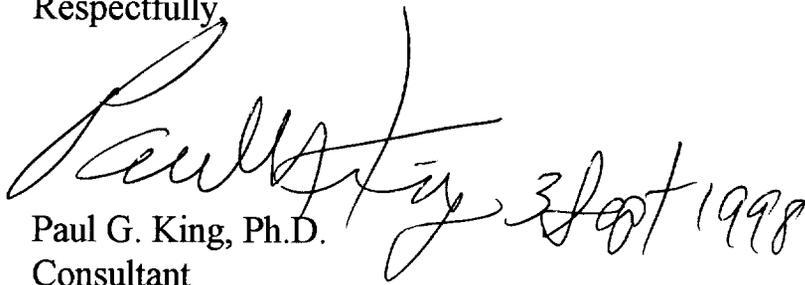
The formal comments on the pages that follow are being submitted in response to the aforementioned request for comment issued in the Federal Register by the Food and Drug Administration.

The comments consist of three sections:

- I. General Comments;
- II. Tabularized Comments On the Objectives Set Forth In The FDA's request for Comments; and
- III. Comments on Specific Sections of FDAMA

Hopefully, these comments will be, for the most part, to the point and helpful to the agency as it endeavors to finalize its initial plan for implementing FDAMA and as it strives to deal with the ongoing issues and competing priorities within the agency.

Respectfully,

 3/20/1998

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I. General Comments

- A.** Overall, the answer to meeting the statutory requirements set forth in FDAMA and those other existing ones that predate FDAMA presupposes that the Agency will be adequately funded, and competently staffed with a cadre of personnel that understand both the scientific/technical realities and the mandated requirements of the regulations and laws governing foods, drugs, medical devices, and cosmetics.
- B.** Unfortunately, even before the passage of FDAMA, the Agency was not adequately funded to discharge many of its preexisting statutory requirements such as at least biannual inspection of all companies listed as drug manufacturers. Moreover, under the administrative governmental reorganization pressures and the legislative budgetary pressures of the early 1990's offered an early retirement program that effectively reduced the overall competency of the Agency's staff and resulted in the Agency's losing many of its most knowledgeable personnel.
- C.** As legislated, FDAMA only exacerbates the Agency's problems as it adds more mandates without explicitly providing any funding for them. Unfortunately, the Agency, unlike the States who have legal recourse to resist Federal "unfunded" mandates, has no effective means to directly address the actions of the government of which it is a part.
- D.** Given the financial and congressional constraints that Congress has and seems committed to imposing upon the FDA, the short-term reality is that whatever the Agency does, the public will suffer as FDAMA, like most recent legislation is aimed at pressuring the FDA to hasten the review process to the point that drugs that should not be approved, are being and will continue to be released for "public use." Effectively, the reality has become that that same "public" is an unwitting participant in truly large-scale experiments from which the manufacturer reaps both direct and indirect financial reward for which the public pays to be in the experiment and, without informed consent, accepts the risks.
- E.** Anyone reading through FDAMA with any understanding of the current regulatory realities should recognize that this statute is replete with language that:
1. Favors the industry, or some special segment of it, like those firms in the area of "Positron Emission Tomography" ("**PET**") who, for no scientifically sound reason, were given an exemption from the regulations governing finished pharmaceuticals,
 2. Constrains the Agency to do more without providing adequate funding and, in some cases, like **PET** and the "annual report" required herein, calculatingly compels the FDA to squander its existing resources in nonproductive work.

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3. Assures that Congress can continue to castigate the FDA for not meeting its mandated deadlines and requirements.
 4. Continues to reduce the safety and level of quality that the products regulated by the FDA do have and are assured of having. More and more, the Agency is being pressured to accept, and seems to be accepting, "risk/benefit" over "safety." [Unfortunately, the patient bears most of the risk, the companies obtain most of the benefit, and, if the ever increasing movement to effectively eliminate the individual's existing rights to sue, singly or collectively, for damages (without limiting any company's right to sue) succeeds, transferring the cost of the damages to the individuals damaged and the taxpayers as a whole.]
- F. Saddest of all, FDAMA does not focus on the key issues of safety and efficacy that should be the overriding goals in any of Congress' mandates to the Agency.

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II. COMMENTS ON THE "OBJECTIVES" THEMSELVES

| Objective Number | "Objective" As Stated In The FR | Comments On The "Objective" |
|------------------|--|---|
| 1 | "Maximizing the availability and clarity of information about the agency application and submission review processes;" | <ol style="list-style-type: none"> 1. Adopt a uniform quality system for all agency application and submission review processes and publish that quality system on the FDA's website. 2. Make certain that that quality system conforms to the format specified in ISO-9001. 3. Make certain that all agency personnel have documented competence in those aspects of the quality system that govern their actions. 4. Make certain that agency standard practices are training-grade documents. 5. Make certain that all agency personnel who interact with the "public" have documented training and demonstrated proficiency to do their job. 6. Incorporate a requirement that supervisory personnel applying to work in the agency's application & submission review processes must have and demonstrate competency in the area in which they are seeking positions. |
| 2 | maximizing the availability and clarity of information for consumers and patients concerning new products; | <ol style="list-style-type: none"> 1. Require the applicants to post comprehensive consumer/patient information, including the substance of all complaints and reported ADR's, written at the third-grade level, on the FDA's website as well as to all of those who dispense said new products. 2. Require that new dispensed products must be identified by lot on each prescription. 3. Provide a form to all patients who receive a new product that asks the patient, or that is patient's caregiver, to document how the new the product affects them as well as to report any adverse reaction to the agency (on a prepaid card provided with each refill) and to their health care provider. 4. Post all adverse reactions and their reported consequences on the internet and alert the manufacturer. |

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7/27/98

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| Objective Number | "Objective" As Stated In The FR | Comments On The "Objective" |
|------------------|--|--|
| 3a | implementing (a) inspection ... provisions of the act; | <ol style="list-style-type: none"> 1. Given the <u>unfunded</u> mandates for training as set forth in Sec. 408 of FDAMA pursuant to, and the existing deficiencies in, training in CGMPs relating to inspections and in the inspections themselves as well as (a) a lack of metric-based competency measures for existing personnel at all levels in the agency and (b) the inability of the agency to meet its current bi-annual inspections, the new routine inspection programs for OTC drug records and for biological products needs to be postponed until the needed training can be provided. 2. Given that the agency has yet to conduct formal training of its inspectors with respect to the requirements of electronic signatures and electronic records and the current lack of training in CGMP as it applies to food, drugs, medical devices, etc., and, by the pending MRA with Europe, that the agency is committed to providing training to their European counterparts, Congress needs to provide funding for a comprehensive training program for all agency personnel from the commissioner on down to provide documented evidence that each agency employee is competent with respect to both applicable regulations governing their activities and the technical understanding to properly discharge their duties. Failing that, the agency cannot perform their functions as the regulations mandate as many of their staff do not even know or understand the explicit requirements of the regulations they are to enforce and are not technically competent to rightly decide if a firm's proposed systems can or do comply. 3. Given FDAMA's directive that the OTC records review be announced, guidance published, and inspection phased in, the postponement of implementation in this area can be easily justified. 4. To assure that the "public" understands that funding is key, all plans should show a funding contingent implementation. |

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| Objective Number | "Objective" As Stated In The FR | Comments On The "Objective" |
|-------------------|--|---|
| 3a (continued) | implementing inspection ... provisions of the act (continued); | <p>5. It is odd that Congress could understand the need for funding and fund the "SEC. 409. CENTERS FOR EDUCATION AND RESEARCH ON THERAPEUTICS," but not seemingly understand the need for added funding for the added programs as well as the added training to effectively implement the added programs.</p> <p>6. A large part of the "root cause" of the loss of effectiveness in the FDA can be traced to the lack of properly trained knowledgeable staff in the agency — but perhaps this is exactly what Congress and the industry wants. If not, then Congress needs to wake up and see the hamstrung FDA that they are helping to create by continually adding more and more duties, reducing the level of funding, and allowing the hiring of less than competent personnel.</p> |
| 3b | implementing ... postmarket monitoring provisions of the act; | <p>1. Implementing the postmarket monitoring provisions as set forth in Section 130 of FDAMA seems to present no significant obstacles other than compliance ones and serves to standardize the reporting time frame requirements.</p> <p>2. Still, Congress should have made additional funds available to support the costs added by the "postmarketing monitoring," tracking and reporting set forth in Section 130 of FDAMA</p> |

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| Objective Number | "Objective" As Stated In The FR | Comments On The "Objective" |
|------------------|--|--|
| 4 | assuring access to the scientific and technical expertise needed to carry out FDA's obligations; | <ol style="list-style-type: none"> 1. This is another area where Congress should have provided significant funding to assure that the FDA can have access to the expertise needed to carry out the FDA's obligations. Since most of those who have the requisite expertise do not work for free, the industry highly compensates many of the independent consultants who have the expertise, and industry, except in their own interest, does not offer its consultants or scientific and technical experts to the agency, the agency would have to have adequate funding to be able to assure the access mandated. Currently, the agency seems to lack the funds to even be able to train its inspection staff in 21 CFR 11, covering electronic records and electronic signatures even though said regulations have been in effect since mid-1997. 2. Moreover, as outlined previously, the FDA's "early retirement" program, triggered by REGO and the budget reductions imposed by Congress, resulted in the loss of many of the agency personnel who were the repositories of much of the agency's scientific and technical expertise. 3. Having lost many of the very personnel who could have passed on their expertise, any FDA plan to increase the agency's expertise in a significant manner would have to rely on recruiting the people from the industry and sending their brightest staff out to get the expertise needed. To make such a plan work, the FDA would need a credible competency-based recruitment and training program coupled with an industry-competitive pay scale — today it has neither. |

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| Objective Number | "Objective" As Stated In The FR | Comments On The "Objective" |
|------------------|--|---|
| 5 | establishing mechanisms, by July 1, 1999, for meeting specified time periods for the review of applications and submissions; | <ol style="list-style-type: none"> 1. Given the current state of the Agency, the only assured way that the FDA could comply with the specified periods for reviewing all applications and submissions would be either to continue to reduce the level of review and increase the current level of "permissive" noncompliance that, through ignorance of the regulations or for other reasons, the current reviewers continue to permit. 2. Even if Congress were to significantly increase the level of funding and the Agency were to raise its new-hire standards to make competency and scientific and technical expertise in the industry prerequisites, to increase the compensation of all of those involved in the review and approval process, and to begin a crash program to upgrade the CGMP training of all their personnel to the point that all personnel had documented proof of their competency, it would take at least two years before the agency's review and approval process could again assure that the products approved do comply with the requirements of the applicable CGMP regs. 3. Currently, the situation is so bad that almost all firms are being permitted to make and sell drugs and other regulated products that are adulterated or misbranded under the act. 4. Lacking the above, any plan that meets the specified timelines will, of necessity, do so be reducing the level of safety and quality in the products whose applications and supplements are being reviewed. More bad drugs will be approved only to be withdrawn shortly after their approval. As with any feedback loop, Companies, seeing that less is required, will continue to do less — thereby lessing both the safety and the quality of their products to "remain competitive" (actually to make more money). The only loser will be the consumer — thankfully, Congress will also at least reap the increased risk that the public will share. For no one can tell by looking whether or not their medications are safe and effective. |

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3/15/99

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| Objective Number | "Objective" As Stated In The FR | Comments On The "Objective" |
|------------------|---|--|
| 6 | eliminating backlogs in the review of applications and submissions. | <ol style="list-style-type: none"> <li data-bbox="880 283 1506 691">1. If the only goal is to eliminate the backlog, then, as alluded to above, the agency need only reduce their already substandard requirements and minimize the level of the scrutiny given to any company's applications, submissions, and their actual practices — make all PAI inspections like the foreign ones (3 to 5 days) with no follow up to make certain that promised corrective actions were implemented and truly addressed the problem for which they were proposed. <li data-bbox="880 697 1506 883">2. In other words, become a passive regulatory body, like the FAA, and only react when the industry's actions result in the loss of 100 (or more lives), or more than 1000 cases of non-reversible injury, or some other numbers. |

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III. COMMENTS ON: CERTAIN LEGISLATIVE SECTIONS OF FDAMA

In the sectional comments, the format that is used is to present the section in a small font with the portion on which a comment is being made being **bolded** followed by the comment in a larger font.

In general, given the time constraints and my principal areas of competence, the comments that follow will be confined to providing comment on areas in Title I and IV.

TITLE I--IMPROVING REGULATION OF DRUGS

Subtitle A--Fees Relating to Drugs

SEC. 101. FINDINGS.

Congress finds that — (1) prompt approval of safe and effective new drugs and other therapies is critical to the improvement of the public health so that patients may enjoy the benefits provided by these therapies to treat and prevent illness and disease; (2) the public health will be served by making additional funds available for the purpose of augmenting the resources of the Food and Drug Administration that are devoted to the process for review of human drug applications; (3) the provisions added by the Prescription Drug User Fee Act of 1992 have been successful in substantially reducing review times for human drug applications and should be — (A) reauthorized for an additional 5 years, with certain technical improvements; and (B) carried out by the Food and Drug Administration with new commitments to implement more ambitious and comprehensive improvements in regulatory processes of the Food and Drug Administration; and **(4) the fees authorized by amendments made in this subtitle will be dedicated toward expediting the drug development process and the review of human drug applications** as set forth in the goals identified, for purposes of part 2 of subchapter C of chapter VII of the Federal Food, Drug, and Cosmetic Act, in the letters from the Secretary of Health and Human Services to the chairman of the Committee on Commerce of the House of Representatives and the chairman of [[Page H10453]] the Committee on Labor and Human Resources of the Senate, as set forth in the Congressional Record.

1. It is sad that Congress continues to provide fees for “faster” development and review without providing much concomitant funding, either by fee or in the budget, to improve the safety and efficacy of drugs or the compliance with CGMP by the industry.

SEC. 102. DEFINITIONS.

Section 735 (21 U.S.C. 379g) is amended —

(1) in the second sentence of paragraph (1) — (A) by striking “Service Act, and” and inserting “Service Act.”; and (B) by striking “September 1, 1992.” and inserting the following: “September 1, 1992, does not include an application for a licensure of a biological product for further manufacturing use only, and does not include an application or supplement submitted by a State or Federal Government entity for a drug that is not distributed commercially. Such term does include an application for licensure, as described in subparagraph (D), of a large volume biological product intended for single dose injection for intravenous use or infusion.”;

(2) in the second sentence of paragraph (3) — (A) by striking “Service Act, and” and inserting “Service Act.”; and (B) by striking “September 1, 1992.” and inserting the following: “September 1, 1992, does not include a biological product that is licensed for further manufacturing use only, and does not include a drug that is not distributed commercially and is the subject of an application or supplement submitted by a State or Federal Government entity. Such term does include a large volume biological product intended for single dose injection for intravenous use or infusion.”;

(3) in paragraph (4), by striking “without” and inserting “without substantial”;

(4) by amending the first sentence of paragraph (5) to read as follows: “(5) The term ‘prescription drug establishment’ means a foreign or domestic place of business which is at one general physical location consisting of one or more buildings all of which are within five miles of each other and at which one or more prescription drug products are manufactured in final dosage form.”;

(5) in paragraph (7)(A) — (A) by striking “employees under contract” and all that follows through “Administration,” the second time it occurs and inserting “contractors of the Food and Drug Administration.”; and (B) by striking “and committees,” and inserting “and committees and to contracts with such contractors.”;

(6) in paragraph (8) — (A) in subparagraph (A) — (i) by striking “August of” and inserting “April of”; and (ii) by striking “August 1992” and inserting “April 1997”; and

(B) in subparagraph (B) — (i) by striking “section 254(d)” and inserting “section 254(c)”;

(ii) by striking “1992” and inserting “1997”; and (iii) by striking “102d Congress, 2d Session” and inserting “105th Congress, 1st Session”; and

(7) by adding at the end the following: “(9) The term ‘affiliate’ means a business entity that has a relationship with a second business entity if, directly or indirectly— (A) one business entity controls, or has the power to control, the other business entity; or (B) a third party controls, or has power to control, both of the business entities.”.

Comments on Section 102:

1. Nothing of consequence except that the definition of although the lumping of all buildings within a “19.5+ sq. mile” area into a single prescription drug establishment seems to be a bit overly broad especially since there is no requirement that the buildings be on a single campus or even on property controlled by the establishment.

SEC. 103. AUTHORITY TO ASSESS AND USE DRUG FEES.

(a) Types of Fees.—Section 736(a) (21 U.S.C. 379h(a)) is amended— (1) by striking “Beginning in fiscal year 1993” and inserting “Beginning in fiscal year 1998”;

(2) in paragraph (1) — (A) by striking subparagraph (B) and inserting the following: “(B) Payment.—The fee required by subparagraph (A) shall be due upon submission of the application or supplement.”;

(B) in subparagraph (D) — (i) in the subparagraph heading, by striking “not accepted” and inserting “refused”; (ii) by striking “50 percent” and inserting “75 percent”; (iii) by striking “subparagraph (B)(i)” and inserting “subparagraph (B)”;

and (iv) by striking “not accepted” and inserting “refused”; and

(C) by adding at the end the following: “(E) Exception for designated orphan drug or indication.— A human drug application for a prescription drug product that has been designated as a drug for a rare disease or condition pursuant to section 526 shall not be subject to a fee under subparagraph (A), unless the human drug application includes an indication for other than a rare disease or condition. A supplement proposing to include a new indication for a rare disease or condition in a human drug application shall not be subject to a fee under subparagraph (A), if the drug has been designated pursuant to section 526 as a drug for a rare disease or condition with regard to the indication proposed in such supplement.”

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"(F) Exception for supplements for pediatric indications. — A supplement to a human drug application proposing to include a new indication for use in pediatric populations shall not be assessed a fee under subparagraph (A)."

"(G) Refund of fee if application withdrawn.—If an application or supplement is withdrawn after the application or supplement was filed, the Secretary may refund the fee or a portion of the fee if no substantial work was performed on the application or supplement after the application or supplement was filed. The Secretary shall have the sole discretion to refund a fee or a portion of the fee under this subparagraph. A determination by the Secretary concerning a refund under this paragraph shall not be reviewable.;"

(3) by striking paragraph (2) and inserting the following:

"(2) Prescription drug establishment fee.—"

"(A) In general.—Except as provided in subparagraph (B), each person that —"

"(i) is named as the applicant in a human drug application; and"

"(ii) after September 1, 1992, had pending before the Secretary a human drug application or supplement, shall be assessed an annual fee established in subsection (b) for each prescription drug establishment listed in its approved human drug application as an establishment that manufactures the prescription drug product named in the application. The annual establishment fee shall be assessed in each fiscal year in which the prescription drug product named in the application is assessed a fee under paragraph (3) unless the prescription drug establishment listed in the application does not engage in the manufacture of the prescription drug product during the fiscal year. The establishment fee shall be payable on or before January 31 of each year. Each such establishment shall be assessed only one fee per establishment, notwithstanding the number of prescription drug products manufactured at the establishment. In the event an establishment is listed in a human drug application by more than one applicant, the establishment fee for the fiscal year shall be divided equally and assessed among the applicants whose prescription drug products are manufactured by the establishment during the fiscal year and assessed product fees under paragraph (3)."

"(B) Exception.—If, during the fiscal year, an applicant initiates or causes to be initiated the manufacture of a prescription drug product at an establishment listed in its human drug application —"

"(i) that did not manufacture the product in the previous fiscal year; and"

"(ii) for which the full establishment fee has been assessed in the fiscal year at a time before manufacture of the prescription drug product was begun; the applicant will not be assessed a share of the establishment fee for the fiscal year in which the manufacture of the product began.;"

and

(4) in paragraph (3)— (A) in subparagraph (A) — (i) in clause (i), by striking "is listed" and inserting "has been submitted for listing"; and (ii) by striking "Such fee shall be payable" and all that follows through "section 510." and inserting the following: "Such fee shall be payable for the fiscal year in which the product is first submitted for listing under section 510, or is submitted for relisting under section 510 if the product has been withdrawn from listing and relisted. After such fee is paid for that fiscal year, such fee shall be payable on or before January 31 of each year. Such fee shall be paid only once for each product for a fiscal year in which the fee is payable.;" and

(B) in subparagraph (B), by striking "505(j)." and inserting the following: "505(j), under an abbreviated application filed under section 507 (as in effect on the day before the date of enactment of the Food and Drug Administration Modernization Act of 1997), or under an abbreviated new drug application pursuant to regulations in effect prior to the implementation of the Drug Price Competition and Patent Term Restoration Act of 1984."

(b) Fee Amounts.— Section 736(b) (21 U.S.C. 379h(b)) is amended to read as follows: "(b) Fee Amounts.— Except as provided in subsections (c), (d), (f), and (g), the fees required under subsection (a) shall be determined and assessed as follows:"

"(1) Application and supplement fees.—"

"(A) Full fees.— The application fee under subsection (a)(1)(A)(i) shall be \$250,704 in fiscal year 1998, \$256,338 in each of fiscal years 1999 and 2000, \$267,606 in fiscal year 2001, and \$258,451 in fiscal year 2002."

"(B) Other fees.— The fee under subsection (a)(1)(A)(ii) shall be \$125,352 in fiscal year 1998, \$128,169 in each of fiscal years 1999 and 2000, \$133,803 in fiscal year 2001, and \$129,226 in fiscal year 2002."

"(2) Total fee revenues for establishment fees.—The total fee revenues to be collected in establishment fees under subsection (a)(2) shall be \$35,600,000 in fiscal year 1998, \$36,400,000 in each of fiscal years 1999 and 2000, \$38,000,000 in fiscal year 2001, and \$36,700,000 in fiscal year 2002."

"(3) Total fee revenues for product fees.—The total fee revenues to be collected in product fees under subsection (a)(3) in a fiscal year shall be equal to the total fee revenues collected in establishment fees under subsection (a)(2) in that fiscal year."

(c) Increases and Adjustments.— Section 736(c) (21 U.S.C. 379h(c)) is amended — (1) in the subsection heading, by striking "Increases and";

(2) in paragraph (1)— (A) by striking "(1) Revenue" and all that follows through "increased by the Secretary" and inserting the following: "(1) Inflation adjustment.—The fees and total fee revenues established in subsection (b) shall be adjusted by the Secretary";

(B) in subparagraph (A), by striking "increase" and inserting "change";

(C) in subparagraph (B), by striking "increase" and inserting "change"; and

(D) by adding at the end the following flush sentence:

"The adjustment made each fiscal year by this subsection will be added on a compounded basis to the sum of all adjustments made each fiscal year after fiscal year 1997 under this subsection.;"

(3) in paragraph (2), by striking "October 1, 1992," and all that follows through "such [[Page H10454]] schedule." and inserting the following:

"September 30, 1997, adjust the establishment and product fees described in subsection (b) for the fiscal year in which the adjustment occurs so that the revenues collected from each of the categories of fees described in paragraphs (2) and (3) of subsection (b) shall be set to be equal to the revenues collected from the category of application and supplement fees described in paragraph (1) of subsection (b).;" and

(4) in paragraph (3), by striking "paragraph (2)" and inserting "this subsection."

(d) Fee Waiver or Reduction.— Section 736(d) (21 U.S.C. 379h(d)) is amended — (1) by redesignating paragraphs (1), (2), (3), and (4) as subparagraphs (A), (B), (C), and (D), respectively and indenting appropriately;

(2) by striking "The Secretary shall grant a" and all that follows through "finds that —" and inserting the following: "(1) In general.—The Secretary shall grant a waiver from or a reduction of one or more fees assessed under subsection (a) where the Secretary finds that —";

(3) in subparagraph (C) (as so redesignated in paragraph (1)), by striking ", or" and inserting a comma;

(4) in subparagraph (D) (as so redesignated in paragraph (1)), by striking the period and inserting ", or";

(5) by inserting after subparagraph (D) (as so redesignated in paragraph (1)) the following: "(E) the applicant involved is a small business submitting its first human drug application to the Secretary for review.;" and

(6) by striking "In making the finding in paragraph (3)," and all that follows through "standard costs." and inserting the following:

"(2) Use of standard costs.—In making the finding in paragraph (1)(C), the Secretary may use standard costs."

"(3) Rules relating to small businesses.—"

"(A) Definition.—In paragraph (1)(E), the term 'small business' means an entity that has fewer than 500 employees, including employees of affiliates."

"(B) Waiver of application fee.—The Secretary shall waive under paragraph (1)(E) the application fee for the first human drug application that a small business or its affiliate submits to the Secretary for review. After a small business or its affiliate is granted such a waiver, the small business or its affiliate shall pay —"

"(i) application fees for all subsequent human drug applications submitted to the Secretary for review in the same manner as an entity that does not qualify as a small business; and"

"(ii) all supplement fees for all supplements to human drug applications submitted to the Secretary for review in the same manner as an entity that does not qualify as a small business."

(c) Assessment of Fees.— Section 736(f)(1) (21 U.S.C. 379h(f)(1)) is amended — (1) by striking "fiscal year 1993" and inserting "fiscal year 1997"; and

(2) by striking "fiscal year 1992" and inserting "fiscal year 1997 (excluding the amount of fees appropriated for such fiscal year)."

(f) Crediting and Availability of Fees.— Section 736(g) (21 U.S.C. 379h(g)) is amended — (1) in paragraph (1), by adding at the end the following:

"Such sums as may be necessary may be transferred from the Food and Drug Administration salaries and expenses appropriation account without fiscal year limitation to such appropriation account for salaries and expenses with such fiscal year limitation. The sums transferred shall be available solely for the process for the review of human drug applications.;"

(2) in paragraph (2) — (A) in subparagraph (A), by striking "Acts" and inserting "Acts, or otherwise made available for obligation.;" and

(B) in subparagraph (B), by striking "over such costs for fiscal year 1992" and inserting "over such costs, excluding costs paid from fees collected under this section, for

fiscal year 1997"; and

(3) by striking paragraph (3) and inserting the following:

"(3) Authorization of appropriations.—There are authorized to be appropriated for fees under this section —"

"(A) \$106,800,000 for fiscal year 1998;"

"(B) \$109,200,000 for fiscal year 1999;"

"(C) \$109,200,000 for fiscal year 2000;"

"(D) \$114,000,000 for fiscal year 2001; and"

"(E) \$110,100,000 for fiscal year 2002, as adjusted to reflect adjustments in the total fee revenues made under this section and changes in the total amounts collected by application, supplement, establishment, and product fees."

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“(4) Offset.—Any amount of fees collected for a fiscal year under this section that exceeds the amount of fees specified in appropriation Acts for such fiscal year shall be credited to the appropriation account of the Food and Drug Administration as provided in paragraph (1), and shall be subtracted from the amount of fees that would otherwise be authorized to be collected under this section pursuant to appropriation Acts for a subsequent fiscal year.”

(g) Requirement for Written Requests for Waivers, Reductions, and Refunds.—Section 736 (21 U.S.C. 379h) is amended —

- (1) by redesignating subsection (i) as subsection (j); and
- (2) by inserting after subsection (h) the following:

“(i) Written Requests for Waivers, Reductions, and Refunds.—To qualify for consideration for a waiver or reduction under subsection (d), or for a refund of any fee collected in accordance with subsection (a), a person shall submit to the Secretary a written request for such waiver, reduction, or refund not later than 180 days after such fee is due.”

(h) Special Rule for Waivers and Refunds.—Any requests for waivers or refunds for fees assessed under section 736 of the Federal Food, Drug, and Cosmetic Act (42 U.S.C. 379h) prior to the date of enactment of this Act shall be submitted in writing to the Secretary of Health and Human Services within 1 year after the date of enactment of this Act. Any requests for waivers or refunds pertaining to a fee for a human drug application or supplement accepted for filing prior to October 1, 1997 or to a product or establishment fee required by such Act for a fiscal year prior to fiscal year 1998, shall be evaluated according to the terms of the Prescription Drug User Fee Act of 1992 (as in effect on September 30, 1997) and part 2 of subchapter C of chapter VII of the Federal Food, Drug, and Cosmetic Act (as in effect on September 30, 1997). The term “person” in such Acts shall continue to include an affiliate thereof.

Comments on Section 103

1. This section, at “(4) Offset—” contains a disincentive for the agency to be more efficient as any “excess” fees collected [presumably caused by the pharmaceutical industry’s submitting an significantly larger number of supplements or applications for which the agency collects fees triggered by a significant increase in FDA review efficiency] in a given fiscal year reduces the amount of fees authorized for the following fiscal year. Thus, if the FDA were to collect \$ 209,200,000 in fiscal 1999 when \$ 109,200,000, their year 2000 fee appropriations budget would be reduced from \$ 109,200,000 to \$ 9,200,000. I do not understand how such a provision will help: a) expedite a controlled review and approval process or b) the FDA in any way operate in a controlled manner.
2. Based on what has been enacted, it seems that Congress is again undermining the ability of the agency to assure that the drugs that are distributed are safe and efficacious — perhaps that is what industry: a) wants and b) is influencing Congress to do.

SEC. 104. ANNUAL REPORTS.

(a) Performance Report.—Beginning with fiscal year 1998, not later than 60 days after the end of each fiscal year during which fees are collected under part 2 of subchapter C of chapter VII of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 379g et seq.), the Secretary of Health and Human Services shall prepare and submit to the Committee on Commerce of the House of Representatives and the Committee on Labor and Human Resources of the Senate a report concerning the progress of the Food and Drug Administration in achieving the goals identified in the letters described in section 101(4) during such fiscal year and the future plans of the Food and Drug Administration for meeting the goals.

(b) Fiscal Report.—Beginning with fiscal year 1998, not later than 120 days after the end of each fiscal year during which fees are collected under the part described in subsection (a), the Secretary of Health and Human Services shall prepare and submit to the Committee on Commerce of the House of Representatives and the Committee on Labor and Human Resources of the Senate a report on the implementation of the authority for such fees during such fiscal year and the use, by the Food and Drug Administration, of the fees collected during such fiscal year for which the report is made.

Comments On Section 104.

1. Given the restrictions set forth in Section 103, none of the collected “fees” can be used in satisfying the requirements set forth herein.
2. Again additional unfunded mandates are being set forth. Thus, Congress continues to burden the FDA with more to do while, almost simultaneously, reducing the agency’s level of funding knowing that this will lead to less personnel to do more and more. Though Congress’ intent may be to punish the FDA, this course of action results in an ever increasing risk to the safety and efficacy of the drug products being supplied to the American consumer.

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Subtitle B — Other Improvements

SEC. 112. EXPEDITING STUDY AND APPROVAL OF FAST TRACK DRUGS.

(a) In General.— Chapter V (21 U.S.C. 351 et seq.), as amended by section 125, is amended by inserting before section 508 the following:

“SEC. 506. FAST TRACK PRODUCTS.”

“(a) Designation of Drug as a Fast Track Product.—”

“(1) In general.— The Secretary shall, at the request of the sponsor of a new drug, facilitate the development and expedite the review of such drug if it is intended for the treatment of a serious or life-threatening condition and it demonstrates the potential to address unmet medical needs for such a condition. (In this section, such a drug is referred to as a ‘fast track product’).”

“(2) Request for designation.— The sponsor of a new drug may request the Secretary to designate the drug as a fast track product. A request for the designation may be made concurrently with, or at any time after, submission of an application for the investigation of the drug under section 505(i) or section 351(a)(3) of the Public Health Service Act.”

“(3) Designation.— Within 60 calendar days after the receipt of a request under paragraph (2), the Secretary shall determine whether the drug that is the subject of the request meets the criteria described in paragraph (1). If the Secretary finds that the drug meets the criteria, the Secretary shall designate the drug as a fast track product and shall take such actions as are appropriate to expedite the development and review of the application for approval of such product.”

“(b) Approval of Application for a Fast Track Product.—”

“(1) In general.— The Secretary may approve an application for approval of a fast track product under section 505(c) or section 351 of the Public Health Service Act upon a determination that the product has an effect on a clinical endpoint or on a surrogate endpoint that is reasonably likely to predict clinical benefit.”

“(2) Limitation.— Approval of a fast track product under this subsection may be subject to the requirements —”

“(A) that the sponsor conduct appropriate post-approval studies to validate the surrogate endpoint or otherwise confirm the effect on the clinical endpoint; and”

“(B) that the sponsor submit copies of all promotional materials related to the fast track product during the preapproval review period and, following approval and for such period [Page H10456] thereafter as the Secretary determines to be appropriate, at least 30 days prior to dissemination of the materials.”

“(3) Expedited withdrawal of approval.— The Secretary may withdraw approval of a fast track product using expedited procedures (as prescribed by the Secretary in regulations which shall include an opportunity for an informal hearing) if —”

“(A) the sponsor fails to conduct any required post approval study of the fast track drug with due diligence;”

“(B) a post-approval study of the fast track product fails to verify clinical benefit of the product;” **“(C) other evidence demonstrates that the fast track product is not safe or effective under the conditions of use; or”**

“(D) the sponsor disseminates false or misleading promotional materials with respect to the product.”

“(c) Review of Incomplete Applications for Approval of a Fast Track Product.—”

“(1) In general.— If the Secretary determines, after preliminary evaluation of clinical data submitted by the sponsor, that a fast track product may be effective, the Secretary shall evaluate for filing, and may commence review of portions of, an application for the approval of the product before the sponsor submits a complete application. The Secretary shall commence such review only if the applicant —”

“(A) provides a schedule for submission of information necessary to make the application complete; and”

“(B) pays any fee that may be required under section 736.”

“(2) Exception.— Any time period for review of human drug applications that has been agreed to by the Secretary and that has been set forth in goals identified in letters of the Secretary (relating to the use of fees collected under section 736 to expedite the drug development process and the review of human drug applications) shall not apply to an application submitted under paragraph (1) until the date on which the application is complete.”

“(d) Awareness Efforts.— The Secretary shall —”

“(1) develop and disseminate to physicians, patient organizations, pharmaceutical and biotechnology companies, and other appropriate persons a description of the provisions of this section applicable to fast track products; and”

“(2) establish a program to encourage the development of surrogate endpoints that are reasonably likely to predict clinical benefit for serious or life-threatening conditions for which there exist significant unmet medical needs.”

(b) Guidance.— Within 1 year after the date of enactment of this Act, the Secretary of Health and Human Services shall issue guidance for fast track products (as defined in section 506(a)(1) of the Federal Food, Drug, and Cosmetic Act) that describes the policies and procedures that pertain to section 506 of such Act.

Comments On Section 112:

1. While, at first glance, the criteria for “fast tracking” under “(a)(1)” seem to be reasonable, a closer reading reveals that, lacking any clear cut definition of key words in the phrase, “it demonstrates the potential to address unmet medical needs,” this section is an invitation to abuse by the industry.
2. Similarly, “(c)” encourages the Secretary to initiate reviews before any application is complete. If implemented, this provision would: a) encourage companies to submit incomplete applications and, thereby minimizing the company’s costs and cost risk if the “new” moiety fails to meet its performance criteria; b) increase the risk that the FDA reviewers would waste even more valuable review effort in a “drug” that subsequently fails to be worth pursuing than the agency does currently.
3. Moreover, “(c)(2),” though the resetting of the review clock would appear to benefit the agency as the agency’s review clock would not start until the application is complete, this clause actually benefits the companies as any patent life extension would be added to the date of the complete application and not the date upon which the partial application began to be reviewed.
4. Further, since “(c)” is discretionary, hopefully the agency, critically short of review resources already, will wisely decline to grant subsection “(c)” reviews.

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5. "d" is another example of an unfunded mandate. Moreover "(d)(2)" is particularly egregious as it directs the Secretary to "establish a program to encourage the development of surrogate endpoints that are reasonably likely to predict clinical benefit for serious or life-threatening conditions for which there exist significant unmet medical needs." Since when should the role of a regulatory agency be to establish programs to encourage the development of "surrogate endpoints" that, although they may predict clinical benefit, do not and cannot predict clinical safety and efficacy. Currently the industry is replete with surrogate endpoint tests and novel modes of action. Unfortunately, these have been used to justify the development and, in some cases, approval of drugs that have significant adverse health consequences including death for some of those who took and, in some cases, still are taking such high-risk products. How many people need to be maimed and killed before a drug's "benefits" are overwhelmed by the real damage done to some who take it? Is it 100? 1,000? 10,000?
6. Section "(b) Guidance —" is another unfunded mandate that provides industry and Congress yet another opportunity to a) complain about the FDA's failure to meet certain goals while b) burying certain pending items that they do not wish to be enacted (such as the proposed revisions to 21 CFR 210 and 21 CFR 211) that should have been issued within 180 days of the close of the comment period in 1996 but are currently being projected to emerge, if at all, in FY 2000 ("the end of 1999) more than 720 days after their publication for review and comment.

SEC. 113. INFORMATION PROGRAM ON CLINICAL TRIALS FOR SERIOUS OR LIFE-THREATENING DISEASES.

- (a) In General.—Section 402 of the Public Health Service Act (42 U.S.C. 282) is amended—
- (1) by redesignating subsections (j) and (k) as subsections (k) and (l), respectively; and
 - (2) by inserting after subsection (i) the following:

"(j)(1)(A) The Secretary, acting through the Director of NIH, shall establish, maintain, and operate a data bank of information on clinical trials for drugs for serious or life threatening diseases and conditions (in this subsection referred to as the 'data bank'). The activities of the data bank shall be integrated and coordinated with related activities of other agencies of the Department of Health and Human Services, and to the extent practicable, coordinated with other data banks containing similar information."

"(B) The Secretary shall establish the data bank after consultation with the Commissioner of Food and Drugs, the directors of the appropriate agencies of the National Institutes of Health (including the National Library of Medicine), and the Director of the Centers for Disease Control and Prevention."

"(2) In carrying out paragraph (1), the Secretary shall collect, catalog, store, and disseminate the information described in such paragraph. The Secretary shall disseminate such information through information systems, which shall include toll-free telephone communications, available to individuals with serious or life-threatening diseases and conditions, to other members of the public, to health care providers, and to researchers."

"(3) The data bank shall include the following:"

"(A) A registry of clinical trials (whether federally or privately funded) of experimental treatments for serious or life-threatening diseases and conditions under regulations promulgated pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act, which provides a description of the purpose of each experimental drug, either with the consent of the protocol sponsor, or when a trial to test effectiveness begins. **Information provided shall consist of eligibility criteria for participation in the clinical trials, a description of the location of trial sites, and a point of contact for those wanting to enroll in the trial, and shall be in a form that can be readily understood by members of the public. Such information shall be forwarded to the data bank by the sponsor of the trial not later than 21 days after the approval of the protocol.**"

"(B) Information pertaining to experimental treatments for serious or life-threatening diseases and conditions that may be available—"

"(i) under a treatment investigational new drug application that has been submitted to the Secretary under section 561(c) of the Federal Food, Drug, and Cosmetic Act; or"

"(ii) as a Group C cancer drug (as defined by the National Cancer Institute)."

"The data bank may also include information pertaining to the results of clinical trials of such treatments, with the consent of the sponsor, including information concerning potential toxicities or adverse effects associated with the use or administration of such experimental treatments."

"(4) The data bank shall not include information relating to an investigation if the sponsor has provided a detailed certification to the Secretary that disclosure of such information would substantially interfere with the timely enrollment of subjects in the investigation, unless the Secretary, after the receipt of the certification, provides the sponsor with a detailed written determination that such disclosure would not substantially interfere with such enrollment."

"(5) **For the purpose of carrying out this subsection, there are authorized to be appropriated such sums as may be necessary. Fees collected under section 736 of the Federal Food, Drug, and Cosmetic Act shall not be used in carrying out this subsection.**"

(b) Collaboration and Report.—

(1) In general.—The Secretary of Health and Human Services, the Director of the National Institutes of Health, and the Commissioner of Food and Drugs shall collaborate to determine the feasibility of including device investigations within the scope of the data bank under section 402(j) of the Public Health Service Act.

(2) Report.—Not later than two years after the date of enactment of this section, the Secretary of Health and Human Services shall prepare and submit to the Committee on Labor and Human Resources of the Senate and the Committee on Commerce of the House of Representatives a report—

(A) of the public health need, if any, for inclusion of device investigations within the scope of the data bank under section 402(j) of the Public Health Service Act;

(B) **on the adverse impact, if any, on device innovation and research in the United States** if information relating to such device investigations is required to be publicly disclosed; and

(C) on such other issues relating to such section 402(j) as the Secretary determines to be appropriate.

Comments On Section 113:

1. At least there is a promise of funding for the data bank itself "(j)(5);" hopefully Congress will honor it as the Agency is not permitted to collect or charge fees for it.

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2. This provision amounts to setting up a major 24-hour "help desk" that promises to offer information to those who have such serious diseases and conditions and the public. However, because participation by the companies is voluntary, there is no assurance that this legislation will provide any public true access and certainly little, if any, oversight.
3. For example, in "(j)(3)(A)," sponsors are supposed to provide certain information "within not later 21 days of the approval of the protocol." However, the legislation provides no penalty if the required information is not provided.
4. "Ironically," section 113(b), another unfunded mandate, addresses actions to include device trails in the data bank and, by inference, in the help desk's scope with demands for information on the adverse impacts on "device innovation and research in the United States, (b)(2)(B), but there is no balancing requirement for the agency to assess the adverse impact on the affected public if this information is not made available — as if Congress was elected by the industry and not by the public.

SEC. 114. HEALTH CARE ECONOMIC INFORMATION.

- (a) In General.— Section 502(a) (21 U.S.C. 352(a)) is amended by adding at the end the following:

"Health care economic information provided to a formulary committee, or other similar entity, in the course of the committee or the entity carrying out its responsibilities for the selection of drugs for managed care or other similar organizations, shall not be considered to be false or misleading under this paragraph if the health care economic information directly relates to an indication approved under section 505 or under section 351(a) of the Public Health Service Act for such drug and is based on competent and reliable scientific evidence. The requirements set forth in section 505(a) or in section 351(a) of the Public Health Service Act shall not apply to health care economic information provided to such a committee or entity in accordance with this paragraph. Information that is relevant to the substantiation of the health care economic information presented pursuant to this paragraph shall be made available to the Secretary upon request. In this paragraph, the term 'health care economic information' means any analysis that identifies, measures, or compares the economic consequences, including the costs of the represented health outcomes, of the use of a drug to the use of another drug, to another health care intervention, or to no intervention."

- (b) Study and Report.—The Comptroller General of the United States shall conduct a study of the implementation of the provisions added by the amendment made by subsection

(a). Not later than 4 years and 6 months after the date of enactment of this Act, the Comptroller General of the United States shall prepare and submit to Congress a report containing the findings of the study.

Comments On Section 114:

This legislation blatantly approves the industry's submission of "health care economic information" that is false or misleading provided it (a) directly relates to an indication approved under section 505 or under 351(a) of the Public Health Service Act for such drug and (b) is based on competent and reliable scientific evidence. Thus, a drug company, having an approved drug for which there are multiple indications, is free to submit biased information based on a comparison of the most economically favorable approved indication to the same indication for competing drugs or to no treatment and to omit the economic consequences that might arise for the other approved uses without worrying about violating the applicable statutes as Congress has granted them that "right." A "right" that is essentially a right to mislead a formulary committee or similar body that makes the decisions as to which of the approved drugs shall be made available to the pharmacies operating under its auspices.

Hopefully, the state formularies will reject such information and demand a comprehensive all indications approach as this provision effectively prevents the agency from acting unless it can prove that the scientific evidence presented is either non-competent or not reliable or both. Perhaps when someone in Congress has a member of their immediate family damaged by a drug that was formulary listed based on its clear economic superiority over its competitors for indication "a" and, therefore, prescribed even though it had rare, but serious, risk when used for treating its approved indication "b" conditions.

This is one amendment that the agency should truly "bring to the attention" of all formulary or related boards.

SEC. 115. CLINICAL INVESTIGATIONS.

- (a) Clarification of the Number of Required Clinical Investigations for Approval.— Section 505(d) (21 U.S.C. 355(d)) is amended by adding at the end the following:

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"If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence for purposes of the preceding sentence."

(b) **Women and Minorities.**—Section 505(b)(1) (21 U.S.C. 355(b)(1)) is amended by adding at the end the following:

"The Secretary shall, in consultation with the Director of the National Institutes of Health and with representatives of the drug manufacturing industry, review and develop guidance, as appropriate, on the inclusion of women and minorities in clinical trials required by clause (A)."

Comments On Section 115:

In (a), the law is changed to permit approval decisions on only one clinical trial of the kind that are currently being conducted in the US (healthy Caucasian males with average weights). This makes industry happy as their development costs could be significantly reduced.

However in (b), in an effort to appease women, who constitute slightly more than half of the US's population and minorities, this statute throws them a bone by mandating the unfunded development of "guidance" on the inclusion of women and minorities into the clinical trials required by clause (A) when, there is more than enough evidence today that all such studies for new drugs to treat diseases common to both men and women should be balanced by approximately doubling the number in the trials and constructing the to study group reflect the make up of the population for whom the drug is intended.

Therefore, the Agency should, to comply with the wishes of Congress, stop approving any clinical trial unless its make up, in general, reflects the target population. Failing this, the agency should mandate that at least one clinical trial must be conducted on a population whose genetic make up mirrors that of the population for which the drug is intended with a size large enough to separate out any major genetic-factor-related treatment effect, outcome, or adverse impact. This approach would neatly sidestep some of the issues of "foreign" clinical trials by not proscribing them but protect the American public by insuring that at least one full-scale clinical trial was conducted on a "healthy" population whose genetic make up matched that of the diverse American public for whom the drug is intended. As an American with a diverse genetic background that includes Jewish, American Indian, Scottish, and Irish influences and who has exhibited "peculiar" responses to some diseases and treatments, I both understand and appreciate the need to include genetic diversity in clinical trials.

Also, the practice of having a "placebo" arm in trails where the "new drug" addresses a disease or condition where there are existing therapeutic alternatives should be proscribed. It should be a crime to knowingly withhold any treatment for a life threatening condition or disease during a clinical trial of a "new drug" when there are approved drugs available for that condition or disease.

SEC. 116. MANUFACTURING CHANGES FOR DRUGS.

(a) **In General.**—Chapter V, as amended by section 112, is amended by inserting after section 506 the following section:

"SEC. 506A. MANUFACTURING CHANGES.

"(a) **In General.**—With respect to a drug for which there is in effect an approved application under section 505 or 512 or a license under section 351 of the Public Health Service Act, a change from the manufacturing process approved pursuant to such application or license may be made, and the drug as made with the change may be distributed, if —"

"(1) the holder of the approved application or license (referred to in this section as a 'holder') has validated the effects of the change in accordance with subsection (b); and" [[Page H10457]]

"(2)(A) in the case of a major manufacturing change, the holder has complied with the requirements of subsection (c); or"

"(B) in the case of a change that is not a major manufacturing change, the holder complies with the applicable requirements of subsection (d)."

"(b) **Validation of Effects of Changes.**—For purposes of subsection (a)(1), a drug made with a manufacturing change (whether a major manufacturing change or otherwise) may be distributed only if, before distribution of the drug as so made, the holder involved validates the effects of the change on the identity, strength, quality, purity, and potency of the drug as the identity, strength, quality, purity, and potency may relate to the safety or effectiveness of the drug."

"(c) **Major Manufacturing Changes.**—"

"(1) **Requirement of supplemental application.**—For purposes of subsection (a)(2)(A), a drug made with a major manufacturing change may be distributed only if, before the distribution of the drug as so made, the holder involved submits to the Secretary a supplemental application for such change and the Secretary approves the application. The application shall contain such information as the Secretary determines to be appropriate, and shall include the information developed under subsection (b) by the holder in validating the effects of the change."

"(2) **Changes qualifying as major changes.**—For purposes of subsection (a)(2)(A), a major manufacturing change is a manufacturing change that is determined by the Secretary to have substantial potential to adversely affect the identity, strength, quality, purity, or potency of the drug as they may relate to the safety or effectiveness of a drug. Such a change includes a change that —"

"(A) is made in the qualitative or quantitative formulation of the drug involved or in the specifications in the approved application or license referred to in subsection (a) for the drug (unless exempted by the Secretary by regulation or guidance from the requirements of this subsection);"

"(B) is determined by the Secretary by regulation or guidance to require completion of an appropriate clinical study demonstrating equivalence of the drug to the drug as manufactured without the change; or"

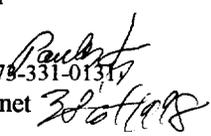
"(C) is another type of change determined by the Secretary by regulation or guidance to have a substantial potential to adversely affect the safety or effectiveness of the drug."

"(d) **Other Manufacturing Changes.**—"

"(1) **In general.**—For purposes of subsection (a)(2)(B), the Secretary may regulate drugs made with manufacturing changes that are not major manufacturing changes as follows:

"(A) The Secretary may in accordance with paragraph (2) authorize holders to distribute such drugs without submitting a supplemental application for such changes."

"(B) The Secretary may in accordance with paragraph (3) require that, prior to the distribution of such drugs, holders submit to the Secretary supplemental applications for such changes."



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“(C) The Secretary may establish categories of such changes and designate categories to which subparagraph (A) applies and categories to which subparagraph (B) applies.”

“(2) Changes not requiring supplemental application.—”

“(A) Submission of report.—A holder making a manufacturing change to which paragraph (1)(A) applies shall submit to the Secretary a report on the change, which shall contain such information as the Secretary determines to be appropriate, and which shall include the information developed under subsection (b) by the holder in validating the effects of the change. The report shall be submitted by such date as the Secretary may specify.”

“(B) Authority regarding annual reports.—In the case of a holder that during a single year makes more than one manufacturing change to which paragraph (1)(A) applies, the Secretary may in carrying out subparagraph (A) authorize the holder to comply with such subparagraph by submitting a single report for the year that provides the information required in such subparagraph for all the changes made by the holder during the year.”

“(3) Changes requiring supplemental application.—”

“(A) Submission of supplemental application.—The supplemental application required under paragraph (1)(B) for a manufacturing change shall contain such information as the Secretary determines to be appropriate, which shall include the information developed under subsection (b) by the holder in validating the effects of the change.”

“(B) Authority for distribution.—In the case of a manufacturing change to which paragraph (1)(B) applies:”

“(i) The holder involved may commence distribution of the drug involved 30 days after the Secretary receives the supplemental application under such paragraph, unless the Secretary notifies the holder within such 30-day period that prior approval of the application is required before distribution may be commenced.”

“(ii) The Secretary may designate a category of such changes for the purpose of providing that, in the case of a change that is in such category, the holder involved may commence distribution of the drug involved upon the receipt by the Secretary of a supplemental application for the change.”

“(iii) If the Secretary disapproves the supplemental application, the Secretary may order the manufacturer to cease the distribution of the drugs that have been made with the manufacturing change.”

(b) Transition Rule.—The amendment made by subsection (a) takes effect upon the effective date of regulations promulgated by the Secretary of Health and Human Services to implement such amendment, or upon the expiration of the 24 month period beginning on the date of the enactment of this Act, whichever occurs first.

Comments On Section 116

1. At first reading and with rereading it seems that all this section does is to place the general SUPAC guidance decision process into the statutes.
2. Based on the preceding, it would seem that the SUPAC guidance documents need only be recast, with some revision, as the requisite regulations and issued. Since the industry has already “bought into SUPAC,” the conversion of SUPAC from guidance to regulation should be straightforward.
3. However, notwithstanding anything that has been said, the crux of the matter, and also the root of the many product problems that exist today, is that the validation must be done on a scientifically sound basis in which (1) a statistically valid number of (2) representative samples are (3) taken by a scientifically sound procedure, (4) examined and (5) tested at unit-dose level. The number of batches produced with the change must also be statistically sound (6). Moreover, (7) from the valid results obtained, (8) based on the application of the appropriate statistics, (9) the product must be shown to conform to (10) specifications appropriate for release (and not to the USP’s article test criteria which, according to the USP, are not release tests) and to (11) appropriate statistical criteria for acceptance or rejection (as set forth in 21 CFR 211.165 and the other applicable sections, governing stability, special testing requirements, reserve samples, and contamination, that follow 21 CFR 211.165).
4. Currently, many of the existing “validation” studies that have been, and are being, carried out are not scientifically sound and do not therefore accurately even accurately reflect the nature of the batches in the validation study much less validly describe or predict the quality of the future batches of drug product made using that process or, for that matter, the capability of the process to operate in control under conditions that permit significant variation in the components used in the processes. Unless the agency moves to correct this major problem, companies, as most do today, will continue to make and distribute batch after batch of adulterated drug product while the agency “looks the other way.”

SEC. 117. STREAMLINING CLINICAL RESEARCH ON DRUGS.

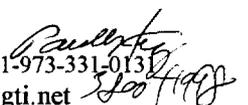
Section 505(i) (21 U.S.C. 355(i)) is amended —

- (1) by redesignating paragraphs (1) through (3) as subparagraphs (A) through (C), respectively;
- (2) by inserting “(1)” after “(i)”;
- (3) by striking the last two sentences; and
- (4) by inserting after paragraph (1) (as designated by paragraph (2) of this section) the following new paragraphs:

“(2) Subject to paragraph (3), a clinical investigation of a new drug may begin 30 days after the Secretary has received from the manufacturer or sponsor of the investigation a submission containing such information about the drug and the clinical investigation, including —”

“(A) information on design of the investigation and adequate reports of basic information, certified by the applicant to be accurate reports, necessary to assess the safety of the drug for use in clinical investigation; and”

“(B) adequate information on the chemistry and manufacturing of the drug, controls available for the drug, and primary data tabulations from animal or human studies.”



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"(3)(A) At any time, the Secretary may prohibit the sponsor of an investigation from conducting the investigation (referred to in this paragraph as a 'clinical hold') if the Secretary makes a determination described in subparagraph (B). The Secretary shall specify the basis for the clinical hold, including the specific information available to the Secretary which served as the basis for such clinical hold, and confirm such determination in writing."

"(B) For purposes of subparagraph (A), a determination described in this subparagraph with respect to a clinical hold is that —"

"(i) the drug involved represents an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation, taking into account the qualifications of the clinical investigators, information about the drug, the design of the clinical investigation, the condition for which the drug is to be investigated, and the health status of the subjects involved; or"

"(ii) the clinical hold should be issued for such other reasons as the Secretary may by regulation establish (including reasons established by regulation before the date of the enactment of the Food and Drug Administration Modernization Act of 1997)."

"(C) Any written request to the Secretary from the sponsor of an investigation that a clinical hold be removed shall receive a decision, in writing and specifying the reasons therefor, within 30 days after receipt of such request. Any such request shall include sufficient information to support the removal of such clinical hold."

"(4) Regulations under paragraph (1) shall provide that such exemption shall be conditioned upon the manufacturer, or the sponsor of the investigation, requiring that experts using such drugs for investigational purposes certify to such manufacturer or sponsor that they will inform any human beings to whom such drugs, or any controls used in connection therewith, are being administered, or their representatives, that such drugs are being used for investigational purposes and will obtain the consent of such human beings or their representatives, except where it is not feasible or it is contrary to the best interests of such human beings. Nothing in this subsection shall be construed to require any clinical investigator to submit directly to the Secretary reports on the investigational use of drugs."

Comments On Section 117

1. There are two problems with the preceding - lack of funding and, the related one, lack of adequate or competent staffing.
2. Again that this is an unfunded mandate requiring a rapid, by FDA standards, (<30 day) decision. Based on the agency's current capabilities, the agency is between a rock and a hard place. If reviewers are diverted from the general review process to assess clinical trial plans to meet its 30-day windows, application and supplement reviews will fall behind; if not, the 30-day time frames will not be met or hasty decisions will be made.
3. The second problem is that, Secretary is again burdened with issuing even more regulations to better define the list of reasons for clinical hold when, at its current funding and staff level, the agency was already falling behind in issuing other promised regulations and in adequately training its personnel.

SEC. 118. DATA REQUIREMENTS FOR DRUGS AND BIOLOGICS.

Within 12 months after the date of enactment of this Act, the Secretary of Health and Human Services, acting through the Commissioner of Food and Drugs, shall issue guidance that describes when abbreviated study reports may be submitted, in lieu of full reports, with a new drug application under section 505(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(b)) and with a biologics license application under section 351 of the Public Health Service Act (42 U.S.C. 262) for certain types of studies. Such guidance shall describe the kinds of studies for which abbreviated reports are appropriate and the appropriate abbreviated report formats.

Comments On Section 118

1. Yet another unfunded mandate.
2. Given that current "full" study reports, at times, contain less information than is needed, perhaps, the current reporting guidance should be reissued under GGP as "Guidance For Abbreviated Reports" and a comprehensive GGP guidance "full study" reporting guidance document would then be issued that mandates complete reporting of all data and findings generated in or adjunct to a study.

SEC. 119. CONTENT AND REVIEW OF APPLICATIONS.

(a) Section 505(b).— Section 505(b) (21 U.S.C. 355(b)) is amended by adding at the end the following:

"(4)(A) The Secretary shall issue guidance for the individuals who review applications submitted under paragraph (1) or under section 351 of the Public Health Service Act, which shall relate to promptness in conducting the review, technical excellence, lack of bias and conflict of interest, and knowledge of regulatory and scientific standards, and which shall apply equally to all individuals who review such applications."

"(B) The Secretary shall meet with a sponsor of an investigation or an applicant for approval for a drug under this subsection or section 351 of the Public Health Service Act if the sponsor or applicant makes a reasonable written request for a meeting for the purpose of reaching agreement on the design and size of clinical trials intended to form the primary basis of an effectiveness claim. The sponsor or applicant shall provide information necessary for discussion and agreement on the design and size of the clinical trials. Minutes of any such meeting shall be prepared by the Secretary and made available to the sponsor or applicant upon request."

"(C) Any agreement regarding the parameters of the design and size of clinical trials of a new drug under this paragraph that is reached between the Secretary and a sponsor or applicant [Page H10458] shall be reduced to writing and made part of the administrative record by the Secretary. Such agreement shall not be changed after the testing begins, except —"

"(i) with the written agreement of the sponsor or applicant; or"

"(ii) pursuant to a decision, made in accordance with subparagraph (D) by the director of the reviewing division, that a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun."

"(D) A decision under subparagraph (C)(ii) by the director shall be in writing and the Secretary shall provide to the sponsor or applicant an opportunity for a meeting at which the director and the sponsor or applicant will be present and at which the director will document the scientific issue involved."

"(E) The written decisions of the reviewing division shall be binding upon, and may not directly or indirectly be changed by, the field or compliance division personnel unless such field or compliance division personnel demonstrate to the reviewing division why such decision should be modified."

"(F) No action by the reviewing division may be delayed because of the unavailability of information from or action by field personnel unless the reviewing division determines that a delay is necessary to assure the marketing of a safe and effective drug."

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"(G) For purposes of this paragraph, the reviewing division is the division responsible for the review of an application for approval of a drug under this subsection or section 351 of the Public Health Service Act (including all scientific and medical matters, chemistry, manufacturing, and controls)."

(b) Section 505(j).—

- (1) Amendment.—Section 505(j) (21 U.S.C 355(j)) is amended —
(A) by redesignating paragraphs (3) through (8) as paragraphs (4) through (9), respectively; and
(B) by adding after paragraph (2) the following:

"(3)(A) The Secretary shall issue guidance for the individuals who review applications submitted under paragraph (1), which shall relate to promptness in conducting the review, technical excellence, lack of bias and conflict of interest, and knowledge of regulatory and scientific standards, and which shall apply equally to all individuals who review such applications."

"(B) The Secretary shall meet with a sponsor of an investigation or an applicant for approval for a drug under this subsection if the sponsor or applicant makes a reasonable written request for a meeting for the purpose of reaching agreement on the design and size of bioavailability and bioequivalence studies needed for approval of such application. The sponsor or applicant shall provide information necessary for discussion and agreement on the design and size of such studies. Minutes of any such meeting shall be prepared by the Secretary and made available to the sponsor or applicant."

"(C) Any agreement regarding the parameters of design and size of bioavailability and bioequivalence studies of a drug under this paragraph that is reached between the Secretary and a sponsor or applicant shall be reduced to writing and made part of the administrative record by the Secretary. Such agreement shall not be changed after the testing begins, except —"

"(i) with the written agreement of the sponsor or applicant; or"

"(ii) pursuant to a decision, made in accordance with subparagraph (D) by the director of the reviewing division, that a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun."

"(D) A decision under subparagraph (C)(ii) by the director shall be in writing and the Secretary shall provide to the sponsor or applicant an opportunity for a meeting at which the director and the sponsor or applicant will be present and at which the director will document the scientific issue involved."

"(E) The written decisions of the reviewing division shall be binding upon, and may not directly or indirectly be changed by, the field or compliance office personnel unless such field or compliance office personnel demonstrate to the reviewing division why such decision should be modified."

"(F) No action by the reviewing division may be delayed because of the unavailability of information from or action by field personnel unless the reviewing division determines that a delay is necessary to assure the marketing of a safe and effective drug."

"(G) For purposes of this paragraph, the reviewing division is the division responsible for the review of an application for approval of a drug under this subsection (including scientific matters, chemistry, manufacturing, and controls)."

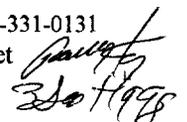
(2) Conforming amendments.— Section 505(j) (21 U.S.C. 355(j)), as amended by paragraph (1), is further amended —

- (A) in paragraph (2)(A)(i), by striking "(6)" and inserting "(7)";
(B) in paragraph (4) (as redesignated in paragraph (1)), by striking "(4)" and inserting "(5)";
(C) in paragraph (4)(I) (as redesignated in paragraph (1)), by striking "(5)" and inserting "(6)"; and
(D) in paragraph (7)(C) (as redesignated in paragraph (1)), by striking "(5)" each place it occurs and inserting "(6)".

The Secretary shall issue guidance for the individuals who review applications submitted under paragraph (1), which shall relate to promptness in conducting the review, technical excellence, lack of bias and conflict of interest, and knowledge of regulatory and scientific standards, and which shall apply equally to all individuals who review such applications."

Comments On Section 119:

1. More unfunded mandates seemingly drafted by the written, submitted to Congress and enacted into law.
2. What is accomplished by issuing "equally applicable" guidance on "knowledge of regulatory and scientific standards" to the reviewers who have not received the appropriate training on said regulations and standards, or who have not demonstrated their competence in any documented measurable manner in understanding said regulations and standards.
3. From a "quality systems" point of view, placing "promptness" ahead of technical excellence and knowledge of regulatory requirements and scientific standards assures that reviewers will continue to be biased and have a built in conflict of interest between making certain that the applications they review meet the regulatory minimums and getting them done as fast as possible.
4. If the agency truly wishes to provide its reviewers proper guidance, then its guidance should begin by making certain that said reviewers are truly competent to review applications. In addition, each reviewer needs to be trained to understand the difference between release specifications and compendial standards as well as what the true statistical requirements are before test results on samples can validly be used to make decisions concerning the current validity of a process or to predict the process capability for the product for future batches. If reviewers truly understood these process fundamental then, contrary to what is the case today, no reviewer would permit the USP's compendial standards to be directly used as the sole release criteria for a batch since they would know (a) that using the USP's criteria is not scientifically sound and (b) that meeting the USP does not satisfy the requirements set forth in 21 CFR 211.165 regarding batch release. Ideally, the agency can use the training mandates set forth in the general section to encourage Congress to recognize the need for and fund a comprehensive Training Program that begins by requiring review and compliance job candidates to establish that they have the training, education and experience required not only in the



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fundamentals in the areas of technical expertise that the job requires for the position but also in the basics of the agency regulations and statutes applicable thereto.

SEC. 120. SCIENTIFIC ADVISORY PANELS.

Section 505 (21 U.S.C. 355) is amended by adding at the end the following:

"(n)(1) For the purpose of providing expert scientific advice and recommendations to the Secretary regarding a clinical investigation of a drug or the approval for marketing of a drug under section 505 or section 351 of the Public Health Service Act, the Secretary shall establish panels of experts or use panels of experts established before the date of enactment of the Food and Drug Administration Modernization Act of 1997, or both."

"(2) The Secretary may delegate the appointment and oversight authority granted under section 904 to a director of a center or successor entity within the Food and Drug Administration."

"(3) The Secretary shall make appointments to each panel established under paragraph (1) so that each panel shall consist of—"

"(A) members who are qualified by training and experience to evaluate the safety and effectiveness of the drugs to be referred to the panel and who, to the extent feasible, possess skill and experience in the development, manufacture, or utilization of such drugs;"

"(B) members with diverse expertise in such fields as clinical and administrative medicine, pharmacy, pharmacology, pharmacoeconomics, biological and physical sciences, and other related professions;"

"(C) a representative of consumer interests, and a representative of interests of the drug manufacturing industry not directly affected by the matter to be brought before the panel; and"

"(D) two or more members who are specialists or have other expertise in the particular disease or condition for which the drug under review is proposed to be indicated. Scientific, trade, and consumer organizations shall be afforded an opportunity to nominate individuals for appointment to the panels. No individual who is in the regular full-time employ of the United States and engaged in the administration of this Act may be a voting member of any panel. The Secretary shall designate one of the members of each panel to serve as chairman thereof."

"(4) Each member of a panel shall publicly disclose all conflicts of interest that member may have with the work to be undertaken by the panel. No member of a panel may vote on any matter where the member or the immediate family of such member could gain financially from the advice given to the Secretary. The Secretary may grant a waiver of any conflict of interest requirement upon public disclosure of such conflict of interest if such waiver is necessary to afford the panel essential expertise, except that the Secretary may not grant a waiver for a member of a panel when the member's own scientific work is involved."

"(5) The Secretary shall, as appropriate, provide education and training to each new panel member before such member participates in a panel's activities, including education regarding requirements under this Act and related regulations of the Secretary, and the administrative processes and procedures related to panel meetings."

"(6) Panel members (other than officers or employees of the United States), while attending meetings or conferences of a panel or otherwise engaged in its business, shall be entitled to receive compensation for each day so engaged, including traveltime, at rates to be fixed by the Secretary, but not to exceed the daily equivalent of the rate in effect for positions classified above grade GS-15 of the General Schedule. While serving away from their homes or regular places of business, panel members may be allowed travel expenses (including per diem in lieu of subsistence) as authorized by section 5703 of title 5, United States Code, for persons in the Government service employed intermittently."

"(7) The Secretary shall ensure that scientific advisory panels meet regularly and at appropriate intervals so that any matter to be reviewed by such a panel can be presented to the panel not more than 60 days after the matter is ready for such review. Meetings of the panel may be held using electronic communication to convene the meetings."

"(8) Within 90 days after a scientific advisory panel makes recommendations on any matter under its review, the Food and Drug Administration official responsible for the matter shall review the conclusions and recommendations of the panel, and notify the affected persons of the final decision on the matter, or of the reasons that no such decision has been reached. Each such final decision shall be documented including the rationale for the decision."

Comments On Section 120:

1. Provided, that the experts appointed are also required to be knowledgeable in the applicable regulations, such expert panels are a good idea.
2. Therefore, based on my experience, training, and education and my in-depth understanding of the regulations and their minimum requirements, I would like to volunteer to serve on any and all scientific advisory panels for drugs under "(n)(3)(B)" and "(n)(3)(C)." To that end, a copy of my current curriculum vitae is being provided as a part of my comments in Appendix A.

SEC. 121. POSITRON EMISSION TOMOGRAPHY.

(a) Regulation of Compounded Positron Emission Tomography Drugs.—Section 201 (21 U.S.C. 321) is amended by adding at the end the following:

"(ii) The term 'compounded positron emission tomography drug'—"

"(1) means a drug that —"

"(A) exhibits spontaneous disintegration of unstable nuclei by the emission of positrons and is used for the purpose of providing dual photon positron emission tomographic diagnostic images; and"

"(B) has been compounded by or on the order of a practitioner who is licensed by a State to compound or order compounding for a drug described in subparagraph (A), and is compounded in accordance with that State's law, for a patient or for research, teaching, or quality control; and"

"(2) includes any nonradioactive reagent, reagent kit, ingredient, nuclide generator, accelerator, target material, electronic synthesizer, or other apparatus or computer program to be used in the preparation of such a drug."

(b) Adulteration.—

(1) In general.—Section 501(a) (21 U.S.C. 351(a)) is amended by striking "; or (3)" and inserting the following:

"; or (C) if it is a compounded positron emission tomography drug and the methods used in, or the facilities and controls used for, its compounding, processing, packing, or holding do not conform to or are not operated or administered in conformity with the positron emission tomography compounding [[Page H10459]] standards and the official monographs of the United States Pharmacopoeia to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, that it purports or is represented to possess; or (3)".

(2) Sunset.—Section 501(a)(2)(C) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351(a)(2)(C)) shall not apply 4 years after the date of enactment of this Act or 2 years after the date on which the Secretary of Health and Human Services establishes the requirements described in subsection (c)(1)(B), whichever is later.

(c) Requirements for Review of Approval Procedures and Current Good Manufacturing Practices for Positron Emission Tomography.—

(1) Procedures and requirements.—

(A) In general.—In order to take account of the special characteristics of positron emission tomography drugs and the special techniques and processes required to produce these drugs, not later than 2 years after the date of enactment of this Act, the Secretary of Health and Human Services shall establish —

(i) appropriate procedures for the approval of positron emission tomography drugs pursuant to section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355); and

(ii) appropriate current good manufacturing practice requirements for such drugs.

(B) Considerations and consultation.—In establishing the procedures and requirements required by subparagraph (A), the Secretary of Health and Human Services shall take due account of any relevant differences between not-for-profit institutions that compound the drugs for their patients and commercial manufacturers of the drugs. Prior to

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establishing the procedures and requirements, the Secretary of Health and Human Services shall consult with patient advocacy groups, professional associations, manufacturers, and physicians and scientists licensed to make or use positron emission tomography drugs.

(2) Submission of new drug applications and abbreviated new drug applications.—

(A) In general.—Except as provided in subparagraph (B), the Secretary of Health and Human Services shall not require the submission of new drug applications or abbreviated new drug applications under subsection (b) or (j) of section 505 (21 U.S.C. 355), for compounded positron emission tomography drugs that are not adulterated drugs described in section 501(a)(2)(C) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351(a)(2)(C)) (as amended by subsection (b)), for a period of 4 years after the date of enactment of this Act, or for 2 years after the date on which the Secretary establishes procedures and requirements under paragraph (1), whichever is longer.

(B) Exception.—Nothing in this Act shall prohibit the voluntary submission of such applications or the review of such applications by the Secretary of Health and Human Services. Nothing in this Act shall constitute an exemption for a positron emission tomography drug from the requirements of regulations issued under section 505(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)).

(d) Revocation of Certain Inconsistent Documents.—Within 30 days after the date of enactment of this Act, the Secretary of Health and Human Services shall publish in the Federal Register a notice terminating the application of the following notices and rule:

(1) A notice entitled "Regulation of Positron Emission Tomography Radiopharmaceutical Drug Products; Guidance; Public Workshop", published in the Federal Register on February 27, 1995, 60 Fed. Reg. 10594.

(2) A notice entitled "Draft Guideline on the Manufacture of Positron Emission Tomography Radiopharmaceutical Drug Products; Availability", published in the Federal Register on February 27, 1995, 60 Fed. Reg. 10593.

(3) A final rule entitled "Current Good Manufacturing Practice for Finished Pharmaceuticals; Positron Emission Tomography", published in the Federal Register on April 22, 1997, 62 Fed. Reg. 19493 (codified at part 211 of title 21, Code of Federal Regulations).

(e) Definition.—As used in this section, the term "compounded positron emission tomography drug" has the meaning given the term in section 201 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321).

Comments on Section 121:

1. The preceding section is but one more example of a special interest drug manufacturing group being able, through legislation, to effectively delay their being regulated for at least four (4) more years as the agency, based on several man years of effort, had properly, with ample opportunity for the special interest's input and little public input, had ascertained that this segment should be regulated.

2. If Congress feels that it must, as it has been doing and is doing, micro manage the FDA, then it should at least accept full personal responsibility for the fruits of its management — the decreased safety that Americans now enjoy because of their actions.

3. Since the agency must start over, it should use the existing documents as their starting point. If the agency truly feels that "P.E.T." drugs should be regulated exactly as any other drug, then the agency should simply re-propose 21 CFR 211 for finished pharmaceuticals as 21 CFR 21x for "P.E.T." drugs with some modifications designed to deal with the short half-life/expiration dating that such drugs have. Moreover, because Congress has mandated that there be separate regulations for radiopharmaceuticals, the "P.E.T." drugs should be addressed as an integral part of the regulations for radiopharmaceutical drugs.

SEC. 122. REQUIREMENTS FOR RADIOPHARMACEUTICALS.

(a) Requirements.—

(1) Regulations.—

(A) Proposed regulations.—Not later than 180 days after the date of enactment of this Act, the Secretary of Health and Human Services, after consultation with patient advocacy groups, associations, physicians licensed to use radiopharmaceuticals, and the regulated industry, shall issue proposed regulations governing the approval of radiopharmaceuticals. The regulations shall provide that the determination of the safety and effectiveness of such a radiopharmaceutical under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) or section 351 of the Public Health Service Act (42 U.S.C. 262) shall include consideration of the proposed use of the radiopharmaceutical in the practice of medicine, the pharmacological and toxicological activity of the radiopharmaceutical (including any carrier or ligand component of the radiopharmaceutical), and the estimated absorbed radiation dose of the radiopharmaceutical.

(B) Final regulations.—Not later than 18 months after the date of enactment of this Act, the Secretary shall promulgate final regulations governing the approval of the radiopharmaceuticals.

(2) Special rule.—In the case of a radiopharmaceutical, the indications for which such radiopharmaceutical is approved for marketing may, in appropriate cases, refer to manifestations of disease (such as biochemical, physiological, anatomic, or pathological processes) common to, or present in, one or more disease states.

(b) Definition.—In this section, the term "radiopharmaceutical" means—

(1) an article —

(A) that is intended for use in the diagnosis or monitoring of a disease or a manifestation of a disease in humans; and

(B) that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons; or (2) any nonradioactive reagent kit or nuclide generator that is intended to be used in the preparation of any such article.

Comments on Section 122:

1. Hopefully, given the agency's limited resources, the mandated regulations for radiopharmaceuticals will also encompass "Positron Emission Tomography" drugs so that only one set of regulations will encompass such drugs. (See comments on section 121.)

SEC. 123. MODERNIZATION OF REGULATION.

(a) Licenses.—

(1) In general.—Section 351(a) of the Public Health Service (42 U.S.C. 262(a)) is amended to read as follows:

"(a)(1) No person shall introduce or deliver for introduction into interstate commerce any biological product unless —"

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- "(A) a biologics license is in effect for the biological product; and"
- "(B) each package of the biological product is plainly marked with —"
- "(i) the proper name of the biological product contained in the package;"
- "(ii) the name, address, and applicable license number of the manufacturer of the biological product; and"
- "(iii) the expiration date of the biological product."
- "(2)(A) The Secretary shall establish, by regulation, requirements for the approval, suspension, and revocation of biologics licenses."
- "(B) The Secretary shall approve a biologics license application —"
- "(i) on the basis of a demonstration that —"
- "(I) the biological product that is the subject of the application is safe, pure, and potent; and"
- "(II) the facility in which the biological product is manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent; and"
- "(ii) if the applicant (or other appropriate person) consents to the inspection of the facility that is the subject of the application, in accordance with subsection (c)."
- "(3) The Secretary shall prescribe requirements under which a biological product undergoing investigation shall be exempt from the requirements of paragraph (1)."
- (2) Elimination of existing license requirement.—Section 351(d) of the Public Health Service Act (42 U.S.C. 262(d)) is amended —
- (A) by striking "(d)(1)" and all that follows through "of this section.";
- (B) in paragraph (2)—
- (i) by striking "(2)(A) Upon" and inserting "(d)(1) Upon" and
- (ii) by redesignating subparagraph (B) as paragraph (2); and
- (C) in paragraph (2) (as so redesignated by subparagraph (B)(ii))—
- (i) by striking "subparagraph (A)" and inserting "paragraph (1)"; and
- (ii) by striking "this subparagraph" each place it appears and inserting "this paragraph".
- (b) Labeling.—Section 351(b) of the Public Health Service Act (42 U.S.C. 262(b)) is amended to read as follows:
- "(b) No person shall falsely label or mark any package or container of any biological product or alter any label or mark on the package or container of the biological product so as to falsify the label or mark."
- (c) Inspection.—Section 351(c) of the Public Health Service Act (42 U.S.C. 262(c)) is amended by striking "virus, serum," and all that follows and inserting "biological product."
- (d) Definition: Application.—Section 351 of the Public Health Service Act (42 U.S.C. 262) is amended by adding at the end the following:
- "(i) In this section, the term 'biological product' means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings."
- (e) Conforming Amendment.—Section 503(g)(4) (21 U.S.C. 353(g)(4)) is amended —
- (1) in subparagraph (A)—
- (A) by striking "section 351(a)" and inserting "section 351(i)"; and
- (B) by striking "262(a)" and inserting "262(i)"; and
- (2) in subparagraph (B)(iii), by striking "product or establishment license under subsection (a) or (d)" and inserting "biologics license application under subsection (a)".
- (f) Special Rule.—The Secretary of Health and Human Services shall take measures to minimize differences in the review and approval of products required to have approved biologics license applications under section 351 of the Public Health Service Act (42 U.S.C. 262) and products required to have approved new drug applications under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(b)(1)).
- (g) Application of Federal Food, Drug, and Cosmetic Act.—Section 351 of the Public Health Service Act (42 U.S.C. 262), as amended by subsection (d), is further amended by adding at the end the following:
- "(j) The Federal Food, Drug, and Cosmetic Act applies to a biological product subject to regulation under this section, except that a product for which a license has been approved under subsection (a) shall not be required to have an approved application under section 505 of such Act." [Page H10460]]
- (h) Examinations and Procedures.—Paragraph (3) of section 353(d) of the Public Health Service Act (42 U.S.C. 263a(d)) is amended to read as follows:
- "(3) Examinations and procedures.—The examinations and procedures identified in paragraph (2) are laboratory examinations and procedures that have been approved by the Food and Drug Administration for home use or that, as determined by the Secretary, are simple laboratory examinations and procedures that have an insignificant risk of an erroneous result, including those that —"
- "(A) employ methodologies that are so simple and accurate as to render the likelihood of erroneous results by the user negligible, or "
- "(B) the Secretary has determined pose no unreasonable risk of harm to the patient if performed incorrectly."

Comments on Section 123:

This most of this section simply reflects mandated language that is congruent with the FDA's goal to treat the review and auditing of "biological products" in the same manner as drugs are treated.

SEC. 124. PILOT AND SMALL SCALE MANUFACTURE.

- (a) Human Drugs.—Section 505(c) (21 U.S.C. 355(c)) is amended by adding at the end the following:
- "(4) A drug manufactured in a pilot or other small facility may be used to demonstrate the safety and effectiveness of the drug and to obtain approval for the drug prior to manufacture of the drug in a larger facility, unless the Secretary makes a determination that a full scale production facility is necessary to ensure the safety or effectiveness of the drug."
- (b) Animal Drugs.—Section 512(c) (21 U.S.C. 360b(c)) is amended by adding at the end the following:
- "(4) A drug manufactured in a pilot or other small facility may be used to demonstrate the safety and effectiveness of the drug and to obtain approval for the drug prior to manufacture of the drug in a larger facility, unless the Secretary makes a determination that a full scale production facility is necessary to ensure the safety or effectiveness of the drug."

Comments on Section 124:

1. This section simply formalizes the practices that some companies have been using, after obtaining agency approval. This wording places the onus on the FDA by requiring it to make a determination each time a firm submits an application for review based solely on pilot-plant or contract manufactured drug.
2. To assure that there is no misunderstanding about the agency's position, the agency should approve all such applications with a stipulation that, post approval, any change of the source of the drug product source or scale would require the applicant to validate that the change did not

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affect the safety, identity, strength, quality, or purity of the active or the process' capability to meet its predetermined specifications, file a supplement, and obtain approval for said change before drug-product from the different source or scale are marketed.

SEC. 127. APPLICATION OF FEDERAL LAW TO PRACTICE OF PHARMACY COMPOUNDING.

(a) Amendment.—Chapter V is amended by inserting after section 503 (21 U.S.C. 353) the following:

***SEC. 503A. PHARMACY COMPOUNDING.**

*(a) In General.—Sections 501(a)(2)(B), 502(f)(1), and 505 shall not apply to a drug product if the drug product is compounded for an identified individual patient based on the unsolicited receipt of a valid prescription order or a notation, approved by the prescribing practitioner, on the prescription order that a compounded product is necessary for the identified patient, if the drug product meets the requirements of this section, and if the compounding —"

"(1) is by —"

"(A) a licensed pharmacist in a State licensed pharmacy or a Federal facility, or"

"(B) a licensed physician, on the prescription order for such individual patient made by a licensed physician or other licensed practitioner authorized by State law to prescribe drugs; or" [[Page H10461]]

"(2)(A) is by a licensed pharmacist or licensed physician in limited quantities before the receipt of a valid prescription order for such individual patient; and"

"(B) is based on a history of the licensed pharmacist or licensed physician receiving valid prescription orders for the compounding of the drug product, which orders have been generated solely within an established relationship between —"

"(i) the licensed pharmacist or licensed physician; and"

"(ii)(I) such individual patient for whom the prescription order will be provided; or"

"(II) the physician or other licensed practitioner who will write such prescription order."

"(b) Compounded Drug.—"

"(1) Licensed pharmacist and licensed physician.—A drug product may be compounded under subsection (a) if the licensed pharmacist or licensed physician —

"(A) compounds the drug product using bulk drug substances, as defined in regulations of the Secretary published at section 207.3(a)(4) of title 21 of the Code of Federal Regulations —

"(i) that—"

"(I) comply with the standards of an applicable United States Pharmacopoeia or National Formulary monograph, if a monograph exists, and the United States Pharmacopoeia chapter on pharmacy compounding;

"(II) if such a monograph does not exist, are drug substances that are components of drugs approved by the Secretary; or"

"(III) if such a monograph does not exist and the drug substance is not a component of a drug approved by the Secretary, that appear on a list developed by the Secretary through regulations issued by the Secretary under subsection (d);"

"(ii) that are manufactured by an establishment that is registered under section 510 (including a foreign establishment that is registered under section 510(i)); and"

"(iii) that are accompanied by valid certificates of analysis for each bulk drug substance;"

"(B) compounds the drug product using ingredients (other than bulk drug substances) that comply with the standards of an applicable United States Pharmacopoeia or National Formulary monograph, if a monograph exists, and the United States Pharmacopoeia chapter on pharmacy compounding;"

"(C) does not compound a drug product that appears on a list published by the Secretary in the Federal Register of drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective; and"

"(D) does not compound regularly or in inordinate amounts (as defined by the Secretary) any drug products that are essentially copies of a commercially available drug product."

"(2) Definition.—For purposes of paragraph (1)(D), the term 'essentially a copy of a commercially available drug product' does not include a drug product in which there is a change, made for an identified individual patient, which produces for that patient a significant difference, as determined by the prescribing practitioner, between the compounded drug and the comparable commercially available drug product."

"(3) Drug product.—A drug product may be compounded under subsection (a) only if —"

"(A) such drug product is not a drug product identified by the Secretary by regulation as a drug product that presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product; and"

"(B) such drug product is compounded in a State —"

"(i) that has entered into a memorandum of understanding with the Secretary which addresses the distribution of inordinate amounts of compounded drug products interstate and provides for appropriate investigation by a State agency of complaints relating to compounded drug products distributed outside such State; or"

"(ii) that has not entered into the memorandum of understanding described in clause (i) and the licensed pharmacist, licensed pharmacy, or licensed physician distributes (or causes to be distributed) compounded drug products out of the State in which they are compounded in quantities that do not exceed 5 percent of the total prescription orders dispensed or distributed by such pharmacy or physician.

The Secretary shall, in consultation with the National Association of Boards of Pharmacy, develop a standard memorandum of understanding for use by the States in complying with subparagraph (B)(i)."

*(c) Advertising and Promotion.—A drug may be compounded under subsection (a) only if the pharmacy, licensed pharmacist, or licensed physician does not advertise or promote the compounding of any particular drug, class of drug, or type of drug. The pharmacy, licensed pharmacist, or licensed physician may advertise and promote the compounding service provided by the licensed pharmacist or licensed physician."

*(d) Regulations.—"

"(1) In general.—The Secretary shall issue regulations to implement this section. Before issuing regulations to implement subsections (b)(1)(A)(i)(III), (b)(1)(C), or (b)(3)(A), the Secretary shall convene and consult an advisory committee on compounding unless the Secretary determines that the issuance of such regulations before consultation is necessary to protect the public health. The advisory committee shall include representatives from the National Association of Boards of Pharmacy, the United States Pharmacopoeia, pharmacy, physician, and consumer organizations, and other experts selected by the Secretary."

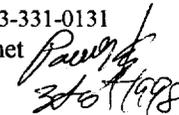
"(2) Limiting compounding.—The Secretary, in consultation with the United States Pharmacopoeia Convention, Incorporated, shall promulgate regulations identifying drug substances that may be used in compounding under subsection (b)(1)(A)(i)(III) for which a monograph does not exist or which are not components of drug products approved by the Secretary. The Secretary shall include in the regulation the criteria for such substances, which shall include historical use, reports in peer reviewed medical literature, or other criteria the Secretary may identify."

*(e) Application.— This section shall not apply to —"

"(1) compounded positron emission tomography drugs as defined in section 201(ii); or"

"(2) radiopharmaceuticals."

*(f) Definition.— As used in this section, the term 'compounding' does not include mixing, reconstituting, or other such acts that are performed in accordance with directions contained in approved labeling provided by the product's manufacturer and other manufacturer directions consistent with that labeling."



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(b) Effective Date.—Section 503A of the Federal Food, Drug, and Cosmetic Act, added by subsection (a), shall take effect upon the expiration of the 1-year period beginning on the date of the enactment of this Act.

Comments On Section 127:

1. The regulations governing compounding should clearly require that the pharmacist or physician must actually perform the compounding personally — that supervision of the compounding is not sufficient nor, as this statute is constructed, permitted.
2. The regulations should also require that, at a minimum, the identity of any and all components must be determined by a specific identity tests (not the USP identity test unless such test is truly specific for the component being tested) for each shipment of each lot.
3. Moreover, at a minimum, the as-is, 99%-lower-bound-confidence-level (based on the formula $Purity_{(lower\ bound)} = Assay_{(avg\ of\ n)} - t_{(0.99, n-1)} \times SD_n / \sqrt{n}$ where “n” is the number of independent Assay determinations, typically 6 or more, from a representative sample) purity (not the USP Assay) of each active ingredient must be determined on representative samples from each shipment of each active pharmaceutical. [Unless this is done, the compounded material is not assured of meeting the requirements of 21 CFR 101, “intent to provide not less than 100 % of” the labeled or targeted amount.]
4. Thus, such compounders would need to have a small lab or to send their samples out to an accredited lab for the requisite testing and obtain documented evidence that the components met their requirements before any component could be accepted and used in compounding.
5. At a minimum, any component must have a certificate that certifies:
 - (a) that it was manufactured under the appropriate CGMP, drug (FDA), excipient (...), food (FDA), nutritional (CRN), etc.;
 - (b) that all testing was done on representative samples from the batch; and
 - (c) reports all individual results and any derived values required pursuant to the USP’s requirements along with the USP or other source specifications used by the component’s manufacturer to release the component for distribution.
6. The regulations should, at a minimum, require that a documented record be kept of the lot numbers for each component, the weights or volumes of each component used in compounding, the general steps taken in compounding and the results including number of dosage-form units or containers produced and their appearance and appropriate physical characteristics.

SEC. 130. REPORTS OF POSTMARKETING APPROVAL STUDIES.

(a) In General.—Chapter V, as amended by section 116, is further amended by inserting after section 506A the following:

***SEC. 506B. REPORTS OF POSTMARKETING STUDIES.**

- (a) Submission.
 - (1) In general.—A sponsor of a drug that has entered into an agreement with the Secretary to conduct a postmarketing study of a drug shall submit to the Secretary, within 1 year after the approval of such drug and annually thereafter until the study is completed or terminated, a report of the progress of the study or the reasons for the failure of the sponsor to conduct the study.

The report shall be submitted in such form as is prescribed by the Secretary in regulations issued by the Secretary.
 - (2) Agreements prior to effective date.—Any agreement entered into between the Secretary and a sponsor of a drug, prior to the date of enactment of the Food and Drug Administration Modernization Act of 1997, to conduct a postmarketing study of a drug shall be subject to the requirements of paragraph (1). An initial report for such an agreement shall be submitted within 6 months after the date of the issuance of the regulations under paragraph (1).
 - (b) Consideration of Information as Public Information.—Any information pertaining to a report described in subsection (a) shall be considered to be public information to the extent that the information is necessary —
 - (1) to identify the sponsor;
 - and
 - (2) to establish the status of a study described in subsection (a) and the reasons, if any, for any failure to carry out the study.
 - (c) Status of Studies and Reports.— The Secretary shall annually develop and publish in the Federal Register a report that provides information on the status of the postmarketing studies —
 - (1) that sponsors have entered into agreements to conduct; and
 - (2) for which reports have been submitted under subsection (a)(1)."
- (b) Report to Congressional Committees.— Not later than October 1, 2001, the Secretary shall prepare and submit to the Committee on Labor and Human Resources of the Senate and the Committee on Commerce of the House of Representatives a report containing —
- (1) a summary of the reports submitted under section 506B of the Federal Food, Drug, and Cosmetic Act;
 - (2) an evaluation of:
 - (A) the performance of the sponsors referred to in such section in fulfilling the agreements with respect to the conduct of postmarketing studies described in such section of such Act; and

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- (B) the timeliness of the Secretary's review of the postmarketing studies;
and
(3) any legislative recommendations respecting the postmarketing studies.

Comments On Section 130:

See Previous Section II 3b Comments Provided In Tabular Form.

TITLE IV — GENERAL PROVISIONS

SEC. 405. INFORMAL AGENCY STATEMENTS.

Section 701 (21 U.S.C. 371) is amended by adding at the end the following:

"(h)(1)(A) The Secretary shall develop guidance documents with public participation and ensure that information identifying the existence of such documents and the documents themselves are made available to the public both in written form and, as feasible, through electronic means. Such documents shall not create or confer any rights for or on any person, although they present the views of the Secretary on matters under the jurisdiction of the Food and Drug Administration."

"(B) Although guidance documents shall not be binding on the Secretary, the Secretary shall ensure that employees of the Food and Drug Administration do not deviate from such guidances without appropriate justification and supervisory concurrence. **The Secretary shall provide training to employees in how to develop and use guidance documents and shall monitor the development and issuance of such documents.**"

"(C) **For guidance documents that set forth initial interpretations of a statute or regulation, changes in interpretation or policy that are of more than a minor nature, complex scientific issues, or highly controversial issues, the Secretary shall ensure public participation prior to implementation of guidance documents, unless the Secretary determines that such prior public participation is not feasible or appropriate. In such cases, the Secretary shall provide for public comment upon implementation and take such comment into account.**"

"(D) **For guidance documents that set forth existing practices or minor changes in policy, the Secretary shall provide for public comment upon implementation.**"

"(2) In developing guidance documents, the Secretary shall ensure uniform nomenclature for such documents and uniform internal procedures for approval of such documents. The Secretary shall ensure that guidance documents and revisions of such documents are properly dated and indicate the nonbinding nature of the documents. The Secretary shall periodically review all guidance documents and, where appropriate, revise such documents."

"(3) The Secretary, acting through the Commissioner, shall maintain electronically and update and publish periodically in the Federal Register a list of guidance documents. All such documents shall be made available to the public."

"(4) The Secretary shall ensure that an effective appeals mechanism is in place to address complaints that the Food and Drug Administration is not developing and using guidance documents in accordance with this subsection."

"(5) Not later than July 1, 2000, the Secretary after evaluating the effectiveness of the Good Guidance Practices document, published in the Federal Register at 62 Fed. Reg. 8961, shall promulgate a regulation consistent with this subsection specifying the policies and procedures of the Food and Drug Administration for the development, issuance, and use of guidance documents."

Comments On Section 405:

1. Pursuant to the highlighted portion of "(h)(1)(B)," the Secretary needs to provide some mechanism that, unlike systems used to generate the present guidance documents, can assure that no guidance document recommends any practice or course of action that is in conflict with:
 - (a) a Federal statute or regulation or
 - (b) that is in conflict with a recognized National or International Standard or the requirements of a recognized pharmacopeia, such as the United States Pharmacopeia, or the National Formulary.
2. Pursuant to ""(h)(1)(C)," notwithstanding any existing policy, the Secretary should, by policy, publish all such guidance documents that have not been open to public comment as "ROUGH DRAFT" documents. Then, after initial comment has been received and reviewed, revise the documents and publish them as "DRAFT" documents for final comment and review before publishing the "FINAL" guidance document,.
3. Pursuant to ""(h)(1)(D)," notwithstanding any existing policy, the Secretary should, by policy, publish all such guidance documents as "DRAFT" documents for final comment and review before publishing the "FINAL" guidance document.

SEC. 408. EDUCATION AND TRAINING.

(a) Food and Drug Administration.—Chapter VII (21 U.S.C. 371 et seq.), as amended by section 407, is further amended by adding at the end the following section:

"SEC. 742. EDUCATION.

"(a) **In General.**—The Secretary shall conduct training and education programs for the employees of the Food and Drug Administration relating to the regulatory responsibilities and policies established by this Act, including programs for—"

"(1) scientific training;"

"(2) training to improve the skill of officers and employees authorized to conduct inspections under section 704;"

"(3) training to achieve product specialization in such inspections; and"

"(4) training in administrative process and procedure and integrity issues."

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"(b) Intramural Fellowships and Other Training Programs.— The Secretary, acting through the Commissioner, may, through fellowships and other training programs, conduct and support intramural research training for predoctoral and postdoctoral scientists and physicians."

(b) Centers for Disease Control and Prevention.—

(1) In general.—Part B of title III of the Public Health Service Act is amended by inserting after section 317F (42 U.S.C. 247b-7) the following:

"SEC. 317G. FELLOWSHIP AND TRAINING PROGRAMS."

"The Secretary, acting through the Director of the Centers for Disease Control and Prevention, shall establish fellowship and training programs to be conducted by such Centers to train individuals to develop skills in epidemiology, surveillance, laboratory analysis, and other disease detection and prevention methods. Such programs shall be designed to enable health professionals and health personnel trained under such programs to work, after receiving such training, in local, State, national, and international efforts toward the prevention and control of diseases, injuries, and disabilities. Such fellowships and training may be administered through the use of either appointment or nonappointment procedures."

(2) Effective date.—The amendment made by this subsection is deemed to have taken effect July 1, 1995.

Comments On Section 408:

1. In my 18+ years of dealing with the agency and agency personnel, the greatest non-addressed weaknesses in dealing with said personnel is their lack of training in and understanding of the requirements of the regulations with which those companies the agency regulates are supposed, at a minimum, comply. Therefore, the agency needs to first train and then establish the competence of all of its employees who are directly involved in the regulatory review and approval process from the commissioner's office on down to the newly hired inspector. If the agency understands the need to mandate that the companies they regulate provide ongoing training in the regulations with which they are to comply, then it should understand the need to have those employees involved in the regulatory process to be fully competent with respect to the requirements with which they are supposed to assure that the companies they are evaluating comply fully.
2. Based on my experience, not only has the problem alluded to in comment 1 always been an issue, it has gotten worse as the agency has retired many of those who were most knowledgeable, is experiencing an increasing rate of turnover, and, because of budgetary constraints and priorities has been forced to minimize training and has apparently opted to pare training in the regulations to the bone. For example, when I attended the 22nd International GMP Conference at the U. of Georgia in March of this year (1998), I heard that inspections for electronic records and electronic signatures were being conducted and that the FDA was planning a training course for its inspectors. As of the end of August 1998, I was told that, because of budgetary constraints, that the course was still in the planning stage but with the FY 1999 budgeting constraints, it might not occur until the end of 1999 (FY 2000). How can there be effective inspections or effective application reviews if the reviewers and the inspectors are untrained?
3. Recently, in again attempting to get the agency to "enforce" the 1978 CGMP regulations as they are clearly written, I encountered many who did not even know exactly what the regulations required.
4. Lacking a fundamental understanding and competency in the clearly written regulations that they are supposed to "enforce," it is easy for me to see how companies have persuaded the agency to "look the other way" in certain critical areas, for the reviewers to approve filings that contain violative practices and specifications, and for the inspectors to accept as compliance practices that the USP itself, in its General Notices, warns against. Thus, before trying to build up their staff, the agency needs to make sure that the foundation training their employees receives results in these employees being competent with the real requirements of the regulations with which the firms they are dealing are supposed to be complying.

SEC. 410. MUTUAL RECOGNITION AGREEMENTS AND GLOBAL HARMONIZATION.

(a) Good Manufacturing Practice Requirements.—Section 520(f)(1)(B) (21 U.S.C. 360j(f)(1)(B)) is amended—

- (1) in clause (i), by striking ", and" at the end and inserting a semicolon;
- (2) in clause (ii), by striking the period and inserting "; and"; and
- (3) by inserting after clause (ii) the following:

"(iii) ensure that such regulation conforms, to the extent practicable, with internationally recognized standards defining quality systems, or parts of the standards, for medical devices."

(b) Harmonization Efforts.—Section 803 (21 U.S.C. 383) is amended by adding at the end the following:

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"(c)(1) The Secretary shall support the Office of the United States Trade Representative, in consultation with the Secretary of Commerce, in meetings with representatives of other countries to discuss methods and approaches to reduce the burden of regulation and harmonize regulatory requirements if the Secretary determines that such harmonization continues consumer protections consistent with the purposes of this Act."

"(2) The Secretary shall support the Office of the United States Trade Representative, in consultation with the Secretary of Commerce, in efforts to move toward the acceptance of mutual recognition agreements relating to the regulation of drugs, biological products, devices, foods, food additives, and color additives, and the regulation of good manufacturing practices, between the European Union and the United States."

"(3) The Secretary shall regularly participate in meetings with representatives of other foreign governments to discuss and reach agreement on [[Page H10473]] methods and approaches to harmonize regulatory requirements."

"(4) The Secretary shall, not later than 180 days after the date of enactment of the Food and Drug Administration Modernization Act of 1997, make public a plan that establishes a framework for achieving mutual recognition of good manufacturing practices inspections."

"(5) Paragraphs (1) through (4) shall not apply with respect to products defined in section 201(ff)."

Comments On Section 410:

1. While I applaud the intent here to harmonize regulatory requirements, I remain appalled at the duplicitous way with which some in the EU seem to be dealing with their US counterparts. After having been forced to hurriedly reply to the FDA's proposed "MRA" enabling regulations because, I was told, that they were under tight time constraints to publish the final regulations by the end of August, I was very disappointed to find out that:
 - (a) the EU side had unilaterally changed the initialed MRA agreements (that all parties had agreed to) to "correct typographical errors" and tried, fortunately unsuccessfully, to have the FDA agree to accept the changes without review;
 - (b) failing that and after further review of what they had agreed to, the EU side next wanted, again *sub rosa*, to change the agreed upon merged definition of "good manufacturing practice" which again the FDA properly resisted as to do so would have reduced "consumer protection" and not been "consistent with the purposes of the act;" and
 - (c) failing that, have, after meeting with government officials other than the FDA, convinced the Commerce Committee to issue requests for FDA documents and to hold hearings on "17 September 1998" (although I have not yet gotten the Republican Side of the Committee to confirm this) at which only testimony concerning the MRA process is to be solicited from the agency only and, judging by the openness with which my request for information as to what was going on and the lack of response from the scheduling party, public attendance is certainly not being solicited and public input is certainly not on the agenda.
2. From my point of view, the agreement that was essentially in place was the most that the US side could do without doing more than risking more than a slight compromise in the consumer safety that the existing MRA agreement (as published by the FDA on their web site and implemented in their proposed regulations, with minor corrections) was already risking.
3. Given the preceding and the fact that most of the pharmaceutical products from the EU are from multinational companies who, for the most part, are head quartered in the EU, I would suggest that the companies be contacted at the highest levels and their management asked to vote on whether or not the MRA is acceptable to them.
4. If they vote against it, then I think that the USTR and Commerce should inform their EU counterparts that, because of their unwillingness to accept the MRA as agreed to by the parties and the opposition of the major multinationals head quartered in the EU, that the US sees no need to pursue said MRA further (see comment 6).
5. If, on the other hand, they vote for it, then, I would leave it up to them to overcome the opposition as they know how to accomplish that much better than we do. Then, after giving these multinationals a month to resolve the issues that the EU side is now raising, (a) the US FDA should go ahead and enact the regulations that are as were agreed to by the parties or, (b) if the EU side is still not swayed, the MRA approach should be tabled (see comment 6.).
6. If the EU cannot now accept the MRA that they agreed to in May of 1998, then the FDA to minimize its inspectional burden in the EU and elsewhere should purpose regulations that would

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require all US drug firms having approved applications that reference a foreign source to (a) conduct annual audits against the US CGMP standards, and (b) provide annual certification that all of their foreign locations listed in any application are operating in full compliance with the US CGMP requirements with the penalty for a false certification being handled under the debarment provisions of the act. After all, **21 CFR 211.22(a)** currently includes language that states:

“The quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company.”

which, in many cases already provides this avenue to the US FDA. If legal review finds that that language is not adequate, then, all that would be needed would be to make a minor change to the language to :

“The quality control unit shall be responsible for approving or rejecting ~~drug products~~ *drugs, in-process intermediate materials, and drug products* manufactured, processed, packed, or held under contract by another company.”

7. Were the FDA to take this course of action, one benefit to the US would be that many of the pharmaceutical manufacturing jobs that are being “exported” to foreign companies would begin to be re-imported and, as the should, the US companies would bear the costs of auditing their foreign sources. This, in turn, would (a) strengthen the US pharmaceutical industry and (b) minimize the number of costly foreign inspections that would need to be done and thus allow the agency to meet its biannual general drug-product CGMP inspection mandates. Finally, because their risk of inspection, and the costs thereof, would increase, the safety and quality of the drugs, in-process intermediate materials and drug products would increase.

SEC. 412. NATIONAL UNIFORMITY FOR NONPRESCRIPTION DRUGS AND COSMETICS.

- (a) Nonprescription Drugs.—Chapter VII (21 U.S.C. 371 et seq.), as amended by section 411, is further amended by adding at the end the following:

“Subchapter F — National Uniformity for Nonprescription Drugs and Preemption for Labeling or Packaging of Cosmetics”

“SEC. 751. NATIONAL UNIFORMITY FOR NONPRESCRIPTION DRUGS.”

“(a) In General.—Except as provided in subsection (b), (c)(1), (d), (e), or (f), no State or political subdivision of a State may establish or continue in effect any requirement —”

“(1) that relates to the regulation of a drug that is not subject to the requirements of section 503(b)(1) or 503(f)(1)(A); and”

“(2) that is different from or in addition to, or that is otherwise not identical with, a requirement under this Act, the Poison Prevention Packaging Act of 1970 (15 U.S.C. 1471 et seq.), or the Fair Packaging and Labeling Act (15 U.S.C. 1451 et seq).”

“(b) Exemption.—”

“(1) In general.—Upon application of a State or political subdivision thereof, the Secretary may by regulation, after notice and opportunity for written and oral presentation of views, exempt from subsection (a), under such conditions as may be prescribed in such regulation, a State or political subdivision requirement that —”

“(A) protects an important public interest that would otherwise be unprotected, including the health and safety of children;”

“(B) would not cause any drug to be in violation of any applicable requirement or prohibition under Federal law; and”

“(C) would not unduly burden interstate commerce.”

“(2) Timely action.—The Secretary shall make a decision on the exemption of a State or political subdivision requirement under paragraph (1) not later than 120 days after receiving the application of the State or political subdivision under paragraph (1).”

“(c) Scope.—”

“(1) In general.—This section shall not apply to —”

“(A) any State or political subdivision requirement that relates to the practice of pharmacy; or”

“(B) any State or political subdivision requirement that a drug be dispensed only upon the prescription of a practitioner licensed by law to administer such drug.”

“(2) Safety or effectiveness.—For purposes of subsection (a), a requirement that relates to the regulation of a drug shall be deemed to include any requirement relating to public information or any other form of public communication relating to a warning of any kind for a drug.”

“(d) Exceptions.—”

“(1) In general.—In the case of a drug described in subsection (a)(1) that is not the subject of an application approved under section 505 or section 507 (as in effect on the day before the date of enactment of the Food and Drug Administration Modernization Act of 1997) or a final regulation promulgated by the Secretary establishing conditions under which the drug is generally recognized as safe and effective and not misbranded, subsection (a) shall apply only with respect to a requirement of a State or political subdivision of a State that relates to the same subject as, but is different from or in addition to, or that is otherwise not identical with —”

“(A) a regulation in effect with respect to the drug pursuant to a statute described in subsection (a)(2); or”

“(B) any other requirement in effect with respect to the drug pursuant to an amendment to such a statute made on or after the date of enactment of the Food and Drug Administration Modernization Act of 1997.”

“(2) State initiatives.—This section shall not apply to a State requirement adopted by a State public initiative or referendum enacted prior to **September 1, 1997.**”

“(e) No Effect on Product Liability Law.—Nothing in this section shall be construed to modify or otherwise affect any action or the liability of any person under the product liability law of any State.”

“(f) State Enforcement Authority.—Nothing in this section shall prevent a State or political subdivision thereof from enforcing, under any relevant civil or other enforcement authority, a requirement that is identical to a requirement of this Act.”

(b) Inspections.—Section 704(a)(1) (21 U.S.C. 374(a)(1)) is amended by striking “prescription drugs” each place it appears and inserting “prescription drugs, nonprescription drugs intended for human use.”

(c) Misbranding.—Subparagraph (1) of section 502(e) (21 U.S.C. 352(e)(1)) is amended to read as follows:

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"(1)(A) If it is a drug, unless its label bears, to the exclusion of any other nonproprietary name (except the applicable systematic chemical name or the chemical formula)—"

"(i) the established name (as defined in subparagraph (3)) of the drug, if there is such a name;"

"(ii) the established name and quantity or, if determined to be appropriate by the Secretary, the proportion of each active ingredient, including the quantity, kind, and proportion of any alcohol, and also including whether active or not the established name and quantity or if determined to be appropriate by the Secretary, the proportion of any bromides, ether, chloroform, acetanilide, acetophenetidin, amidopyrine, antipyrine, atropine, hyoscyne, hyoscyamine, arsenic, digitalis, digitalis glucosides, mercury, ouabain, strophanthin, strychnine, thyroid, or any derivative or preparation of any such substances, contained therein, except that the requirement for stating the quantity of the active ingredients, other than the quantity of those specifically named in this subclause, shall not apply to nonprescription drugs not intended for human use; and"

"(iii) the established name of each inactive ingredient listed in alphabetical order on the outside container of the retail package and, if determined to be appropriate by the Secretary, on the immediate container, as prescribed in regulation promulgated by the Secretary, except that nothing in this subclause shall be deemed to require that any trade secret be divulged, and except that the requirements of this subclause with respect to alphabetical order shall apply only to nonprescription drugs that are not also cosmetics and that this subclause shall not apply to nonprescription drugs not intended for human use."

"(B) For any prescription drug the established name of such drug or ingredient, as the case may be, on such label (and on any labeling on which a name for such drug or ingredient is used) shall be printed prominently and in type at least half as large as that used thereon for any proprietary name or designation for such drug or ingredient, except that to the extent that compliance with the requirements of subclause (ii) or (iii) of clause (A) or this clause is impracticable, exemptions shall be established by regulations promulgated by the Secretary."

(d) Cosmetics.—Subchapter F of chapter VII, as amended by subsection (a), is further amended by adding at the end the following:

"SEC. 752. PREEMPTION FOR LABELING OR PACKAGING OF COSMETICS."

"(a) In General.—Except as provided in subsection (b), (d), or (e), no State or political subdivision of a State may establish or continue in effect any requirement for labeling or packaging of a cosmetic that is different from or in addition to, or that is otherwise not identical with, a requirement specifically applicable to a particular cosmetic or class of cosmetics under this Act, the Poison Prevention Packaging Act of 1970 (15 U.S.C. 1471 et seq.), or the Fair Packaging and Labeling Act (15 U.S.C. 1451 et seq.)."

"(b) Exemption.—Upon application of a State or political subdivision thereof, the Secretary may by regulation, after notice and opportunity for written and oral presentation of views, exempt from subsection (a), under such conditions as may be prescribed in such regulation, a State or political subdivision requirement for labeling or packaging that —"

"(1) protects an important public interest that would otherwise be unprotected;"

"(2) would not cause a cosmetic to be in violation of any applicable requirement or prohibition under Federal law; and"

"(3) would not unduly burden interstate commerce."

"(c) Scope.—For purposes of subsection (a), a reference to a State requirement that relates to the packaging or labeling of a cosmetic means any specific requirement relating to the same aspect of such cosmetic as a requirement specifically applicable to that particular cosmetic or class of cosmetics under this Act for packaging or labeling, including any State requirement relating to public information or any other form of public communication."

"(d) No Effect on Product Liability Law.—Nothing in this section shall be construed to modify or otherwise affect any action or the liability of any person under the product liability law of any State."

"(e) State Initiative.—This section shall not apply to a State requirement adopted by a State public initiative or referendum enacted prior to September 1, 1997."

Comments On Section 412:

1. Since California's prop 65 is (a) exempted for both nonprescription drugs and cosmetics and (b) does represent a sound scientifically based source of the human exposure risk for carcinogenicity and reproductive risks to the fetus and the population at large, I would recommend that the Secretary, in the interests of protecting the health of the consumer, promulgate regulations that would require that labeling of any nonprescription drug or cosmetic reflect such warnings if the manufacturer provides them for product sold in California.
2. In recent dealings with the industry, it has seemed odd to me that firms shipping product into California have, in many cases, opted to have a "special" California label when for cost and control reasons, a single label would be more effective. Given the reality of "prop 65," it would seem that if firms were truly interested in label uniformity and control and cost efficiency that they would use a unified label system.
3. Therefore on both practical grounds and in the interests of providing all Americans the protections that the citizens of California currently have, such regulations should be enacted as are necessary to provide the "prop 65" information to all US consumers.

SEC. 415. CONTRACTS FOR EXPERT REVIEW.

Chapter IX (21 U.S.C. 391 et seq.), as amended by section 214, is further amended by adding at the end the following:

"SEC. 907. CONTRACTS FOR EXPERT REVIEW."

"(a) In General.—"

"(1) Authority.—The Secretary may enter into a contract with any organization or any individual (who is not an employee of the Department) with relevant expertise, to review and evaluate, for the purpose of making recommendations to the Secretary on, part or all of any application or submission (including a petition, notification, and any other similar form of request) made under this Act for the approval or classification of an article or made under section 351(a) of the Public Health Service Act (42 U.S.C. 262(a)) with respect to a biological product. Any such contract shall be subject to the requirements of section 708 relating to the confidentiality of information."

"(2) Increased efficiency and expertise through contracts.—The Secretary may use the authority granted in paragraph (1) whenever the Secretary determines that use of a contract described in paragraph (1) will improve the timeliness of the review of an application or submission described in paragraph (1), unless using such authority would reduce the quality, or unduly increase the cost, of such review. The Secretary may use such authority whenever the Secretary determines that use of such a contract will improve the quality of the review of an application or submission described in paragraph (1), unless using such authority would unduly increase the cost of such review. Such improvement in timeliness or quality may include providing the Secretary increased scientific or technical expertise that is necessary to review or evaluate new therapies and technologies."

"(b) Review of Expert Review.—"

"(1) In general.—Subject to paragraph (2), the official of the Food and Drug Administration responsible for any matter for which expert review is used pursuant to subsection (a) shall review the recommendations of the organization or individual who conducted the expert review and shall make a final decision regarding the matter in a timely manner."

"(2) Limitation.—A final decision by the Secretary on any such application or submission shall be made within the applicable prescribed time period for review of the matter as set forth in this Act or in the Public Health Service Act (42 U.S.C. 201 et seq.)."

Comments On Section 415:

Paul G. King Consulting
33 Hoffman Avenue
Lake Hiawatha, NJ 07034-1922

**Paul G. King's
Formal Comments On Docket Number: 98N-0339**

Given that the limitations imposed in Sec. 907(b)(2), it would seem that the "experts" would have to be retained to evaluate well before they were given any particular application, or part thereof, to evaluate. To assure that these "experts" were indeed technically competent and understood the true requirements of the applicable regulations, the agency needs to develop metrics by which potential experts could be qualified and establish a database for such regulatorily qualified experts. Moreover, to assure an unbiased review, the reviewers would have to have no direct or indirect monetary interest in the issues that they are to consider. Hopefully, the Secretary will promulgate policies and, if needed regulations that will properly address these areas.

SEC. 417. REGISTRATION OF FOREIGN ESTABLISHMENTS.

Section 510(i) (21 U.S.C. 360(i)) is amended to read as follows:

"(i)(1) Any establishment within any foreign country engaged in the manufacture, preparation, propagation, compounding, or processing of a drug or a device that is imported or offered for import into the United States shall register with the Secretary the name and place of business of the establishment and the name of the United States agent for the establishment."

"(2) The establishment shall also provide the information required by subsection (j)."

"(3) The Secretary is authorized to enter into cooperative arrangements with officials of foreign countries to ensure that adequate and effective means are available for purposes of determining, from time to time, whether drugs or devices manufactured, prepared, propagated, compounded, or processed by an establishment described in paragraph (1), if imported or offered for import into the United States, shall be refused admission on any of the grounds set forth in section 801(a)."

Comments On Section 417:

My only concern is that any such "cooperative agreements" should be demonstrable an improvement over the system currently in use, provide the same or a higher level of consumer protection, facilitate FDA "for cause" and "confirmatory" audits of any establishment covered by the agreement in any foreign country that enters into such an agreement, and require that there be FDA-comparable inspections in said foreign country including the issuance of inspectional findings and establishment inspection reports that would be available in the US in English under FOI. If nothing else, history has shown us that governmental activities concerning public matters that are allowed to operate in the dark usually do so because they really do have something to hide.

JOINT EXPLANATORY STATEMENT OF THE COMMITTEE OF CONFERENCE

Title I--Improving Regulation of Drugs

Prescription Drug User Fee Act (Subtitle A) The conferees believe it is important to place the PDUFA reauthorization provisions of the Act in the overall context of the budgetary agreements which have been put into place by the 1997 Balanced Budget Agreements (BBA). This Act preserves the original PDUFA adjustment factor and therefore the basic understanding behind the 1992 enactment of this provision:

that is, the industry willingness to pay user fees for enhanced performance in the drug approval process.

Nevertheless the conferees acknowledge that the 1997 BBA places tight constraints on the appropriations process, particularly in the out years. The conferees expect the appropriators will make every effort to meet the trigger so that FDA is allowed to collect and expend user fees. However, it must be acknowledged that particularly in the fifth year of BBA, budgetary pressures on all discretionary spending will be great.

Breakdowns of the actual spending levels at FDA have not traditionally been provided to the appropriators, making it difficult to conduct oversight.

Beginning in Fiscal Year 1998, appropriators will require FDA to submit a directed operating budget as part of the annual budget request. This will serve as a functional breakdown of how appropriated dollars are spent, similar to the report FDA submits annually to show how the agency spent collected PDUFA user fees.

The conferees expect the President's budgetary request for FDA for salaries and expenses to meet the PDUFA levels specified for each of these years and not be based on any assumption of the enactment of new substitutive user fees on other FDA regulated industries.

Comment On The Bolded Portion of the "JOINT EXPLANATORY STATEMENT OF THE COMMITTEE OF CONFERENCE":

Hopefully, the FDA will make their directed budget available to the public: (a) as they submit to Congress and (b) after Congress appropriate funds for each portion so that the public can see if either the FDA or Congress is truly interested in protecting the consumer or has puts the interests of other groups ahead of those of the public as a whole.

APPENDIX A

CREDENTIALS

For

Paul G. King, Ph.D.

Paul G. King

SUPPORT IN CHEMICALS & PHARMACEUTICS

SPECIALIZING IN SUPPORT TO INDUSTRY IN:

QUALITY: *Auditing, GMP/GLP Compliance, Systems, Work Flow Analysis & Validation [IQ/OQ/PQ]*

GENERATION OF: *Mission Statements, Policies, Protocols, Standard Operating Procedures [SOPs] & Work Instructions*

REGISTRATION: *DMFs, ANDAs & NDAs*

METHODS, PROCESSES and PRODUCTS: *Design, Development, Definition & Improvement*

LABORATORY SYSTEMS: *Design, Construction, Equipping, Staffing, Training, Revision, Management & Regulatory Compliance.*

AREAS OF EXPERTISE :

1. ***Quality Aware:*** An ASQC Trained Quality Auditor with an in-depth knowledge of and understanding of CGMP, GLP, GMP, ISO 9000 - 9004, ISO 10011, ISO/IEC Guide 25, Taguchi target orientation toward quality, Simple Charting and SPC, and Validation.

[Have: Audited contract laboratories and manufacturing facilities for CGMP and GLP compliance. Performed foreign pre-FDA audits of facilities in Shanghai, Nantong, Haimen, Jaijong, and Han Zhou (Peoples Republic of China) and overseen the creation of both Type I and Type II Drug Master Files as well as Participated in FDA Pre-Approval Inspections (PAIs) and the response to FDA letters of deficiency in the bulk pharmaceuticals chemicals area. Developed validation SOPs for lab and process areas. Trained Laboratory Personnel in all aspects of quality. Generated and administered simple short-answer and fill-in-the-blank tests for the CGMP regulations for Finished Pharmaceuticals. Generated Screening Questionnaires for use in the hiring of personnel. **Directed projects for the selection, purchase, installation, operation, and maintenance of computerized systems including multi-site LIMS and LAS systems in regulated environments requiring both hardware and software validation.** Developed and evaluated a "validation issues" questionnaire that was sponsored by NAPM.]

2. ***FDA Aware:*** Understand FDA intent/bent/direction and reasons behind them as well as cognizant of FDA GMP enforcement in the areas of bulk drugs and pre-approval inspections. [Able to elicit cogent answers from the Head of Foreign Inspections, about GMP guidance for BPCs and APIs, in general, and the impact on foreign inspections, in particular.] Understand that FDA's priorities include media oriented events that are designed to improve the FDA's public image.

3. ***Technical Documents:*** Mission Statements, Policies, Standard Operating Procedures, Test Methods, Work Rules, Reports, Publications, Compendial Inquires, Letters to FDA, Type I and Type II DMFs, CMC Sections of filings (ANDA, AADA, and NDA), and, in 1990, Guidelines for BPC GMP Compliance (pseudo "GMP for Bulk Pharmaceutical Chemicals"), similar to the 1996 draft guidance on APIs, as well as formal responses to FDA "Form 483" observations and other FDA concerns.

4. ***Written and Verbal Communications:*** Administrative Procedures, Teaching Simple Techniques, Advising Fellow Workers and Subordinates, Ability to elicit direct answers from Regulatory bodies (FDA, EPA, and NJDEP), Education of foreign personnel (Spanish-speaking and Chinese) and Auditing of Foreign Companies.

5. ***Finding Mistakes/Omissions/Deviations:*** Auditor of Production Records, Laboratory Records, Regulatory Submissions, and Regulatory Answers in the United States, Puerto Rico, and China.

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AREAS OF EXPERTISE: [CONTINUED]

6. Understanding Problems: Production, Process, Laboratory, Warehouse, Raw Material, In-Process, Finishing, Sampling, Validation (including Cleaning and Computerized Systems), Experimental Design [using Minimal Experiments and/or Direct Search Optimization (EXPLEX and REXPLEX version of the SIMPLEX Direct-Search Algorithms), and Process Capability]

7. Persuasive: Able to convince an FDA Administrator (Joel Davis) of the validity of a key analytical method which I had developed over the strong objections of two of the FDA's Technical Staff (key point was the, then current, affirmation by the United States Supreme Court that an FDA Administrator does **not** have any latitude in enforcing a REGULATION). Able to convince Chinese to change their production process and to implement two key in-process controls in a manner that they did not lose "face." Have, with the help of my interpreters, been able to persuade some Chinese companies to commit to quality and to GMP.

8. Systems Development and Implementation: Grew a Quality Control Laboratory from an unstructured environment into a "GLPS" structured Lab with bar-code sample tracking, automatic test list assignment, computerized batch tracking and control of release generation, logs of all equipment usage, training logs, and departmental operating procedures for all aspects of the Lab from administrative to technical protocols. Designed and implemented organizational systems (including titles, responsibilities, reporting relationships, initial compensation levels and compensation policies for overtime, and work hours). Upgraded reporting and data integrity controls so as to assure that the requisite tests, and records thereof, are performed and retained in a way that is a) acceptable to the FDA, b) complies with regulations, and c) is cost and time effective.

9. Finding Good Solutions: Regulatory Answers, GMP Compliance Issues, Production Process Development, Process Controls, Product Formulation, Lab Problems, Methods, Lab Design, Personnel Staffing to Comply with EEO while operating the lowest cost per Analyst QC Lab with the lowest turnover (among 3 NJ Labs)

10. Methods Development using most appropriate technology (myself and by directing others):
Examples: **A.** A robust part-per-trillion cleaning-verification method. **B.** Structure of Sucralfate by solid-state Aluminum NMR (^{27}Al). **C.** Sub-ppm determination of a Penicillin in a Cephalosporin. **D.** Analytical procedure for Cinoxacin using polymeric columns. **E.** Method for Flucloxacillin Sodium using HPLC. **F.** HPLC method for the level of a herbicide in a formulation which successfully resolved a low-level, highly toxic impurity from the major component. **G.** GC Method for a substituted aziridine. **H.** LN_2 -cooled Injector and column for injection-desorption focusing of volatile components (designed the injector). **I.** Method for the Detection and Semi-Quantitation of Sub-ppm N-Nitroso and N-Nitro Amines using both LC/Thermal Energy Analyzer (TEA) and GC/TEA systems. **J.** An improved electrode preparation procedure for the preparation of a solid-billet electrode for argentometric titrations. **K.** Improved methodology for the determination of the purity of components being detected by a LC/diode-array system. **L.** Developed my own empirical chromatographic theory for LC that is based on "site specific" exchange interactions (from 1975 to 1979) and have used it to develop methods for pharmaceuticals, new molecular entities, impurities, isomers, degradation products, and intermediates. **M.** Used hot-stage microscopy to establish that an apparently pure compound (by both capillary GC and GC/MS) was, in fact a mixture of isomers which could not be resolved by conventional GC (100m capillary column coated with a polar phase (OV-17) using hydrogen as the carrier gas. **N.** An organic-solvent-based, Atomic Adsorption method for Potassium which, when coupled with a UV method, was successfully used to control the reflux/bottoms purge ratio to assure the safe distillation of a base-washed crude nitration product. **O.** A robust HPLC method for separating a derivatized pair of enantiomers that have a conformationally shielded optically active center.

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AREAS OF EXPERTISE: [CONTINUED]

11. *Laboratory Design, Construction, Equipping, Staffing, and Management:*

A. Lab Design and Construction:

Have designed 5 Quality Control, 1 Validation and 1 Process Support Lab starting from the building shell up to final structure (benches, cabinets, hoods, ventilation systems, electrical systems, DI water and gas distribution systems, sinks, eye wash/safety showers, fire extinguishers and equipment placement layouts) as well as the renovation of other Labs and the designing of shipboard sampling systems for the for the study of high-temperature (> 1000 °C) incineration.

B. Equipping:

Responsible for the equipping of several Labs including some of those which I designed and oversaw the construction of. Responsible for the selection of equipment in the positions which I have held. Responsible for selecting and evaluating equipment for clients.

C. Staffing and Management:

Have been, at various times, responsible for the staffing of up to three (3) Labs in different locations (ca. 100 persons), the staffing of a ca. 50-person 3-shift Quality Control Lab, a BPC Quality Control and Environmental Lab, and two Hazardous Waste Testing Labs. In various capacities, I have always been able to staff and/or utilize the existing staff in a productive manner while actively growing personnel from within by mentoring as well as proactively complying with EEO Guidelines. Have been able to build quality in by: developing screening questionnaires; empowering Lab personnel; leadership; structuring; establishing self-evaluation performance reviews and analyst commitment to improvement; and providing proactive training in leadership to my direct reports.

12. *Mentoring/Teaching:* Have helped personnel grow upward within Companies, outward to other Companies, and within by encouraging them to go to, or back to, College, take courses, and/or training them myself. Provide short courses, lectures, and small group mentoring to clients on scientific, regulatory, and process and production technologies. Provide explanations of the validity of Company practices to FDA personnel in Pre-approval and Compliance Inspections.

Committed to addressing your needs in a cost-effective manner that is driven by a commitment to customer-based quality.

My mission is to assist you in finding and implementing solutions that effectively address your concerns and solve your problems.

Paul G. King

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Credentials for Paul G. King, Ph.D.

UNIVERSITY EDUCATION

1. FROM about September of 1973 until the end of 1975, Dr. King worked at THE UNIVERSITY OF GEORGIA in Athens, Georgia as a Postdoctoral Fellow to Dr. L. B. (Buck) Rogers, Graham Perdue Professor. There he was, among other things, the System Manager, Systems Analyst, and Programmer for a Multi-User HP Minicomputer. His research efforts included the design and the construction of a computer-controlled system for constant-temperature (± 0.01 °C) comparative study of enzymatic reaction rates of immobilized enzymes to the rates using the soluble enzyme.
2. From mid-May of 1971 through: August of 1973, Dr. King attended EMORY UNIVERSITY in Atlanta, Georgia in a Ph.D. program under Dr. Stan Deming (who is currently at The University of Houston) that awarded him a Ph.D. in December of 1973 that was officially conferred upon him in June of 1974. Dr. King's major field of endeavor was Analytical Chemistry with minors in Inorganic Chemistry and Physical Chemistry. In Dr. King's Ph.D. program, in addition to helping others with their projects, he:
 - 2.1 Partially designed and then constructed, installed, debugged, and validated a full (84 signals) bi-directional parallel multiplexed external interface to a PDP-9 Minicomputer.
 - 2.2 Designed, constructed, installed, debugged, and validated a remote interface to **PDP-9** for the robot, **MADAM** (**M**achine for the **A**utomated **D**evelopment of **A**nalytical **M**ethods).
 - 2.3 Designed and constructed the power systems, controls and critical components for **MADAM**.
 - 2.4 Debugged the operation of **MADAM** and validated that **MADAM** met or exceeded its hardware design specifications.
 - 2.5 Working from a version of **FOCAL**[™] (a DEC interactive, interpretative language similar to BASIC) written for a **PDP-15** (**FOCAL.LAL**), Dr. King researched this computer's machine language; dissected the core coding needed for his project; and generated his own version of **FOCAL** (**FOCAL.PGK, version 1**).
 - 2.6 Wrote, debugged, and validated key machine-code patches to his **FOCAL.PGK (Version 1A)** for the required data acquisition and control subroutines that provided real-time control and data acquisition capabilities for **MADAM**.
 - 2.7 Generated, programmed, debugged, and verified the performance of his own "**SIMPLEX**" direct-search algorithms that were used by the robot to adaptively search for an "Optimum" as defined by Dr. King.
 - 2.8 Selected a simple colorimetric analysis method for the determination of formaldehyde for his initial study; prepared the reagents needed by the robot, primed the eight (8) reagent delivery pumps and checked that the robot's component systems for acquisition (1) and system control (8) were operating as designed; generated a simple "optimum" (Absorptivity of the colored reaction product); started the robot's search for the optimum "greatest Absorptivity" using "**EXPLEX**," his modified **SIMPLEX** search algorithm; and monitored the performance of **MADAM** as the robot first found the region of optimum Absorptivity and then tracked it.

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RELEVANT UNIVERSITY EDUCATIONAL BACKGROUND [CONTINUED]

- 2.9 After MADAM had adaptively tracked the optimum for two days, then programmed a factorial mapping experiment set and had the robot acquire the data needed.
- 2.10 Following mapping, reviewed and verified all of the data and generated the appropriate reports.
- 2.11 Then selected a more complicated colorimetric test having more variables and repeated steps 8 through 10.
- 2.12 Finally, wrote his dissertation summarizing his research and findings, submitted the final document for review by the department, and defended his dissertation and findings in an open discussion that included faculty from all divisions of the Chemistry Department.

In recognition of Dr. King's contribution to science in Chemistry, automation, and process control, his dissertation, "*Automated Development of Analytical Methods*," received a *SIGMA XI's* annual award for scientific excellence.

3. In addition, Dr. King holds:
 - 3.1 An M.S. Degree in Inorganic Chemistry under Dr. Ronald C. Johnson from Emory University (awarded in 1969) as well as
 - 3.2 An ACS Certified B.A. in Chemistry with a minor in Physics from Vanderbilt University, Nashville, Tennessee (awarded in 1967).

ADDITIONAL TRAINING

1. **Dr. King is an ASQC Trained Quality Auditor** ([1995]), with competence certified by formal ASQ written examination in 1995 for Certified Quality Auditor..
2. The numerous formal Technical Courses which Dr. King has taken include:
 - 2.1 Current FDA Views on Pharmaceutical Laboratory Operations and CGMPs (1998);
 - 2.2 Computer Validation and Various Aspects of Process and Equipment Validation (1997);
 - 2.3 Interfacing with the FDA (1997);
 - 2.4 Pre-Approval Inspection (1996);
 - 2.5 Quality Auditing (1995);
 - 2.6 Pharmaceutical Validation (1995);
 - 2.7 Software Audits (1993), "TESTING COMPUTER SYSTEMS IN PHARMACEUTICAL APPLICATIONS," given by **Confidence in Software**. Their three-day course covered:
 - 2.7.1 FDA Requirements,
 - 2.7.2 Planning Validation,
 - 2.7.3 Validation Preparation,
 - 2.7.4 Testing Modules,
 - 2.7.5 Testing Interfaces,
 - 2.7.6 Challenging Functions,
 - 2.7.7 Challenging the System,
 - 2.7.8 Conducting the Challenge, and
 - 2.7.9 Acceptance Testing.

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ADDITIONAL FORMAL TRAINING [CONTINUED]

- 2.8 Various Aspects of the Pharmaceutical Industry (1991);
- 2.9 Quality Assurance for Laboratories (1989);
- 2.10 *Perkin-Elmer LIMS/CLAS System Management and Operation* (1984) (Laboratory Information management System [“LIMS”] and Computerized Laboratory Acquisition System [“CLAS”]);
- 2.11 Laboratory Automation and Quality Control (1984);
- 2.12 Personnel Supervision (1981);
- 2.13 General Management (1978); and
- 2.14 **A Technical Degree in “Computer Programming and Systems Analysis”** (1971) [Computer Learning Centers, Inc., Rockville, MD] (this intensive course covered:
 - 2.14.1 The formalized process by which software is defined, stated, written, debugged, tested and verified in a controlled documented manner;
 - 2.14.2 Programming in several IBM System 360 languages (including Basis Assembly Language [BAL], FORTRAN 66, COBOL, and PL/1;
 - 2.14.3 The Fundamentals of Systems Analysis including project planning, PERT charting, project auditing and review, and systems’ standards).

ASSOCIATIONS AND SOCIETIES

- 1. *American Chemical Society (ACS)*;
- 2. *AOAC International*;
- 3. *American Society for Quality (ASQ)*, formerly the American Society for Quality Control (ASQC)
- 4. *International Society for Pharmaceutical Engineering (ISPE)*; and
- 5. *Institute for Validation Technology*.

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DOCUMENTS AND PUBLICATIONS

In addition to publications on **ISO/IEC Guide 25** and other aspects impacting on the operation and auditing of laboratory operation, his thesis and one publication from it, his dissertation and two publications therefrom, Dr. King has published on a variety of topics including: "Intelligence in Instruments," computerization, and the interactions between computerization and regulations (GLPS [Good Laboratory Practice Standards] and CGMP [Current Good Manufacturing Practice regulations]).

Except for the articles in preparation on "method validation," "cGMP training programs," "dissolution," "practical HPLC methods and their validation," "purity determination," and stimuli to the USP's revision process, Dr. King's principal documents and publications are as follows:

1. *"The Coordination Chemistry of Tantalum (V)," Ann Arbor Press, 1969, 48+ pages (master's thesis).*
2. *"Coordination Compounds of Niobium(V) and Tantalum(V) Chloroalkoxides with Ligands Related to beta-Diketones," Journal of Less-Common Metals, Volume 19 (1969), pages 141-149 with R. C. Johnson et al.*
3. *"Computers and experimental Optimization," Research/Development, Volume 25 (1974), Number 5, Cover and pages 22-24 & 26 with Stanley N. Deming.*
4. *"Automated Development of Analytical Methods," Ann Arbor Press, 1974, 443+ pages (Ph.D. Dissertation that won a Sigma XI Award for Excellence).*
5. *"UNIPLEX: Single-Factor Optimization of Response in the Presence of Error," Analytical Chemistry, Volume 46 (1974), Number 11, pages 1476-1481 with Stanley N. Deming.*
6. *"DIFFICULTIES IN THE APPLICATION OF SIMPLEX OPTIMIZATION TO ANALYTICAL CHEMISTRY," Analytical Letters, Volume 8 (1975), Number 5, pages 369-376 with Stanley N. Deming and Stephen L. Morgan.*
7. Internal Publications including several key methods and two research project reports - **including one (for which he received a bonus) on the detection of known and unknown N-Nitroso and N-Nitro Amines in materials at sub-ppm levels.**
8. Several research reports and a key method as well as improvements to other methods and the Standard Operating Procedures ("SOPs") and **a crucial LIMS Project Assessment Report** on which a major international German corporation based its LIMS buying plan for its worldwide agricultural divisions.
9. *"Laboratory Automation and Information Management," Analytical Instruments and Computers, Volume 1 (1984), pages 45-47.*
10. *"Laboratory Computerization and Good Laboratory Practise Standards (GLPS)," Analytical Instruments and Computers, Volume 2 (1984), pages 14-15.*
11. *"Quality Assurance and Computerization in the Regulated Laboratory," Computerized Applications in the Laboratory, Volume 2 (1984), pages 298-304.*

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DOCUMENTS AND PUBLICATIONS [CONTINUED]

12. Research reports and a key HPLC method.
13. *"Intelligence in Instruments," Instruments & Computers*, Volume 3 (1985), pages 4-5.
14. Numerous SOPs, methods, training, audits and tests as well as key reports, processes, process controls, and project reports as well as LIMS Project Definition, Requests for Proposal (RFP), Vendor Response Evaluations, System Selection, Installation, Training, Checkout, Acceptance Testing, Implementation, Database Definition & Redefinition, Backup, Tracking, Maintenance, Problem Identification, Problem Resolution, and Routine Reporting Documents. In addition, a validated FORTRAN 77 program for properly correcting HPLC data for systematic or periodic drift even in cases where there is a non-zero-intercept relationship between analyte amount and detector response. Implemented proficiency testing and the critical evaluation of all test data.
15. Numerous SOPs, methods, training, employee prescreening questions, and detailed **CGMP** tests as well as several critical reports, controls, and project reports and the original process, cleaning, and methods validation SOPs.

Oversaw all aspects of laboratory function including the selection of personnel, equipment and methods; the training of laboratory personnel; the validation of lab equipment; the development and validation of methods and procedures; and the management of the Raw Material, In-Process, Release, Stability, Validation, and Micro groups.

Directed a LAS Computerization Project from Design Qualification (DQ) [requirements specification, **RFP**, pre-purchase evaluation and testing]; System and Support Contracting; Installation Qualification (IQ) [pre-installation, installation, installation verification, and post-installation checkout]; Operation Qualification (OQ) [validation by vendor under supervision by Company of performance to both the vendor's and the Company's specifications as well as defined the programs for system challenge, exception generation, handling, and resolution and for the training of personnel]; Performance Qualification (PQ) [intensive operation testing and the monitoring of all functionality (even of those functions that were not presently in use)]; Maintenance Qualification (MQ) [the monitoring of the ongoing performance of all critical system components by either periodic calibration challenge or performance tracking or both]; and Closure Qualification (CQ) [planning for, and initial studies of the problems with , upgrade from the current version of the software to the newer version in a controlled manner].

Also, directed a similar project to install a centralized temperature and humidity monitoring system for controlled areas. Developed an improved drug release test method that minimized the decomposition of the drug during the test (the change raised recoveries from about 75 % to more than 95 %).

Designed a bench-scale photolysis system for the rapid determination of the photolytic stability of the active ingredients under "natural" conditions.

Implemented an ISO-25-like quality system that included the auditing of all contract test laboratories and challenging their systems by the use of blinded "surrogate" samples.

Assisted Quality Assurance in the generation of "vendor audit" and in the review and handling of production, laboratory and customer problems.

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DOCUMENTS AND PUBLICATIONS [CONTINUED]

16. Drug Master Files, Type I and Type II documents and related SOPs, for Primidone USP as well as **CGMP audits** and audit reports, FDA support, and FDA 483 responses from consulting visits to the People's Republic of China as well as related matters.
17. Draft SOPs on SOPs, Stability and Weight Variation; memos; reports; blend homogeneity tracking spreadsheets; and product tracking spreadsheets as well as the training of their key personnel in the fundamentals of blend and blender size matching.
18. Several articles in *The AOAC International's* periodical, The Referee, in 1996 on:
 - 18.1 **Business and the Laboratory**;
 - 18.2 **Twentieth International Good manufacturing Practices Conference** (in two parts);
 - 18.3 **ISO/IEC Guide 25 and Laboratory Competence**; and
 - 18.4 **Safe Handling of Hazardous Materials, Carcinogens and Biohazards**.
19. Detailed **Validation Protocol SOPs** and **DRAFT Validation Protocols** for clients. 1996 - .
20. Data audit reports and suggestions on how to word **regulatory submission documents** and how to address **FDA-related labeling** issues for clients. 1996 - .
21. "Altered Dynamics for USP Apparatus 2," Dissolution Technologies, Volume 3 (1996), No. 3, pages 8-12.
22. "Bringing a Chinese Bulk Pharmaceutical Chemical Manufacturer Up to FDA Expectations," J. cGMP Compliance, Volume 1 (1997), Number 3 (April), pages 38-43.
23. "The Future of Validation A Validation 'Life Cycle' Journey," J. Validation Technology, Volume 3 (1997), Number 3 (May), pages 296-297.
24. "ISO/IEC Guide 25, An International Quality System Standard, and the FDA-Regulated Laboratory," J. cGMP Compliance, Volume 1 (1997), Number 4 (July), pages 25-35.
25. "INTRODUCTION TO 'DISSOLUTION'," a 33-page training course syllabus, July 1997.
26. "Equipment Validation A Logical Approach to the Pharmaceutical 'Life Cycle' Journey - Part I of a Series -," J. Validation Technology, Volume 3 (1997), Number 4 (August), pages 345-354.
27. Formal comments on the FDA's "Current Good Manufacturing Practice; Proposed Amendment of Certain Requirements for Finished Pharmaceuticals, in September 1997.
28. "Process Validation for Existing Processes A Logical Approach to the Pharmaceutical 'Life Cycle' Journey - Part II of a Series -," J. Validation Technology, Volume 4 (1997), Number 1 (November), pages 53-64.
29. "Process Validation for New Processes A Logical Approach to the Pharmaceutical 'Life Cycle' Journey - Part III of a Series -," J. Validation Technology, Volume 4 (1998), Number 3 (May), pages 234-242.
30. "Improving cGMP Training Programs, A White Paper, November 1997 (from which two papers, one appearing in the J. cGMP Compliance in July 1998 and the other in preparation were derived).

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DOCUMENTS AND PUBLICATIONS [CONTINUED]

31. ***“Method Validation By Example A Logical Approach to the Pharmaceutical ‘Life Cycle’ Journey - Part IV of a Series -,”*** A White Paper, December 1997 (part of the white paper is “in press” for publication in J. Validation Technology in 1998).
32. ***“Formal Method Validation A Logical Approach to the Pharmaceutical ‘Life Cycle’ Journey - Part V of a Series -,”*** in preparation, December 1997 (part of the white paper is “in review” for publication in J. Validation Technology in 1998).
33. ***“Valid HPLC Methods, Part I Practical Method Development Recommendations and Insights,”*** A White Paper, December 1997.
34. ***“Valid HPLC Methods, Part II PRACTICAL LINEARITY, LINEAR RANGE, STANDARD PLACEMENT AND LIMITS Recommendations and Insights,”*** A White Paper, December 1997.
35. ***“In-Process ‘Powder’ Blend Sampling And Evaluation (And Appropriate In-Process and Final Release Specifications),”*** A White Paper, January 1998. [This white paper was submitted to certain key industry, financial, and FDA administrators at the Twenty-Second International GMP Conference held in March at the University of Georgia in Athens, GA; the Agency has agreed to review and comment on, has reviewed and is in the process of preparing a formal answer, and has committed to providing a written response to the key Agency and CGMP-compliance and legal issues raised.]
36. ***“The Blending Of ‘Dry’ Solids,”*** A White Paper, February 1998.
37. ***“HPLC METHOD DEVELOPMENT AND VALIDATION: A Direct Procedure For Determining An HPLC Method’s ‘Linear Through Zero’ Range,”*** A White Paper, April 1998 (from which three papers were derived and submitted for consideration in three periodicals; at present, one is published in June of 1998; another has been reviewed and should be published before the end of 1998; and the third declined to consider the article for publication because it did not fit that periodical’s editorial goals).
38. ***“Sampling And Testing ‘Size,’ For In-Process Blends: Legal, Regulatory and Industry Realities, A Call To Action,”*** A White Paper, May 1998.
39. Formal comment on FDA’s proposed 21 CFR 26, ***“Mutual Recognition of Pharmaceutical Good Manufacturing Practice Reports, Medical Device Quality System Audit Reports, And Certain Medical Device Premarket Evaluation Reports Provide By European Community Member State Regulatory Authorities And European Community Conformity Assessment Bodies”*** in May 1998.
40. ***“A Direct Approach to Determining The Valid Linear Range for A Comparative Method that Uses a Single Standard,”*** Scientific Computing & Automation June 1998, pages 63-64.
41. ***“Improving cGMP Training Programs – Part One of a Two-part Series – ,”*** J. cGMP Compliance Volume 2, 1998, Number 4 (June), pages 56-63.
42. ***“IN-PROCESS FINAL-BLEND SAMPLING AND EVALUATION (AND APPROPRIATE IN- PROCESS AND FINAL RELEASE SPECIFICATIONS),*** A White Paper, June 1998.

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DOCUMENTS AND PUBLICATIONS [CONTINUED]

43. *"The Blending Of 'Dry' Solids - II,"* A Revised White Paper, June 1998.
44. "Purity Determination For Pharmaceutical Ingredients," A Confidential White Paper, June/July 1998.
45. Formal "Standard Practice for Standard Practices" guidance document for confidential client, July 1998.
46. Formal "Standard Operating Procedure for Standard Operating Procedures" basis document for confidential client, July 1998.
47. Project draft proposal, "Design, Installation, and Operational Qualification" for a computerized test apparatus where the software was developed using the "waterfall" model and ISO 9000-3 was the firm's basis standard, July 1998.
48. "Scientifically Sound, A Prerequisite For Compliance With 21 CFR 211," A White Paper, July 1998.
49. "Formulation Component Complexity," A White Paper, August 1998.
50. "Improving cGMP Training Programs – Part Two of a Two-part Series – ," J. cGMP Compliance, Volume 3, 1998, Number 1 (October), pages 78-85, in press.
51. "Weight-Percent Purity Determination For Active Pharmaceutical Ingredients (APIs)," A White Paper, August 1998.

In addition, I have prepared numerous documents for clients that have been adopted with minor or no modifications and published within the applicable clients' operations (SOPs, policy statements, mission/vision/value statements, validation protocol documents, *etc.*) or, in a few cases, externally in periodicals such as Pharmaceutical Technology. These include formal validation protocol documents, validation master plans, validation test formats, and validation review documents.

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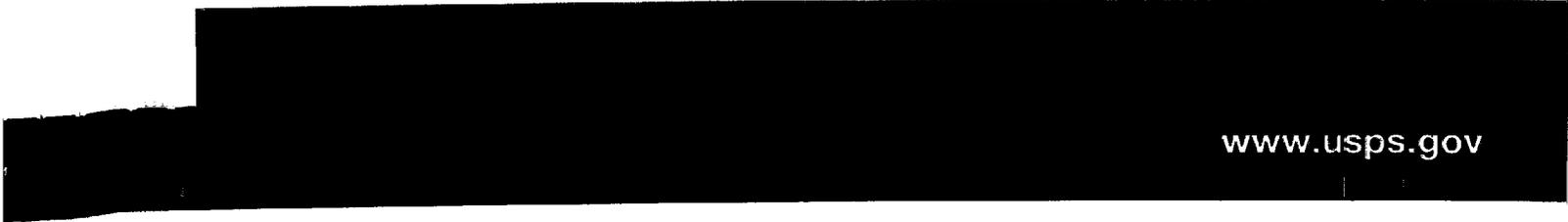
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