

April 19, 1996

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H.R. 3201
"MEDICAL DEVICE REFORM ACT OF 1996"¹

SEC. 1. SHORT TITLE; REFERENCE; TABLE OF CONTENTS

SEC. 2. FDA MISSION AND ANNUAL REPORT

- Section 2(a), the mission statement establishes efficient review and approval and global harmonization as primary FDA goals.

The agency's core mission is not to approve products, but rather to thoroughly and fairly evaluate them and render impartial decisions about their safety and effectiveness. The mission statement should include protecting the public from products that do not have the requisite approval prior to marketing -- i.e., products that are unsafe and ineffective or have not been shown to be safe and effective.

- Section 2(b) requires the Secretary to, in connection with the submission of an annual budget, submit to the Commerce Committee in the House and the Committee on Labor and Human Resources in the Senate, an annual report that (1) reviews FDA's performance in meeting its mission and developing policies to implement such mission; (2) reviews FDA's performance in meetings its own performance standards (including meeting statutory deadlines); (3) describes FDA's staffing and resources and lists third parties that have been accredited to perform product reviews [drug, rather than device, provisions are listed] and GMP inspections and to conduct investigations; (4) describe FDA's harmonizations goals, activities, and accomplishments; and (5) compares FDA's performance in approving innovative products with that of the most "successful" agency performing similar functions in other countries and compares the resources used by such agencies.

The agency does not disagree with the principle that the agency must be held accountable. The concern is that some of the requirements set forth in this provision are not clearly defined and/or possibly not feasible. For example, the requirement that FDA compare its performance in approving innovative products with that of the most "successful" agency performing similar functions in other countries is

¹ H.R. 3201 includes a number of supportable concepts. The emphasis of this section-by-section analysis, however, is on the problematic provisions in the bill.

vague and may be difficult, if not impossible, to meet. The term "successful" is not one that provides much guidance. Moreover, it is uncertain whether such data are available from other countries or if such data are available, whether a comparison is possible. Finally, what devices another country might consider to be innovative could be considered passe (or dangerous) in the U.S. and vice versa.

SEC. 3. DISPUTE RESOLUTION

- Section 3 provides that whenever an "impasse" exists in the review of an application, device sponsors may seek dispute resolution before an advisory committee or a special government employee or a nongovernmental person who is qualified to mediate or arbitrate and who is acceptable to the Secretary and the applicant. It requires the Secretary to refer the dispute to an advisory committee or third party on receipt of a notification from the applicant that a dispute exists. The panel or third party has 60-90 days to provide the Secretary a report containing recommendations on the matter. Within 30 days of receiving the panel or third party recommendation, the Secretary must, in writing, confirm or modify the panel or third party recommendation providing reasons and reference to data before the committee or third party for any modification. The panel or third party recommendation automatically becomes the Secretary's unless the Secretary acts within 30 days of receipt of the recommendation.

The section begins by referencing 510(k) submissions and IDE applications (section 520(g)), but it later references PMA's (section 515). It is unclear whether it applies to all three. It also is not completely clear that the provision operates to toll the clock on the review of 510(k), IDE and PMA submissions. (Tolling seems to be contemplated because the bill allows up to 120 days for resolution of a dispute and thus decisions on 510(k)s would be delayed beyond the statutory time period of review.)

The concept of an effective appeals process is supportable. However, this section would duplicate (and if the sponsor chooses would supersede) existing dispute resolution procedures. It does not appear to require a sponsor to first go up the administrative ladder. Its use is not limited to significant scientific issues. It has the potential for inundating the agency with requests for advisory panel meetings, which have significant resource implications. The advisory committee or third party should have the ability to turn down requests for dispute resolution.

SEC. 4. INVESTIGATIONAL DEVICE EXEMPTIONS

- Section 4 directs FDA to amend its IDE regulations (within 120 days) to permit the use of investigational devices in the diagnosis or treatment of life threatening or irreversibly debilitating conditions by any treating doctor who determines that the risk of not using the device exceeds the probable risk of using it.

CDRH comments indicated that it already permits use of an investigational device in life-threatening situations pursuant to 21 CFR 812.35(a). This has been interpreted to cover organ threatening and sight threatening situations as well as situations in which patients may suffer irreversible debilitation. **Does this mean that 812.35 has been interpreted to permit the use of investigational devices outside of a protocol. It refers to persons who are "subjects" of the investigation. DISCUSS.**

- New Paragraphs (B) and (C) of section 520(g)(6), added by this provision, require the agency to review, within 30 days, pre-IDE submissions (including protocols). Within the 30 days, the agency must not only review but also explain in writing how a deficient protocol may be corrected.

CDRH agrees with the concept of pre-IDE conferences. In fact, the provision mirrors current Center policy. However, the bill seems to require IDE sponsors to submit a quasi-formal application and to require that FDA respond to that in writing. It requires FDA to expend significant resources into responding to an informal submission -- i.e. FDA must respond to what a company might do.

- Pursuant to new paragraph (D), submitters may challenge the agency's response by appealing to a classification panel at its next scheduled meeting.

This provision seems to "elevate" the agency's response to an informal submission. (Note IDE decisions go to an advisory committee or a third party (see section 3); these pre-IDE decisions go to a classification panel.)

- Paragraph (E) on page 8 would require FDA to permit changes to investigational devices without an additional IDE or supplement if there is not a "significant change" in design or basic principles of operation.

This provision, which is substantially similar to a parallel section in S.1477 (Sec. 303.), gives sponsors wide latitude to make changes to an

investigational device during the course of a clinical trial without prior approval by FDA, a third party, or an IRB. This generally is FDA's practice. **Shouldn't (E) also require that there not be an affect on the validity of the data and patient safety?**

- Paragraph (F) will permit changes to clinical protocols that do not affect the validity of the resulting data and do not alter the risk/benefit relationship for the patient.

This provision also is substantially similar to a parallel section in S.1477 (Sec. 303.). It gives sponsors wide latitude to make changes to a study protocol during the course of a clinical trial without prior approval by FDA, a third party, or an IRB. The result may be study data that is a mixture of results from the various mid-study changes. This could complicate or undermine FDA's ability to make rational determinations about the safety and effectiveness of the investigational device. Even more problematic is that fact that it would permit sponsors to significantly increase the patient population in a study and thus, because sponsors are permitted to recover developmental costs, would in effect permit sponsors to use the IDE to market their product. Because there would be widespread commercialization, there would be no need for sponsors to come to FDA for approval.

SEC. 5. SPECIAL REVIEW OF CERTAIN DEVICES

- Within 6 months of enactment, FDA must promulgate regulations establishing priority review of breakthrough or other important technologies for life-threatening or irreversibly debilitating conditions. This provision establishes a 60 day comment period and gives the agency 60 days to publish final rules.

Expedited review of important new devices is a supportable concept. CDRH currently has an expedited review policy in effect (for both 510(k) and PMA devices), which is predicated on essentially the same criteria as in the bill and which is yielding the kind of results apparently contemplated by the provision. The abbreviated schedule for developing and promulgating regulations, as called for in the bill, could detract from current expedited review activities because the people involved in both activities would likely be the same. [Also this must be considered along with the abbreviated promulgation schedules that appear several places in this bill.]

SEC. 6. EXPANDING HUMANITARIAN USE OF DEVICES

- In 1990, Congress passed the humanitarian use device exemption (HUD) to encourage the discovery and use of devices intended to benefit patients in the treatment and diagnosis of diseases or conditions that affect a relatively small number of individuals. The provision exempts HUD manufacturers from the requirement for demonstrating "effectiveness" for devices subject to the PMA and performance standards provisions. Section 6 amends the current provision of the statute by establishing a 30 day time period for agency review of HUD applications, and eliminating any time limit on the HUD exemption (the current law establishes a renewable 18 month term). It also changes the program from a 5 year pilot to a permanent provision and eliminates the requirement for regulations prior to implementation.

CDRH currently is preparing a regulation implementing the 1990 provision. The regulation would treat these devices as PMA products without the effectiveness requirement. The bill's 30-day review deadline is not realistic. It does not allow enough time to do a credible job of assessing a HUD application. It certainly does not allow enough time to take the issue before an advisory committee. Moreover, it would create an artificially high priority for products that are targeted to benefit a small group of patients who may not have serious diseases or conditions and potentially displace work on products for larger groups of patients with serious diseases or conditions. The elimination of a term for the exemption also is problematic. A use may become widespread -- and at some point no longer meet the definition for a humanitarian use.

SEC. 7. PERFORMANCE STANDARDS

- This section strikes current section 514 of the Act and substitutes a requirement that the Secretary publish notices recognizing standards that can be applied to any approval or compliance determination under the Act. The agency would have to recognize "applicable nationally or internationally recognized consensus standards" through this process and accept certifications that devices conform with these standards. An applicant would be free to use other data to establish safety and effectiveness or compliance with the Act.

*no agency
determining
review*

This section differs significantly from the Senate version, which maintains the portions of 514 that permit the agency to promulgate performance standards and which establishes criteria for standard-setting bodies as well as provisions for what should be included in a performance standard. In light of the fact that the agency has never promulgated a performance standard, the deletion of current 514 may

not make a great deal of difference. However, it is not clear how much discretion FDA has in recognizing performance standards. (i.e., the bill says "shall" but leaves open the possibility that the Secretary has discretion to determine what is "applicable," "recognized," and represents "consensus"). Regulations that establish criteria for what standards are acceptable and when recognition of standards may be revoked seem essential.

Nothing in the section appears to prohibit the Secretary from requiring third party certification of conformance with standards. However, that point should be clarified.

SEC.8. EFFECTIVENESS DETERMINATION

- ~~Section 8 changes the current effectiveness standard to include a maximum of one clinical investigation and establishes that no clinical investigation will be required unless the Secretary first consults with a classification panel.~~

Although one pivotal trial generally can demonstrate effectiveness, there are times when more than one study is needed. Forcing the agency to consult with advisory panels on a device-by-device basis will introduce substantial administrative burdens. **DISCUSS**

- Section 8 also restricts any clinical trial to controls that are appropriate for labeled uses. **Discuss the implications of this?**
- New section 513(a)(3)(C)(1) prohibits FDA from evaluating clinical data for devices, unless the device is labeled as having a therapeutic effect to the person for whom it is intended. 7 0

This appears to eliminate the agency's ability to require and evaluate clinical data for devices. This emasculates the present system that requires devices be shown to clinically perform as intended and produce useful outcomes for patients. It is a move to the EU system, which looks only at engineering aspects of a device. Without well-designed and well-conducted studies, FDA will be hampered in making well-informed decisions about the clinical efficacy of devices, a situation strongly criticized by the Congress earlier in this decade. This will ultimately impair clinical decision-making by health care providers.

- Add (ii) and (iii) and explain that this is current practice.

- New section 513(a)(3)(C)(iv) also provides that the review of a device application cannot include the evaluation of any use not included in the labeling.

This appears to prohibit FDA from including, in the labeling, warnings about indications for which a product is dangerous or known not to be effective.

SEC. 9. PRE-MARKET NOTIFICATION

- Subsection (a)(1) exempts all Class I devices from the requirement of submitting a premarket (section 510(k)) notification. Subsection (a)(3) requires FDA to publish a list of exempt Class II devices within 30 days. It gives anyone the right to petition for other Class II devices to be exempt, and provides 120 days for the Secretary to review such petitions.

Re: Class I devices: FDA has already exempted 572 class I devices from premarket notification. Many of the devices that FDA has not exempted, were not exempted for public health reasons. For example:

1. FDA needs to review tests on the technical performance of hearing aids to ensure that they function as intended.
2. Rebreathing devices are used as components within certain anesthesia machines, volume ventilators and resuscitation devices. Certain rebreathing devices have been directly related to death, serious injury, and serious illness resulting from complications caused by their design, performance, etc.
3. Patient examination gloves have a significant history of defects such as hole not readily detected by the user. This is unacceptable for a device that is important in the prevention of HIV and other blood borne diseases.

The Senate bill gives FDA 15 days from the date of enactment to publish in the Federal register a list of Class I devices that FDA determines require a 510(k) to protect the public health. A similar provision should be added to the House bill.

Re: Class II, the provision is almost identical to S. 1477, Sec. 702 (a). There is no opportunity for public comment on the exemptions. Moreover, under the House version, however, a petition for a Class II exemption is deemed granted if the Secretary does not respond within

120 days.

- Subsection (a)(2) permits device sponsors to submit 510 (k) notifications to third parties.
- Subsection (b)(1) (initial classification) is essentially identical to the Senate version (Sec. 702 (b) of S. 1477), except that a panel recommendation automatically becomes a final order if the Secretary does not make a determination within 10 days.

The same concerns that were raised with respect to the Senate version apply to this section: i.e., it is not desirable from a scientific or resource perspective to have every NSE decision go to a panel; the time frames are unreasonable.

- Subsection (b)(2) authorizes third parties to review 510(k) submissions for Class II devices. The third party's determination that a device is Class II shall be considered an order of the Secretary initially classifying the device. If the third party determines that the device should be classified as Class III, such person must refer the report to the Secretary.

*3rd Party
Review of
Class II*

The bill authorizes manufacturers of class II devices to obtain market clearance from third parties, whose decisions are binding and devoid of any FDA review and concurrence. This sets up the possibility that a high risk device that should be in class III may be found by a third party to be "classifiable" in class II and the decision of the third party would be implemented without any input from FDA, its advisory panel, or the public.

- Subsection (b)(2) also provides for third party review of Class III devices. It gives third parties 60 days to review 510(k) submissions for Class III devices and submit a recommendation regarding initial classification to the Secretary and to the submitter. The third party's recommendation becomes a final order unless the Secretary determines that the device is NSE and issues an order within 30 days of receiving the recommendation. Such order must provide a detailed explanation and justification for the basis of the Secretary's disagreement with the third party. If the Secretary does nothing, the recommendation of the third party becomes a final order 90 days following the Secretary's receipt of the third party report. [It is unclear how this 90 day time period relates to the 30 days in which the Secretary must act.]
- Subsection (b)(2) also prohibits the Secretary from withholding a substantial equivalence determination because of failure to comply with GMPs.

This is similar to provision in Sec. 702 (a) of Senate bill. It prevents FDA from ascertaining GMP compliance prior to market clearance and to thereby have a reasonable assurance that a device is substantially equivalent or that the firm can reliably and consistently produce high quality devices.

- Subsection (c) -- device modification-- eliminates the requirement that a manufacturer file a 510(k) for any modification other than a major change in intended use if the modification is supported by appropriate data and can be shown not to adversely affect the safety and effectiveness of the device. Records of data supporting the change must be kept for commercial life of device.

Under the bill, unless the manufacturer's own data shows that the safety and effectiveness were to diminish, FDA could not require data on the modified product. This would eliminate FDA's role in assuring that modifications made to a product do not adversely affect its safety and effectiveness. Thus, changes to biomaterial, power sources, and control mechanisms would be permitted and FDA would not see data. This provision creates an enormous loophole to the 510(k) requirement.

This is a lower standard than the modified Senate version. Unlike the House version, the Senate provision on device modification (sec. 702 (d)) includes the following as 510 (k) triggers: significant change in operating principles; significant change or modification in design; significant change in manufacture (assuming the word "manufacture" was accepted by the Senate committee). In addition, the Senate version requires the manufacturer's supporting data to include information demonstrating compliance with GMPs and to maintain supporting data for a least 2 years.

- Subsection (c) -- the substantial equivalence provision -- would specify that each use included within a general use for a predicate device be deemed a legally marketed use for purposes of premarket notification.

This would allow a device originally marketed for one clinical indication to later be marketed for other indications, even high risk ones. Add example

This is similar to the Senate provision on general use/specific use (S. 1477, Sec. 702 (c)), with the significant omission of language similar to that of the Kennedy amendment, which was intended to clarify that it is up to the Secretary to determine whether a specific use is "reasonably" included within a general use. The Senate version is also more explicit

about the fact that the requirement to submit a 510 (k) still pertains.

- Subsection (c) also changes the substantial equivalence provision by providing that data required to show substantial equivalence may be either "scientific" or "clinical" and changes the term "efficacy" to "effectiveness."

SEC. 10. CLASSIFICATION PANELS

- Section 10 requires the Secretary to schedule 6 meetings a year for each classification panel and scientific advisory panel. This section establishes equal access for all persons to panel members and equal participation in meetings. This section also establishes a 30 day time frame for FDA review of a panel recommendation.

The requirement for advisory panels to meet six times per year is unrealistic. CDRH manages over 20 different panels. Even if half of the meetings could be accomplished electronically, the logistics of pre-panel preparation and scheduling would be formidable. The time demands imposed by the bill on advisory panels could have a negative affect on the willingness of existing panels to continue to serve in their present capacities and have a chilling affect on FDA's ability to recruit future panel members. The 60 day timeframes are unrealistic. It is one half that required by S. 1477.

The provision assumes that all matters presented to advisory committees are susceptible to "final" determination. This is not always true. A better approach would be to require FDA to make a determination within __ days or to notify the affected persons of the reason why a decision has not been made and the timetable by which a decision will be made.

- Section 10 provides sponsors direct contact with classification panel members.

This provision would allow sponsors to lobby classification panel members.

SEC. 11. PREMARKET APPROVAL

- Subsection (a) of this section establishes the scope of third party authority for premarket approval. Third parties will handle the receipt, filing, and review of the PMA, as well as classification panel presentations and evaluations of classification panel recommendations. The third party must make a

recommendation to the Secretary within 30 days following receipt of a classification panel recommendation. The third party's recommendation about a PMA, i.e., whether it should be approved or denied, is considered an order of the Secretary unless the Secretary finds that there is a "reasonable probability that the device is not safe or effective," and provides a detailed explanation of the basis of the finding.

This standard requires the Secretary to establish a negative instead of finding that the application does not provide reasonable assurance of safety and effectiveness. This provision implicitly negates the bases set forth in current 515 (d)(2) as grounds for disapproval by the Secretary when a PMA is reviewed by a third party.

- Subsection (b) establishes interim deadlines for the Secretary to meet to ensure that a PMA is reviewed within 180 days. It provides that the 180 day timeframe shall not be enlarged by any amendment to the application.

This is substantially similar to Sec. 707 (a) of the Senate bill, with additional provisions for situations in which a PMA is reviewed by a third party. It requires numerous meetings and includes unrealistic timeframes. For example, by requiring FDA to meet with companies within 90 days and to present a description of deficiencies in the application and "what information is required to bring the application into a form that would require approval," the bill actually requires FDA to do a comprehensive review in one half the current statutory timeframe.

The prohibition against enlargement of time poses a special concern in cases when major deficiencies are discovered or unsolicited major amendments (e.g., new intended uses) are submitted. Under the bill the review clock cannot be reset.

- Subsection (b) also requires a report to the Commissioner and Secretary every time an interim deadline is not met. The report is due within 10 days of the missed deadline and it must fully explain the reason that the timeframe was not met. Within 10 days of receipt of the report, the Commissioner must provide an explanation to the applicant of the reasons for the failure to meet the deadlines and set forth the date for satisfying the scheduled review times. The Secretary must submit an annual report to Congress that summarized each time a requirement was not met, explains the reasons for the failure, and provides proposals to ensure that deadlines will be met.

An administrative nightmare.

- Subsection (c) requires FDA to promulgate regulations to amend 21 CFR Part 814 to conform to this section of the bill and to eliminate the need for PMA supplements for changes that "do not actually affect device safety or effectiveness."

This language is looser than the similar Senate provision, which links the exemption from supplement filing to a demonstration through data that changes will not adversely affect safety or effectiveness. The House version requires regulations to be promulgated on an expedited schedule.

This provision, for all practical purposes, eliminates the requirement relating to PMA supplements for manufacturing changes and other changes that do not actually affect product safety and effectiveness. In effect, this relieves manufacturers from seeking FDA approval despite changes in manufacturing processes, sites of manufacture, sterilization procedures, etc.

It is worth noting that this change is in contradiction to EU's medical device directive, which requires manufacturers to inform notified bodies of the kind of changes described above and to submit to assessments by the notified bodies for the purpose of verifying that the changes do not affect the firm's compliance standing. Thus, this provision can actually undermine harmonization efforts.

SEC. 12. ACCREDITATION OF THIRD PARTIES

- Subsection (a) requires the Secretary to promulgate regulations to establish procedures for accrediting third parties to review PMAs and perform GMP inspections. It establishes certain criteria for accreditation of third parties relating to conflict of interest, competency, and protection of information. It also requires the Secretary to provide for accreditation through government or qualified non-government entities.

This section does not establish how the third parties are to be compensated for services. It lacks clearly defined criteria for establishing the qualifications of third parties. It does not provide sufficient safeguards against conflicts of interest. The provision is vague as to whether FDA can inspect third parties or require third parties to maintain records. It also is unclear as to whether third parties can be given access to privileged information that is in the custody of FDA. In addition, it appears that the intention is not to have the Secretary accredit any particular entity, but rather to have the

Secretary designate agencies or organizations who will then perform the accreditation process.

- Subsection (b) amends the prohibited acts section of the FDC Act to add a new section relating to actions by third parties. Under proposed 301 (w), a third party would violate this section if it submitted a materially false or misleading report, disclosed trade secret confidential commercial information, or accepted a bribe or performed any other corrupt act in connection with its delegated responsibility.

SEC. 13. RECLASSIFICATION OF PREAMENDMENT DEVICES

- Section 13 sets an 18 month deadline for the agency to complete the reclassification of Class III pre-amendment devices. At the end of that time period, this provision requires the Secretary to reclassify these devices into Class II if they have not been the subject of a 513 (i) (2) rule down-classifying or retaining the device in Class III.

The provision mandates completion of a resource-intensive activity without consideration as to priority, benefit, or workload. It would be virtually impossible for CDRH to evaluate and act on incoming data for over 30 devices that are presently considered to be candidates for reclassification. The net result would be that a high percentage of these would be retained in class III.

SEC. 14. DEVICE TRACKING

- Section 14 amends the device tracking provision to require a regulation for imposing a tracking requirement, limits tracking to class II and III devices, changes the criteria for a tracking requirement, and eliminates FDA's discretion to apply the provision to "any other device."

Section 14 parallels Sec. 704 of the Senate bill but makes it more difficult to designate a device for tracking. Instead of requiring a potential device failure to be "reasonable likely" to be life-threatening or have "serious adverse health consequences," the House version requires the failure to be life-threatening or have permanently debilitating effects. The provision eliminates the "discretionary" category, which now includes infusion pumps, breast implants, and other silicone related devices. The Senate language is preferable, but it could be improved by changing the "permanently implantable" language to "implanted for more than 30 days."

SEC. 15. POSTMARKET SURVEILLANCE

- Section 15 eliminates the old discretionary category and makes the old mandatory category discretionary. It also further limits the type of device that can be the subject of postmarket surveillance

Section 15 parallels Sec. 705 of S.1477, but further limits the type of device that can be the subject of postmarket surveillance. The House version eliminates the catch-all category in the Senate bill for devices that potentially present a serious risk to human health or create public health concerns that justify surveillance.

Another problem with the provision is that it only permits FDA to require postmarket surveillance for devices "first introduced or delivered into interstate commerce after January 1, 1991." The date restriction would exclude Shiley heart valves, breast implants, and Landmark catheters. This cut off was eliminated from the Senate bill.

- Paragraph (b) limits the scope of the surveillance to information "necessary to determine the occurrence of unforeseen events" and limits surveillance to 18 months

This is narrower than the current standard ("data or other information necessary to protect the public health and to provide safety and effectiveness data"), which is in S. 1477. Certain devices (e.g., implantable hips) have long latency periods and the frequency of adverse events cannot always be detected within this 18 month timeframe.

SEC. 16. HARMONIZATION

- Paragraph (a) adds a requirement that GMP regulations conform "to the extent practicable" with international standards.
- Paragraph (b) requires the Secretary to meet with other countries to discuss methods and approaches to reduce regulatory burdens, harmonize regulatory requirements, and seek appropriate reciprocal arrangements. Within 180 days of enactment, the Secretary must make public a plan that establishes a framework for achieving mutual recognition of GMPs. The Secretary also must provide 60 day notice to the Committee before executing any agreements with foreign countries.

SEC 17. GOOD MANUFACTURING PRACTICE INSPECTIONS

- Subsection (a) amends section 704 of the FDC Act to permit third parties to conduct gmp inspections. It also amends the section to require a 10 day waiting period after any inspection (whether by a third party or FDA?) to give the subject an opportunity to respond to any observations. The agency may not take any regulatory action following an inspection until it has reviewed a timely response from the subject of the inspection, unless there is a reasonable probability that a device would cause serious, adverse health consequence or death or that any regulated article could present an unreasonable and substantial risk. The Secretary must also provide a detailed assessment of the response submitted by the subject of the inspection within 30 days.

In general, requiring a 10 day waiting period, a review of the manufacturer's response, and a detailed response in 30 days may have a significant impact on agency workload (for the inspections the agency would continue to do). Because a warning letter is considered regulatory action, this provision would stop FDA from issuing one until this process is complete. This may not significantly slow down current time frames for issuing warning letters, but it has the potential to hamper agency action.

- A third party performing a GMP inspection does not submit a copy of its observations to the Secretary. However, if the findings indicate a serious problem, the third party must immediately notify the Secretary unless the person subject to the inspection immediately ceases distribution, notifies health professionals and device user facilities, and undertakes all corrections identified by the third party. When such compliance is completed, the third party provides a certification of compliance, a copy of which is provided to the Secretary. The Secretary may not perform another gmp inspections for 2 years after the date of the certification unless justified by good cause.

As it is drafted, the agency never becomes involved in compliance matters when a third party has undertaken the original inspection. The third party oversees corrections and certifies to the Secretary that the company is in compliance. The Secretary may not conduct a GMP inspection for 2 years after the date of this certification, "unless justified by good cause."

SEC. 18. USE OF SCIENTIFIC AND MEDICAL INFORMATION

- Section 18 amends 502(f) to make it legal to disseminate medical texts, journal articles, and government information, and to make presentations at medical and scientific meetings about off-label uses. These activities would not constitute misbranding and would not trigger the need to file a 510 (k) or

PMA unless the person "in addition" encourages the unapproved use of a legally marketed device through labeling, advertising, or other means of promotion. The provision also establishes that knowledge of an off-label use would not trigger any obligation for the manufacturer to change the labeling or amend a marketing application. The section also makes it permissible for sponsors of IDEs and their agent to disseminate materials, make presentations, and display investigational devices at trade shows so long as the sponsor or agent does not "encourage the use of the device".

This section assumes that the various activities it permits are not promotion and do not encourage off-label uses or uses of investigational products. The provision will make it possible for sponsors to promote off label uses and investigational products without filing marketing applications or IDEs. The provision eliminates incentives for manufacturers to conduct studies needed to demonstrate the safety and effectiveness of new uses and to go through the regulatory process at all for off-label uses.

SEC. 19. REPORTS

- Section 19 (a) eliminates reporting requirements for distributors.

Eliminating distributor reporting is not objectionable.

- Section 19 (b) eliminates reports of malfunctions when the available information clearly shows (presumably to the satisfaction of the manufacturer or importer) that the failure was caused by improper servicing or maintenance as determined by review of the device labeling.

Eliminating this reporting requirement would have a crippling effect on FDA's ability to identify and insure correction of serious device problems.

- Subsection (d) eliminates user reporting requirements and requirements relating to annual certification and reports of removals and corrections.

The elimination of user facility reporting is problematic. The certification requirements and reports of removals and corrections also serve important oversight functions and they hold manufacturers accountable for compliance with the law.

SEC. 20. G.M.P. AND DEVICE REPORTS

- Section 20 eliminates civil penalty liability for misbranding a device by failing to make required reports or for adulterating a device by failing to comply with GMPs if the person acted in good faith, had no reason to believe the law was being violated, and had no prior notice from the Secretary that the acts constituted violations.

The reference to 301(g)(1)(B) does not make sense.

SEC. 21. CIVIL PENALTIES

- Paragraph (1) gives the Secretary discretion to direct a person subject to civil money penalties to apply the amount to the correction of violations, as verified by an independent auditor.

The intent of this provision is unclear. Is the idea to allow violative companies to benefit? Doesn't this then create an incentive to violate the law? Would the money be used to compensate persons injured by the device?

- Paragraph (2) adds the right to discovery for particular violations concerning the distribution of growth hormones to minors.

What is this intended to accomplish and why is it in the device reform bill?

SEC. 22. INFORMATION SYSTEM

- Section 22 requires FDA to establish a system to track the status and progress of each application. The system must permit access by the applicant.

This section raises concerns re: protecting the confidentiality of applicant information. In addition, there are resource implications re: set-up and maintenance.

SEC. 23. ENVIRONMENTAL IMPACT REVIEW

- Section 23 eliminates the requirement to prepare an environmental analysis unless the Secretary demonstrates that because of extraordinary circumstances, the action will have a significant effect on the human environment and the consideration of such significant effect will directly affect the Secretary's decision on the action.

This is similar to Sec. 406 of the Senate bill, but the House version

makes it harder to require an environmental impact review because it requires the Secretary to demonstrate that the action "will have a significant effect on the human environment."

SEC. 24. INFORMAL AGENCY STATEMENTS

- This section prohibits the Secretary from relying on policy statements, guidance documents, and similar statements to require any action to satisfy a provision of the FDC Act. It also requires the Secretary to publish notice of availability of such statements and to make them accessible electronically.

FDA's position is that guidance documents are not binding on the Agency or the public. FDA recently issued a Federal Register notice that affirms this position and has agreed to take steps to ensure that the agency and the public know and understand this principle. To the extent that this provision is reaffirming that position it is not problematic. To the extent that it is saying that FDA cannot issue guidance that explains how it believes compliance with the Act may be accomplished, it is problematic -- particularly for the industry. FDA will no longer be able to provide guidance and there is a risk of non-uniformity in the application of the laws and regulations that FDA is tasked with implementing.

SEC. 25. RESEARCH AND EDUCATION; PRACTICE OF MEDICINE

- New section 908(a) requires FDA to train and educate its employees.

FDA currently does this through staff colleges etc.

- New section 908(b) limits FDA's research activities to research directly related to the implementation of the FDC Act.
- New section 909 states that nothing in the FDA Act shall limit or interfere with a health care practitioner's authority to prescribe or administer legally marketed drugs or devices.

SEC. 26. PUBLICATION OF NOTICE DEVIATION

- Section 26 prevents FDA from making public any information regarding a notice that informs a regulated person of a purported deviation from a requirement of the Act until after the Secretary has completed the investigation

of such deviation.

This provision calls into question the agency's long-standing practice of making 483s, warning letters, and correspondence with regulated industry available to the public. Such a radical change in FDA's public information procedures and regulations could hamper the agency's ability to carry out its public health mission effectively. The difficulty the agency currently has with respect to prohibitions on public disclosure of information contained in marketing applications would extend to disclosure of information about observed violations and enforcement initiatives.

MONDAY, FEBRUARY 6, 1995

"WE DON'T WANT ANYONE INTERFERING WITH
OUR SALES"



Edward M. Kennedy

Prescription for Disaster

Republican legislation in Congress to "reform" the Food and Drug Administration would dramatically weaken the FDA's ability to protect the public health. The

it on the FDA is particularly serious, because the agency is responsible for the safety of a quarter of all the products in the American economy—especially the food we eat and the prescription drugs we take.

The Republican bills would water down requirements that guarantee these products are safe and effective. They would turn over many of the FDA's most important functions to private industry, with built-in conflicts of interest. They would give preference to products approved in Europe and other foreign countries, where the public is less well protected. And they would saddle the agency with so many new bureaucratic requirements and so much red tape that it would be unable to do its job. If the Republican proposals are enacted, Americans can expect many more drug disasters like thalidomide and DES, medical device failures like the Dalkon shield, lethal vaccines like the Cutter polio vaccine,

threats to the blood supply and even threats to the food supply, such as the "mad cow disease," which has rocked the British beef industry.

The Republican proposals, by eliminating essential FDA oversight of the production of medical products, threaten the safety of drugs, medical devices, blood and vaccines. A minor manufacturing change that alters the solvent used to kill viruses in blood products can result in ineffective sterilization of the blood, risking the transmission of AIDS or hepatitis. A change in the filters used to produce vaccines can turn a protective vaccine into a killer. A change in filters used to produce the Cutter polio vaccine resulted in 200 cases of polio in the 1950s, before the FDA required more rigorous standards. Under the Republican bills, the agency would no longer be permitted to review such manufacturing changes in advance to ensure that the public is protected.

The House Republican bill eliminates existing requirements for the FDA to approve certain products that can be dangerous to public health—such as leaky surgical gloves or faulty diagnostic tests. In recent weeks, it was revealed that a defective new AIDS test kit was distributed to 2 million patients abroad. American consumers, however, were spared exposure to this dangerous product.

The Senate bill gives the FDA only 90 days

to review certain new food additives, even though these additives can result in the involuntary exposure of millions of Americans to potentially harmful substances.

The Dalkon shield, used to prevent pregnancy, injured 90,000 women because of a design flaw. This tragedy led to legislation strengthening FDA oversight of medical devices. The Shiley heart valve proved vulnerable to breakage, killing the patients. Before the valve was withdrawn, the manufacturer proposed a new version six times more dangerous than the original. The FDA rejected it, but 4,000 patients received it in Europe. Under the Republican bills, the FDA's ability to prevent such tragedies would be seriously compromised.

The House bill would reduce standards for approving a new use for a drug already approved for another purpose. The lower standard would restore the pre-1962 requirements that brought us DES. In recent years, drugs approved for life-threatening heart arrhythmias were widely prescribed for mild arrhythmias. This "off-label" use of the drug has been estimated to have caused as many as 50,000 deaths.

Both the Senate and the House bills contain an inherent and outrageous conflict of interest. They are designed to shift responsibility for product approval from the independent experts

at the FDA to private businesses. The profitability of these firms would depend on the fees they attracted from the very companies whose products they review. The Senate bill pretends to give the FDA final approval of the decisions of these private reviewers, but the time frames for action are so short and the rules for oversight so limited that the agency would be reduced to little more than a rubber stamp. The House bill is even more extreme, removing the FDA from certain product approvals altogether.

As hard as it may be to believe, another provision in the bills would prohibit the FDA from requiring companies to make information available to patients on possible dangers of prescription drugs. At a time when hospitalizations from improper use of prescription drugs by senior citizens cost Medicare \$20 billion a year, it is foolish to deny patients information they need to monitor their use of medications.

The Republican bills also contain provisions to micromanage the agency. The strategy of the Republicans and their special interest constituency is clear: Set up procedures that make it impossible for regulatory agencies to protect the public, and then use their failures as an excuse to dismantle them.

The assault on the FDA is fueled by a well-funded campaign alleging that patients are suffering because foot-dragging by the agency is denying them needed drugs already approved in foreign countries. Much of the funding for this campaign comes from tobacco companies, who have their own reasons to discredit the FDA. In fact, FDA drug review time was cut by 40 percent between 1987 and 1993. According to the nonpartisan congressional General Accounting Office, by 1993 the United States was reviewing drugs as fast as, or faster than, Great Britain and other foreign countries. Review times in the United States have dropped even farther since.

And unlike foreign approval authorities, the FDA has combined speed with safety. Between 1970 and 1992, 56 drugs were introduced in France, Germany, Great Britain and the United States that subsequently had to be withdrawn because they were unsafe. Only nine had been approved in this country, compared with 31 in France, 30 in Germany and 23 in Great Britain.

The FDA is not perfect, but it is still renowned as one of the most effective regulatory agencies in the world. There is always room for improvement, but the Republican proposal is a blueprint for demolition, not modernization, and Congress should reject it.

The writer is a Democratic senator from Massachusetts



The Boston Globe

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The FDA and Shannon McDermott

Janet McDermott is waging a valiant struggle to get medication that will prevent the seizures suffered by her daughter Shannon. But Shannon's plight should not encourage support for a bill in Congress that would force the Food and Drug Administration to speed up the approval process for new drugs.

The McDermotts, who live in Marshfield, have tried every treatment recommended by Shannon's doctors to relieve the seizures. The latest drug prescribed for the 8-year-old is Sabril, not yet approved in the United States. Shannon's mother must go to Canada for it.

Mrs. McDermott has also traveled to Washington, at the expense of a pharmaceutical trade group, to lobby on behalf of a bill that would shift the balance of regulatory power at the FDA. This measure would apply to every experimental medicine, from cancer treatment to baldness cure, and to medical devices like heart valves or prostheses.

Under present law, the FDA is exceedingly careful about which drugs it qualifies for use. Before an application can be accepted, medicines must undergo animal tests and at least two clinical trials on people. Approval for Sabril was delayed when the first use on animals showed that it might cause holes in the brain. Subsequent tests showed that this condition did not apply to humans.

It is reassuring that federal law demands rigorous testing. The legislation, which just cleared the Senate Labor Committee over the objections of Sen. Edward Kennedy, would change the em-

phasis of the FDA from review to approval. In the most extreme case, the FDA would have to accept a drug cleared by the European Union unless it can state in writing why approval for the medicine should be withheld.

Only four years ago, Congress imposed a user fee on the drug industry. The money is being spent to hire 600 additional reviewers, and approval times have been reduced to 16 months, compared with 33 months in the late 1980s.

In response to public pressure, the FDA has already expedited approval of drugs that fight AIDS and cancer. Other improvements in the process may well be in order, but these are best recommended by an unbiased group before being considered by Congress. An independent review of FDA procedures should be undertaken only when the impact of the user fee can be assessed.

As for Sabril, an FDA spokesman, James O'Hara, says the drug could be offered to Shannon McDermott on a special, individual testing basis. Hoechst-Marion-Roussel, the manufacturer, demurs, saying that it would rather devote resources to testing the drugs on large groups. Shannon would not qualify for such group trials.

That decision is well within the company's rights as a maker of medicine. Julie O'Dell, a company spokeswoman, says the Sabril work should be completed by the end of the year and the drug available for widespread use in 1997. That's a long time in the life of an 8-year-old, but in matters of drug safety, caution is better than haste.

The FDA Legislation

UNTIL RECENTLY, the Senate bill to streamline some drug and device approval procedures for the Food and Drug Administration was moving forward cautiously. The bill that emerged from committee, though, is incautious—loaded with last-minute changes that destroy any claim to judiciousness.

An amendment by Sen. Dan Coats (R-Ind.) seizes on and vastly expands what would have been an FDA pilot program—an experiment allowing companies to opt for a private third-party route that might speed up the more onerous parts of the approval process, whose results the FDA would then look at before giving the final sign-off. The Coats amendment turns this into a procedure in which any manufacturer could request the third-party review for any device, could itself choose the private company or companies to perform the review and could decide how much to pay for it—a process that gives huge and obvious incentives to third-party review companies to be as fast and undemanding as possible. And under this scheme, the chosen outside reviewers, not the FDA, would effectively have the final say. (The FDA would have to prove harm in order to prevent a device's coming to market, rather than, as now, the manufacturer's having to prove safety.)

The idea of prodding the FDA to offer third-party review as a road to efficiency, without recklessly dismantling safeguards, was at least

consistent with the stated argument from “reform” proponents that the purpose is not to weaken safety protections but merely to serve industries’ and patients’ interests better by bringing the long, drawn-out approval process to conclusion more quickly. Accordingly, the pilot program would have limited the experiment to devices classed low or moderate risk already, limiting the chances of danger in case the untested system proved too porous. The Senate committee, though, changed that, extending eligibility for the third-party system to all devices—including the ones classed as high risk.

These risks aren't exactly abstractions. Medical devices get embedded in the human body, hold people's bones together, are carried in the body for years. Does anyone seriously think for a moment that there is a public outcry for the removal of incentives to double-check the safety of things that shunt fluids from the human brain, clear heart patients' veins, are buried in the skin of people's arms? Or, for that matter, for the removal of an independent check on the safety of drugs and the food supply?

Arguments over efficiency and how best to get the job done are legitimate, but the public interest in having the FDA ride herd effectively on the safety of these miraculous medical devices and incredibly powerful drugs remains high. The Senate committee add-ons don't sufficiently recognize or respect that fact.

Streamlining the F.D.A., Safely

The Clinton Administration is making it easier for cancer patients to get promising drugs that have not been fully tested. By loosening some of the Food and Drug Administration's rules to accelerate access to experimental drugs, the White House may defuse more sweeping and dangerous reforms under consideration by Congress.

The F.D.A.'s job is to insure that drugs and medical devices are safe and effective and that food additives are risk-free. The agency gives approval only after lengthy clinical trials by the manufacturer. But many companies complain that the F.D.A. is slow to respond, escalating costs. In addition, some groups representing AIDS and cancer patients say that its bureaucracy denies them faster access to promising remedies.

Congress, the companies and the agency are now struggling to get drugs and medical devices to needy patients as quickly as possible without jeopardizing public health or sacrificing the standards of safety and efficacy that give consumers confidence in F.D.A.-approved products.

The Clinton Administration proposes faster approval for cancer-fighting drugs. Previously, the F.D.A. asked for proof that an experimental drug would help a patient's chances for survival or improve that patient's quality of life. Under the new rules, a drug can be approved based on a "partial" positive response, like shrinkage of a tumor. In addition, companies making experimental drugs that have already been approved overseas can seek permission to distribute those drugs to American cancer patients even before the F.D.A. has given final approval. These measures, which need no further approval, will take effect immediately and could apply to about 100 drugs under study.

The new initiatives are welcome but unlikely to appease Congress, which is pressing for more sweeping F.D.A. reform. Last month the Senate Labor and Human Resources Committee approved a bill sponsored by Nancy Kassebaum, Republican of Kansas, that calls on the agency to expedite clinical investigations of new drugs, devices and biological products as well as breakthrough drugs for life-threatening diseases. If the agency fails to review most applications within six months, the product sponsors could force it to contract with outside experts to complete the process.

Similarly, a bill being pushed on behalf of the House G.O.P. by James Greenwood of Pennsylvania sets tight approval deadlines and would turn over some F.D.A. review authority to third parties.

The F.D.A. would retain a supervisory role. But the outside experts and "third parties" envisioned in both the Senate and House bills could, under the guise of regulatory reform, lead to the privatization of many of the F.D.A.'s functions and undermine its role as an independent government protector of public health.

The drive to reform the F.D.A. comes at a time when the agency has been improving its performance. In 1994, 96 percent of new drug applications were approved within the 12 months allotted under current law, and the agency has been streamlining many of its internal procedures. Important life-enhancing drugs and medical devices should obviously get to consumers as quickly as possible. That is what the Administration's new cancer drug initiative aims to do. But safety and effectiveness should not be sacrificed for efficiency. At the moment, the Administration seems more mindful of that than Congress.

Don't let Congress cripple the FDA

By JOE GRAEDON
and TERESA GRAEDON

Americans are an impatient people. We have grown accustomed to instant coffee, one-hour photo processing, fast food and fares.

Delay is irritating. If you don't believe us, just try stepping into the express checkout lane with more than 13 items.

Obsessed with speed, we tend to forget there can be risks to rushing. We see every innovation as progress and rarely pause to examine its potential problems.

This may explain why the current legislative proposals to "streamline" the Food and Drug Administration seem so appealing. Everyone wants a quick cure for cancer, AIDS, Alzheimer's disease and arthritis. In its haste to hurry the FDA's approval process, Congress may well hamstring this critical agency.

We are not big fans of the FDA. We often criticize this bureaucracy for its insensitivity and inflexibility. But without this watchdog, Americans would be at far greater risk of injury and illness.

Even under the current system, there are flaws. A General Accounting Office study revealed that more than half of the new drugs approved by the FDA are later found

People's Pharmacy

to have serious or even life-threatening consequences that did not show up in the original data.

It is estimated that more than 100,000 Americans die each year as a result of prescription drug problems. That's the equivalent of a 727 going down every day. If that many people were dying in plane crashes, there would be an outcry for the Federal Aviation Administration to crack down.

Prescription drug companies are aggressively promoting their products directly to consumers in magazines, newspapers and TV. In addition, many drugs that were once available only by prescription are now sold over the counter. Instead of cutting back on the FDA's oversight, this country needs better protection of the public health.

Millions of women are worried about the unresolved question of whether female hormones promote breast cancer. Reports that Ritalin and a common ingredient in laxatives cause cancer in animals has consumers concerned. And some people are frightened about the possibility that certain blood pressure pills may increase the risk of heart attacks.

Whether Congress cuts the FDA's authority, consumers are more vulnerable today than ever before. Doctors, overwhelmed with paperwork, have a hard time staying current on powerful new drugs. Pharmacists are being stretched to their limits, and managed care is affecting everyone.

As eager as we all are to have new and better treatments, cutting back on drug testing and speeding FDA review may not improve health overall.

Q: My husband has been on Mevacor for years to lower his cholesterol. We read that this drug causes cancer in animals. Is there any danger?

A: We wish we knew. An article in the Journal of the American Medical Association (vol. 275, p. 53-60) noted that lovastatin (Mevacor) and related drugs produce tumors in rodents. Whether this is a problem for humans remains controversial. The FDA does not have a good system for evaluating such long term risks.

Joe Graedon is a pharmacologist. Teresa Graedon holds a doctorate in medical anthropology and is a nutrition expert. *The People's Pharmacy* with Joe and Teresa Graedon is a call-in show syndicated to many public radio stations.

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The New Haven Register

March 21, 1996

EDITORIAL

Keep hands off drug safety checks

Bill before Congress would strip away basic protections on new drugs, medical devices.

Here's a one-word reason why U.S. Sen. Christopher J. Dodd, D-Conn., should vote against a radical overhaul of the Federal Food and Drug Act: thalidomide.

Between 1959 and 1961, thousands of pregnant women in Europe, where the drug was approved, took it for nausea. They and American women, taking the drug in trials, gave birth to some 10,000 infants with deformities ranging from legless torsos to toes and hands attached directly to the body.

In 1962, Congress passed a law requiring that companies prove drugs are safe and effective before being sold in the United States. It's hard to imagine such a basic health protection being stripped away.

However, a bill before the Senate's Labor and Human Resources Committee on which Dodd sits, would do just that. Drugs already approved in Europe, as was thalidomide, would be approved for use here if the Food and Drug Administration did not meet stringent review deadlines.

The possibility of another thalidomide baby tragedy is just one of the horrific possibilities raised by this bill.

In 1976, Congress again expanded the FDA's authority to regulate medical devices after another medical disaster, the Dalkon Shield. Before the birth control device was withdrawn, thousands of women were left infertile and an estimated 15 died of injuries it

caused.

Again, protection from a similar catastrophe would be stripped away by the pending legislation if an FDA review isn't speedy enough.

This bill would also end the FDA's approving medicines for specific uses. However, a drug that is safe for one use may not be safe for another.

This legislation is deliberately destructive of basic medical safeguards. It demands cuts in time taken for reviews by a third. But, it offers no extra money for staff to do the reviews effectively.

While the FDA review process has been laggard, Congress solved much of the problem with 1992 legislation that has let the FDA work with pharmaceutical companies to speed reviews. Ten years ago, it took nearly three years for FDA action. Now, most new drugs are approved within 12 months.

In recent years, the FDA has actually approved new drugs more quickly than Germany or Great Britain. Further, the FDA has a far better safety record. Between 1970 and 1992, only nine drugs were withdrawn because of safety reasons in the United States. In Great Britain, 32 dangerous drugs had to be taken off the market; in Germany, 30. The most serious side effects of the withdrawn drugs were death, paralysis, heart attacks and liver damage.

The FDA's speed and procedures can use improvement. But the alternative in this bill is nothing short of a medical hell of unnecessary death and tragedy.

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The Des Moines Register

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THE REGISTER'S EDITORIALS

Rushing drugs to market

**If the FDA speeds approval,
mistakes are more likely.**

The nation's drug companies invest fortunes in researching new drugs, and every day that the Food and Drug Administration delays approval of marketing the drugs, it causes the makers to lose big bucks.

It also saves lives. But that gets little attention.

A bill in the Senate would speed up the approval process, forcing the FDA to meet tighter deadlines. If the FDA missed the deadline on a drug already approved for use in Europe, use here would be approved by default. Because European standards are not as tough as the FDA's, that could be dangerous. Thirty years ago, thalidomide was approved here on an experimental basis after approval in Britain. A few paid an agonizing price in birth deformities.

The Senate bill would enable "off-label" use of any drug for a purpose other than that for which it was developed and approved, even if the off-label use had not been tested. In the late 1980s, two drugs approved for treatment of abnormal heartbeats began to be routinely prescribed for milder heart problems, based on the as-

sumption it was safe, although the FDA had not completed testing for such use. What the agency discovered was that use of the drugs for the "off-label" condition doubled the patient's risk of dying.

The FDA has speeded its drug-approval process markedly in recent years. But there are limits, rooted in safety. The agency is already approving drugs for life-threatening ailments in less time than the bill would require. But an unending push for more speed can be satisfied only at the expense of care. "One of these days," said FDA Commissioner David Kessler, "we are going to make a mistake."

The bill poses the FDA as the national enemy, pitted against the best interests of the drug firms and the ill. In truth, FDA is a national guardian, protecting the public from the consequences of undue haste.

The speed-up bill, sponsored by Kansas Republican Nancy Kassebaum, is up for a vote Thursday in the Senate Committee on Labor and Human Resources. Iowa's Senator Tom Harkin is a committee member. He and his colleagues should vote "no."

The Washington Post

AN INDEPENDENT NEWSPAPER

Prodding the FDA

IF YOU'VE heard the ideological fervor with which anti-regulatory types habitually attack the Food and Drug Administration, you might be surprised at the sorts of issues that are occupying the warring sides on FDA "reform" legislation in the Senate. The bill, sponsored by Sen. Nancy Kassebaum (R-Kan.), has little in common with the plans that came out of Speaker Newt Gingrich's Progress and Freedom Foundation or the Heritage Foundation last year. Those groups regard the FDA as a particularly noxious and burdensome example of regulatory excess, and their visions include stripping or privatizing the FDA's enforcement powers or eliminating the requirement that a drug be "efficacious" as well as "safe" in order to go on the market.

None of these approaches got the support of the mainstream pharmaceutical industry, which relies on the FDA and gleans both legal and marketing advantages from its stamp of approval both here and abroad. What the drug companies, the medical-device companies and the young biotechnology industry wanted was to prod the agency out of longstanding habits of bureaucratic backlog, foot-dragging and unnecessary paperwork. The Kassebaum bill does this by a complicated system of deadlines, structural changes and

"hammers"—points in the development process at which the FDA would have to approve or disapprove a drug or explain why it hadn't acted. As it happens, these are areas where the FDA has itself made strides, with agency head David Kessler instituting reforms to reduce backlogs and bottlenecks.

The Hill fight turns out to be mostly about whether this is happening fast enough, how much further and faster it can safely be pushed and who—FDA or Congress—should have final say over its shape. Parts of the bill are designed to speed up the progress of big drug trials and reduce the time needed to file certain kinds of applications. The questions here are simple scientific ones: What is the optimum setup for a big drug trial involving 4,000 college students? Can that number be safely cut to 1,500 students?

It may very well be, as the drug companies complain, that years of FDA caution have "barnacled" the process till a push like this was needed to get things moving faster. But aside from the motivational qualities of the threat of legislation, you've got to wonder whether these are questions best settled by a legislative body containing, on the Senate side at least, exactly one doctor.

The New York Times

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NEW YORK, TUESDAY, MARCH 12, 1996

Go Slow on F.D.A. Reforms

Americans who remember the thalidomide disaster in England 35 years ago, when many mothers who had taken the drug had babies with serious birth defects, were grateful that the Food and Drug Administration kept it off the market in this country. But now the F.D.A. has come under fire for taking too long to approve drugs and medical devices. Congress is considering legislation that is designed to speed things up, but that may go too far in loosening regulatory safeguards.

The F.D.A. aims to insure that drugs and medical devices are safe and effective and that food additives are safe. Companies applying for approval of new drugs and devices submit their research data to the F.D.A., which assembles expert advisory committees to help determine whether the safety and efficacy standard has been met.

But over the years there have been complaints that the agency's regulatory machinery grinds far too slowly. Many companies that manufacture drugs and medical devices complain that the process often takes years. Some patients with serious or terminal diseases like cancer or AIDS have been frustrated by agency rules that prevent them from trying experimental drugs.

Senator Nancy Kassebaum, Republican of Kansas, recently introduced legislation designed to ease the rules. Her proposal would set a deadline of four months for the review of breakthrough drugs, down from the present six months. It would cut approval time for all other drugs from 12 to 6 months. In addition, the proposed bill would allow approval of medical devices on the basis of less rigorous research than is now required.

If the agency fails to meet the specific review times, a company could still market its product on the basis of approval by the European Union. That's a return to the days before the agency was required by a 1962 law to make an affirmative finding of safety and not just rely on the testing of others.

Dr. David Kessler, the F.D.A. Commissioner, insists that internal management reforms have already brought good results. Approval time for new drug applications was reduced from an average of 33 months in 1987 to 19 months in 1992. In 1994, 96 percent of new drug applications were acted on within the allotted 12 months. With the F.D.A. already making good progress, Congress should be wary of pressing it to move too fast in approving new drugs. Haste could prove hazardous.

Sugar-Coating a Bitter Pill

Sweet Talk Aside, the GOP and the Pharmaceutical Industry Want to

By Thomas J. Moore

THE DRUG industry and its allies call it "streamlining the Food and Drug Administration." Patients are promised they will get new drugs more quickly. Hidden behind this slick sales pitch is the most frightening effort to roll back drug safety and efficacy laws since federal regulation began in 1906.

With Senate Republicans promising floor action as early as next month, this legislative blitz may succeed before a broader public realizes what's at risk. On Wednesday the Senate Labor Committee meets to mark up its bill. While described in some press accounts as "moderate," it would achieve an unprecedented cutback in drug testing requirements. The House Commerce Committee—whose chairman is highly critical of the FDA—has promised to get a bill to the floor promptly. The Pharmaceutical Research and Manufacturers Association and its allies already have a major lobbying campaign in high gear. It features ads attacking the FDA, a letter-writing effort and the usual generous campaign contributions. Industry lobbyists are even rounding up patients dying of serious diseases or their relatives and flying them to Washington to plead with key members of Congress.

Indeed, why do we insist on a powerful FDA that requires elaborate clinical testing of each new drug that can take 10 years to complete and a year to evaluate? Why not let medical researchers, doctors and patients make the judgments about drugs with minimum government interference? We test because prescription drugs regularly cause the most painful injuries imaginable—hideous birth defects, irreversible brain damage, life-long addiction and thousands of preventable deaths.

Other damage is less severe but more widespread. For example, 20 of the 200 most commonly prescribed drugs cause sexual dysfunction. Two of the most widely used

classes of drugs—beta-blockers and benzodiazepine tranquilizers—unpair judgment and the ability to think clearly. Painkillers, including aspirin, cause thousands of hospitalizations each year for perforated ulcers or internal bleeding.

Having recently studied the toll of death and injury from prescription drugs under existing law, I shudder at proposals to weaken an already inadequate system. Based on my research, I estimate that each year prescription drugs injure about 5 million Americans enough to require medical treatment. Another 1 million are injured so severely they require hospitalization. Deaths could be 100,000 or more. Overall, you are 10 times more likely to be severely injured by a prescribed drug than in an automobile accident.

These figures have to be approximations because there is no systematic monitoring of the adverse effects of drugs. In most states, you must report an auto accident with a few hundred dollars damage. But when a prescription drug is suspected of causing death or serious injury, neither doctors nor hospitals have any legal obligation to report it. In one famous study of Rhode Island doctors, only 55 of 27,000 significant adverse drug reactions believed to have occurred in one year were ever reported. Injuries occur when anything goes wrong in the complex system that requires thorough clinical testing, intensive FDA review, effective post-market surveillance, alert physicians and knowledgeable patients. But without adequate clinical testing the whole system is crippled from the start.

Thousands of lives are also at risk when drugs that the FDA-approved for one medical condition become widely prescribed for another. This is called "off-label" use, and two Senate bills being championed by the industry would encourage still more of this practice. Such off-label use helped create the nation's worst drug disaster.

A family of drugs that were FDA approved for life-threatening heart rhythm disturbances were widely pre-

scribed for patients with mild irregular heart beats. In 1989, a government-sponsored clinical trial proved conclusively that two of these drugs killed 6 percent of the heart patients who took them in just one year's time. That would mean an estimated 50,000 deaths among similar patients taking all brands of these drugs in just a few year's time—a death toll comparable to U.S. losses in the Vietnam War.

Cripple Safety Testing

Another loophole in existing law allows drugs to be sold for long-term use without long-term clinical testing. The most frequently prescribed drug today is conjugated estrogen, a hormone that women take after menopause. Last year a large—but not definitive—epidemiological study showed that taking estrogen increased the risk of breast cancer. On the other hand, another study—also not definitive—suggested estrogen may cut the risk of death from heart disease. Here is a drug on sale for decades to millions of people and generating hundreds of millions of dollars in revenue every year. But because even now we haven't done the proper clinical studies—costing a fraction of those sales—we don't know whether it is harmful or beneficial over the long term.

Even more lives are at stake in new questions about the safety of calcium

channel blockers—a family of heart drugs taken to lower blood pressure and prevent chest pains. They are taken daily by 7 million Americans. Last year three studies appeared in peer-reviewed medical journals suggesting that some—or possibly all—of these agents may cause heart attacks instead of preventing them. The evidence persuaded an expert panel at the National Institutes of Health to issue an unusual warning, saying the safety of all calcium channel blockers was "unclear" and urging doctors to avoid one of them, short-acting nifedipine (sold as Procardia and Adalat). It doesn't do us any good to get new drugs quickly if we can't tell their effects.

The experience with Prozac, Paxil and other anti-depressants shows that even when a drug proves beneficial, we also need to take a careful measure of its adverse effects. Talk to patients who are taking these popular drugs and you will often get passionate testimonials about the benefits. But you will also hear the sorrow of those who say they've lost their interest in sex. At last official count, there were 242 different adverse effects of Prozac, including 39 separate problems related to genital or urinary systems. About 1 in 5 people who take Prozac experience an adverse effect.

All this explains why clinical testing is so essential, but not why it is so expensive or needs to take so long. Despite its aura of high-tech wizardry, drug research remains a hit-or-miss game where researchers grope in the dark, wrestling with immensely complex biological systems that no one yet understands. This is one reason why 90 percent of drugs that enter human testing fail to win FDA approval. "Drug

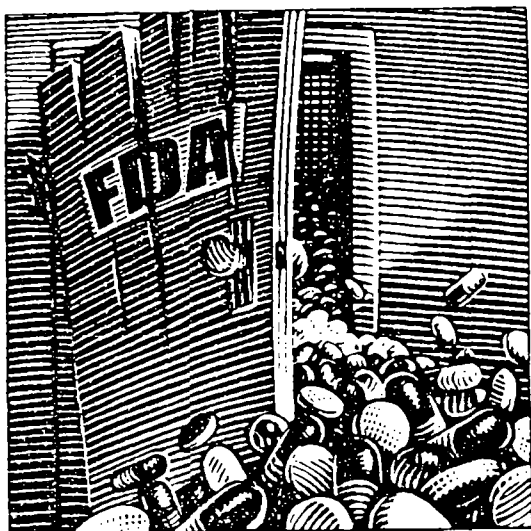


ILLUSTRATION BY JEFFREY M. HARRIS FOR THE WASHINGTON POST

development is like watching people who learned how to make a transistor but don't yet know how a radio works," notes experimental pathologist Christian Haudenschild. Biological ignorance is an argument for more drug testing not for less.

Escalating costs of drug development is often used to justify less test-



BY JOHN MCKINLEY FOR THE WASHINGTON POST

ing. A Tufts University study estimated it costs \$291 million to bring a new drug to market—and the industry claims it costs even more. But the amount spent on the actual human and long-term animal tests is less than \$16 million. Where did the rest go? To test the other nine drugs that didn't make it, to ongoing research and to the interest costs of the money over the full period.

Costs are also driven up by drug companies scrambling to copy someone else's winner. There are currently in development 127 drugs that work on the same mechanisms as Prozac or Elavil. Most will never make it to market, but they will help run up the research bill. And finally, testing is so expensive because the effects of many popular drugs are so small that it takes observing thousands of people for several years to detect any measurable effect. Cholesterol-lowering drugs are the classic example. Look at the evidence from the clinical trial of Pravacol, one of the most effective: Among the 3,302 people who took it for five years, there were 74 fewer heart attacks and deaths. Those promoting the drug can say correctly that it reduces the risk of death or heart attack by 31

percent. But of every 1,000 persons who take Pravacol for one year, 995 get no benefit. To produce just this evidence involved screening 81,000 patients, took more than five years and cost millions.

With the health of millions of people at stake, certifying that a drug is safe and effective is one of the most difficult and complex scientific judgments made in our society. Not only do we need rigorous clinical studies, we also need an expert and impartial FDA to judge them. If the final tests of a drug show tell-tale signs that it might be dangerous, I want an agency smart and tough enough to stand up to a powerful pharmaceutical giant with millions already invested.

In the User Fee Act of 1992, Congress showed that we can indeed speed drugs to patients without cutting corners on safety and clinical testing. Using fees collected from industry, the FDA has hired more experts to review drugs—which are now being approved in about half the time it took in 1987. But much still remains to be done.

We need a coherent program to reduce the hundreds of thousands of preventable deaths and severe injuries from drugs. The whole system needs an impartial oversight agency modeled on the National Transportation Safety Board. We need expert panels to identify the drug studies that are too expensive—or not potentially profitable enough—for a drug company to undertake. We need to fix the information system that buries doctors under an avalanche of often biased and unnecessarily complicated data while depriving patients of basic facts about the drugs they take. Prescription drugs remain the biggest commercial source of accidental injury and death for which there is little or no hope of compensation.

Congress is now heading in the wrong direction. We should encourage drug companies to do more testing and less marketing, not enact a law that would achieve the reverse.

Thomas Moore is a senior fellow at the Center for Health Policy Research at George Washington University and the author of "Deadly Medicine: Why Tens of Thousands of Heart Patients Died in America's Worst Drug Disaster."

Allison M. Zieve
And Sidney M. Wolfe

Don't Weaken The FDA Laws

In his Feb. 1 op-ed piece, "Keeping Doctors Up to Date on Drugs," Sen. Bill Frist tries to sell the public on a dangerous idea. He wants to remove the 34-year-old ban that ensures that drug companies do proper testing before they promote a drug or medical device for a particular medical use. The proposal touted by Frist—that drug and medical-device companies be permitted to promote their products for uses never approved by the FDA—strikes at the heart of the processes used to ensure that drugs and medical devices are safe and effective. Not surprisingly, the drug and medical device industries have been pushing this idea for some time.

Referring to "FDA-approved products," Frist misunderstands the federal drug- and device-approval systems. The approval processes do not evaluate the safety and effectiveness of a product in general, but only for a specified use. The FDA weighs the benefits of that use against the risks to determine if, on balance, doctors should be prescribing it for that particular purpose. Manufacturers are permitted to promote and advertise their products only for approved uses—those uses that have been evaluated for safety and effectiveness.

Experimenting with an unapproved (off-label) use exposes patients to unknown risks, usually without their consent or knowledge. A few years ago, thousands of physicians prescribed Tambocor and Enkaid to treat patients

Taking Exception

with mild irregular heartbeats—an off-label use of a drug intended for life-threatening heart conditions. The doctors and drug companies hoped these drugs would prevent cardiac arrest. They were proven tragically wrong when a study funded by the National Institutes of Health discovered that the drugs frequently caused cardiac arrest in recent heart attack survivors. The death toll—measured in thousands—would have been even higher if the companies had been free to promote the drugs even more aggressively for this off-label use, as Frist advocates.

Frist also errs in suggesting that prohibiting sponsors from disseminating information about unapproved uses suppresses discussion or publication in journals of studies concerning off-label uses. In fact, the FDA's policy ensures that such discussion is objective and honest, untainted by the economic self-interest of a manufacturer seeking to expand its product's market. Under the FDA's recent draft policy statement, physicians are free to attend seminars on off-label uses and to publish and read articles on such uses. The product's manufacturer, however, cannot be involved in preparing, financing the dissemination of, or disseminating the material.

To permit written promotion of unapproved—including specifically disapproved—uses would be to pay mere lip-service to existing product-approval requirements and the clear intent of previous Congresses to protect the public from dangerous and unproven drugs and devices. Adoption of Frist's proposal would quickly halt much of the expensive clinical testing of unapproved uses needed to ensure safety. What corporation would invest millions of dollars in safety testing that might detect serious problems with its product when promotion for unapproved uses offers a faster, cheaper route to increased sales?

Finally, Frist states that a busy physician may not have time to seek out the latest information on all drug uses, apparently referring to unapproved drug uses. Yet he wants to relax the restrictions on off-label promotion because, he says, physicians should be trusted "to sort out" the information on unapproved uses. Senator, you cannot have it both ways. If physicians do not have time to seek out the latest information and are dependent on manufacturers sending them material on unapproved uses, manufacturers are likely to monopolize the information flow to physicians. Thus, these busy doctors will not see the complete story on the new use but only the information hand-picked by the manufacturers to increase their products' sales.

In short, the purpose of the approval processes is to prevent doctors and their patients from being misled by unproven health claims. No system of after-the-fact enforcement would be adequate to that task. When an unproven assertion of safety and effectiveness is made and relied on, the resulting injury is often irreparable. Our strong pre-market approval system is essential to protect our health and safety. The proposal Frist advocates threatens that system.

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The Washington Post

Next Round on the FDA

A DRUMBEAT continues for what's being called "reform" of the Food and Drug Administration. Sen. Nancy Kassebaum (R-Kan.) introduced a bill in December that would push the FDA toward what her spokesman characterizes as "creating a collaborative process" with drug companies and device manufacturers and tightening the deadlines on the process by which the agency certifies drugs as safe and effective. A group called Citizens for a Sound Economy released a spatter of radio ads. Characters representing the worried families of sick people engaged in mournful dialogues about how the FDA still hasn't approved "that new treatment" and how maybe "Congress needs to shake them up, too."

Though the players are new, this is yet another round of a long-running oscillation between the two dangers any government confronts in regulating drug safety: being too careful and not being careful enough. The most famous public health disaster from not-careful-enough drug regulation was, of course, thalidomide. It was followed by years of increasing caution and eventually a fair amount of bureaucratic slowdown at the FDA. This brought the agency under attack from AIDS activists in the 1980s and the vice presidential government-reinvention initiative in the 1990s.

Between them, these two attacks have caused the pendulum to swing a considerable way back. The

former sought and eventually got fast tracks for experimental drugs that, though they might be dangerous, offered hope to the dying. A General Accounting Office report last month certified that the FDA had all but eliminated its backlog and cut approval times by as much as half, in large measure because of a 1992 law that charged drug companies "user fees" to put more analysts on the case.

The restructuring bill seeks to push this process farther and faster and, in some cases, to remove the safeguards that make such speeded-up approval feasible. The Kassebaum bill proposes among other things to cut approval times sharply by bringing drug companies into the process, not merely of doing the experiments (they already do this) but of clearing and evaluating the results that are submitted to the agency for review. It also would lift restrictions on advertising for "off-label" or unapproved uses of drugs. Under current law, a doctor can prescribe a drug for any purpose, whether or not it's the purpose the FDA has tested and cleared, but the drug makers can advertise only where there is some evidence of effectiveness.

You can't do too much of this without careful attention to the safeguards that public health demands. Those weighing FDA "reform" should look carefully at the steps already taken before deciding whether to go farther down the path.

THE

"USA TODAY hopes to serve as a forum for better understanding and unity to help make the USA truly one nation."

—Allen H. Neuharth
Founder, Sept. 15, 1982



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Today's debate: REGULATING DRUGS

Rx for disaster: Peddling drugs for unapproved uses

OUR VIEW Easing regulation of prescription drugs isn't the lifesaver the drug merchants claim.

Hot on the heels of legislation recently introduced in Congress, the nation's \$55.5-billion pharmaceutical industry is angling behind every closed door it can find to ease controls on the marketing of prescription drugs. If it succeeds, more Americans will be mismedicated; more will suffer unforeseen side effects; and more will die.

Briefly, drug makers want the right to tell doctors about studies that support "off-label" use of their products — uses not approved by the Food and Drug Administration. Experience says such studies can be flawed. And such uses can be dangerous:

► Flecainide and encainide, two drugs approved for specific types of abnormal heartbeats, were routinely prescribed for other heart problems in the late 1980s — until follow-on research indicated that such use more than doubled the risk of death.

► Centoxin, a drug engineered to fight septic infection, had to be yanked off the market in Europe. The FDA decided that the first clinical trials were insufficient, and a second set found many more patient deaths than predicted.

► Clonidine, an adult high blood pressure medicine, was prescribed off-label more than 200,000 times in 1994 to treat children with attention deficit disorders. Now, research has uncovered severe side

effects and a handful of deaths.

Why risk more of the same?

Physicians are already free to prescribe for off-label uses; half the 2.1 billion prescriptions written each year are such. Within existing limits, most doctors can judge the benefits and risks of off-label uses.

But giving drug makers carte blanche to market their products for unapproved uses will swamp doctors with inadequate studies. Who should the public depend upon: the FDA and its objective mission to evaluate new drugs, or the companies that have wagered millions developing those drugs?

If drug companies can sell drugs based on studies of their choice, they have no reason to seek FDA approval for any use except the narrowest, easiest ones. That done, it would be simple to market the drug for another, more dangerous use.

Drug industry briefing papers say that "pharmaceutical companies ... are in the best position to provide current, scientifically accurate information about (their) products." Maybe, but that's a handy prescription itself — for conflict of interest.

The industry also says that seeking FDA approval for every use is time-consuming and costly. Reforms are in order, but off-label marketing doesn't repair the FDA; it just destroys the agency's quality controls.

There are many reasons why this idea, now in the formative stages in Congress, should be snuffed out. It undermines drug safety and endangers consumers. It also means lower costs for makers, who would spend less on trials and studies. But who do you think will pay *that* price?

THE LANCET

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EDITORIAL

In defence of the FDA

The US Food and Drug Administration (FDA) has a massive remit and is a huge organisation. It regulates 25 cents of every dollar spent by the American consumer, or about \$1 trillion worth of goods and services annually. To do that FDA employs over 9000 people and has a budget of \$1 billion. The agency's regulatory and enforcement successes are too much for the anti-government minions. For example, the speaker of the US House of Representatives, Newt Gingrich, has accused the FDA of "Stalinist" tactics and has called its commissioner, David Kessler, "a thug and a bully". Wrong.

Kessler has managed to speed a government bureaucracy in the right direction. The perennial complaint that new-drug approval takes too long is now outdated. Since passage of the Prescription Drug User Fee Act of 1992, median approval time for new drug applications has fallen from 27 months in 1992 to 19 months in 1994. Alendronate was approved in 6 months (see p 1028). For applications handled through the user fees process (not all are), the 1994 median was 13½ months. A backlog of nearly 700 drugs awaiting FDA action in 1992 has been cut to zero, right on schedule. And the improved performance extends to generic drugs, biological agents, and medical devices. An automated cervical-screening system was approved in just 7 months (see p 1029).

Not content with or perhaps frustrated by this impressive record, FDA critics have stooped to irresponsibility. One Congressman recently announced that "2888 Americans have died needlessly because the FDA took too long to approve the coronary stent". A conservative lobby group has bought newspaper space to proclaim "If a murderer kills you, it's homicide. If a drunk driver kills you, it's manslaughter. If the FDA kills you, it's just being cautious". The advertisement continues: "during the seven years it took to approve tacrine, thousands of Alzheimer's patients gradually lost their memories . . . 14 000 heart-attack victims so far have died who could have been saved by the cardiac-pump during the two years the FDA has delayed approval". *Lancet* readers will not have appreciated stents were uniformly successful, that

tacrine was a wonder drug, or that the pump was such a marvellous invention. And readers will have seen enough drug tragedies to have learned the need for caution. 56 drugs were withdrawn from US, UK, German, and French markets in 1970-92; only 9 were US withdrawals.

The FDA has also been accused of slowing the pace of drug development in the USA by prolonging the pre-approval stages of pharmaceutical research. However, everywhere such development is taking more time. World wide, the lag from synthesis to marketing of a new drug increased from an average of 8 years in the 1970s to at least 12 by 1990. Of the 44 new drugs approved by the FDA in 1993/94, 17 were marketed first in the USA. Among the other 27 were 13 whose applications were not even filed with the FDA until an average of 7 years after they were introduced in another country. Indeed, the greener grass claimed to be growing in Europe seems less fertile to those who do business there. European pharmaceutical and biotechnology companies are pouring money into the USA.

Perhaps FDA critics would be silenced if other public health agencies—such as the Centers for Disease Control and Prevention—took up the slack of enforcement. The reforms that the FDA is making are streamlining drug development and approval; some of the more punitive measures that the industry finds burdensome are being lifted; and restrictions on minor drug manufacturing changes that pose no threat to public health are being eased. An additional goal is to speed device approvals by implementing user fees. And the FDA's stand against allowing drug companies to promote "off label" use of their products—surely an invitation to dangerous drug marketing—is welcome too. Much work remains to be done. For example, the acceptance of placebo-controlled evidence in preference to comparator drug trial data is a serious flaw in the regulatory process. Yet the absurd proposal that FDA functions be privatised needs fierce resistance, lest public debate over what is prescribed for patients be governed in private by the profit-makers.

The Lancet

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EDITORIALS

FDA REFORM

Agency needs moderate, not massive, change

Nobody — nobody sane — wants to abolish the Food and Drug Administration. America's admirably safe food supply depends on the agency's work. It ensures the safety of billions of dollars' worth of cosmetics, medical devices, and human and veterinary medicines. Without the FDA, snake oil would sit alongside antihistamines and bactericides on pharmacy shelves.

Nobody, however, says the FDA can't improve. Pharmaceutical companies complain that FDA's drug approval process costs too much in time, money and frustration. Some patient advocacy groups concur. Bioengineers voice similar gripes about winning approval for new medical devices and biomaterials. Many in Congress yearn to overhaul the agency — including Speaker of the House Newt Gingrich, who has inaccurately labeled the FDA "the leading job-killer in America."

Congress shouldn't base reform on such false and misleading claims. Instead, lawmakers should study how medicine has changed in this century. They must encourage the FDA's internal attempt to streamline drug approvals. Last, reformers must acknowledge what FDA Commissioner David Kessler calls "the inherent tension" between the agency's intertwined goals: to

protect consumers against unsafe or useless products, and to make new medical technologies available as quickly as possible.

Here are some reforms Congress should support:

- Expand programs that allow patients access to conditionally approved drugs that appear effective against serious illnesses.
- Continue efforts to harmonize the drug approval process among members of the World Trade Organization.
- Relax some reporting and review requirements for slightly modified versions of previously approved drugs and devices.
- Create new and appropriate standards for judging the safety and efficacy of medical devices and, particularly, biomaterials.

Consider revising the large human clinical trial process for new drugs that have appeared safe and effective in earlier phases of lab, animal and human testing.

Congress should note: These are incremental changes, not attempts to gut the agency. Americans may not like bureaucracy, but they're not enthused about unsafe medicines either. Lawmakers must be careful that their "cures" for the FDA don't make Americans sick.



First of three parts

End of the line in sight for FDA?

The new Republican Congress is naturally antipathetic to the US Food and Drug Administration, but radical change will not be easily accomplished, which is just as well.

THERE are several reasons why the present US Congress distrusts the Food and Drug Administration. One is simple and ideological; the FDA is a bureaucracy, a device for administering government regulations (on the safety and efficacy of new medicines and medical equipment and on the quality of foodstuffs offered for sale). It is staffed by people who, of necessity, add nothing but their salaries and fringe benefits to the gross domestic product. Another reason is that the activities of the FDA most directly affect the pharmaceutical companies chafing at the delays between the development of new drugs and their arrival on the market. When the Congress returns from its summer break, there will be many who will have woken up to the fact that President Bill Clinton's new war against tobacco (see *Nature* 376, 539-540; 1995) relies crucially on FDA's willingness to classify tobacco as a harmful substance and nicotine as a cause of addiction. The grumbling about FDA in the first year of the new Congress will become louder in the second. Even now, there will be congressmen seeking to win a little publicity for themselves by preparing bills that would abolish the agency altogether.

The reality is that, as always, there is room for reform, but that abolition of FDA would compel the need to reinvent at least substantial parts of it. The contentious issues mostly arise from the procedures for licensing new drugs for sale, by prescription or otherwise. These are the procedures that require manufacturers to spend large sums of money on clinical trials to demonstrate both the safety and the efficacy of the drugs they seek to have licensed. The delays occasioned are in themselves expensive, and may also be held to affect adversely the health of those who might have benefited from them if early licensing had been allowed. Yet the inventor of a new kitchen gadget, or a cleaning fluid, is not required by the present law to demonstrate the safety and efficacy of his products in advance. If they should prove unsafe, those who suffer damage from them can pursue product liability suits in the courts. If they prove ineffectual, the market (aided no doubt by consumer organizations) will quickly recognize that much, whereupon sales will collapse. Why not follow the same principles for medicines?

Safety

Whatever the logic (and it is not strong), FDA's most severe critics must be aware that it would not carry

weight in the United States. One of the enduring legends of the nineteenth century is that of the snake-oil salesmen appearing regularly at country fairs, milking credulous audiences of their spare cash with promises of relief from this or that ailment. FDA is modern America's answer to those dubious characters. Or is part of an answer; the general craving for good health, longevity and even immortality has provided a rich market for those offering naturally occurring vitamins and natural oils of various kinds as recipes for continued health. The objection to letting modern synthetic medicines find their level in the market is that they do not enjoy the presumption of safety that applies to natural products, and that even the law of tort on product liability does not prevent suppliers from escaping their obligations behind the protection of the bankruptcy laws. In a country that specifies the safety equipment motor-car manufacturers must embody in their products, there is no political possibility that drug manufacturers would be freed from comparable restraints.

Efficacy

It is relevant, and even now important, that in the early 1960s Senator Estes Kefauver would have gone a substantial step further. In a seemingly endless series of congressional hearings, he set out to devise a way in which manufacturers would be discouraged from seeking licences for "Me-too!" drugs by requiring that the efficacy of a new drug should be demonstrated, in clinical trials, to be superior to others on the market. In the event, that goal would have been impracticable; even the most elaborate clinical trials are rarely so precise. But Kefauver was sustained in his long campaign by a groundswell of public opinion that is unlikely to have vanished in three decades. Even now, the opinion that the effectiveness of newly licensed medicines should be demonstrated in advance is likely to be widely shared by every congressman's electorate.

So is there nothing to be done to simplify the present procedures for licensing new drugs? As Republican luck will have it, the opposite is the truth. Everybody (FDA included) has learned a great deal from the special arrangements made five years ago for the licensing of drugs thought relevant to the treatment of AIDS; when no proven remedies are available, the seriousness of the condition to be treated must moderate the standards to

be satisfied by the proof of efficacy (as distinct from safety) required of a new drug.

Two other considerations arise. First, compounds offered as new medicines whose design is based on a testable physiological rationale deserve an inside track — a partial presumption of efficacy. That is already an important issue in biotechnology, where many of the compounds waiting in the wings for approval are synthetic versions of naturally occurring proteins, but the queue will become more clamant when more is known of the natural function of genes that, in mutated forms, are linked with important genetic diseases. If, for example, further study and understanding should suggest that there is a replacement therapy for Alzheimer's disease, what formal proof of efficacy would be considered necessary?

The second new opportunity is offered by means in which the design of clinical trials can be made less formal. 'Meta-analysis' is the slogan. The truth is that once the safety of a proposed new medicine has been established, an assessment of its effectiveness can be reached by the careful gathering of data in its tentative use. The outcome is neither as clean nor as decisive as that from a regular clinical trial, but none the less useful on that account. A few exercises of this kind might enable FDA (and similar organizations elsewhere) further to speed up the approval of new drugs. The difficulty, for the radical wing in the US Congress, is that neither of these opportunities can be enshrined in new legislation, but must be decided by a technically expert organization — one like FDA, for example. □

Care in the community

There will be no quick answer to the British government's call for better care for the psychiatrically ill.

THE British government's Department of Health has woken up to a scandal that has been simmering away for the past four years — the plain truth that its humane programme for moving people with chronic psychiatric illness from long-stay hospitals into the community at large is not working as intended. Last week, in the wake of two critical reports by differently constituted teams of inspectors, the minister at the department, Mr Gerald Malone, wrote to Britain's hospital trusts urging them to do better. He is right to ask. Whether he or his successors will be satisfied with the response is another matter.

That the policy of community care is enlightened is beyond dispute. In the bad old days, institutionalization was a disease in its own right, but in the absence of palliatives of psychiatric illness, also a necessity of a kind. Now that manic depression and clinical depression are reasonably well dealt with by means of drugs, and even schizophrenia is controlled by the phenothiazines and their derivatives, it makes good sense that those affected should live in circumstances comparable with those that others of their age enjoy. For any government, community care also

offers potentially huge economic benefits; even psychiatric hospitals are expensive to staff and run, while circumstances usually dictate that they should be a public expense. So there is nothing wrong with the ambition that most of those suffering from psychiatric illness should live in the community rather than in hospitals. The difficulties lie in the way in which the policy is carried out.

When the British version of these arrangements was decreed in 1990, it was intended that health authorities and the social services departments of local authorities should devise a joint plan for dealing with the community care of psychiatric patients in their areas. The hope was that there would also be plans for individual patients, offering them programmes of health care, social support and even occupational activity. Last week's report of the Department of Health's own Social Services inspectorate is based on five local-authority social services departments; it says that only one of the five departments had drawn up such a plan, and that even that had been in place for just over a year.

Shameful though that may seem, it is not surprising (nor at odds with anecdotal evidence emerging in the past few years). The Health Service has been in the throes of huge administrative upheaval and is no position to seek out extra work to do, while even those local authorities with expertise in, say, the care of the elderly have not known enough to anticipate the needs of the psychiatrically ill. And among those, it is plain the people with schizophrenia habitually draw the short straw; the Department of Health's Clinical Standards Group (which acts as a kind of auditor of clinical standards) based a detailed survey of the treatment of schizophrenia in eleven health-service administrative units; none was found to be unequivocally "good", although four approached that ranking. Others were frankly "poor" in the quality of the care they provided for schizophrenia.

Extenuating circumstances abound. The administrative changes of the past few years have not helped. The attention paid to the needs of psychiatric patients as distinct from other claimants on public services almost inevitably depends on the fuss that individuals make. And psychiatric illness is still in many places a tainted kind of disability. But the real difficulty is the lack of adequately trained people able and willing to work peripatetically, as community care requires. Sadly, for the psychiatrically ill, that deficiency will not be quickly remedied. When they are found in sufficient numbers, they will turn out to be expensive. Then the government will be wondering whether it can afford the extra cost, and its critics will be saying that it cannot afford not to afford it. That is at least a tangible difficulty. The less tangible, and therefore the less easily remediable, is the persisting suspicion of psychiatric illness even in enlightened administrations such as the British. People with schizophrenia, who are notoriously awkward customers, are especially likely to be short-changed. But wishing that they would go away will serve no purpose. The lifetime suicide rate may be 15 per cent, but numbers are constantly renewed. □

ONCE OVER

No, the FDA is not killing people

In the early 1960s, an alert scientist at the U.S. Food and Drug Administration kept the sleeping pill thalidomide off the market in the U.S. That protected untold numbers of children from being born deformed in this country. Several thousand European children weren't as lucky.

Since then, the FDA has enjoyed a public profile as a stalwart guardian of public health and a scourge of quacks and profiteers. That is, until the past few months.

The FDA is being attacked by politicians and by foundations with funding from drug companies. They include the Washington Legal Foundation, the Progress and Freedom Foundation, the Competitive Enterprise Institute, and Citizens for a Sound Economy. Such organizations accuse the FDA of menacing Americans' lives and health by tying up beneficial treatments in interminable red tape.

The most lurid charges have come in ads from the Washington Legal Foundation. Next to images of coffins and tombstones,

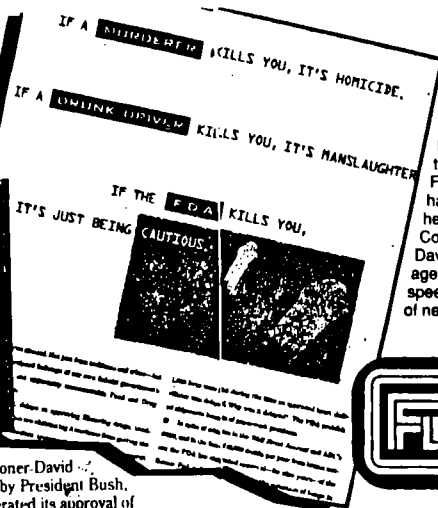
the ads say: "If a murderer kills you, it's homicide. . . . If the FDA kills you, it's just being cautious. . . . The problem with health care in America is the FDA."

The solution, suggests the Progress and Freedom Foundation, formed by close political associates of House Speaker Newt Gingrich, is to turn most of the FDA's work over to private firms. But we have yet to see any proposal that makes clear how those companies would be held accountable and free of conflicts of interest. Some advocates would even let manufacturers sell any drugs they want, leaving customers to sue doctors or manufacturers if the drugs did harm. (At the same time, some in Congress have long wanted to make it tougher to file such suits.)

The FDA, spending \$900-million a year, is a powerful agency with an awesome responsibility. And it was infamous not long ago for taking years to decide whether products got to market. But the bashing it's now getting isn't justified.



Under Commissioner David Kessler, appointed by President Bush, the FDA has accelerated its approval of genuine breakthrough drugs. Last year, 17 of the 22 drugs it approved were these "priority" compounds. For 10 of those drugs, processed under a new user-fee system, the average approval time was cut in half; to less than a year. The agency also fares well in international comparisons. Last year, of the world's dozen new drugs considered the most



Attack ads: Recent ads like this suggest the FDA's red tape is hazardous to your health. But under Commissioner David Kessler, the agency has actually speeded up approval of new drugs.

notable therapeutic advances, five were first introduced in the U.S., compared with three in Japan and no more than one in any other country.

The FDA also seems effective at keeping unsafe drugs off the market. Public Citizen's Health Research Group recently studied the 56 drugs withdrawn from the

market in the U.S., England, France, and Germany since 1970 because of safety problems. Only nine had made it onto the market in the U.S., compared with 23 in England, 30 in Germany, and 31 in France.

The FDA's review procedures have revealed time and again that not every promising therapy turns out to work or to be safe. The Washington Legal Foundation's ads claim that people died because specific drugs or medical devices were trapped too long in the review process. Those assertions are misleading.

The foundation claims that "the lives of more than 150,000 heart attack victims may have been saved" if the agency had been faster to approve TPA, a drug that dissolves blood clots. In fact, another, almost equally effective drug, streptokinase, was already on the market before the FDA even started reviewing TPA. Any doctor or hospital was free to use it.

The ad complains that the FDA has "obstructed" approval of the Sensor Pad, a silicon-filled plastic pad that supposedly helps women feel breast lumps, while the product was released for sale in Canada "in less than 60 days." In fact, the FDA kept the product off the market because its manufacturer was unable or unwilling

to do tests to show the pad worked as claimed. Last year, Canadian officials asked for the same information the FDA had sought. They couldn't get it either, and ordered the Sensor Pad off the market.

One gripe with some validity is that the FDA stopped tests of a portable heart resuscitation pump because test subjects—people who collapsed suddenly of massive heart attacks—couldn't, for obvious reasons, give "informed consent" to participate. The agency has belatedly promised new regulations to permit experimentation with resuscitation drugs and equipment.

Those organizing the assault on the FDA insist their motives are philosophical, based on a belief that such government regulation is wrong. But the anti-FDA groups are getting money from drug and medical-device companies that could profit from deregulation. These companies include Burroughs Wellcome, Eli Lilly, Genzyme, Glaxo, Johnson & Johnson, Pfizer, Searle, Siemens, and Solvay. The companies we contacted refused to endorse any of the specific proposals being floated, but said they are interested in hearing the groups' ideas. One company, Merck, has said it opposes dismantling the FDA.

CO detectors: Are some too sensitive?

Carbon monoxide detectors are essential safety devices in any household with oil or gas heat, a woodstove, or a gas range. But they may sometimes do their job too well, sounding off when exposed to low levels of the colorless, odorless gas.

To mitigate problems that have been blamed on ultra-sensitive detectors or improper installation, Underwriters Laboratories has proposed some significant changes to the standards governing the way the devices work. The changes, due to take effect next October, would require:

1. Detectors to withstand exposure to 15 parts per million of CO for at least 30 days without alarming. The current standard tests only eight hours' exposure.

2. A Hush or Reset button on all new detectors to temporarily quiet the alarm. Most AC-powered detectors already have that feature.

3. More-detailed instructions, urging people who have no symptoms of CO poisoning to immediately contact a qualified technician when the alarm goes off. Manufacturers currently advise people to call the fire department.

Nuisance alarms made headlines last winter in Chicago, the only major municipality that requires a CO detector in most dwellings. Alarms sounded thousands of times—most at benign levels of gas. The worst outbreak occurred during 48 hours in December, when

officials officials responded to some 2300 calls during a temperature inversion—a freak weather pattern in which atmospheric conditions trap pollutants from vehicle exhausts and other sources.

City officials voiced particular concern over the sensitivity of *First Alert* detectors. The Chicago Department of Consumer Affairs says the sensor in *First Alert* detectors is prone to CO buildup over time, which could cause the alarm to react to even low levels of the gas.

First Alert detectors do meet the UL standard. The company acknowledges that the detectors use a very sensitive sensor. But they say that isn't necessarily a drawback, since it provides the maximum level of protection.

Our tests last year—and those for a July report—have shown *First Alert* detectors to be somewhat slow to respond. But once they do, they need several hours to recover after the air clears. Other detectors—including the *American Sensors COS-200* we top-rated last year—clear themselves in a matter of minutes.

First Alert attributed the high incidence of alarms to several factors, including poorly maintained furnaces and appliances, blocked or damaged chimneys and flues, and detectors placed too close to a range or furnace.

As a goodwill gesture, *First Alert* offered refunds until January 31 to Chicago-area residents who were unhappy with their purchase.

CU needs a video engineer

We have an opening in our electronics department for an experienced video engineer. The person we hire must have at least a bachelor's degree in electrical engineering, with 10 or more years of experience in consumer-electronics engineering and testing, primarily in television and video. Applicants must have strong written and verbal skills and be proficient in the use of computers for test-data acquisition and analysis. A hobby background in electronics is desirable.

The salary will be commensurate with experience; CU also offers an excellent benefits package.

To apply, please send a detailed résumé and salary requirements to: Consumers Union, Box HC, 101 Truman Ave., Yonkers, N.Y. 10703. Consumers Union is an equal-opportunity employer.

Benefactors & Lifetime Members

Every few months in this space, we acknowledge our Benefactors & Lifetime Members, individuals whose generosity helps make CU's work possible.

Our newest Benefactors are: Charles Bailey, Conn. Gladys H. Cervoni, Fla. F. W. Higgins, Pa. Ray J. Schmitz, Ill. Harold A. Tower, Ariz. William S. Warfield, IV, Mont. Stephen D. Weinroth, N.Y. Nadine H. Wray, N.Y. In addition, eight Benefactors wish to remain anonymous.

Our newest Lifetime Members are: James Acri, Pa. Henry S. Adanick, Mo. Paul E. & Sherrill Allen, Calif. Brenda & David Anderson, Calif. Diana B. Anderson, Wisc. Dwan D. Applegate, N.J. Mr. & Mrs. James D. Aspaugh, Colo.

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Dismantled FDA: A bitter pill we shouldn't swallow

In the war against excessive federal regulations, the most intense battle is being fought over the rigorous reviews by the Food and Drug Administration.

FDA regulations hit close to home, covering the processed food, drugs and cosmetics we buy every day. Because U.S. standards are the world's highest, we have the safest food and drugs on the planet.

The effort to streamline drug approvals is led by conservatives who consider the FDA an enemy of free markets. They want to curtail its powers or have it privatized and contract the review work to research companies.

"Every year, tens of thousands of Americans die while the FDA delays approval of drugs readily available in Europe," says Citizens for a Sound Economy, a conservative think tank.

At a congressional hearing this week, Republican Rep. Jack Kingston of Georgia said the FDA does more to impede medical progress than to protect public health.

"You don't have a can-do attitude, you have a can't-do attitude," he said, addressing

FDA Commissioner David Kessler.

That remark hit a nerve.

"You don't think I want to get devices that are important to save lives out there? Who do you think works at the FDA — (we are) real physicians who have lost real patients," Kessler replied.

The agency says its average drug approval in 1994 took 19 months — a 21 percent



STEVE WILSON

Republic Columnist

improvement over the previous year.

Critics consider that statistic misleading. Drug companies say it takes up to 12 years and \$400 million to bring new drugs from the laboratory to the market.

I have no trouble believing that the FDA's 9,300 employees could work more efficiently. Many of its rules are decades old and ill-suited to today's biotechnology. I imagine approvals could be speeded up without significant risk.

But anyone who wants to gut the agency or grease the review skids ought to read a chilling new book, *Deadly Medicine*, by Thomas Moore, a health-policy researcher at George Washington University.

The book tells the story of a medication called Tambocor, which came on the market in 1985 as a treatment for arrhythmia (irregular heartbeat).

The FDA studied the drug for 34 months before approving it. Moore says the agency initially decided to give approval only for patients with life-threatening arrhythmia.

But its manufacturer, 3M Co., persuaded the FDA to permit its use for a much larger

range of heart patients, Moore claims.

He says Tambocor and similar drugs produced "America's worst medical disaster," accounting for some 50,000 deaths. Instead of suppressing irregular heartbeat and preventing heart attacks, the drugs sometimes produced fatal heart attacks, he writes.

While the extrapolated death toll is disputed, there's no question that the drug caused many cases of cardiac arrest.

Moore believes additional testing could have prevented most of the deaths, a view supported by a National Institutes of Health study in 1989. Six percent of patients who took the drug for more than a year died, a rate 250 percent higher than a control group taking a placebo. FDA approval for Tambocor was narrowed in response to that study.

Moore argues that the Tambocor experience shows that, despite the FDA's elaborate review process, the system is still biased in favor of getting new drugs to market, since all parties — manufacturers, doctors and patients — are eager to reap the benefits.

As Congress debates whether to bust up the FDA, it might also think about another medicine with unforeseen effects: thalidomide.

That drug, a sedative developed in Europe and rushed into experimental use in America, caused severe birth defects and some deaths when taken by women during pregnancy. As a result of those 1960s tragedies, the FDA received more regulatory teeth.

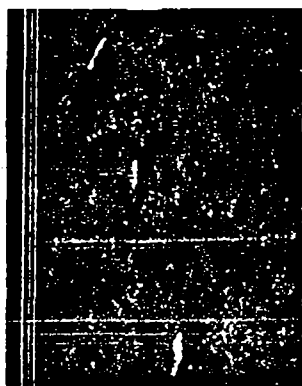
I'm sure the pharmaceutical industry has valid complaints about the FDA bureaucracy. We're not well-served when excess caution keeps lifesaving medicine out of reach.

But as more-powerful drugs with more-potent side effects are being developed, and as all facets of health care become more dollar-driven, the need for safety assurance today seems greater than ever.

Drug companies don't want to sell harmful products, but neither do they want to see a competitor beat them to market.

The FDA's job is to check their homework and at times put on the brakes. The agency can be fine-tuned without being dismantled.

Can the "Grinch" steal the FDA?



Alvin P. Shapiro, M.D.

At the University of Pittsburgh School of Medicine in 1960, we started a program in clinical pharmacology in the department of medicine, at the urging of Jack Myers and with the generous support of a training grant from The National Institutes of Health (NIH). The discipline of clinical pharmacology was then in its infancy but rapidly expanded due to an "explosion" of new therapies developed in the ensuing decade, many of them related to my own major clinical and research interests, namely the diagnosis and treatment of hypertension. Together with Dr. Robert McDonald we conducted the program for about 20 years, teaching medical students and residents the principles of drug evaluation; the appropriate use of potent medications; and the pathopharmacology of side effects and drug interactions. We also trained 18 fellows who either went on to academic pursuits or to practice in broad areas of internal medicine.

Among our tasks in clinical pharmacology was understanding the work of the Food and Drug Administration (FDA), the federal agency charged since 1906 with the regulation of new drugs coming on the market. The purpose of the FDA is to protect consumers from quackery and "therapeutic misadventures" and to guide healthcare providers in prescribing medications. Originally it dealt only with interstate transfers of mislabeled drugs and adulterated foods, but in 1938, federal regulations requiring demonstrations of safety of new drugs were enacted after a disaster involved with a toxic preparation of sulfonamide. In 1962, the Kefauver-Harris amendments were added, which additionally required evidence of efficacy—a not unreasonable request!

The process of drug acceptance is now well-outlined and does indeed take some time, perhaps several years, but occasionally longer from "bench to bedside" as the drug undergoes: *animal testing*; *Phase I* trials in man, usually normal volunteers, to determine biological activity and metabolism; *Phase II* trials in selected patients to determine dosage

range and duration; and *Phase III* trials to compare efficacy to known drugs and/or placebos in a controlled, often "double blind," fashion. If these phases establish safety and efficacy (the latter not necessarily better than

The FDA is not a political issue but a medical necessity . . . we must as physicians oppose Newt on this question.

an older drug) it can be released, but as it is broadly used, the drug may now become subject to a *Phase IV* surveillance, and the FDA can then order its withdrawal if new problems appear.

These regulations are now well known to pharmaceutical companies who by and

large deal with them honestly and cooperatively, although with some grumbling about the time and expense involved. Occasionally, consumers fret about delays, most recently concerning drugs to treat AIDS. But the basic reason for the regulations are to protect the consumer and guard against extravagant and sometimes fraudulent claims about new "wonder drugs."

All of which leaves me, as a clinical pharmacologist, an internist, and a citizen, rather aghast at the pronouncements of Newt Gingrich that the authority of the FDA should be eliminated or "privatized" because its activities are expensive and result in "restraint of trade."¹⁻⁴ I do not sympathize with many of Newt's suggestions to "downsize," but I am particularly distraught by his attack on the FDA, which has a long history of protection of the public (e.g. the prevention of thalidomide use in the U.S.). After all, Newt is a historian and should know the background of the laws and the chaos which existed prior to their passage.

Under the leadership of Dr. David Kessler (originally a Republican appointee), the agency has upgraded itself further in recent years and made itself more visible, and hence perhaps more subject to attack by what must be a powerful drug company lobby; I do not think Newt has come to this on his own. The FDA is not a political issue but a medical necessity. If we are to continue the high standards of drug development in the U.S., we must as physicians oppose Newt on this question.

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Needed nitpicking

Before the drug industry emasculates the FDA
remember the Thalidomide babies

By FRANK H. BOEHM, M.D.

RECENTLY certain members of Congress have become concerned that the Food and Drug Administration (FDA) inhibits job growth by being overly strict on releasing certain drugs and technical devices to the public.



BOEHM

As a result, these members of Congress are trying to eliminate the FDA and replace it with an industry-dominated agency. Because of this, I feel compelled to tell an old but well known story.

It was 1960, and the FDA had received an application to market in this country a tranquilizer called Thalidomide. Believed by many to be a miracle drug, Thalidomide not only induced sleep but also had no known side effects. It was a very popular drug in Europe and Great Britain, and its manufacturers, the William B. Merrill Co., wanted the drug approved for sale in the United States. There was one small problem. Dr. Frances Kelsey, a newly hired employee of the FDA and an expert in the science of drugs, was given the application. Dr. Kelsey was not intimidated by Merrill's demand to speed things up, and she certainly was no pushover.

By law, Dr. Kelsey had only 60 days to study the Thalidomide application and render an opinion. Only if additional information was needed could that time frame be extended. Dr. Kelsey was concerned by the fact that, while Thalidomide induced sleep in humans, it did not do so in animals. Perhaps there were similar differences in animals and humans, and therefore the fact that no birth defects were noted in animals did not reassure her.

Dr. Kelsey was also concerned about a letter written to a British medical journal in which a physician noted inflammation of the nerves of fingers in individuals who had taken Thalidomide for an extended period of time. She wanted more information from Merrill about similar possible fetal effects. The Merrill Co. executives were not happy.

As later revealed, unbeknownst to the general medical profession, in 1959, 12 grossly deformed babies were born throughout Germany. This malformation was called phocomelia, a condition in which babies are born without arms or legs. At the time, no connection, however, was made between this

extremely rare birth defect and any drug usage.

Meanwhile, West German clinics recognized that 83 cases of phocomelia had been reported by the end of 1960. The connection between Thalidomide and phocomelia was finally made by a West German pediatrician who noted that 50% of mothers interviewed who delivered babies with this birth defect remembered that they had taken Thalidomide early in their pregnancy.

Physicians from Australia and Scotland quickly confirmed this correlation and suddenly the William B. Merrill Co. notified the FDA that they were withdrawing their Thalidomide application.

Unfortunately, considerable damage had already been done. Because of Thalidomide, 10,000 deformed babies were born throughout Europe. Fortunately, because of a "bureaucratic nitpicker" (as Morton Mintz of *The Washington Post* referred to Dr. Frances Kelsey), babies born in the United States were spared such horrors. For her work, President Kennedy gave Dr. Kelsey a Distinguished Federal Civilian Service

Award in 1962.

Since those Thalidomide days, the FDA has demanded considerable proof of safety as well as efficacy before releasing drugs and medical devices to the public. Because of these stringent rules and regulations outlined by the FDA, less drugs are withdrawn from the market in the United States because of serious previously undetected side effects than in comparable countries such as France, Germany and the United Kingdom.

Of 56 drugs withdrawn from the market in these countries between the years 1970 and 1992, 31 were withdrawn in France, 30 in Germany, 23 in the United Kingdom and only nine in the United States. This should indicate to our politicians that the FDA is doing its job in keeping more unsafe drugs from reaching the public than other similar industrialized countries. It should also reassure all of us that the FDA is doing its job well.

Go ahead Congress, reform medical care. We need it. And while you're at it, reform and simplify some of the FDA's truly burdensome regulations. But for all our sakes, let the FDA and its employees like Dr. Kelsey continue doing what they have always done best — protecting Americans! ■

(Boehm is professor and director of maternal/fetal medicine at Vanderbilt University Medical Center, and chairman of its ethics committee.)

Critics of FDA Are Out of Line

Public health is a national interest. The American people deserve the oversight of an agency such as the Food and Drug Administration.

Yet, listening to those who challenge the way the FDA operates and even its necessity, a careless person might believe the FDA is paternalistic, bad for business—and dangerous.

While there is always room for improvement—which the FDA contends it has been doing—FDA critics are themselves overzealous and, in some cases, self-serving.

The critics include an unlikely coalition of AIDS activists, Republican-linked think tanks and public policy groups such as the Washington Legal Foundation and Newt Gingrich's Progress and Freedom Foundation. They charge the FDA is overcautious in approving life-saving drugs and medical devices and that delays have cost lives. They claim the process is swifter in other nations and, thereby, better for patients and the pharmaceutical industry.

True, there have been approval delays. But charges of deaths as a result are often hyperbole and in some cases, misrepresentation.

As the new forces in Washington tighten their grip on a smaller, less-restrictive vision of government, the FDA is a natural target because of its broad involvement in many health areas. However, drugs and devices must be judged for effectiveness, not merely harmlessness, as some attackers suggest. And yes, the process ought to be speeded up, not simply for savings to business but to further help those who may benefit from new medications.

Yet the FDA must not be dissuaded from its invaluable role against fraud, quackery and outlandish claims. We have the right to expect our government to act in the best interests in the health of its people, not just in the best interests of business.

The new forces in Washington must be cautious about dismantling or emasculating the agency, at least as long it continues its own efforts to face new challenges successfully.

Gingrich & Co.'s attack on the FDA can make anybody sick

One of the more preposterous and yet revealing proposals to surface in the still-evolving Gingrich manifesto is one that would greatly alter if not eliminate the federal Food and Drug Administration (FDA).

The FDA, among many other duties, has the responsibility of assuring the safety and effectiveness of the vast array of prescription drugs used in the United States. To ensure, for example, that there will not be an incidence in this country of the terrible experience in Europe that resulted from use of Thalidomide, the FDA requires exhaustive laboratory and animal studies before any new drug may enter the U.S. market.

This insistence on rigorous research consumes time — to which many pharmaceutical firms and patients object. The drug houses say that because of the delay they are losing money, while patients fear they are losing a cure.

It was the kind of complaint from a constituent which first got Rep. Newt Gingrich interested in challenging the FDA. As spelled

out in two separate reports by two separate reporters for the Wall Street Journal in late January, his involvement says much about its inspiration.

In the summer of 1993, according to these reports, Gingrich introduced legislation designed to suspend duties on several drug components imported by Solvey Pharmaceuticals, Inc., which is headquartered in Gingrich's home district. Shortly thereafter, the company was approached by the president of the Progress and Freedom Foundation for a contribution. About six months later, Solvey gave \$30,000 to the Foundation.

The Foundation president had been executive director of Ging-



rich's political action committee, Gopac. The Foundation is described as a conservative think tank created by Gingrich associates; its major functions are sponsorship of his nationally televised classroom lectures and the separate National Empowerment Television talk show.

The Wall Street Journal reports claim that a consequence of the Solvey contribution, and a host of similar contributions from other major pharmaceutical firms, is that the Foundation now also has the large task of preparing proposals to revamp or replace the FDA.

Gingrich's early explanation of why the FDA should be eliminated or radically changed was that its work should be taken away from "bureaucrats" who were wasting time and put into the hands of industry, which knew how to get things done.

What that proposal chooses to ignore is that once upon a time the responsibility belonged wholly to the private entrepreneur. Government stepped in only when it became evident that those creat-

ing products for profit, too easily measured their product only in terms of profit and not in terms of safety or effectiveness for the consumer. Too many worthless, even harmful products were marketed. Although business prospered, consumers suffered.

Moreover, human nature being what it is, there is every reason to expect that if nearly a century of

protection by the FDA was terminated, the old practices would be quickly resumed. In just the last decade, a leading American manufacturer of baby food discovered a production error and was only narrowly prevented from marketing bottles labeled "apple juice," but which contained only sugared water. Some in the company protested that "It wouldn't hurt anyone," but would cost the firm millions to correct.

In this era when the bottom line has become the sole measurement of the success of a business administration — and a cost-benefit limitation would be placed on regulation — consumer protection would vanish virtually overnight.

This prospect fits neatly into columnist George Will's defense of "Engine" Charlie Wilson's declaration of forty years ago that "What's good for General Motors, is good for the country." Under that definition, the business came first while the country and its people became an after-thought — a "trickle-down" relationship. The sole criteria for any program's worth would be the volume of profit it allows.

While it may be revealing to some how rewarding it can be to "take care" of a constituent in this "new" Washington scene, most people will realize they've heard this song before.

Most people are consumers — and even his most indiscriminate supporters must wonder if they really want to lose their protections just so Gingrich & Co. can enjoy those "rewards."

No creation of man is perfect, and all of them can profit from honest periodic reexamination. If done in this case, it seems a sure bet that more would be found in the Food and Drug Administration to praise than to change.

In this case, however, the agency is damned in advance.

Tom Bigler is professor of communications at Wilkes University and a Times Leader columnist. His column appears on Sundays and Wednesdays.

February 15, 1995

THE REGISTER'S EDITORIALS

Don't hamstring the FDA

**It's all that protects the public
from snake-oil peddlers, and worse.**

It has been more than 30 years since the thalidomide disaster. Drug manufacturers assume it's a safe bet that America has forgotten. As a result, some of them and their allies in Congress, including House Speaker Newt Gingrich, think it's time once again to try to destroy the U.S. Food and Drug Administration.

The FDA is all that protects the public from the peddlers of snake oil and worse. In the 1960s, a single FDA official — Dr. Frances Kelsey — blocked a catastrophe. She refused to license U.S. sales of thalidomide, a tranquilizer formulated in Germany and intended for use by women in early pregnancy to combat nausea and insomnia. The drug, Kelsey argued, had not been adequately checked for side effects.

Those effects were finally noted — too late. Thousands of babies, including 5,000 in Germany alone, were born with gross deformities. Some lacked arms or legs.

While Kelsey kept thalidomide off the shelves of American drugstores, trial samples were sent to 1,800 U.S. doctors in 50 states. Results for American children were tragic.

Pharmaceutical manufacturers argue that that single instance has been the FDA's excuse for being far too cautious, withholding new drugs from the market for years during testing. They have a point. As one observer noted, caution will be rewarded far more often than haste.

Delay is costly to the manufacturers, because the 17-year patent life of a drug is ticking away while it awaits clearance.

Congress recognized that long ago, adopting "patent restoration" legislation that puts years back on the clock to compensate for time lost to the approval process.

While the drug makers go through their poverty routine, Forbes Magazine's 1995 "Annual Report on American Industry" shows drug making to be the most profitable arm of the health industry, which in turn leads the field of 21 industrial groups in profitability over the past five years. Return on equity for drugs over the five-year span was a whopping 22.8 percent.

They'd show greater profits yet, of course, if their congressional allies succeed in emasculating the FDA.

Still, the manufacturers have a point: The quicker a worthwhile new product gets to market, the quicker the afflicted can benefit. Thus, the approval process should be handled as speedily as possible, giving priority to true "breakthrough" drugs and drugs developed to combat burgeoning epidemics. That argues for a stronger, better staffed and more efficient FDA. But the industry and its allies argue instead for dismantling it.

The campaigners are spending millions and their tactics are crude — likening the FDA to murderers for delaying new drug approval.

"These are inflammatory campaigns meant to terrify people," said Sidney Wolfe of the advocacy group Public Citizen. And if the campaign succeeds, consumers will have reason to be terrified.

Taking apart the FDA

One could guess merely from reading his donor list that House Speaker Newt Gingrich would turn out to be an enemy of the Food and Drug Administration.

In 1993-'94, Gingrich introduced three separate bills to suspend duties on chemicals used by a drug company that gave his think tank \$30,000. He also went to

EDITORIALS

characterized the head of the FDA as "a thug." He also has called for a new agency to regulate drugs, one that would give faster approval with less testing and monitoring.

Gingrich is joined by a number of new right groups who are taking out ads urging the evisceration of the agency.

Their tone is similar to an ad by the Washington Legal Foundation which says: "If a murderer kills you, it's homicide. If a drunk driver kills you, it's manslaughter. If the FDA kills you, it's just being cautious."

Whew. That's high-octane rhetoric. But if FDA inaction can be worrisome, an FDA that allows dangerous drugs on the market is much scarier. Even though a weak FDA would allow fast profits for a few drug companies, it could damage the market for new drugs in the long run.

Most consumers take drug safety for granted in the current regulatory climate.

In a deregulated market, however, customers would resist new drugs because they would not have confidence in their safety. The result would make new drug discoveries a hard sell.

Chances are Gingrich's new-style toothless FDA would last only until the next time a drug with dangerous side-effects is released.

But why should we allow that to happen?

The FDA could stand procedural reforms and regulatory streamlining, but it's doing a generally good job of keeping dangerous products with misleading claims off drugstore shelves.

The U.S. Food and Drug Administration should not be taken apart because a few special interests are giving big money to Newt Inc.

"WE DON'T WANT ANYONE INTERFERING WITH OUR SALES"



4A — THE NEWS-JOURNAL Tuesday, February 14, 1995

bat for the company before the FDA. Gingrich has dismissed the connection as mere constituent service for a company with headquarters in his district.

But that isn't all. Another drug company donated \$41,690 to the Gingrich-controlled GOPAC, or GOP Political Action Committee. Pharmaceutical companies have poured hundreds of thousands of dollars into GOPAC.

Not surprisingly, the speaker and his allies have talked about weakening and dismantling the FDA. Gingrich has

EDITORIALS

Hard to swallow

For a disturbing example of what special-interest money can buy in Washington, look no further than the growing effort to dismantle the Food and Drug Administration. An unholy alliance of irresponsible drug companies and ultraconservative political organizations is bankrolling a congressional effort to gut the FDA's regulatory powers. If that effort succeeds, millions of Americans will no longer have any real reason for confidence in the safety or effectiveness of the prescription drugs, food additives, nutritional supplements and other products they consume.

Drug companies often are frustrated by the time it takes the FDA to test and approve new drugs that hold the promise for great medical breakthroughs — and great profits. But it is irresponsible to suggest, as some interest groups are now, that Americans would be better served if the FDA was abolished or neutered.

The FDA often is the only government agency standing in the way of distribution of a dangerous or ineffective drug. To take just one horrific example, when the tranquilizer Thalidomide went on the market in Britain in the 1960s without adequate review, pregnant women who used it gave birth to terribly deformed babies. Our government's stricter review process kept Thalidomide out of the American market. Those now advocating the dismantling of the FDA should explain how American consumers would be protected from the next Thalidomide if the practical testing of drugs were left to the marketplace.

The FDA is a prime candidate for constructive reform. It has been slow to adopt

new rules to streamline the testing of drugs to treat AIDS, some kinds of cancer and other terminal illnesses. The agency also has developed a habit of embroiling itself in issues that have more to do with social policy than protection of the nation's health.

Despite those problems, the FDA's responsible critics acknowledge that it would be a terrible mistake to abolish the agency's central regulatory functions. "The tenets FDA enforces, and we live by, ought to remain in place," Dr. Eve Slater, head of regulatory affairs for the drug giant Merck & Co., told the *New York Times*. She supports managerial reforms at FDA but defends the agency's mission.

But some drug-industry interests have a more radical agenda, and they have contributed heavily to members of Congress who are willing to target the FDA as part of a broader effort to deregulate big business. And those same companies are also pushing for legislation that would serve to insulate them from large damages in future lawsuits. If those unscrupulous interests have their way, the victims of future drug scandals will be unable to receive fair compensation in court.

The attack on the FDA is being sold as a populist crusade, but it is anything but. This is a scheme to make a few rich drug companies even richer — even if it means jeopardizing the health of millions of Americans.

Before you swallow this anti-government line, remember how much you take the FDA's work for granted every time you swallow a prescription drug.

EDITORIALS

Dangerous Schemes To Overhaul the FDA

THE ZEAL FOR reduced government has turned reckless with sudden serious discussion in Washington of proposals to weaken or abolish the federal Food and Drug Administration.

For years, drug industry representatives have broached the idea of removing power from the FDA, the agency charged with overseeing the safety and effectiveness of

drugs, medical devices and food. They charge that lives — and profits — have been lost because of the lengthy amount of time it takes to get products approved.

In the past, Congress has wisely ignored the call to undermine the agency, mindful that the FDA —

or even dismantle the agency are suddenly being taken seriously.

The Health Industry Manufacturers Association — which represents the medical-device industry — is circulating a proposal to "semi-privatize" the FDA by creating government-certified approval boards.

The Gingrich-affiliated Progress and Freedom Foundation, which has received hefty contributions from pharmaceutical companies, is writing a study on how to turn over many FDA functions to private industry, an obvious conflict of interest that would rob the process of supervision over life-and-death products of its independence and eliminate current FDA prohibitions against interested parties being involved in the regulation process.

Worse still, the Competitive Enterprise Institute, whose representatives testified before a House appropriations subcommittee last week seeking a cut in the FDA budget, wants to allow companies to market products without FDA approval. It would be up to doctors and patients to decide the risk.

FDA officials admit that the approval process was due for reform and that there is need to speed it up. But they have reacted to that need. Last year, they report, overall drug approval was faster by 21 percent and approval of drugs containing active substances never marketed in the United States was speedier by almost 50 percent. But they are right to insist that public safety must always be their prime concern.

Improvement is one thing. An overreaction that threatens the health and safety of Americans is quite another. As Charles Edwards, FDA commissioner during the Nixon administration said recently, "People who suggest that you can dismantle the FDA or piecemeal its work out to other agencies don't know what they're talking about." They also are dangerous.

*People who
say you can
dismantle
the FDA
'don't know
what they're
talking
about'*

while not perfect — has for almost 90 years proved a bulwark against tainted food, drugs that maim or kill and medical appliances that do more harm than good.

It was an FDA officer, Dr. Frances Kelsey, who prevented the use in the United States of thalidomide, a sleeping pill that was widely used in Europe in the 1960s and that was later shown to have caused birth defects in thousands of babies. Such protection continues. Daily, the FDA and its 9,300 doctors, inspectors and other employees keep harmful products away from consumers and allow life-saving ones to reach the market.

But House Speaker Newt Gingrich has made the FDA a target, describing the agency as "the leading job-killer in America" and calling FDA Commissioner David Kessler a "bully and a thug." Proposals to trim

Don't undermine the FDA; it's a needed protection

Speeding drugs to market isn't the only concern

THERE CAN BE a legitimate debate over whether the U.S. Food and Drug Administration is too cautious — or not cautious enough — in approving new drugs and medical devices for use in the United States.

But there's no justification for the assault on the agency that's being launched by right-wing groups and self-interested manufacturers intent on ruining it. It's an insidious campaign meant to tarnish the FDA as a death-dealing agency because it doesn't rush its approval of drugs and devices that manufacturers are anxious to market.

One of those in the forefront of the anti-FDA campaign is House Speaker Newt Gingrich, D-Ga., who wildly calls the agency "the leading job-killer in America" and FDA Commissioner David A. Kessler "a bully and a thug."

As it happens, executives and lobbyists for seven FDA-regulated companies are among the top money contributors to GOPAC, the controversial Republican political fund-raising arm headed by Gingrich.

Meanwhile, Gingrich's Progress and Freedom Foundation — so wondrously named — is working out a proposal to privatize the drug-approval process, an idea that should scare every American. Another bad notion would let any new device or drug be marketed as long as it is labeled "not FDA-approved."

Much of the criticism stems from the FDA's unwillingness to approve some specific drugs and devices in use in Europe. There may indeed be examples of undue caution by the regulators. But there are also cases where the go-slow approach paid off.

Americans with long memories are still thankful to the FDA for its caution in 1960 and 1961. The FDA held off approving a tranquilizer called Thalidomide because of its unusual chemical structure; the agency didn't think it had been tested enough. Europe raced ahead and used the drug. By late 1961, it was evident that Thalidomide had caused terrible deformities in about 10,000 newborn children in Europe and elsewhere. Americans were spared.

Gingrich is hot under the collar because the FDA has withheld approval of a Danish heart pump that is supposed to increase survival chances of those suffering a heart attack. It could have saved 14,000 lives so far, he insists. But the FDA contends conventional CPR provides as much benefit.

No human institution is perfect, and the FDA is no exception. It might, for instance, be quicker in approving drugs that could help bring relief to people with diseases that so far have proven to be terminal.

Overall, however, the FDA performs a tough balancing act well. It must decide in each case whether there is enough evidence that a drug is safe and effective to merit its sale to Americans. The ultimate buyers of drugs and medical devices are ordinary people who have to rely on its unbiased judgment. Public protection — not fast action to satisfy manufacturers — must be the agency's chief objective.

The FDA has a timetable for quickening its pace in reviewing new drugs and devices, but if speed is made the only criterion, Americans are clearly at risk.

Americans should not fall for the attacks on the FDA.

Abroad at Home

ANTHONY LEWIS

Reform Or Wreck?

BOSTON

In 1960 the Food and Drug Administration received an application to market in this country a tranquilizer called Thalidomide, said to induce calm and sleep with no side effects. Described as a miracle drug, it had been on sale in Europe for two years.

Dr. Frances Kelsey of the F.D.A. was given the application to review. She was cautious because Thalidomide had an unusual chemical structure. She asked the Merrell Company, which wanted to market it, for more information.

Early in 1961 Dr. Kelsey saw in a British medical journal a doctor's letter saying that patients who had used Thalidomide for a long time developed a nerve inflammation in their fingers. She wondered whether fetuses would be similarly affected if pregnant women took the drug. She

asked more questions, irritating Merrell officials.

Over the previous year or two a strange medical phenomenon had appeared in West Germany and Britain. Children were born with grotesque deformities, lacking arms and legs. No one knew the reason.

Then, in November 1961, a German doctor traced the cause to Thalidomide. Women who took the drug early in pregnancy were liable to have deformed children. Thalidomide was withdrawn from the market.

An estimated 10,000 deformed children were born in Europe and elsewhere because of Thalidomide. But except for one trial distribution, the drug was kept out of the United States — kept out by a skeptical, determined F.D.A. doctor who was denounced, Morton Mintz of The Washington Post wrote at the time, as "a bureaucratic nitpicker."

If Newt Gingrich and his supporters have their way, no F.D.A. doctor like Frances Kelsey will again be able to block distribution of a drug like Thalidomide. For the F.D.A. is a prime target of the radical Republicans.

Speaker Gingrich has described the F.D.A. as "the leading job-killer in America." That encapsulates a right-wing view that delay in approving new drugs and medical devices is hurting American manufacturers.

Mr. Gingrich and other critics say the agency kills not only jobs but

people. On NBC's "Meet the Press" last month he showed a Danish cardio-pump that he said increased the survival chances of heart-attack victims "by 54 percent" but that the F.D.A. "makes illegal." In fact, recent medical studies have shown no more benefit from the device than from conventional cardiopulmonary resuscitation.

Two weeks ago the right-wing Washington Legal Foundation ran a full-page newspaper advertisement that called the F.D.A. a killer. It cited the cardio-pump (saying it could have saved "14,000 lives so far") and other equally dubious matters. It said the American Heart Association estimated that delayed approval of a heart defibrillator cost "at least 1,000 lives"; the Heart Association denied making such a claim and deplored the ad.

The tone of the attacks on the F.D.A. is uncommonly brutal. Speaker Gingrich has called its Commissioner, David A. Kessler, who was appointed by President Bush, "a thug."

In all this we can see the real nature of the radical Republican strategy. The talk is of reforming Government. The real intention is to destroy many of its important functions.

Thus there are proposals to eliminate the F.D.A., replacing it with an industry-dominated agency; or to farm out the approval process to private bodies; or to let new drugs and medical devices be sold with a warning that they have not been approved.

Reform and simplification of Federal regulations are necessary. Some have become far too detailed and burdensome. When Washington tries to regulate minutely the practices of thousands of universities all over this vast country, for example, it is as likely to do harm as good.

But there are some things that a civilized society needs government to do. One of them is to protect its citizens from untested drugs that may do terrible harm.

In 1962 President Kennedy gave an award to Dr. Kelsey of the F.D.A. for her "high ability and steadfast confidence" in saving Americans from the Thalidomide tragedy. I do not believe that Americans really want to retreat from that standard to the age of carnival elixirs — or worse. □

A cautionary
tale about
weakening
the F.D.A.

Our perspective

Risky reform

Go slow in making FDA changes

In 1955, while preparing a new anti-polio vaccine, Cutter Laboratories of Berkeley, Calif., accidentally introduced live polio viruses into what was supposed to be a dead-virus serum. More than 100 patients contracted the disease and 11 died before the tainted vaccine could be pulled from distribution. Congress responded by greatly expanding the authority of federal regulators to scrutinize every step of a drug's development and manufacture.

Those powers are among dozens that would be curtailed by a far-reaching Republican proposal to streamline — indeed to weaken — the federal Food and Drug Administration. The agency approves new drugs, medical devices and food additives.

The legislation goes way too far, way too fast.

A package of bills, moving separately through both houses of Congress, would tighten FDA deadlines, ease the paperwork burden on medical manufacturers, sweep aside state regulations that exceed federal standards, greatly expand the use of private laboratories to test new drugs and medical devices, and reduce the FDA's powers in a variety of ways.

The reforms are propelled in part by a legitimate concern: that FDA paperwork may keep promising drugs off the market and hamper American manufacturers in the race for cutting-edge technology. But these bills rely on untested techniques and remove too many of the safeguards that keep risky products off the market. Making modest changes, in the direction the FDA is already heading, is the way to go.

If the problem is a bottleneck in new-product approvals, for example, why not give the FDA more staff or the power to employ outside laboratories? These bills allow manufacturers to hire private labs directly, then submit their results to the FDA. If private labs come to depend on repeat business from manufacturers, the potential for conflict of interest is simply too great.

If the goal is merely to expedite FDA review, why do the bills allow manufacturers to shield basic test results

unless the FDA specifically asks for them? Currently, this "primary" clinical data is part of the routine application. Separating that data only adds an extra step to the review process and invites the suspicion that companies have something to hide.

And if the legislation's authors don't mean to dilute FDA standards, why do they shift the burden of proof — from the manufacturer who must now prove a product safe before bringing it to market, to the FDA, which would have to prove that a product is dangerous before blocking its introduction?

The bills' sponsors say these measures are necessary because the FDA is incapable of reforming itself. But that is demonstrably false. Since 1987, the FDA has cut approval time for new drugs by half, to 16.5 months, and has cut the review time for most new medical devices by more than one-fourth. A recent study by the General Accounting Office found that in 1994, the FDA approved new drugs faster than its counterparts in Great Britain, Germany, France and Japan.

This is not to say that FDA reform is unnecessary. The review process for new medical devices remains tortuous and overlong. Manufacturers such as Minnesota-based Medtronic deserve a more "transparent" FDA so they can track their applications through the regulatory pipeline. And, as Rep. Jim Ramstad, R-Minn., has pointed out, third-party review has been used successfully by other agencies and could be expanded at FDA with proper safeguards.

Under some pressure from Congress and industry, the FDA has started pilot projects to expedite medical-device approval and use outside labs for new-drug applications. Those pilot projects should be expanded and accelerated. But it's too soon to say that the risk of good drugs kept off the market outweighs the risk of bad drugs unleashed on it. Since the subject is science, the FDA deserves to be tested by scientific method, not reformed by untested methods.

EDITORIALS

Sniping at the FDA

REPUBLICANS have gotten themselves into such a snit about the excessive amount of time the Food and Drug Administration spends reviewing new drugs that they are in danger of losing sight of the big picture.

Namely, the agency has tackled the problem itself, done a lot to streamline the review process and continues to move in the right direction.

GOP critics say patients and businesses are hurt because the FDA takes too much time to approve drugs and medical devices. No one disputes that in the past the agency has moved slowly. However, some GOP spin doctors overlook the fact that the median approval time for new drug applications has been cut in half. Today some drugs are approved in just six months.

Furthermore, the agency has an excellent track record for safety. Its regulators are very careful, but their thoroughness pays off in quality and patient confidence. Drugs approved by

government regulators in Great Britain, Germany and France have had to be withdrawn far more often than those that have won the FDA's stamp of approval.

Also to their credit, officials of the FDA are making special efforts to speed up federal approval of cancer drugs — aiming to knock a year off the process. And they're doing more to make cancer drugs that have been declared safe abroad available here.

Even so, frenzied House and Senate Republicans press ahead with demands to overhaul the FDA as though none of this were going on. Particularly troubling is the insistence on requiring faster reviews and permitting some parts of the drug-approval process to be contracted out to private vendors.

Certainly these accomplishments need to be understood. It's hard to believe that congressional Republicans could try to undercut such efforts — unless their goal is political gain rather than the health of America's people.

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How We SEE IT

Keep watchdogs on job

Imagine going to court against a powerful manufacturer only to learn that the judge had been selected and paid by your opponent with promises that if he handled the case appropriately he'd likely be hired again. Does that sound like justice? Does it sound fair? Of course not. But that would be the result of three bills currently under consideration by the U.S. House of Representatives to privatize the Food and Drug Administration's review functions.

Pity the chickens: If the measures pass, the safety of drugs, medical devices and foods would be controlled not by the public's watchdogs at the FDA but by industry-retained reviewers. The foxes themselves wouldn't be watching the henhouses, but they would be writing the guards' job descriptions and paying for their work. Meanwhile, all of us chickens would become fair game.

The contention among pharmaceutical companies, medical device manufacturers and certain food producers is that it takes too long to receive approval for new products, and they've pumped thousands of dollars into the political campaigns of many legislators to influence their votes.

On the other side are the FDA and many consumer groups who fear what could happen to public health if monied special interests determine which products could go on the market and when.

Fastest approvals: According to the General Accounting Office, in 1987 the average approval time for new drugs was 33 months. In 1993, approval time had been reduced to a median of 16.5 months. For the 15 highest priority drugs, the median approval time was six months. Studies both by the GAO and the British-based Centre for Medicines Research all demonstrate that American patients have access to therapeutically important new drugs that have been proved safe and effective sooner than the citizens of any other nation.

While the three bills under consideration are called "reform" bills, none of the so-called reforms does anything to improve public health or safety. Currently, FDA reviews are conducted by scientists, engineers and medical researchers who work for the public. They comply with stringent financial disclosure and conflict-of-interest requirements designed to protect the decision-making process against bias.

A reviewer paid by a drug company to decide the future of that company's products can hardly be unbiased. We don't think the public good is served by such an arrangement.

Make sure new drugs are safe

Don't sacrifice FDA safeguards for speed and profit

THE FEDERAL Food and Drug Administration has made considerable progress in loosening its regulatory strings to approve new products faster to the potential benefit of patients and consumers.

Changes in the process used to approve cancer drugs and to provide quicker access to drugs already approved in other countries are among sensible reforms already implemented at minimal risk to the public.

However, changes being pushed now in Congress go too far, too fast. They risk the public's health in a mad rush to deregulate without due regard for the consequences.

The FDA's historic mission has been to protect the public from dangerous drugs, medical devices and food additives. Proposals in the House to shift much of that duty to the private sector — the same sector that profits from new products — are akin to having the fox guard the medical hen house.

One, for instance, would shift the burden of proof for new food additives. Instead of manufacturers having to prove that products are reasonably safe, the FDA would be saddled with having to show that additives are unsafe. That's a nearly impossible standard to meet for products on which not enough studies had yet been done.

Another proposal would take the impartial FDA out of the business of doing safety reviews for new products. Instead, the reviews would be done by an FDA-approved contractor to be picked by the very company seeking the approval.

It doesn't take much imagination to see the potential for chicanery and conflict of

interest there. But even assuming the private sector is strictly scrupulous, FDA Commissioner David Kessler is persuasive when citing another shortcoming.

Kessler notes that FDA workers who review data about various products have a broad base of knowledge to draw on when assessing a new item's claim. For example, he said, an FDA reviewer a few years ago uncovered fraudulent data being used to push a skin cream designed to protect U.S. soldiers from chemical attack. The FDA specialist was able to spot the phony data only because they were out of line with results from other products he had reviewed.

That kind of safeguard would be lost with the congressional proposal to let independent contractors take over the task. When high-risk products are involved, the results could be deadly.

The FDA already is further streamlining its operations. It has begun work on pilot projects to involve third parties in reviewing low- and moderate-risk products. New, less rigorous standards for testing and using cancer drugs were announced a few weeks ago. And approval time for drugs has been significantly reduced.

Republican prodding and anti-regulatory fervor no doubt played a part in many of those improvements, and most make sense.

But reform can go too far. These do, and so do some of the other efforts being pushed by a House subcommittee on health. Congress should heed Kessler's warnings and let the FDA keep putting safety first

April 19, 1996

DRAFT DRAFT DRAFT

H.R. 3200

"FOOD AMENDMENTS AND THE ANIMAL DRUG AVAILABILITY ACT"¹

TITLE I – FOOD AMENDMENTS

SEC. 101. FDA MISSION AND ANNUAL REPORT

- Section 2(a), the mission statement establishes prompt and efficient review and approval and global harmonization as primary FDA goals.

The mission does not include traditional FDA objectives of ensuring that food is wholesome and properly labeled or that consumers are protected from fraud. The mission statement should include protecting the public from products that do not meet the applicable statutory standards because they lack the requisite approval prior to marketing -- i.e., products that are unsafe and ineffective or have not been shown to be safe and effective.

- Section 2(b), requires the Secretary to, simultaneously with the submission of an annual budget, submit to the Commerce Committee in the House and the Committee on Labor and Human Resources in the Senate, an annual report that (1) reviews FDA's performance in meeting its mission and developing policies to implement such mission; (2) reviews FDA's performance in meetings its own performance standards (including meeting statutory deadlines); (3) describes FDA's staffing and lists third parties that have been accredited to perform product reviews; (4) describes FDA's harmonization goals, activities, and accomplishments; and (5) compares FDA's performance with that of the most "successful" agency performing similar functions in other countries and compares the resources used by such agencies.

The agency does not disagree with the principle that the agency must be held accountable. The concern is that some of the requirements set forth in this provision are not clearly defined and/or possibly not feasible. For example, the requirement that FDA compare its performance with that of the most "successful" agency performing similar functions in other countries is vague and may be difficult, if not impossible, to meet. The term "successful" is not one that provides much guidance. Moreover, it is uncertain whether such data are

¹ H.R. 3200 includes a number of supportable concepts. The emphasis of this section-by-section analysis, however, is on the problematic provisions in the bill.

available from other countries or whether if such data are available, a comparison is possible.

SEC. 102. ACCESS TO DISEASE PREVENTION INFORMATION

- Section 102 amends the section 403(r)(3) standard for authorizing health claims by adding the sentence: "significant scientific agreement does not require consensus or unanimity."

This concept is [supportable]. FDA does not interpret significant scientific agreement as requiring consensus or unanimity. FDA clearly stated this in the preamble to its final rule on health claims. If the agency did not follow this view, it could not have approved the eight health claims currently allowed on the food label. In each case, there were scientists that objected to the claims. For example, there was not complete agreement on the relationship between folic acid and neural tube defects, yet the agency has approved this claim for use on the food label.

- Section 102 allows any materials prepared or distributed by a government agency (such as NIH, CDC, or the National Academy of Science) to serve as the basis for a health claim -- i.e., to fulfill the significant scientific agreement requirement.

This provision fundamentally alters the criteria for health claims that were so carefully worked out in the Nutrition Labeling and Education Act of 1990. Under the bill, there would be no single body to make decisions on health claims, and the result could be inconsistent decisions by different organizations using different standards. Companies would be allowed to pick and choose among government bodies. This provision is likely to result in the type of consumer confusion and misinformation that was abundant before passage of the NLEA.

In addition, the provision is vague and overly broad. The bill would appear to allow ANY information prepared for whatever reason (i.e., not specifically for the purpose of a diet/disease claim evaluation) to form the basis of a health claim. For example, materials relating to a particular diet disease relationship prepared and distributed as background for a hearing by the NAS or a briefing by NCI could be used as the basis for a health claim. Moreover, information contained in pamphlets written by a private organization and distributed by Federal health agencies or the NAS could form the basis for a health

claim under this provision. Information could be taken out of context.

There appears to be no remedy for FDA if it disagrees about a claim evaluation made by another agency.

SEC. 103. ACCESS TO NUTRIENT DESCRIPTOR INFORMATION

- Section 403 of the Act currently permits foods labeling to include nutrient content claims using descriptors that have been defined by FDA. Section 104 amends that provision to permit synonyms of those defined terms, provided they are not false or misleading.

The bill provides no mechanism for determining appropriate synonyms. Because there is no standard for companies to meet before using a new descriptor, the burden would be on the agency to prove that a term is not a synonym for a defined term and that the term is false or misleading. The result of this provision would be a large increase in the number of nutrient content descriptors. The uniformity that the NLEA created would be lost. Such a plethora of uncontrolled terms would confuse consumers by diminishing the usefulness of the defined terms. Consumers would be confused as to the nutrient content of a particular food. For instance, is "lots of fiber" a synonym for "excellent source of fiber" or "good source of fiber?"

FDA's current regulation permit a company to petition for the use of synonyms. In addition, FDA recently proposed to amend its nutrient content claim regulations to permit manufacturers to use synonyms of defined nutrient descriptors as long as such synonyms are not false and misleading and the synonym is "anchored" to the defined term -- i.e., the defined term must appear prominently on the label. The agency's proposal properly balances the concern of unbridled uses of synonyms that can lead to consumer confusion with industry's need for greater flexibility to market the healthful aspects of their products.

SEC. 104. SPECIAL LABELING TO PROTECT PUBLIC HEALTH

- Section 104 prohibits FDA from using its misbranding or food additive authority to require food manufacturers to include a description of a method of production or an ingredient other than in the statement of ingredients, unless such disclosure is necessary to protect the public health.

The effect of this provision will be food labeling that is not complete.

For example, FDA has historically taken the position that if a food production process changes the characteristics of a food, information about that process should be made available to the consumer on the label. The homogenization and Pasteurization notations on milk labels are such examples. This provision might also prohibit FDA from including the olestra statement (which would help consumers connect possible (not medically significant) GI effects with olestra consumption) and irradiation labeling (which is designed to inform consumers that the food has been processed).

In addition, this provision may conflict with other provisions of federal law. For example, section 403(i) requires percent juice labeling to appear on the label. Yet, proposed section 403(t) would prohibit such a disclosure because it is not "necessary to protect the public health."
[DISCUSS]

SEC. 105. ACCREDITED PERSON REVIEW

- Subsections (a) and (b) of Section 105 authorize the review of health claims petitions by third parties. The third party has 120 days to make a recommendation on the petition and the third party's recommendation shall be deemed the recommendation of the Secretary unless the Secretary finds that it is contrary to the findings required by the Act and provides a detailed explanation for the basis of the finding.

This provision creates an implicit presumption in favor of a third party's recommendation and expands FDA's burden to deny a petition for a claim subject to third party review in that the agency would need to show why the third party's recommendation was wrong.

- Subsections (c) and (d) of section 105 authorize the review of food additive and color additive petitions by third parties accredited by FDA. In reviewing a food additive petition, the third party shall determine whether there is a reasonable assurance that the food additive may be safely used under the proposed conditions of use. The third party shall submit a report to the Secretary within ____ days. In reviewing a color additive petition, the third party shall decide whether it meets the requirements of the act. The third party shall submit a report to the Secretary within 120 days. With respect to both food and color additives, the third party's recommendation shall be deemed the decision of the Secretary unless FDA finds that there is a reasonable probability that it is not safe and provides a detailed basis of that finding.

This provision changes the food additive standard (for these additives subject to third party review) from a reasonable certainty of no harm to a reasonable assurance that the food additive may be safely used.

This provision shifts the burden of proof from the additive manufacturer to FDA. Under 3200, FDA can only deny approval of a food or color additive that has been reviewed by a third party if it can demonstrate that there is no "reasonable probability" that the additive is "not safe." Since 1958 and 1960, when Congress passed the Food and Color Additive Amendments, it has been the responsibility of additive manufacturers -- those who profit from the additive use -- to demonstrate to the Agency that the additives they propose to add to food are safe. FDA's responsibility has been to review this evidence and either approve the additive if the agency concurs that the additive is safe or refuse to approve the additive if, in the agency's opinion, safety has not been demonstrated. To require the agency to demonstrate that an additive is not safe is to require it to prove a negative.

The deadline provisions in the bill are confusing.

SEC. 106. ACCREDITED PERSONS

- Section 106 addresses the accreditation process. Within 180 days of enactment, the Secretary must promulgate regulations establishing procedures for the accreditation of third parties for purposes of (1) reviewing health claims petitions, food and color additives petitions, new animal drug applications, and (2) conducting GMP inspections to assess conformance with regulations promulgated under section 402.

This section does not establish how the third parties are to be compensated for services. It lacks clearly defined criteria for establishing the qualifications of third parties. It does not provide sufficient safeguards against conflicts of interest. The provision is vague as to whether FDA can inspect third parties or require third parties to maintain record. It also is unclear as to whether third parties can be given access to privileged information that is in the custody of FDA. In addition, it appears that the intention is not to have the Secretary accredit any particular entity, but rather to have the Secretary designate agencies or organizations who will then perform the accreditation process.

- Section 106 (b) amends the prohibited acts section of the FDC Act to add a new section relating to actions by third parties. Under proposed 301(w), a

third party would violate this section if it submitted a materially false or misleading report, disclosed trade secret confidential commercial information, or accepted a bribe or performed any other corrupt act in connection with its delegated responsibility.

SEC. 107. IMPROVING THE DELANEY CLAUSE

- Section 107 changes the Delaney clause standard from "no risk" to "negligible or de minimis risk." Within 180 days of enactment, FDA must propose regulations establishing criteria for the standard. The proposal will become final unless within 18 months of enactment, FDA issues a final regulation.

[ADD]

SEC. 108. NATIONAL UNIFORMITY

- Section 108(a) prohibits states from establishing any requirements (including prohibitions) for any food, drug, or cosmetic that is of the type authorized or required under the adulteration, misbranding, or new drug provisions of the FDC Act or any regulation implemented thereunder if it is not identical to a requirement imposed under the FDC Act.

This provision would prohibit state action even in areas where FDA is not very active.

- Subsection (b) prohibits states from imposing any notification requirement for a food, drug, or cosmetic that provides for disclosure of the constituents, source, or method of production or processing such product or for a warning concerning the safety of the product or any component or package thereof unless such requirement is identical to a requirement prescribed under the FDC Act.

This provision would preclude notifications pursuant to state laws and initiatives, such as California's Proposition 65.

- Section 108 allows the Secretary to provide an exemption under this section of is it justified by compelling and unique local conditions, protects and important public interest that would otherwise be unprotected, would not cause any food, drug, or cosmetic to be in violation of the FDA Act, and would not unduly burden interstate commerce.

SEC. 109. HARMONIZATION

- Section 109 requires the Secretary to regularly and continuously participate in harmonization efforts and to report those efforts to Congress as well as provide 60 day notice to the Committee before executing any agreements with foreign countries. It also requires the Secretary to, within 180 days, make public a plan that establishes a framework for achieving mutual recognition of good manufacturing practices.

SEC. 110. INFORMAL AGENCY STATEMENTS

- Section 110 prohibits the Secretary from relying on policy statements, guidance documents, and similar statements to require any action to satisfy a provision of the FDC Act. It also requires the Secretary to publish a notice of availability of such statements and to make them accessible electronically.

FDA's position is that guidance documents are not binding on the Agency or the public. FDA recently issued a Federal Register notice that affirms this position and has agreed to take steps to ensure that the agency and the public knows and understands this principle. To the extent that this provision is reaffirming that position it is not problematic. To the extent that it is saying that FDA cannot issue guidance that explains how it believes compliance with the Act may be accomplished, it is problematic -- particularly for the industry. FDA will no longer be able to provide guidance and there is a risk of non-uniformity in the application of the laws and regulations that FDA is tasked with implementing.

SEC. 111. COLORED MARGARINE

- Section 111 repeals section 407 of the Act.

TITLE II -- ANIMAL DRUGS

SEC. 201. EVIDENCE OF EFFECTIVENESS FOR ANIMAL DRUGS

- Section 201(a) amends Section 512(d) of the FDC Act to redefine the "substantial evidence" criteria that currently must be met to establish efficacy. The provision changes the substantial evidence requirement from adequate and well-controlled studies to scientifically sound studies. The requirement that the

studies fairly and reasonably show effectiveness has been changed to a requirement of a reasonable assurance of efficacy. The provision also eliminates the requirement for field investigations unless FDA justifies in writing the need for such investigations to show the effectiveness of animal drugs.

A lower standard for effectiveness is not acceptable. What would be acceptable is a change to current law that clarifies that only one adequate and well controlled study may be necessary and that field investigations be necessary only where appropriate.

- Section 201(c) would eliminate the requirement to show effectiveness of animal drugs intended for uses in minor species or for minor uses.

Elimination of a requirement to show effectiveness takes us back to 1962. There is no point to having available drugs that cannot be shown to be effective. In fact, the availability of ineffective animal drugs has implications for animal health and creates a significant potential for public health hazards. The use of ineffective animal drugs in minor species or for minor uses can lead to the suffering and death of animals and an increase in the potential for the transmission of zoonotic diseases to humans and the development of antimicrobial resistance.

- Section 201(d) would change the standards for approving combination animal drugs.

Although the information necessary to establish effectiveness of combination animal drugs could be narrowed in some instances, this provision is written too broadly. It would permit a sponsor to market a combination animal drug containing two or more drugs that are targeted to the same indication without having to show that each drug provides some additional benefit. Moreover, it would not require the sponsor of a animal drug combination to establish the safety of the combination to the animal targeted to receive the combination.

- Section 201(f) includes a provision relating to presubmission conferences. It directs the agency to provide at the request of the sponsor a presubmission conference during which the agency identifies the studies that a sponsor must conduct to show that a drug is safe and effective. The provision further directs that such decisions regarding what studies are needed are binding on the agency unless FDA by order determines that a documented scientific requirement essential to the determination of safety or effectiveness of the animal drug has appeared after the conference.

The concept of presubmission conferences is supportable. The binding nature of decisions regarding studies is problematic. The agency may be unable to determine with certainty what studies are necessary until the results of some preliminary studies are evaluated.

SEC. 202. TIMEFRAME FOR APPROVAL FOR ANIMAL DRUGS

- Section 202 cuts the timeframe for approval of new animal drug applications in half (from 180 days to 90 days).

The 90 day timeframe is unrealistic.

SEC. 203. DISPUTE RESOLUTION

- Section 203 permits the sponsor of a new animal drug to seek dispute resolution before an advisory committee or a special government employee or a nongovernmental person, acceptable to FDA and the applicant, who is qualified to mediate or arbitrate whenever an "impasse" exists in the review of an application. It requires FDA to refer the dispute to an advisory committee or other third party on receipt of a notification from the applicant that a dispute exists. Within 30 days of receiving the panel or third party recommendation, the Secretary must, in writing, confirm or modify, the panel or third party recommendation providing reasons and reference to data before the committee or third party for any modification.

It is unclear whether the dispute mechanism is workable for CVM because CVM has only one standing advisory committee to which it refers disputes. In addition, the number of experts on a particular subject may be rather limited.

SEC. 204. LIMITATION ON RESIDUES

- Section 204 amends section 512(d)(1)(F) to permit dose ranges, with endpoints based on human and animal safety, to be used on animal drug labels.

This would eliminate the requirement that CVM set a tolerance limit based on an optimal dose, the minimum dose at which there is a maximum effect for the particular indication. Thus, CVM can approve a product with dose ranges that allow veterinarians to exercise professional judgment in treating animals. Permitting the use of dose ranges will reduce the potential for public health problems by reducing the risk of developing antimicrobial resistance and allowing effective

treatment of diseases transmitted from animals to man. The provision is supportable.

SEC. 205. VETERINARY FEED DIRECTIVES

- Section 205 adds new section 504, which provides statutory authority for a new class of animal drugs intended for use in animal feed that would be restricted to use in accordance with a "veterinary feed directive."

This new class is needed because certain animal drugs administered through an animal's feed can only be approved for use under a veterinarian's supervision and thus, cannot be sold over the counter. The regulation of most animal feeds under traditional prescription systems is not practical.

Add The Following REGO Related Provisions Not Currently in the Bill:

Feed Mill Licensing

Would substitute site licensing for medicated feed applications that currently are required to be submitted by feed mills for individual medicated feeds. The proposal would save both agency and industry resources.

Import Tolerances for Veterinary Drug Residues in Food

Would provide FDA specific legislative authority to establish import tolerances to allow importation of food from animals treated with drugs not approved in the U.S. rather than requiring companies to seek approval of the drug's use in the U.S. The establishment of import tolerances would alleviate the unnecessary burden and cost of obtaining unnecessary new animal drug application approval for drugs that are not manufactured and used in the U.S. without compromising food safety.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

APR 17 1996

NOTE TO: Jerry Mande

SUBJECT: Premarket Notification Modification Document

Attached is the second draft of the premarket notification (510(k)) modification document. The document is intended to provide direction to manufacturers, specification developers, and distributors who are making a change to their device, including a change in the manufacturing process, and are in the process of deciding whether the change requires the submission of a new 510(k).

FDA and the industry have both recognized that the criteria are not well defined for deciding whether a given device modification requires a new 510(k). This is because the statute sets forth a subjective standard, to be determined by the manufacturer, of whether a device modification "could significantly affect safety and effectiveness." In response to requests from industry for clarification of how FDA interprets this standard, we developed a "straw" proposal that was disseminated for public comment in April 1994. Based on comments received, the new draft proposes a more clearly defined decision-making process that is presented in flowchart format. A notice announcing the availability of the second draft was published in the Federal Register on October 16, 1995. Comments received on the second draft are favorable.

Please call me if you need additional information.


Joe Levitt

Attachment

cc: Bruce Burlington, M.D.

**Deciding When to Submit a 510(k)
for a Change to an Existing Device**

Draft #2

August 1, 1995

Draft...August 1, 1995

Preface

On April 8, 1994, FDA circulated for comment the first draft of a document intended to provide guidance to manufacturers on deciding when to submit a new 510(k) for changes to an existing device. That draft was the subject of an FDA/FDLI teleconference on May 12, 1994, and also was the subject of discussion at several trade and industry association meetings. The invitation to comment on the draft guidance elicited over 60 distinct comment letters.

Six of the letters FDA received were from organizations representing multiple manufacturers, while the remainder were from individual manufacturers, consultants and other interested parties. Almost all of these letters contained detailed and thoughtful comments on the guidance and its role in a manufacturer's 510(k) decision making. No attempt will be made here to detail the hundreds of specific comments and changes that were suggested and how they have been incorporated in the second draft of the guidance document, which follows. Nevertheless, FDA staff have attempted to include all pertinent suggestions in this draft of the guidance, and individual submitters of comments should easily recognize where their specific suggestions have lead to revisions.

The comment letters, however, reflected several general themes and concerns regarding the philosophy of 510(k) decision making (particularly for changes to existing products) as well as the respective roles of the manufacturer and FDA in this process. These themes and concerns warrant a discussion since they are a large part of the underpinning of this new draft of the guidance document.

Several writers believed that the April 8 draft ignored the language of the current regulations on premarket notification, Section 807.81(a)(3), where it is stated that manufacturers must submit a premarket notification whenever their product is "about to be significantly changed or modified in design, components, method of manufacture, or intended use." The text of this part of the regulations is provided on the first page of this document and was also provided on the first page of the April 8 draft. The previous draft did not ignore the regulations, but rather, it was an attempt to expand on the phrases "could significantly affect," "major change," "significant change," etc. The April 8 draft as a whole was intended to better define these terms, at least from the FDA reviewer's point of view. Thus, the document did not ignore the regulations, but tried to demonstrate how compliance with the regulation could be achieved. The current draft tries to correct those areas where the April 8 draft fell short of this goal and should provide a reasonable basis for a manufacturer's decision making.

Draft...August 1, 1995

Some of the authors believed that the decision-making process had been inappropriately shifted from the manufacturer to FDA. Although this was not the intent of the April 8 draft, some of the statements can be interpreted in this way, especially when taken out of context. FDA still believes that it is important to define as clearly and carefully as possible when manufacturers ought to submit a 510(k) for a change to an existing device. In some instances, FDA's advice to manufacturers is clear cut, and when asked whether a 510(k) is necessary, FDA's response will always be "yes" or "no." In other instances, the response will depend on a variety of factors. This document attempts to provide for manufacturers FDA's response, were the manufacturer to ask FDA the question of whether a 510(k) would be appropriate for a particular type of change. It is still the manufacturer's responsibility to make that decision for, indeed, the manufacturer knows more about its product and that product's use than anyone else. The guidance contained in this document is only intended to be FDA's best advice. FDA believes that the changes made to the April 8 draft will demonstrate this fact. FDA notes, however, that confusion exists in some of the comments regarding what is the manufacturer's and what is FDA's decision-making responsibility. Manufacturers have the responsibility for determining when a change to their product is significant enough to merit submission of a premarket notification. (If FDA finds, after the fact, that a change was significant and the manufacturer did not submit a 510(k), FDA retains the right to notify the manufacturer of this fact and to require the submission of the 510(k).) FDA's responsibility is the determination of substantial equivalence, based upon the evidence submitted by the manufacturer in a premarket notification.

Several letters noted that FDA's GMP regulations provide adequate control over most design and process changes. They believe that it is unnecessarily duplicative to submit 510(k)s for most changes and that the 510(k) process and the GMP regulations should perform complementary functions. FDA completely agrees with this philosophy. In the April 8 draft, an attempt was made to make explicit the complementary nature of the 510(k) and GMP regulations. Obviously, that attempt was made clear to some reviewers and not to others, since some of the comments complimented FDA for trying to rely more on GMP than upon premarket notification. This difference in viewpoint may derive from individual biases regarding the limits of design validation for changes. In this draft guidance, the reliance on design validation of changes under GMP is much more explicit, and, in many instances, the results of design validation activities are identified as indicators of when a change is significant enough to merit a premarket notification.

The comments also discussed what should be included in a 510(k), once the decision to submit a new 510(k) has been made. The statement in the April 8 draft that "when any one change requires the submission of a 510(k), then a 510(k) incorporating all the changes, including any prior incremental changes, must be submitted...the new 510(k) should incorporate the old 510(k) and identify and

Draft...August 1, 1995

discuss all the changes made to date." caused some confusion. In some instances, the statement was interpreted to mean a description would be necessary of each and every engineering change made since the most recent 510(k) submission. This was definitely not intended. The 510(k) for the changed product, however, must discuss all of the differences between the old and the new product, in order for a determination of substantial equivalence to be possible. In most instances, this is currently accomplished by the provision of a table describing major differences in performance specifications and indications for use or other labeling issues. Further, it is not necessary to "physically" include the old 510(k) with the new 510(k), but the original 510(k) should always be identified and referenced.

The question of consultation with FDA was discussed at great length. In order for this or any other guidance to work well, it is important that feedback be provided to FDA of where it works well and where it does not work so well. The April 8 draft was intended to stimulate manufacturers to contact FDA with those decisions where the guidance was not useful (called decisions in the gray area) in order to refine the guidance at some future date. It was not intended that manufacturers refrain from their decision-making pending an FDA determination; the choice of words in the April 8 draft was unfortunate in this regard. Manufacturers certainly make their own decisions on whether to submit a premarket notification, however, in those instances where this guidance does not prove useful, FDA would like to be notified so that these issues can be clarified in future revisions.

The model that was discussed in the April 8, 1994, document was described as a matrix model. In reality, the model combined the use of a flowchart with a matrix-like array of advice for each type of device and device change to guide decision making. The advice contained in the matrix was whether to submit a 510(k) or merely to document the decision-making under the current Good Manufacturing Practices regulation (21 CFR 820) for changes in device design, components, packaging or labeling.

The current model no longer contains the matrix. This was done for two reasons. First, the changes made as a result of the comments diminished the need to rely on a matrix-like illustration of the advice being given. A more generic approach was taken in the model, and there was less need to differentiate among specific device types. In the few instances where the type of device would have an impact on the guidance, this was taken into account in the flow diagram. Thus, the flow diagram in this model is more complex than the April 8 version, but the matrix has been eliminated.

Second, the use of a matrix appeared to confuse many more people than it helped. If the purpose of a guidance document is to clarify regulatory responsibilities, elimination of any source of confusion is beneficial, thus the demise of the matrix.

Draft...August 1, 1995

Many of the writers believed that this guidance is of sufficient importance that it is necessary to provide notice and comment through the Federal Register. FDA does not believe that this document constitutes either a substantive or procedural rule, and, consequently, notice and comment through the Federal Register is not necessary. FDA is cognizant, however, of the potential widespread use of this document, and, therefore, a Notice of Availability has been prepared for publication in the Federal Register to announce the second draft of this guidance for further public comment.

TABLE OF CONTENTS

<u>SECTION</u>	<u>PAGE</u>
Preface	i
Introduction	1
The 510(k) Process and Good Manufacturing Practices	2
Scope of the Proposed Guidance	3
Assumptions/Axioms	4
Proposed Model	5
Labeling Changes	7
Technology or Performance Changes	10
Materials Changes	13
Materials Changes in In Vitro Diagnostic Products	16
Flowchart Definitions	18
Figures	23
Appendix A	28

Introduction

Almost from the enactment of the Medical Device Amendments to the Federal Food, Drug and Cosmetic Act in 1976, FDA staff have attempted to define with greater accuracy when a change in a medical device would trigger a need for a manufacturer to submit a premarket notification (510(k)) to the Agency. The regulatory criteria contained in §807.81(a)(3) state that a premarket notification must be submitted when:

Statutory

(3) The device...is about to be significantly changed or modified in design, components, method of manufacture, or intended use. The following constitute significant changes or modifications that require a premarket notification:

(i) A change or modification in the device that could significantly affect the safety or effectiveness of the device, e.g., a significant change or modification in design, material, chemical composition, energy source, or manufacturing process.

(ii) A major change or modification in the intended use of the device.

The key issue here is that the phrase "could significantly affect the safety or effectiveness of the device" and the use of the adjectives "major" and "significant" sometimes lead to subjective interpretations. Because of this, manufacturers have frequently expressed the need for more specific guidance in applying the regulatory standard in their decision making.

Previous internal attempts to develop such guidance on interpreting the regulation have focused generally on defining broad issues or principles that should be used in deciding when to submit a 510(k). These attempts have been only partially successful in clarifying the situation. The primary reason for partial success is that the variety of device types currently marketed, as well as the myriad changes that occur as technology evolves, are so diverse that one or two unifying principles cannot possibly account for all decision-making opportunities.

To be certain that a decision on when to submit a 510(k) is correct, one would probably need to enumerate all device types and all potential types of changes and then match each combination of device and change with a decision. Given that there are thousands of individual device types and possibly tens or hundreds of enumerable changes, this would be an extremely difficult task. Furthermore, the resultant guidance would fill volumes, would probably be difficult to use and would be unlikely to keep pace with an ever-changing technology.

Draft...August 1, 1995

Between the two extremes of broad principles and detailed enumeration is the area where models can be developed to assist in the decision making. If created and used properly, such a model could provide guidance leading toward a rational answer as to whether a 510(k) is necessary in the large majority of circumstances. This document proposes a flowchart model that can be used by manufacturers in their decision making to analyze how changes in devices may affect safety or effectiveness. In the model, we attempt to address changes to devices at a level detailed enough so that application of the broad principles espoused by the agency would assure a very high percentage of "correct" decisions. The goal of the model is to provide guidance in answering a manufacturer's (or other 510(k) holder's) questions on whether a 510(k) is necessary for a particular type of change and to minimize the number of situations where the answer would be uncertain.

The 510(k) Process and Good Manufacturing Practices

Any guidance on 510(k)s for changes to a marketed device must consider the role of the Good Manufacturing Practices (GMP) regulation in changes in device design. For some types of changes to a device, the Agency continues to find that a 510(k) is not necessary and that reliance on existing GMP requirements may reasonably assure safety and effectiveness of the changed device.

It is important to note that the current GMP regulation does not directly address the original design of a device. In fact, it was the recognition of the need for this type of control for many types of devices that led to the inclusion of pre-production design controls in the Safe Medical Devices Act of 1990.¹ The recently proposed new GMP regulation will implement the new authority and directly address design controls for new devices.

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The current GMP regulation, however, is not silent on device design. It requires manufacturers to document in the device master record (§820.181) any changes (and internal approval to changes) to device design and any associated testing (§820.100). It also requires process validation to assure that products meeting the designed quality characteristics will consistently be produced (§820.5 and §820.100). Finally, manufacturers must have a formal approval procedure for any change in the manufacturing process of a device (including those dictated by design changes) (§820.100(b)(3)).

The net effect of the GMP regulation is to require that, when manufacturers make a change in the design of a device, they must have a process in place to demonstrate that the manufactured product meets the change in design specifications (or the original specifications, if no change was intended). They must keep records, and these records must be made available to an FDA inspector. Thus, although the current GMP regulation does not address the initial design of a device (the proposed

Draft...August 1, 1995

revision to the GMP regulation does address the need for design controls for many products), it does impose certain requirements when changes to a device are implemented. For many types of changes to a device, it may be found that a 510(k) is not necessary, and the Agency may reasonably rely on the existing GMP requirements to assure safety and effectiveness of the changed device. This reliance is enhanced when manufacturers document their decision making based on their testing results or other design validation criteria.

Scope of the Proposed Guidance

The guidance outlined in this document has been developed to aid manufacturers, specification developers or distributors of class I, class II or pre-enactment class III devices (for which premarket approval has not yet been required under section 515(b)) who intend to modify their device and are in the process of deciding whether the modification meets the statutory threshold for requiring a new 510(k) submission. This guidance for changes to an existing device is intended to supplement the general guidance on submitting 510(k)s contained in the ODE bluebook memorandum on the premarket notification program.²

The types of modifications addressed in this document include modifications to design as well as modifications to device labeling, such as modified indications for use, claims for safety and effectiveness, etc. Furthermore, this guidance can be applied to those situations when a legally-marketed device is recalled and a change in device design or labeling is indicated and has not been previously evaluated by the Agency.

This guidance is not intended to apply to device kits (as defined by the 510(k) certification policy memo of April 23, 1994)³, nor is it intended to apply to combination products, such as drug/device or biologic/device combinations. Furthermore, this guidance is not intended to address the need for submitting 510(k)s by refurbishers or remanufacturers of devices. FDA intends to develop additional guidance specific to these situations.

This document attempts wherever possible to incorporate existing guidance and policy regarding when 510(k)s are necessary for modifications to a currently legally-marketed device.⁴ In some cases, the existing guidance derives from advice given to only a few manufacturers for a limited number of devices. In such instances, we have attempted to generalize the concepts to apply to a broader range of devices. However, special cases exist where both manufacturers and FDA have worked to establish definitive guidance for modifications to specific devices, e.g., for daily wear contact lenses.⁵ This guidance is not intended to supplant such existing device-specific guidance.

Good examples?

Assumptions/Axioms

In developing this guidance for aiding in the decision on when to submit a 510(k), a number of assumptions had to be made. Some derive from existing 510(k) policy and are widely known, others are necessary for using the logic scheme contained in this guidance. Thus, anyone using this guidance needs to bear in mind the following assumptions:

- Any person required to register under 21 CFR 807.20, who plans to market a device requiring premarket notification, will always have to submit a new 510(k). (Note that private label distributors and repackagers are exempt from submitting a 510(k) if they satisfy the requirements of 21 CFR 807.85(b).)
- The guidance applies to the change intended by the manufacturer and not any unforeseen results of implementing that change (although unforeseen results may impact safety and effectiveness and, thus, may be key in deciding to submit a 510(k)).
- The basis for comparison of any changed device is the device described by a cleared 510(k) (or a legally marketed pre-1976 device). That is, manufacturers may make a number of changes without having to submit a 510(k), but each time they make a change, the device they should compare to is their most recently cleared device (or their pre-1976 device), not the current legally marketed device. Although a single incremental change to a device may not substantially affect safety or effectiveness, the sum of many incremental changes can have a substantial effect on safety or effectiveness. Thus, manufacturers can only assure themselves that the last change has not had a significant effect by comparing to the most recently cleared device (or the device marketed prior to May 28, 1976). In effect, manufacturers need to submit a new 510(k) only when the sum of the incremental changes (taken together as though they were in fact one change) exceeds the regulatory threshold, described by the phrase, "could significantly affect the safety or effectiveness," for submitting a new 510(k). ✧
- Because many simultaneous changes may be considered in the evolution of device design, each type of change must be assessed separately, and, when any one change leads a manufacturer to decide to submit a 510(k), then a 510(k) incorporating all the current changes and comparing the new device to the originally cleared device (or one marketed prior to May 28, 1976) must be submitted. Note that this comparison may be done via a

table or other means. The new 510(k), once cleared, would form the basis of comparison for the next sequence of changes.

- Whenever manufacturers change their device, they must comply with the Good Manufacturing Practice regulation.⁶ This regulation requires that specification changes be subject to controls as stringent as those applied to the original design specifications of the device, and that such changes be approved and documented by a designated individual(s), which includes the approval date and the date the change becomes effective (21 CFR 820.100(a)(2)). This means that when a change is made to the device, there is verification through testing that the change does not adversely affect the device's safety or effectiveness. Only then can manufacturers assure an accurate assessment of the change(s) in the device in applying this guidance. They must maintain records of the validation under the current GMP. It is this validation of the changes and the documentation maintained by manufacturers that can support the decision on whether to submit a 510(k).
- To derive maximum benefit from this guidance, manufacturers should have in place a mechanism for evaluating whether a proposed change meets the regulatory threshold for a new 510(k). This mechanism could also document use of this guidance, if applicable, or other decision-making aids or bases for deciding whether a 510(k) is necessary.
- This guidance can not address every type of change to every type of device. No matter how ingeniously this guidance is applied, there will still be decisions in the "gray areas" that manufacturers will have to make. If manufacturers notify the Office of Device Evaluation of these instances, the gray areas can be better defined and understood, and, ultimately, this guidance can be refined to encompass the new areas.
- Manufacturers should understand that, even though they use this guidance and submit a 510(k), a substantial equivalence determination is not assured. Some changes to a device may be sufficiently significant that the changed device would be determined to be not substantially equivalent and a premarket approval application would be required before the device could be marketed.

Proposed Model

The model proposed here uses a flowchart to help manufacturers through the logic scheme necessary to arrive at a decision on when to submit a 510(k) for a change to an existing device. A single

Draft...August 1, 1995

flowchart containing all the logical steps necessary is large and cumbersome and could be quite daunting. Therefore, it is not included in this document. Rather, for ease of use, Figure 1 depicts the three logical breakouts of changes that might be made to a device:

- labeling changes,
- technology or performance specifications changes ,and
- materials changes.

The reader is referred to Figure 2 for labeling changes and to Figure 3 for technology or performance specifications changes. Materials changes are addressed by the flowchart in Figure 4, with the exception of materials changes for in vitro devices (IVDs), which are addressed by the flowchart in Figure 5.

To use the model, one must answer the questions posed in the flow chart until either directed to consider submitting a 510(k), document the decision-making, or notify the Agency of the change being effected. This last option occurs for the addition of a contraindication and the necessary documentation would constitute an administrative addition to the 510(k) currently on file. ✓

When contemplating changes to a device, manufacturers should use the flow chart for each individual type of proposed change, e.g., performance specification change, material change, etc. If any one of the changes results in a manufacturer's decision to submit a 510(k), then the 510(k) should be submitted and should incorporate all of the intended changes, as well as a comparison of the changed device to the originally cleared device described by the 510(k) currently on file with the Agency. If a manufacturer's consideration of all proposed changes results in a decision merely to document the decision-making, it should document the application of the model along with the necessary records of the validation of changes to the device.

For those circumstances where the proposed change is not addressed in the flow chart or in a device-specific guidance document, manufacturers are encouraged to contact the Office of Device Evaluation in CDRH to find out whether other, specific, guidance exists or if additional help is available.

Before using the flowchart, the reader is reminded that specific guidance has been developed for changes to a legally-marketed device that result from a recall. That guidance has been developed separately, but its philosophy is similar to this document in that changes to a product that are intended to bring a product back to its original specifications and that can be validated under GMPs

Draft...August 1, 1995

do not require a 510(k). On the other hand, changes in specifications that raise issues of safety or effectiveness would require a 510(k).

Note that the flowchart entries, "new 510(k)" and "documentation," are written in this way only for conciseness. The reader should interpret "new 510(k)" as **strongly consider submitting a 510(k)** and "documentation" as **document your analysis and file it for future reference**. This is, after all, a guidance document, and it is not intended to be prescriptive. It is intended only to provide the outline of a logic scheme for enhancing the likelihood of good decisions.

Each of the questions listed on the detailed flowcharts (Figures 2-5) are identified by the flowchart letter (A through D) and a sequential number. Those questions on the main spine of the flow charts relate to major questions to be asked and are identified by a letter and an integer, such as **A1, A2**, etc. Subsidiary questions that are asked in response to a "yes" answer are identified by the integer for the question, a decimal point and a sequential integer, e.g., **C2.1** in Figure 3 labels a decision point containing the question "(Is there a) Change in device performance specifications?" which follows the determination made in decision point **C2** that a change in material type is contemplated.

Labeling changes

As noted above, the types of changes are divided into labeling changes, technology or performance specifications changes, and materials changes. All labeling changes are handled with a separate logic scheme that concentrates on changes in indications for use as the threshold for contemplating the submission of a 510(k). Other labeling changes are more frequently recommended for documentation only.

Chart A (Figure 3) describes the logic scheme to be used when contemplating the need for a 510(k) for a labeling change. Changes in device labeling often pose the most difficult questions to be addressed by device manufacturers when deciding whether a new 510(k) submission is necessary. Frequently, a rather subtle change in a device labeling can have a significant impact on the safe and effective use of the device.

A 1 Is the labeling being revised for clarity, safer use or effectiveness? Device labeling may be changed for a multitude of reasons. Probably, most labeling changes result from attempts to clarify instructions or to make the device easier, safer or more effective to use. In most instances, such labeling changes would not result in the need to submit a 510(k). For example, the instructions for use of an automated clinical chemistry analyzer may be

modified to clarify how routine batch testing operation may be temporarily interrupted to allow efficient processing of high priority samples. No 510(k) would be necessary in this instance. If the question of a 510(k) submission did arise, however, manufacturers should document the rationale for their decision.

- A 2** Does the change affect the indications for use? Changes in the indications for use section of labeling raise more agency concern than any other aspect of labeling. In fact, changes in this part of the labeling will in most instances require the submission of a 510(k). For all practical purposes, the only substantial change in the indications for use that could occur without the submission of a 510(k) is when the change limits use to within the currently cleared indication. For example, the device was cleared for use with three specific indications and the firm decides to market the device for only two of those indications. Another example would be further limiting the patient population by age or weight. In determining whether a change to the indications for use raises issues of safety and effectiveness, the manufacturer should ask whether the specific uses pose any additional risks or expand the use to a new patient population.

Confusion often results when discussing the distinction between "indications for use" and the "intended use" of the device. The regulatory term, "intended use," refers to objective intent of the persons legally responsible for the labeling of the device. Intent may be determined by written expressions or may be shown by the circumstances surrounding the distribution of the device. The concept of intended use has particular relevance in determining whether a device can be cleared for marketing through the premarket notification (510(k)) process or must be evaluated in a premarket approval application (PMA). Manufacturers should recognize that if a particular labeling change results in a "new" intended use for the device, the Agency will find the device to be not substantially equivalent and require premarket approval.

For the purpose of this guidance, we have elected to avoid referring to "intended use" as a determinant in deciding when to submit a 510(k). We have chosen, rather, to identify the specific changes or modifications that we believe have a major impact on intended use and thus would require the submission of a 510(k) (§807.81(a)(3)). Two common labeling changes that impact intended use and would usually require submission of a 510(k) are:

- (1) reuse of devices previously labeled "single use only;" and
- (2) changes from prescription to over the counter or OTC.

One exception to (2) above is providing home-use instructions for devices that remain prescription and whose movement to use in the home is accepted medical practice in the United States. Many prescription devices are used in the home with increasing frequency and the Agency believes that 510(k)s are not necessary for the labeling changes. The reader is referred, however, to the FDA publication, "Write It Right,"⁷ for techniques to provide clear and understandable home use instructions.

- A 3 Is it a change in warnings or precautions?** In order to facilitate a continuous upgrading in device labeling, manufacturers should monitor device usage and promptly revise the warnings and precautions section based on use experience. 510(k)s for such changes are generally unnecessary unless new issues of safety or effectiveness have arisen to cause the change in labeling, however, manufacturers should document these changes in their files.
- A 4 Does the change add a contraindication?** While all changes in the labeled contraindications for device use should be reviewed by the Agency, CDRH recognizes that the addition of a contraindication based on new information is important to public health and should be implemented immediately. Because of this, manufacturers are encouraged to add new contraindications to their labeling and to notify existing users of their device as expeditiously as possible whenever a pressing public health need arises. The new labeling can be submitted to FDA after the fact as an addition to the existing 510(k) (indicating that the change is already effected). Manufacturers may continue to market their product with the modified labeling, unless otherwise notified by FDA. Manufacturers should be thoroughly familiar with what constitutes a true contraindication to do this.
- A 5 Does the change delete a contraindication?** On the other hand, deletion of a contraindication usually requires the submission of a 510(k) prior to effecting the change. In effect, deletion of a contraindication expands the Indications for use and, thus, would normally require submission of a new 510(k).

FDA believes that, if manufacturers follow this approach to changes in device labeling, the maximum number of necessary 510(k)s (those changes that pose the potential to significantly impact safety and effectiveness) will be submitted while minimizing the submission of unnecessary 510(k)s (those where safety and effectiveness are unlikely to be affected). At the same time, manufacturers should be able to retain the flexibility to update and clarify their labeling to maximize the safe and effective use of their devices.

Technology or Performance Changes

Chart B illustrates the decision making logic scheme for technology or performance specifications changes to a device.

B1 Is it a control mechanism change? Almost all changes in the control mechanism for a device raise questions of safety and effectiveness. Therefore, such changes will normally require the submission of a new 510(k). This is also true for changes in operating principle (decision point B2) as well as for changes in energy type (decision point B3). (This last was recognized as a significant change both in the statute⁸ and the implementing regulations.⁹) Changes of these types tend to be more revolutionary than evolutionary.

One obvious example of a control mechanism change that would raise new questions of safety and effectiveness would be the change from analog to digital control of a medical device. While the change to digital control can markedly improve device performance specifications and effectiveness, the integration of a digital control into a previously all analog system is complex and usually undertaken only as part of a major redesign of a product. Thus, it would be rare that a new 510(k) would not be necessary. Most often, such changes in control mechanism represent the introduction of a new product line.

Other changes in control mechanism of a similar nature would also lead to submission of a new 510(k). Examples of such changes would be the change from pneumatic to electronic control of a respiratory care device or a change from manual power to compressed gas power for a mechanical surgical stapler.

B2 Is it an operating principle change? Similar to a control mechanism change, a change in operating principle would also normally lead to the submission of a 510(k). A typical example of a new operating principle for a device would be changing the image reconstruction algorithm used in a computed tomography x-ray system from simple back projection to a new, more radiation-efficient method. In this case, testing both at the bench and in the clinic would be necessary to support a finding of substantial equivalence for the new device. Such changes may also be accompanied by significant labeling changes and, sometimes, by a need for operator retraining to assure continued safe and effective operation. Note, however, that some minor changes to the algorithm that can easily be validated by the manufacturer may not require the submission of a 510(k). Such incremental software changes are discussed under decision point B8 below.

- B3** Is it a change in energy type? Here, too, the submission of a 510(k) will be the likely result of a manufacturer's decision making. For example, changing from AC to battery power is usually part of a redesign to provide a portable device that can be used under different environmental conditions than the original device. Such a change would normally be accompanied by significant labeling changes, including a new or expanded indication for use. Note that this type of change does not include a change from 3V to 9V operation or a change from NiCad to lead acid storage batteries. Such changes would be considered changes in performance specifications or technical specifications and are discussed at decision point **B5** below.
- B4** Is it a change in environmental specifications? See **B8** below.
- B5** Is it a change in performance specifications? See **B8** below.
- B6** Is it a change in ergonomics of the patient/user interface? See **B8** below.
- B7** Is it a change in dimensional specifications? See **B8** below.
- B8** Is it a change in software or firmware?

The types of changes identified at decision points **B4** through **B8** have frequently been called design changes or engineering changes. They encompass everything from the routine specification changes necessary to maintain or improve device performance as a result of feedback from users, field or plant personnel, etc., up to and including significant product redesign. The major difficulty lies in sorting out which of these changes is significant enough to trigger the need for a 510(k). The logic scheme that follows is intended to lead a manufacturer through a thought process that will allow routine engineering change orders to occur, while identifying those changes for which a 510(k) would be indicated.

- B8.1** Does the change affect the indications for use? As with a labeling change, if the indications for use are affected, a 510(k) is probably necessary. An example of this would be changing the length of a surgical scissor from 4 inches to 12 inches so that the device could be used in laparoscopic procedures. The original indication was for open surgical procedures, while the new indication is for closed, endoscopically-controlled, procedures. Note that even though a surgical scissor is exempt from 510(k) by classification rule, one must still evaluate the change to assure that the change does not affect the device's classification.

B8.2 Are clinical data necessary to establish safety and effectiveness for purposes of substantial equivalence? Whenever a manufacturer recognizes that clinical data are needed and that bench testing or simulations are not sufficient to establish the substantial equivalence of a new design, it is clear that a 510(k) is necessary.

B8.3 Are clinical data necessary to show continuing conformance to a recognized standard? Although the need to collect clinical data for establishing substantial equivalence usually means a 510(k) is necessary, the mere fact that clinical data are collected does not imply the same thing. Frequently, clinical data of some sort may be necessary to demonstrate that device performance continues to conform to a voluntary standard. This frequently occurs for relatively minor changes to *in vitro* diagnostics that are labeled as meeting particular NCCLS standards. Such changes do not normally require a new 510(k).

B8.4 Do results of design validation raise new issues of safety and effectiveness? All changes to product design will require some level of design validation to assure that the product continues to perform as intended. The successful application of routine design validation activities will logically result in manufacturers documenting their efforts and proceeding with the design change, i.e., no issues of safety or effectiveness are raised. Occasionally, however, either routine design validation activities produce unexpected results or otherwise prove to be inadequate to validate the design change. In such instances, questions of safety and effectiveness may be associated with the design change, and the manufacturer may need to submit a new 510(k).

For example, a manufacturer sees the need to add a higher kilovoltage position on the control of a conventional diagnostic x-ray system. The results of the design change are predicted based on models, calculations, etc. The new system is used to image a phantom and all results are as predicted. The manufacturer documents the efforts and proceeds to production. On the other hand, a manufacturer of monitoring devices wants to use a more sensitive comparator circuit and makes other design changes to accommodate the more sensitive component. Tests with a simulator produce unexpected results, and additional work is necessary to rationalize what has occurred. The manufacturer should carefully assess what has been done and whether new questions of safety or effectiveness have been uncovered. One key to the answer (but not the only one) is whether a significantly different scheme for design validation was necessary.

- B9** Is there a change in packaging or expiration dating? Generally, changes in device packaging or changes in the expiration date for device use usually do not result in the need for a new 510(k). Such changes are properly within the function of GMPs. This is true whether the manufacturer applies an expiration date because of package integrity considerations or because of finite shelf life of the device. The reader should note however, that changes in packaging wherein two or more separately packaged products are combined as a kit will be addressed in a separate guidance document on kits.¹⁰
- B10** Has there been a change in sterilization? Changes in sterilization have the potential for affecting the safety or effectiveness of the device and, thus, must be carefully assessed.
- B10.1** Has there been a change in performance specification of the device or in the sterility assurance level attained as a result of the change in sterilization? Changes in the method of sterilization have the potential for changing performance characteristics of a device. This is particularly true of materials properties of plastics. When manufacturers make changes in sterilization methods, they must document that important properties of the device do not change as a result. In addition, if the sterility assurance level is changed, manufacturers must assess whether device safety or effectiveness may have been compromised by the new (lower) level. Manufacturers need, in these instances, to assess critically the need for a new 510(k) for their product.

Materials Changes

Firms making changes to the materials from which their device is manufactured first need to consider the other types of changes discussed above and their impact on the decision regarding the need for a new 510(k). For example, a change of a material type, as discussed below, might also engender a change in the labeling of the device, e.g. the removal of a contraindication or the addition of a new warning. These changes should be considered first, before applying the logic scheme described in this section. See Chart C.

- C1** Is the device an in vitro diagnostic product (IVD)? If the device is an IVD, refer to the later section of this Guidance which is specific to materials changes in IVD's (Chart D).
- C2** Is this a change in type of material from which the device is manufactured? Is the generic type of material being changed? There is considerable discussion available regarding what is meant by generic materials types. FDA is developing a Biomaterials Compendium for

implant devices which will give form and structure to this discussion. The goal of this Compendium is to relate the type of device to the materials of manufacture. Appendix A to this Guidance is a draft of the current tables of generic materials from that Compendium. (It is anticipated that the tables from the Biomaterials Compendium will become final by the time this guidance on when to submit a 510(k) becomes final.)

C2.1 Is there a change in performance specifications? Frequently, a change in materials is made to purposefully alter the performance specifications of a device. In this case, decision point **B5** should be used (in addition to this one) to help decide whether a 510(k) is necessary. Sometimes, however, changes in materials can inadvertently affect performance of a device. Under GMPs, manufacturers are responsible for assessing this possibility. If performance specifications are inadvertently changed, it is possible that a new 510(k) is necessary. Manufacturers should still use the logic scheme beginning at decision point **B5** to help decide whether a 510(k) is necessary.

C2.2 Is the device an implant? Implant devices are those described in the "permanent contact" category of ISO 10993-1.¹¹

C2.2.1 (Since the device is an implant) Will the material of the affected part of the implant be likely to contact body tissues or fluids? Changes in materials that contact body tissues or fluids may critically affect the device's safety or effectiveness, either because of potentially new interactions of the device material on the body or because of the body's environmental effects on the new material in the device. Except in very restricted circumstances, manufacturers are likely to opt for submitting a new 510(k) in this instance. Examples of devices for which changes in material type would normally require a new 510(k) are total joints or their components. On the other hand, changes in materials of an implant that are not intended to contact body tissues or fluids are not likely to require a 510(k). Examples of such changes in material type are changes in the interior materials of an implantable electric stimulator (e.g., a single chamber cardiac pacemaker) which are sealed from ingress of body fluids or tissues.

C2.3 Will the material of the affected part of the device be likely to contact body tissues or fluids in vivo? Since the decision in box **C2.2** above sorted from consideration the implant devices, the remaining devices, i.e. those for which a "yes" answer is appropriate, include both "limited exposure" and "prolonged exposure" devices, as described in ISO 10993-1: Biological Evaluation of Medical Devices, Part 1: Evaluation and Testing. Examples of prolonged

exposure devices which might contact in vivo fluids or tissues are: a parenteral feeding catheter; a wound drain; an infusion catheter; sutures; etc.

C2.3.1 Considering that the material is likely to contact in vivo body tissues or fluids and the requirements of ISO 10993-1, is additional testing required? ISO 10993-1 outlines a rational process by which a manufacturer can determine which types of biological evaluation should be performed on a device prior to its use with patients. Proper consideration of the various aspects of this evaluation should lead the manufacturer to consistent decisions regarding the changes to the material and the necessity of additional testing. If such additional testing is required, a 510(k) is usually necessary.

C3 Is this a change in the formulation of the material, but not a change in material type?

These are changes within a single generic material type that can affect the chemistry, metallurgy or other property or stability of the material. These do not include changes in processing aids, catalysts, residual contaminants or manufacturing aids that are not intended to be part of the material. An example of a change in material formulation is a change from one type of polyurethane to another or a change from a AISI Type 316 stainless steel to a AISI type 400 stainless steel. To determine the need for a 510(k) for a change in material formulation, the same logic used for a change in material type should be followed. (See C2.1 above.)

C4 Is there a change in the vendor of the raw material from which the device is manufactured? Changes in the suppliers of raw materials to the manufacturers of medical devices are described in both the existing GMP Regulations and 510(k) Regulations. These regulations establish the responsibility of the device manufacturer to purchase those materials against a materials specification. Such a specification requires performance characteristics of the raw materials related to the desired performance of the finished device. The controlling aspect of the logic scheme for this change is the existence of such a material specification.

C4.1 Is the new material being supplied to a specification? If the material is being supplied to a specification, a 510(k) is probably not required. For example, a device manufacturer might include a transparency requirement in the purchase specification for tubing for an implantable catheter. Such a requirement might be related to the later processing of the tubing into the finished device. To change the supplier of that material, the specification must include a transparency requirement, and the device manufacturer's design validation, as required by the GMP regulation, must describe the rationale for that transparency requirement. Further, the manufacturer should document that component specifications are

still met and that the performance specifications (characteristics) of the device are not significantly affected.

Materials Changes for In Vitro Diagnostic Products

D.1 Is there a change in performance specifications? Changes in the material used in an IVD can affect the performance of the product and should be assessed as to their impact on safety and effectiveness.

D.1.1 Does the change in performance specifications of the IVD affect its indications for use? A change in the indications for use will likely include a change in the labeling for the IVD. Examples of changes in indications for use that require a new 510(k) are: the expansion of the use of the test to a new population of clinical applications; and the addition of a new matrix for analysis, e.g. for an IVD approved for serum, the addition of use with other matrices. An example of a change in an indication for use not requiring a new 510(k) is the expansion of the use of the test to other equivalent instrumentation beyond that noted in the original submission. (For details on the procedure to be followed for this change, see "FDA Guidance for Review of Primary and Secondary Reagents.")¹² *It should be noted that a reduction in the indications for use for an IVD will not always trigger the need for a 510(k).*

D.1.2 Does the change in the performance specifications of the IVD mean that new clinical data will be necessary to establish the safety and effectiveness of the device for the purpose of demonstrating substantial equivalence? An example of a change where a new 510(k) would be required is if the material change results in a change in cut-off. In that case, clinical testing would be required, and the results should be part of the new 510(k). (Note that clinical testing refers to testing of clinical samples either at the manufacturing site or at sites of intended use.) An example where new clinical data are necessary, but a new 510(k) is not necessary, is when the testing of the new material, using splits of patient specimens, is necessary to compare the new material to a previously used material.

D.1.3 Does the change in the performance specifications of the IVD mean that new clinical data will be necessary to show continuing conformance of the device to a recognized standard? Voluntary standards such as those developed by the National Committee of Clinical Laboratory Standards (NCCLS), the National Cholesterol Educational Program and other professional groups may be the basis of a substantial equivalence determination for an IVD.

Deviation of IVD performance specifications from the performance values of the standard may indicate that substantial equivalence of the device is in question.

- D.1.4 Do the results of the design validation performed as a result of this change in materials raise new questions of safety and effectiveness?** As noted above, design validation is required when changes are made to any device, including an IVD. The results of such a validation showing that questions of safety and effectiveness have been raised may indicate that the performance of the device is not known or well established, and a 510(k) may be necessary.
- D.2 Does the change in material alter the operating principle of the IVD?** Examples of changes in materials that alter the operating principle of the device and would routinely require a 510(k) are: changes from liquid to solid reagent; change from an RIA to a non-RIA; changes in the source and type of an antibody, e.g. from one animal species to another or from polyclonal to monoclonal or vice-versa; change from immunofluorescence to ELISA; and a change in conjugates. Examples of changes that might affect the operating principle of the IVD are changes in reaction components or materials such as calibration materials and quality control materials or changes in methods such as specimen pretreatment, incubation times and temperatures. If these result in changes in the reporting of performance in labeling, they would require a new 510(k). Examples of changes in materials which do not affect the operating principles are changes in preservatives and changes in formulations of the existing materials.

Flowchart Definitions

The following definitions are provided to clarify the meaning of all terms used in the flow chart and to assist in determining when a 510(k) is necessary for a change to an existing device. Wherever possible, existing definitions from the Food, Drug and Cosmetic Act, the medical device regulations or ODE Bluebook memoranda have been used. In some cases, where regulatory definitions are unavailable, we have relied on strict dictionary definitions of terms.

1. Indications for use: An indication for use is "a general description of the disease or condition the device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the device is intended."¹³ The indications include all the labeled patient uses of the device, as for example:

- the condition(s) or disease(s) to be screened, monitored, treated or diagnosed,
- prescription versus over-the-counter use,
- part of the body or type of tissue applied to or interacted with,
- frequency of use, or
- physiological purpose (e.g., removes water from blood, transports blood, etc.).

The indications for use are normally found in the indications section of the labeling, but indications may also be inferred from other parts of the labeling such as the precautions, warnings or the bibliography sections. In some instances, a change in the indications for use may imply a change in the intended use for the device, in which case, the 510(k) for the change would be found not substantially equivalent and a premarket approval application or a reclassification petition would be necessary.¹⁴

2. Labeling: *The term "labeling" means all labels and other written, printed, or graphic matter (1) upon any article or its containers or wrappers, or (2) accompanying such article.*¹⁵ This can include, among other things, any user or maintenance manuals, as well as advertising and promotional literature.

3. Warnings, precautions and contraindications:

- Warnings describe serious adverse reactions and potential safety hazards that can occur in the proper use or misuse of a device, along with consequent limitations in use and mitigating steps to take if they occur.

- ° Precautions describe any special care to be exercised by a practitioner or patient for the safe and effective use of a device.
 - ° Contraindications describe situations in which the device should not be used because the risk of use clearly outweighs any reasonably foreseeable benefits.¹⁶
4. Documentation: Recording the results of applying the model to proposed changes in a device. Consideration of each decision point should be recorded, as well as the final conclusions reached. A copy of this documentation should be maintained for future reference.
 5. Control Mechanism: The manner by which the actions of a device are directed. An example of a change in control mechanism would be the replacement of an electro-mechanical control with a microprocessor control.
 6. Operating Principle: The mode of operation or mechanism of action through which a device fulfills (or achieves) its intended use. An example of a change in operating principle would be using a new algorithm to compress images in a picture archiving and communications system.
 7. Energy Type or Character: The type of power input to or output from the device. Examples of a change in energy type or character would be a change from AC to battery power (input) or a change from ionizing radiation to ultrasound to measure a property of the body (output).
 8. Environmental Specifications: The (range of) acceptable levels of environmental parameters or operating conditions under which the device will perform safely and effectively. Examples of changes in environmental specifications would be expanding the acceptable temperature range in which the device will operate properly or hardening the device to significantly higher levels of electromagnetic interference.
 9. Performance Specifications: The performance characteristics of a device as listed in device labeling or in finished product release specifications. Some examples of performance specifications are measurement accuracy, output accuracy, energy output level, stability criteria, etc.
 10. Ergonomics of Patient/User Interface: The way in which the device and the patient/user are intended to interact. Examples of this would be the various audible or visible alarms intended to alert the user to a hazardous condition, the layout of a control panel, or the mode of presentation of information to the user.

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11. Packaging: Any wrapping, containers, etc., used to protect, to preserve the sterility of, or to group medical devices.

12. Expiration date: The date beyond which there are no data to assure that the product may perform safely or effectively.

13. Method of Sterilization: The physical or chemical mechanism used to achieve sterility or to achieve a specific sterility assurance level (SAL).

14. Software: The set of instructions used to control the actions or output of a medical device, to provide input to or output from a medical device, or to provide the actions of a medical device. This definition includes software that is imbedded or permanently a part of a medical device, software that is an accessory to a medical device, or software that is itself a medical device.

15. Material Supplier: The firm supplying the raw material to a finished device manufacturer.

16. Reuse: Use of a device more than once on a single patient or on more than one patient. Actions necessary for reuse of a device may include instructions for assembly/disassembly, on-site sterilization or disinfection, etc. This definition does not include the refurbishing or repair of a device for redistribution or resale.

17. Material Type: The generic name of the material from which the device is manufactured. (Use the generic name in the biomaterials compendium.) An example of a material type change would be the change from natural latex rubber to synthetic rubber.

18. Material Formulation: The base polymer formulation or the alloy, additives, colors, etc., used to establish a property or the stability of the material. This does not include processing aids, mold release agents, residual contaminants, or other manufacturing aids that are not intended to be a part of the material. An example of a change in material formulation would be a change from a series 300 stainless steel to a series 400 stainless steel.

19. Dimensional Specifications: The physical size and shape of the device. Such specifications may include the length, width, thickness or diameter of a device, as well as the location of a part or component of the device.

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20. Implant: A device which is intended to reside within a surgically or naturally formed channel or cavity of the human body for a period of 30 days or more (excluding dental restoration materials).

21. In Vitro Device: *Those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body.*¹⁷

22. Change: As used in the model, this means a proposed change and not the impact of a proposed change. Important impacts of a proposed change are identified on the flow chart. For example, a manufacturer may propose a change in method of sterilization. This change could impact on performance specifications because of potential chemical or physical damage to the device. The proposed change (in method of sterilization) is the change that must be used in the model.

Draft...August 1, 1995

1. Section 520(f) of the Food, Drug and Cosmetic Act.
2. ODE Bluebook Memorandum No. K86-3 (June 30, 1986), "Premarket Review Notification Program."
3. "Kit Certification and Information for Kit 510(k)s," memorandum to manufacturers(?), June 7, 1993.
4. See, for example, ODE Bluebook Memoranda K86-3, K90-1, etc, as well as device-specific guidance documents.
5. "Premarket Notification Document (510(k)) for Daily Wear Contact Lenses," May 12, 1994.
6. 21 CFR Part 820.
7. "Write It Right, Recommendations for Developing User Instruction Manuals for Medical Devices Used in Home Health Care," HHS Publication (FDA) 93-4258, August 1993.
8. Section 513(i)(1) of the Food, Drug and Cosmetics Act.
9. 21 CFR 807.81(a)(3).
10. (Reference to draft guidance on Kits).
11. ISO 10993-1, Biological Evaluation of Medical Devices, Part 1: Evaluation and Testing.
12. "FDA Guidance for Review of Primary and Secondary Reagents."
13. 21 CFR 814.20(b)(3)(i).
14. ODE Bluebook Memorandum K86-3, "Guidance on the CDRH Premarket Notification Review Program."
15. Section 201(m) of the Food, Drug and Cosmetic Act.
16. For further information see ODE Bluebook Memorandum G91-1, "Device Labeling Guidance.
17. 21 CFR 809.3(a).

WHEN TO FILE A 510(K) AFTER A CHANGE TO AN APPROVED DEVICE

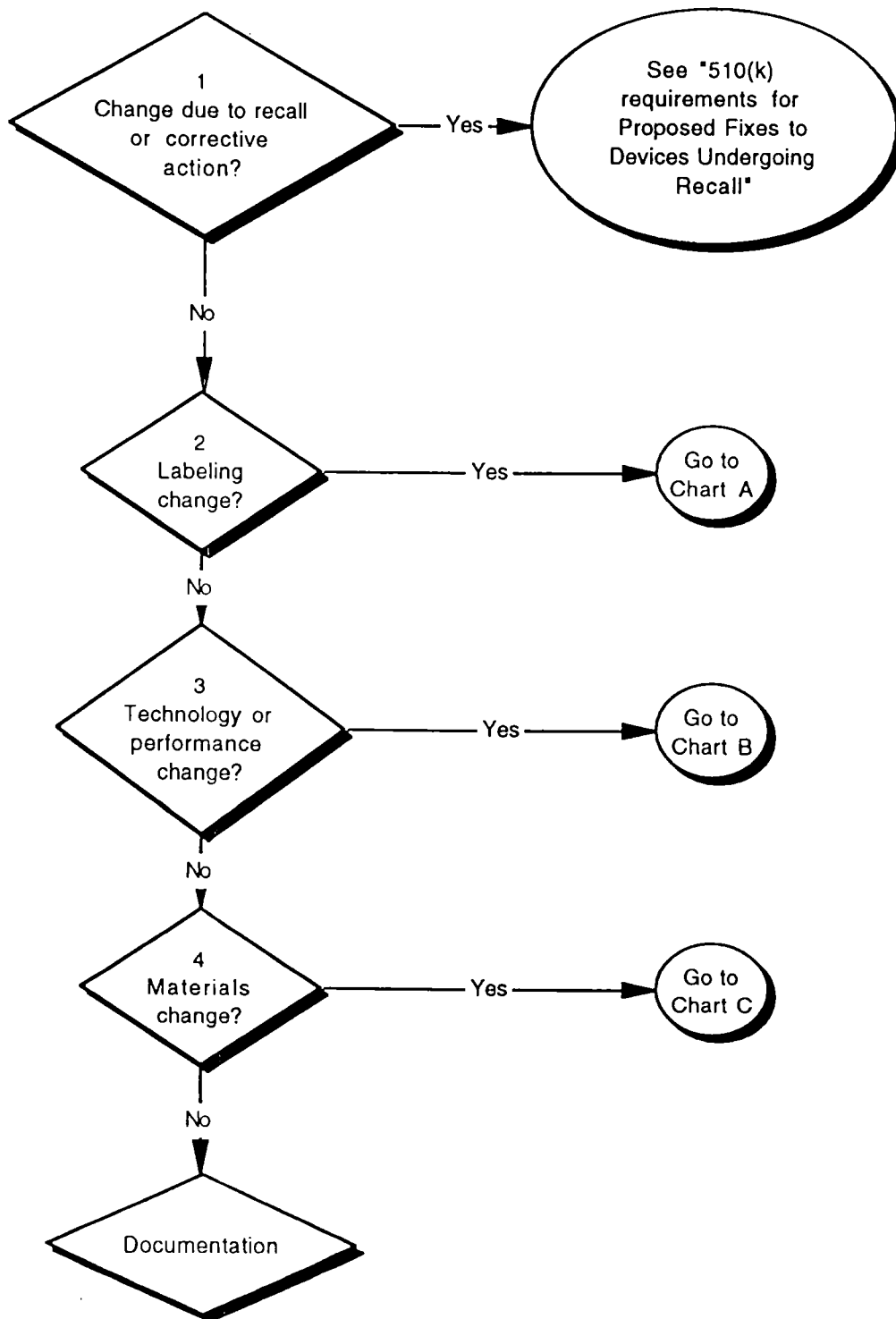


Figure 1

CHART A - IS IT A LABELING CHANGE?

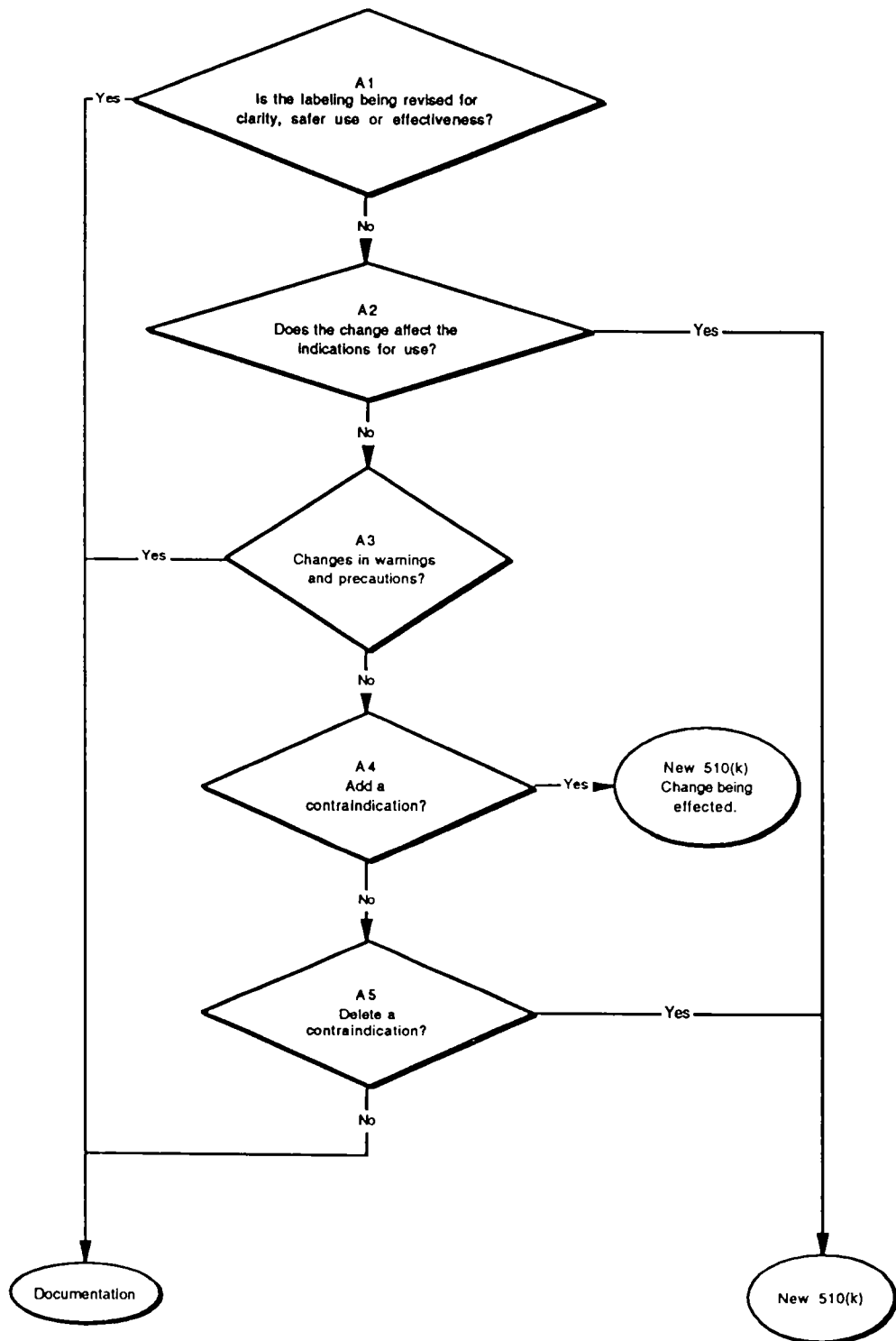


Figure 2

CHART B - IS IT A TECHNOLOGY OR PERFORMANCE CHANGE?

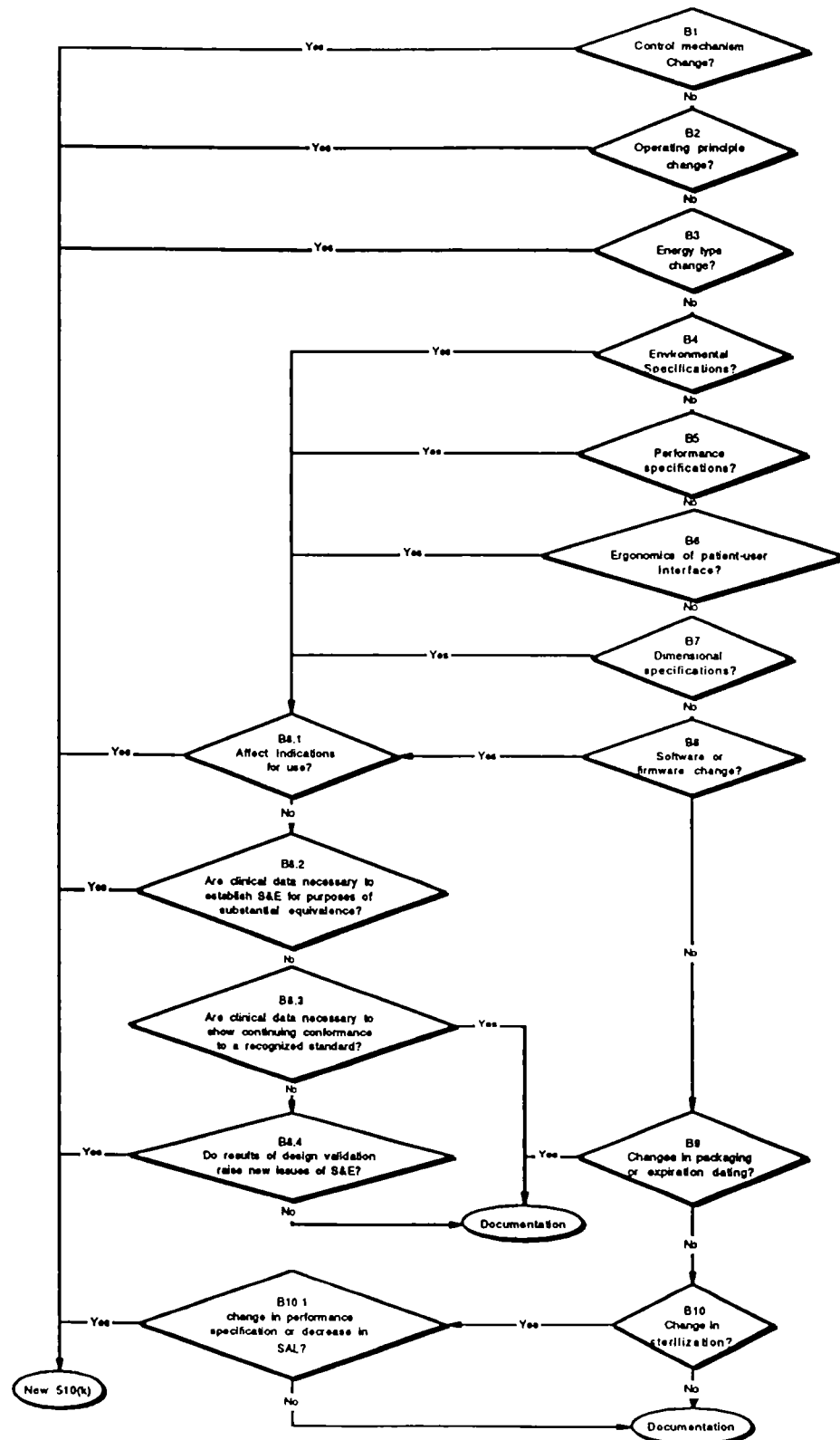


Figure 3

CHART C - IS IT A MATERIALS CHANGE?

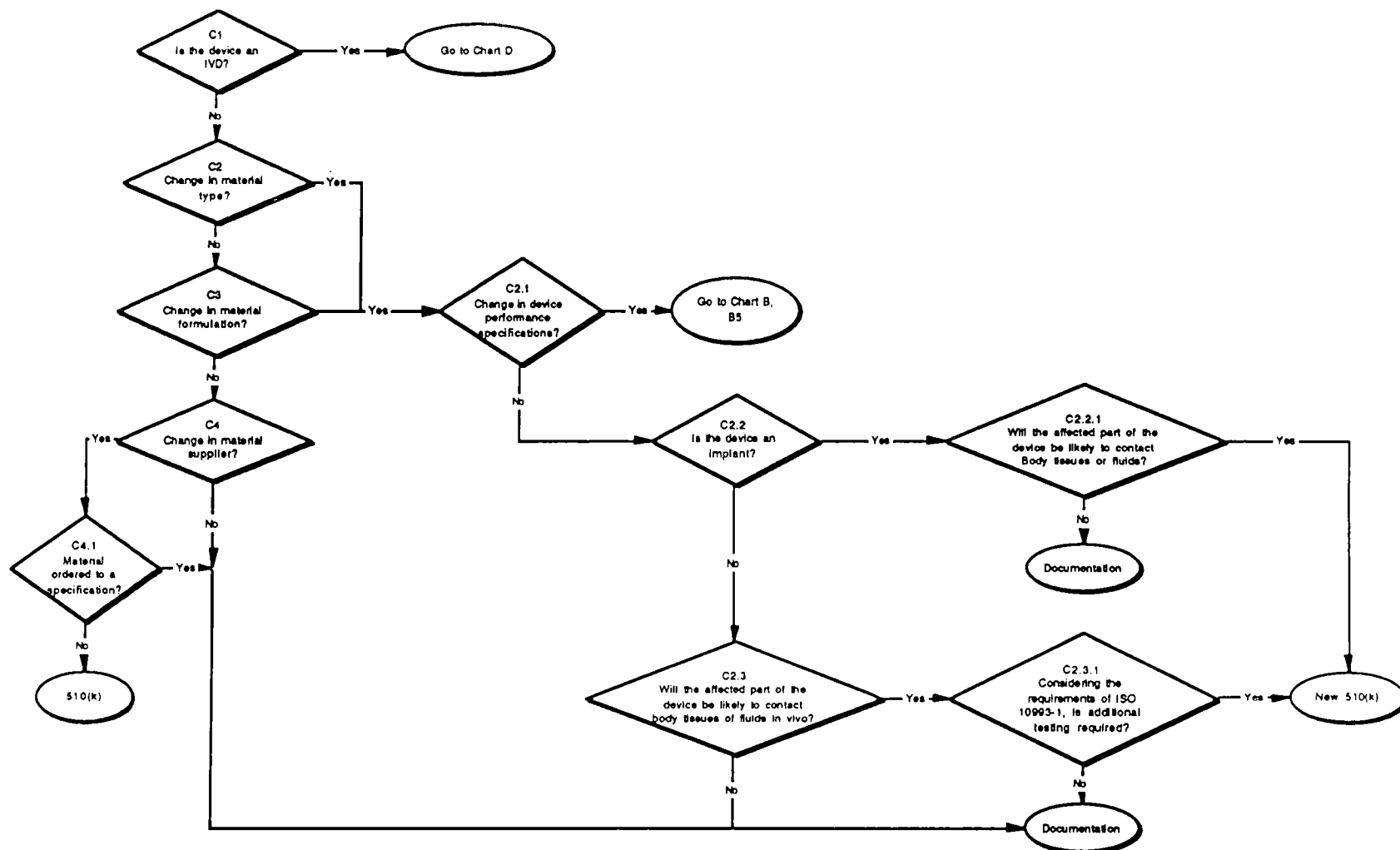


Figure 4

CHART D - MATERIALS CHANGE FOR AN IVD

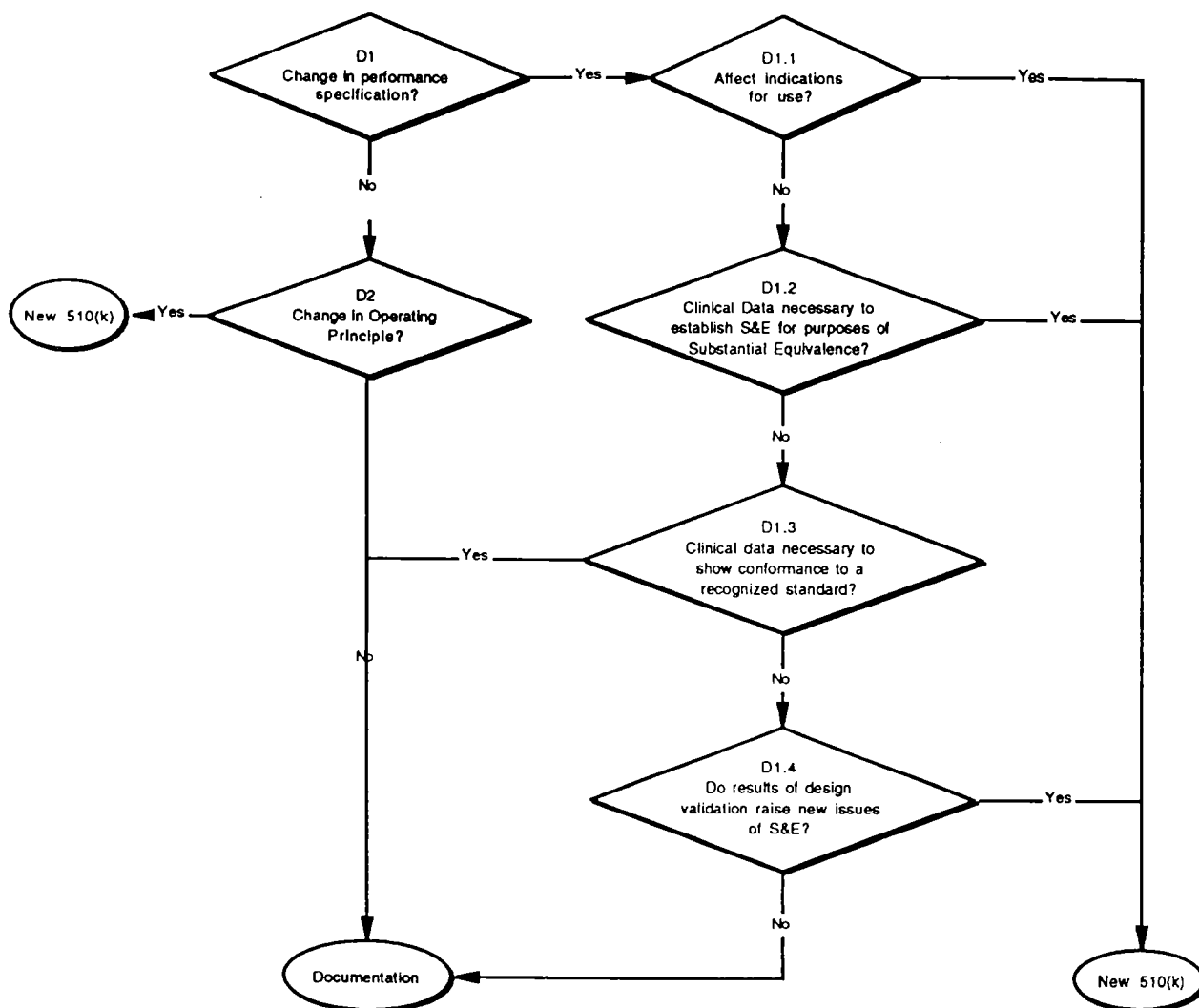


Figure 5

Draft...August 1, 1995

**APPENDIX: DRAFT CONTROLLED VOCABULARY FROM THE FDA BIOMATERIALS
COMPENDIUM**

Material Class

metal
polymer
ceramic
composite
biological origin

Material Subclasses

Metals

stainless steels
co & ni alloys
titanium alloys
zirconium alloys
tantalum alloys
precious metals
amalgams

Polymers

thermoplastics
thermoset/elastomers
absorbable
adhesives
fluids

Ceramics

Al compounds
Ti compounds
Zr compounds
Ca compounds
carbons
glasses

Composites

polymer matrix
metal matrix
ceramic matrix

Biologic Origin

allograft
xenograft
engineered tissues
biomolecules

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METALS

Generic Material Names

Stainless Steels

316L FeCrNiMo
nitrogen strengthened
ferritic ppt hardened
?martensitic, ptt hardened

Co & Ni Alloys

CoCrMo period
CoCrWNi
CoNiCrMo
CoNiCrMoWFe
CoCrNiMoFe

Ti Alloys

CpTi (grade 1-4)
Ti 6Al 4V
Ti 6Al 7Nb
Ti 5Al 2.5 Fe
Ti 3.8Al15Mo5Zr
Ti 13Nb13Zr
Ti 12Mo6Zr2Fe
Ti 15Mo2.8Nb.2Si
NiTi alloy

Zr Alloys
Zr2.5Nb

Ta Alloys
unalloyed Ta

Precious/Noble
gold
silver
platinum
palladium
iridium
Pt/Ir

Amalgams

*Ag-Hg amalgams

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POLYMERIC MATERIALS

Thermoplastic

acetals
*acrylic, powder/liquid
acrylic, PMMA
acrylic, hydrogels
fluorocarbons
polyamides (nylons)
poly(aryl)ether ketones
poly(aryl)sulfones
polycarbonate
parylene
polyesters (PET, PBT)
polyethylene
polyethylene, UHMWPE
polyimides
polypropylene
polystyrene
polyurethane
polyvinyl alcohol
polyvinyl chloride PVC
polyvinylidene chloride

PEO hydrogel

Adhesives

cyanocrylates
acrylic based
epoxy
silicone

Thermoset/Elasto

butyl
epoxy
hydrogel based
natural hevea
polyesterurethanes
polyetherurethanes
polyurethanes (other)
polyisoprene
rubbermodified acrylic
silicone gel
silicone elastomer
bis/GMA

Fluids

polyvinylpyrrolidone
silicone (PDMS)

Absorbable

polyesters
polyethers
polyanhydrides
polyorthoesters
polyetheramide

copolymers

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CERAMICS and COMPOSITES

CERAMICS

Al Compounds

polycrystalline alumina
sapphire
ruby

Ti Compounds

titanium dioxide
TiN
titanium carbide

Zr Compounds

zirconium dioxide
MG-PSZ
Y-TZP
CaO stabilized

Ca Compounds

Beta-TCP
Ca phosphate
Ca hydroxyphosphate
calcium aluminate
gypsum
HA/TCP
hydroxylapatite

Carbons

fibers
graphite
LTI pyrolytic
LTI-Si alloy
ULTI pyrolytic
vapor deposited
vitreous

Glasses

bioactive glass
silica based

COMPOSITES

Polymer Matrix

CFR epoxy
CFR poly(etherketones)
CFR poly(imide)
CFR Poly(sulfone)
glass reinforced
ceramic particle reinforced
metal fiber reinforced
PUIPC
*PTFE composites
CFR UHMWPE
bis/GMA composites
urethanedimethacrylate

Metal Matrix

*Ta-Eigiloy wire
Ag-MP35 I?

Ceramic Matrix

carbon-carbon
zinc phosphate cement
porcelains
*zinc oxide eugenol
glass ionomer cements

zinc polycarboxylate cement

EXECUTIVE OFFICE OF THE PRESIDENT

05-Apr-1996 08:10am

TO: Sally Katzen

FROM: Jonathan Winer
Office of Mgmt and Budget, OIRA

CC: John F. Morrall, III
CC: Daniel J. Chenok
CC: Elizabeth E. Drye

SUBJECT: FDA ANNOUNCES PILOT INITIATIVES TO IMPROVE MEDICAL DEVICE RE

FDA ANNOUNCES PILOT INITIATIVES TO IMPROVE MEDICAL DEVICE REVIEW PROCESS
The Food and Drug Administration April 3 announced plans to implement initiatives designed to streamline regulation of medical devices (61 FR 14786, 14789, 14922).

One initiative is a pilot program to assess whether reviews by third-party organizations will improve the efficiency of FDA's medical device review process and conserve resources. The pilot program will run for two years, beginning Aug. 1, according to the Federal Register notice. Besides studying whether third-party organizations can safely and efficiently complete reviews of new devices, FDA will evaluate whether conflict-of-interest rules can be maintained in a third-party review process. The pilot project will be limited to reviews of low- and moderate-risk medical devices--electronic thermometers and surgical gloves, for example--for which no clinical safety and effectiveness data is required. Manufacturers of these products submit premarket notifications, also known as 510 (k)s, in order to show that their products are substantially equivalent in safety and efficacy to existing approved products. HHS estimated that FDA receives approximately 1,500 510(k)s each year.

The third-party pilot program will operate on a voluntary basis--manufacturers can request third-party review or leave the process to FDA. According to HHS, companies opting for third-party review will be able to choose from among the FDA-certified companies to review 510(k) applications under the pilot program.

The third-party company will review the product, submitting the marketing application, the results of its review, and its recommendations to FDA for assessment. FDA will make a decision on the application within 30 days. This would eliminate the first phase of FDA's traditional review process, HHS said.

Proposals Test Public Health Protections
FDA has been sharply criticized by members of Congress and industry groups for the lengthiness of its medical device review process and provisions addressing the issue appear in FDA reform legislation introduced in both the House and Senate (S 1477, HR 3201).

In a statement issued by the Department of Health and Human Services, FDA Commissioner David A. Kessler commented, "The test for any reform is whether it protects the public health. Our proposal will test whether this speeds up

the process and if the integrity of the review can be maintained.''
HHS Secretary Donna E. Shalala described the initiatives as ``another example of FDA's innovative regulatory strategy for the 21st century.''
``It explores how the agency can best review low-hazard products while enabling the agency to target its resources where risks are high,' she added. These initiatives also respond to goals set out in the National Performance Review's Reinventing Government effort headed by Vice President Gore, which aims to improve the way the federal government works while reducing costs. Comments on the FDA's proposal to implement a third-party review test program, Docket No. 96N-0025, should be submitted by June 3 to the Dockets Management Branch (HFA-305), FDA, 12420 Parklawn Dr., Room 1-23, Rockville, Md. 20857.

Companies interested in applying for recognition as a third-party reviewer should send applications to the Division of Small Manufacturers Assistance (HFZ-220), Attn: Third-Party Recognition, Center for Devices and Radiological Health, FDA, 1350 Piccard Dr., Rockville, Md. 20850.

To help prospective third-party reviewers prepare their applications, FDA will hold an informational briefing April 15. Registration forms for the briefing are available by fax from CDRH's Facts on Demand, (800) 899-0381 or (301) 827-0111. The registration forms are found on FDA's home page, <http://www.fda.gov>, under the Medical Devices and Radiological Health category, Third Party Review option.

Manufacturers who want to submit 510(k)s for review by third party firms should send their applications to the Document Mail Center (HFZ-401), Attn: Third Party Review, CDRH, FDA, 9200 Corporate Blvd., Rockville, Md. 20850.

Inspection Procedure Changes

~~FDA's second initiative, which was developed in conjunction with a task force of medical device industry representatives, would apply to manufacturers having a good history of compliance with FDA regulations.~~

~~The initiative proposes changing FDA's inspection process to:~~

- ~~o Give manufacturers advance notification of inspections, rather than conducting unannounced inspections;~~
- ~~o Allow firms to note on official inspection reports any previous violative findings that were corrected immediately; and~~
- ~~o Require FDA to issue a letter to companies informing them they successfully passed the inspection.~~

~~The inspection initiative will be implemented immediately and last throughout 1996. Although FDA initially is limiting the pilot inspection program to medical device companies, it will be expanded to other product areas, if it is found to be effective after evaluation.~~

~~According to the Federal Register, medical device inspections currently done under contract by California, Colorado, and Texas will not be included in the pilot program.~~

~~Comments on the proposed inspection pilot program, Docket No. 96N-0086, should be submitted to the Dockets Management Branch at the address noted above.~~

~~FDA also is proposing to streamline requirements that medical device manufacturers must meet under the National Environmental Policy Act. According to HHS, the proposal will apply to all FDA-regulated products and is designed to reduce the number of environmental assessments industries must prepare and submit to FDA. This change could result in yearly savings of approximately \$15 million for medical device manufacturers and save FDA \$1 million as well, HHS said.~~

PMA Approval Process Suspensions

Meanwhile, under a final rule scheduled to appear in the April 5 Federal Register, FDA has established procedures for temporarily suspending approval of a premarket approval application (PMA) or PMA supplement. FDA received new authority to halt temporarily the PMA process from the Safe Medical Devices Act of 1990 (PL 101-629). Under SMDA, FDA can take action after an informal hearing if ``there is reasonable probability that continued distribution of a device would cause serious, adverse health consequences or death.'' After temporarily suspending the PMA, FDA has 60 days to permanently withdraw the approval of the PMA or PMA supplement. The final rule becomes effective 30 days after publication of the notice in the Federal Register. For more information, contact Lisa A. Rooney, CDRH (HFZ-84), FDA, 2094 Gaither Rd., Rockville, Md. 20850; (301) 594-4765, extension 164.

Hazardous Materials

[Federal Register: January 29, 1996 (Volume 61, Number 19)]
[Proposed Rules]
[Page 2739-2748]
From the Federal Register Online via GPO Access [wais.access.gpo.gov]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
21 CFR Parts 314, 600, and 601

[Docket No. 95N-0329]
RIN 0910-AA57

Changes to an Approved Application

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the biologics regulations for reporting changes to an approved application in order to reduce unnecessary reporting burdens on applicants holding licenses approved in the Center for Biologics Evaluation and Research (CBER) under the Public Health Service Act (the PHS Act) to manufacture biological products. In addition, FDA is proposing to amend the corresponding drug regulations for submitting supplements for and reporting changes to an application approved under the Federal Food, Drug, and Cosmetic Act (the act) for well-characterized biotechnology products reviewed in the Center for Drug Evaluation and Research (CDER) to harmonize the drug and biologics regulations. These actions are part of FDA's continuing effort to achieve the objectives of the President's "Reinventing Government" initiatives.

DATES: Written comments on this proposed rule by April 29, 1996. Submit written comments on the information collection requirements by February 28, 1996, but not later than March 29, 1996. The agency proposes that any final rule that may issue based on this proposal become effective immediately upon its date of publication in the Federal Register.

ADDRESSES: Submit written comments on this proposed rule to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857. Submit written comments on the information collection requirements to the Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, Attn: Desk Officer for FDA.

FOR FURTHER INFORMATION CONTACT:

Tracey H. Forfa or Timothy W. Beth, Center for Biologics Evaluation and Research (HFM-630), Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852-1448, 301-594-3074
or;

Yuan Yuan Chiu, Center for Drug Evaluation and Research (HFD-820), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-3510.

SUPPLEMENTARY INFORMATION:

I. Introduction

A. Background

This proposed rule is issued in accordance with the principles set forth in the Regulatory Flexibility Act of 1990 (Pub. L. 96-354),

Executive Order 12866; the President's memorandum of March 4, 1995, announcing the ``Regulatory Reinvention Initiative;'' the President's memorandum of April 21, 1995, entitled, ``Regulatory Reform--Waiver of Penalties and Reduction of Reports;'' the April 1995 Publication ``Reinventing Drug and Medical Device Regulations, and the November 1995, Presidential National Performance Review report ``Reinventing the Regulation of Drugs Made From Biotechnology.'' The Regulatory Flexibility Act requires Federal agencies to consider the burden a rule may have on small business entities through a regulatory flexibility analysis and to periodically review its rules to determine if regulatory burdens may be reduced. Executive Order 12866 directs Federal agencies and the Office of Information and Regulatory Affairs (OIRA) to implement measures that will reform and make the regulatory process more efficient. -

Under Executive Order 12866, FDA published a document in the Federal Register on January 20, 1994 (59 FR 3043), that announced FDA's plan to review and evaluate all significant regulations for their effectiveness in achieving public health goals and in order to avoid unnecessary regulatory burden. FDA published two documents in the Federal Register of June 3, 1994 (59 FR 28821 and 28822), that announced the review of certain general biologics and blood and blood product regulations by CBER to identify those regulations that are outdated, burdensome, inefficient, duplicative, or otherwise unsuitable or unnecessary.

The President's memorandum of March 4, 1995, entitled ``Regulatory Reinvention Initiative'' sets forth four steps toward regulatory reform, one of which instructs agencies to revise those regulations that are in need of reform. FDA believes that this proposed regulation is in keeping with these principles without compromising the agency's duty and commitment to protect the public health. The President's memorandum of April 21, 1995, directs Federal agencies to reduce the frequency of regularly scheduled reports that the public is required, by rule or policy, to provide to the Federal government. In addition, the November 1995, Presidential National Performance Review report entitled ``Reinventing the Regulation of Drugs Made From Biotechnology,'' focused on FDA's efforts to reform the regulation of biotech drugs used for therapy.

FDA also held a public meeting on January 26, 1995, to discuss the retrospective review effort. The public meeting was a forum for the public to voice its comments regarding the retrospective review of regulations being undertaken by CBER.

Many of the comments submitted to the public docket regarding the CBER retrospective regulations review were requests to revise Sec. 601.12 Changes to be reported (21 CFR 601.12). Most of those comments requested revision of the regulation to reduce the burden on applicants of reporting changes to an approved application. As part of the CBER regulatory review initiative, and in response to the comments received, FDA published in the Federal Register of April 6, 1995 (60 FR 17535), a document entitled, ``Changes to Be Reported for Product and Establishment License Applications; Guidance.'' The guidance document set forth FDA's current interpretation of Sec. 601.12 and was intended to reduce the reporting burden as well as facilitate the timely implementation of certain changes by manufacturers. The guidance document was the first step in a reinventing Government initiative outlined in the April 1995 publication ``Reinventing Drug and Medical Device Regulations.''

Concurrently, CBER's Office of Blood Research and Review (OBRR), in letters to applicants and an industry trade organization and in presentations at a January 30 and 31, 1995, ``Licensing Blood Establishments'' workshop,

[[Page 2740]]

communicated FDA's interpretation of Sec. 601.12 as it applies to blood establishments. OBRR discussed categories of changes that blood establishments could implement without supplement submission and FDA approval. These categories include noncritical standard operating procedures, certain personnel changes, and some facility changes. During a 9-month period (October 1994 to June 1995), CBER received over 850 such submissions that were not required to await FDA approval.

The agency is proposing to revise Sec. 600.3 (21 CFR 600.3) and Sec. 601.12 to permit more substantial report reduction as the second step in the President's reinvention initiative. FDA is also proposing to add Sec. 314.70(g) (21 CFR 314.70(g)) which would apply to well-characterized biotechnology products approved under the act to harmonize CDER and CBER postapproval reporting requirements. FDA published a definition of a well-characterized therapeutic recombinant deoxyribonucleic acid (DNA)-derived and monoclonal antibody biotechnology product in a document published in the Federal Register of December 8, 1995, (60 FR 63048), as follows: -

A chemical entity(ies) whose identity, purity, impurities, potency, and quantity can be determined and controlled.

Identity:

a. Recombinant DNA Biotechnology Products -

The primary structure is known (i.e., amino acid sequence), and

The secondary structure is known (e.g., disulfide linkage), and

Post-translational modifications are known (e.g.,

glycosylation), or

b. Monoclonal Antibodies

The identity can be determined by rigorous physicochemical and immunochemical characterization without fully knowing its chemical structure

Purity and impurities:

The purity is quantifiable.

The impurities are quantifiable, and identified if feasible

Potency and quantity:

The biological activity is measurable.

The quantity is measurable.

Well-characterized therapeutic recombinant DNA-derived or monoclonal antibody biotechnology product require proper raw materials controls, process validation and controls, and sensitive and validated test methods and specifications.

FDA plans to hold an open public meeting that will be announced in a future issue of the Federal Register during the comment period of this proposed rule to facilitate public discussion.

B. Summary of the Proposed Rule

1. Summary of Changes to Sec. 600.3--Definitions

There has been much confusion regarding the use of the words "supplement" and "amendment" in relation to license applications for biological products approved under section 351 of the PHS Act. In order to clarify the use of these terms, and to facilitate a clearer understanding of the proposed revision of Sec. 601.12, FDA is proposing to amend Sec. 600.3 (21 CFR 600.3) to include definitions of "supplement" and "amendment." Previously, a change submitted to an approved biological product license application (PLA) or establishment license application (ELA) was termed an "amendment." In order to achieve consistency with CDER in implementing the Prescription Drug User Fee Act of 1992 (PDUFA) (21 U.S.C. 301, et seq.), CBER began using the term "amendment" to refer to a change submitted to a pending license application or supplement, and the term "supplement" to refer to a change submitted to an approved license application. A change to an unapproved (pending) new drug application (NDA) is also referred to as an "amendment" and a change submitted to an approved NDA is also

referred to as a ``supplement.'' Under this proposed rule, Sec. 600.3(ff) would define the term ``amendment'' as the submission of information to an unapproved license application or supplement. Such information could include additional information or reanalysis of data previously submitted, to revise or modify the application as originally submitted. Section Sec. 600.3(gg) would define a ``supplement'' as a request to the Director, CBER, to approve a change to an approved license application. A supplement would ordinarily contain a description of the proposed change and the data and information supporting the change.

FDA believes that defining these terms in the regulations will simplify the approval process for applicants, minimize misunderstanding between CBER and the biologics industry, and harmonize the use of the terms within CBER and CDER.

2. Section 314.70--Changes to an Approved Application

To ensure consistent treatment of well-characterized biotechnology-derived products within CBER and CDER, conforming amendments to Sec. 314.70 are also being proposed. Specifically, FDA is proposing an exception in Sec. 314.70(g) for well-characterized biotechnology products that provides that manufacturing changes to these products would be handled as described in proposed Sec. 601.12(b), (c), and (d) with regard to preapproval, notification, and submission in annual reports instead of as described in Sec. 314.70 (a), (b), (c), and (d). However, labeling changes would not be affected by the proposed change.

3. Summary of Proposed Sec. 601.12--Changes to an Approved Application

Section 601.12 currently requires that important proposed changes in location, equipment, management and responsible personnel, or in manufacturing methods and labeling, be reported to the Director, CBER, not less than 30 days in advance of the time such changes are intended to be made. Proposed changes in manufacturing methods and labeling may not become effective until notification of acceptance is received from the Director, CBER.

In comments made to the public docket and at the January 26, 1995, public meeting, representatives from the biologics industry requested that FDA modify Sec. 601.12 to be more flexible and less burdensome. The representatives also asked that a category system of changes to be reported be implemented, which would include changes that could be made without prior approval and those that would be required to be described in an annual report. Several comments requested that CBER make the reporting process comparable to Sec. 314.70 Supplements and other changes to an approved application which sets out three categories of notification of changes that are reported to FDA. These include: Supplements requiring FDA approval before the change is made, supplements for changes that may be made before FDA approval (changes being effected), and changes described in an annual report. Another comment stated that regulations should not stand as a barrier to manufacturing process improvement by requiring the filing of a supplement and CBER approval for even minor changes and improvements in the manufacturing process.

The regulatory scheme that the agency is now proposing responds to these and other requests from the public. In response to the comments, FDA undertook an informal review of the types of changes that had historically been subject to prior approval and the impact such changes had on products and establishments. FDA also examined the existing requirements applicable to drugs and devices approved under the act; in particular, the regulations found in Secs. 314.70 and 814.39 (21 CFR,

[[Page 2741]]

814.39). FDA used this information to develop categories of reportable changes and criteria for assigning a change to the appropriate category.

FDA is now proposing a three-category scheme for changes in the product, production process, equipment, facilities, or responsible

personnel that would eliminate FDA approval of certain reportable ^① changes and create a category of changes that would be described in an annual report. In addition to these two categories, there is a category ^② of changes which would require approval prior to distribution. ^③ The agency believes that this proposed rule reduces unnecessary reporting and approval of changes for biologics licensed under the PHS Act consistent with the corresponding regulations applicable to drugs and devices approved under the act. These categories would include: (1) Supplement submission and approval prior to distribution of a product made using a proposed change that has a substantial potential to have an adverse effect on a product's safety, purity, potency, or effectiveness; (2) notification not less than 30 days prior to distributing a product made using a change that has a moderate potential to have an adverse effect on a product's safety, purity, potency, or effectiveness; and (3) an annual report describing changes that have minimal potential to have an adverse effect on a product's safety, purity, potency, or effectiveness. The agency does not intend that this rule would apply to normal maintenance and repair which would continue to be documented as it is now by firms under applicable current good manufacturing practice (CGMP) regulations (21 CFR parts 210, 211, 606, and 820). The proposed revision also includes new Sec. 314.70(g) for well-characterized biotechnology products to make the requirements for changes made to such products consistent within CBER and CDER.

The proposed revision also sets out a separate, three-category reporting system for biological product labeling changes. This scheme differs slightly from the scheme for proposed changes in the product, production process, equipment, facilities, or responsible personnel, and is consistent with requirements for labeling changes applicable to drugs approved under the act. A change to a product package label, container label, or package insert would require one of the following: (1) Submission of a supplement with FDA approval required prior to product distribution; (2) submission of a supplement with product distribution allowed prior to FDA approval; or (3) submission of the final printed label in an annual report. Promotional labeling and advertising would be required to be submitted in accordance with the requirements of Sec. 314.81(b)(3)(i) (21 CFR 314.81(b)(3)(i)).

Although the proposed decrease in reporting and approval requirements and the corresponding reduction in the agency's role in reviewing changes before they are implemented does present some risks to product safety, purity, potency, and effectiveness, the agency believes that these risks are minimal. Under the proposed rule the applicant would be required to document that each change has no adverse effect on the safety, purity, potency, or effectiveness of the product. Such documentation would include appropriate validation and/or other studies. In some cases clinical data would be necessary and in other cases it would not. Applicants would be required to maintain records of the validation and study data under existing CGMP requirements. For those changes no longer requiring supplement approval, FDA review would shift to postmarketing review including inspections of manufacturing facilities.

The proposed rule includes some specific examples of changes that fall into a particular category, but does not attempt to set out a comprehensive list of the changes included in each category. The agency recognizes that scientific and technological advances may change the need for supplement approval and/or reporting of many types of changes. Moreover, the potential for a particular change to adversely affect a product's safety, purity, potency, or effectiveness may differ for different products. FDA recognizes that a change made to a less well-characterized product could fall into a different reporting category than the same change made to a product that was adequately characterized using analytical and functional tests. For example, scale up of a purification process may have a greater impact on a live virus

vaccine than it may on a well-characterized recombinant DNA-derived purified protein. The agency believes that it can more readily respond to advances in technology, differences among products, and knowledge gained from experience by creating a rule that sets out general categories of changes. FDA recognizes, however, that applicants need clear guidance on how the agency intends to interpret the rule in order to efficiently produce products and adhere to regulatory requirements. Accordingly, FDA intends to make available guidance documents to describe the agency's current interpretation of specific changes falling into each category and to modify the documents as needed to reflect changes in science and technology. Notices of availability for drafts of guidance documents for reporting changes to most biological products and to well-characterized recombinant DNA-derived and monoclonal antibody biotechnology products are published elsewhere in this issue of the Federal Register. FDA is seeking comment on the use of guidance documents in conjunction with a final rule that may result from this proposal. FDA is also soliciting comment on the appropriate categorization of specific changes enumerated in this proposal and the guidance documents. In the Federal Register of October 25, 1995, (60 FR 54695), FDA announced that a workshop would be held on December 11 through 13, 1995, to discuss the definition of a well-characterized biotechnology product. Information from this workshop will help FDA to refine its definition of a well-characterized biotechnology product.

FDA also anticipates that applicants could consult with the office which has product or establishment responsibility in CBER, or the Office of New Drug Chemistry in CDER, regarding appropriate objectives and design of studies to validate and document the potential for adverse effect of a proposed change for a particular product prior to committing the resources for such studies. Guidance on the appropriate reporting mechanism would also be available from these offices.

The proposed rule would authorize the Directors of CBER and CDER, or their designees under 21 CFR part 5, to make decisions under the provisions of the rule as they apply to their respective centers.

The agency expects that applicants would update their marketing applications in an annual report to assure that they accurately reflect current conditions. FDA is seeking comments on mechanisms that industry and the public believe may be appropriate for the periodic update of marketing applications. This proposed rule would require that some changes in manufacturing be submitted annually. CBER does not currently require, nor would this proposed rule require, that the annual report include additional information that is submitted for a drug approved under the act under Sec. 314.81(b)(2). FDA requests comment on whether the annual report for a biological product licensed under the

[[Page 2742]]

PHS act should include the information described in Sec. 314.81(b)(2).

The proposed rule does not address requirements for submitting changes to a pending license application or supplement. Applicants currently submit amendments to pending applications in order to comply with the requirement in the PHS Act that a biologic product distributed for sale, barter, or exchange in interstate commerce must be manufactured in accordance with its license, and the regulations in Sec. 601.2 that set out the information and data that must be submitted in such license applications. FDA intends to consider whether specific requirements for submitting amendments to pending applications should be included when the agency undertakes a review of the licensing requirements in part 601 (21 CFR part 601).

4. Analysis of Sec. 601.12--Changes to An Approved Application--

a. Changes requiring supplement submission and approval prior to distribution of product made using the change. Currently, all important

proposed changes made by applicants must be reported not less than 30 days in advance of the time such changes are intended to be made. Such changes in manufacturing methods and labeling may not become effective until notification of acceptance is received from the Director, CBER. Accordingly, CBER requires approval of all important changes in manufacturing methods and labeling before such changes are implemented. FDA continues to believe that it is important that the agency review data regarding any change that has a substantial potential to have an adverse effect on the safety, purity, potency, or effectiveness of the product, prior to distribution of the product made using the change, to assess whether the change will have a detrimental impact on the licensed product with regard to its safety, purity, potency, effectiveness, and consistency in biological and clinical characteristics. -

Proposed Sec. 601.12(b)(1) would require an applicant to submit a supplement for approval to the Director, CBER, for any proposed change in the product, production process, equipment, or facilities that has a substantial potential to have an adverse effect on the product's safety, purity, potency, or effectiveness. These changes have the highest probability to adversely affect the product's safety, purity, potency, or effectiveness, and, in most instances, are integral to the manufacturing process or product production equipment. Proposed Sec. 601.12(b)(1) would require the applicant to submit a supplement containing a detailed description of the proposed change, the products involved, the manufacturing sites or areas affected, a description of the methods used and studies performed to evaluate the effect of the change on the product's safety, purity, potency, and effectiveness, the data derived from clinical and/or nonclinical laboratory studies, relevant validation protocols and data, and a reference list of the relevant standard operating procedures (SOP's). Approval of the supplement by the Director, CBER, would be required prior to distributing product made using the change.

FDA proposes to enumerate the following changes that have a substantial potential to have an adverse effect on a product's safety, purity, potency, or effectiveness: A new indication, route of administration, dosing schedule, dosage form, or formulation; the addition, removal, or reordering of the step(s) of the licensed production process; and the conversion of a single product manufacturing area to a multiproduct manufacturing area. The agency believes that the need for FDA premarket approval of these significant changes is unlikely to vary with technological advances or due to differences among products, and that these changes should be enumerated in the rule.

Other examples of changes that have caused detrimental effects on the safety, purity, potency, or effectiveness of products, even where applicants performed validation or other studies, include process changes or changes in analytical methods that result in a change of specification limits and addition of a new location for manufacture. FDA believes that the agency's continued prior review and approval of such changes is currently necessary to protect the public from products whose safety, purity, potency, or effectiveness may be compromised. However, FDA is proposing to describe these, and additional, specific examples of changes that CBER currently believes have substantial potential to adversely affect the product, in guidance, rather than enumerate them in the rule. FDA anticipates that scientific advances and future experience may reduce the need for premarket approval of certain changes and believes that the agency will be able to respond readily to changed circumstances by revising guidance that interprets the rule.

b. Changes requiring notification not less than 30 days prior to distributing product made using the change. FDA believes that the public health can be adequately protected by eliminating agency approval of changes that have only a moderate potential to have an

adverse effect on the safety, purity, potency, or effectiveness of a product. Changes that have moderate potential to affect a product's safety, purity, potency, or effectiveness are changes that do not have as high a probability for causing an adverse effect as those for which the agency proposes to require supplement approval. Under current Sec. 601.12, the agency requires FDA approval of all important proposed changes to a product, and requires that all important proposed changes in manufacturing methods and labeling await such approval before they may be distributed. FDA is now proposing to require that applicants notify the agency not less than 30 days prior to distributing a product made with a change in the product, production process, equipment, facilities, or responsible personnel that has moderate potential to have an adverse effect on the product, but to permit a product to be distributed after the 30-day period has elapsed without awaiting FDA approval. These notifications would not be considered supplements requiring approval. Thus, many changes that now require FDA approval as supplements could be implemented rapidly through the notification process without the prior submission of a supplement. For example, based on FDA's experience in reviewing submissions, the agency currently believes that minor changes in fermentation batch size using the same equipment and resulting in no change in specifications of the bulk or final product, and increases or decreases in the purification scale, not associated with a process change or different equipment, have moderate potential to have an adverse effect on the product. -

In the notification, an applicant would be required to provide the agency with a clear description of the change, the product or products involved, the manufacturing sites or areas involved, a brief description of the validation and/or other clinical and/or nonclinical laboratory studies conducted to analyze the effect of the change on the safety, purity, potency, and effectiveness of the product, the dates of any such studies, reference to any SOP's used to complete the studies, and a summary of the relevant data or information. During the 30-day period, FDA would review the notification to determine if it was properly submitted as a notification. If FDA agreed that the change described was of the type that had moderate potential to adversely affect the safety, purity, potency, or effectiveness of the product, and the notification included

[[Page 2743]]

all of the required information, the applicant could begin distribution of a product made using the change 30 days after FDA's receipt of the notification.

Under the proposed rule, FDA would ordinarily contact the applicant before the expiration of the 30-day period if the agency determined that the change was improperly submitted as a notification. If FDA informed the applicant within the 30-day period that the submission did not meet the requirements for a notification, the applicant would be required to correct the deficiencies in the information submitted before distributing the product. Depending on the problem, FDA would respond in one of two ways: (1) If the change was of the type that presented a substantial potential to adversely affect the safety, purity, potency, or effectiveness of the product, the agency would inform the applicant that the change should be submitted as a supplement and the applicant would be required to await FDA approval before product produced with the change could be distributed; or (2) if the change was of the type that could properly be submitted as a notification, but the required information was incomplete, the applicant would be required to supply the missing information and wait until FDA determined compliance with this section before distributing the product.

FDA intends, during the 30 days, to focus its review on determining whether the applicant reported the change under the appropriate mechanism, and, if so, whether any of the required information was

missing. Under the proposed rule, FDA would not ordinarily contact the applicant if the notification was properly submitted in accordance with Secs. 601.12(c) or 314.70(g)(2). FDA anticipates that applicants would use a method of delivery for notifications that would allow confirmation of the submission having been received by FDA.

FDA would also ordinarily review the substantive information contained in a notification and request the applicant to clarify the submission if necessary. If the agency's review determined that additional studies or information were necessary to document the lack of an adverse effect on the safety, purity, potency, or effectiveness of the product, the agency could request that additional data be collected. Failure to comply with the proposed requirements and existing CGMP requirements to properly validate the change could result in enforcement action. Following the agency's review, FDA would send to the applicant a stamped copy of the cover letter for the notification indicating that FDA had placed the submission in the applicant's license application file. FDA anticipates that the agency could conduct a more extensive review of data supporting the notification during inspections if necessary.

FDA believes that a notification process, as described above, for changes that have a moderate potential to affect the safety, purity, potency, or effectiveness of the product would protect against the distribution of unsafe or ineffective products while speeding the availability of improved products. Under the proposed rule, applicants would be required to demonstrate, through appropriate validation or other studies, that a change has no adverse effect on the safety, purity, potency, and effectiveness of the product. Applicants would be required to briefly describe the studies and data in the notification. While a full description of the studies would not be required to be submitted in a notification, as it generally would be in a supplement, applicants would be required to maintain the data in records that are available for FDA inspection under existing CGMP's. The 30-day period that would be required to elapse before products made using the change could be distributed would permit the agency to redirect submissions for changes that could substantially affect product safety, purity, potency, or effectiveness to the supplement approval process before the product entered the market. In addition, the agency could identify applicants that, through an incomplete submission, failed to establish that they had followed the necessary steps to validate and implement a change. Applicants would be required to submit the missing information before they could distribute the product.

c. Changes to be described in an annual report. FDA recognizes that there are changes in the product, production processes, equipment, facilities, and responsible personnel that have minimal potential to have an adverse effect on the product's safety, purity, potency, or effectiveness. Under the current Sec. 601.12, the agency has required many of these changes to await supplement approval before they could be implemented. FDA believes that prior agency approval of these changes is unnecessary, and is proposing in Sec. 601.12(d) that such changes would not be required to be approved by the agency. FDA continues to believe that it is important that such changes be documented and validated so that there is a mechanism for assessing the consequences of the change. FDA is therefore proposing that changes that have minimal potential to have an adverse effect on the product's safety, purity, potency, or effectiveness be required to be described by the applicant in an annual report. The annual report would be required to be submitted each year within 60 days of the anniversary date of approval of the application. FDA believes that the agency can effectively assess compliance with this section and CGMP requirements for changes that have minimal potential to adversely affect the product's safety, purity, potency, or effectiveness by having ready access to information regarding such changes through the submission of an annual report and by inspection. Applicants would be required to

include in the annual report a listing of all products involved, a brief description of and reason(s) for the change, the manufacturing sites or areas involved, the date each change was made, and a cross-reference to any validation protocols and/or SOP's. Both the applicant and FDA could use this information to assess whether problems which may arise with products are related to such changes. Under proposed Sec. 601.12(a), the applicant would be required to perform appropriate validation or other studies to demonstrate the lack of adverse effect on the safety, purity, potency, and effectiveness of the product. Applicants would maintain records of such studies under existing CGMP requirements.

As a result of FDA's experience in reviewing changes, the agency believes that changes that have a minimal potential to have an adverse effect on the product would include such changes as a change in storage conditions of in-process intermediates based on data derived from studies following a protocol in the approved license application; modifications in analytical procedures with no change in the basic test methodology or existing release specifications; relocation of analytical testing laboratories within a licensed facility; and area upgrades such as the installation of improved finishes on floors or walls.

d. Labeling. Under the current Sec. 601.12, all important proposed labeling changes are required to be submitted for FDA approval before they may be implemented. The agency recognizes, however, that some labeling changes may not have a substantial impact on the safe and effective use of the product. For other changes, such as updates of important safety information, it is important that prescribers and patients have access to current information as soon as it becomes available. Therefore, the agency is proposing to revise the biological products reporting requirements for

[[Page 2744]]

labeling changes. The regulations in Sec. 314.70(b), (c), and (d), governing how labeling changes are reported for products regulated by CDER, are not affected by the proposal. In fact, the proposed revision of Sec. 601.12(e) is consistent with requirements for labeling changes applicable to drugs approved under the act.

Changes to labeling would be submitted to CBER in one of the following ways: (1) A supplement requiring FDA approval prior to distribution of product with the revised labeling, (2) a supplement requiring FDA approval but permitting the distribution of product with the accompanying revised labeling prior to such approval, or (3) submission of final printed labeling in an annual report. It is expected that proposed Sec. 601.12(e) would significantly decrease the number of labeling submissions that currently require approval prior to use of the labeling.

Under proposed Sec. 601.12(e)(2), an applicant would be required to submit a supplement, but could disseminate the revised labeling with the product, at the time the supplement was submitted. Such revisions to the labeling would include any information that adds or strengthens a contraindication, warning, precaution, or adverse reaction; adds or strengthens a statement about abuse, dependence, psychological effect, or overdose; adds or strengthens an instruction about dosage and administration that is intended to increase the safe use of the product; or deletes false, misleading, or unsupported indications for use or claims for effectiveness.

FDA believes that permitting these labeling changes to be effected and product distributed prior to FDA approval would facilitate labeling changes intended to adequately inform prescribers and patients of the risks and benefits of a biological product and thereby allow prescribers and patients earlier access to important new information on the safe use of the product. Proposed Sec. 601.12(e)(2) would require that the supplement clearly identify any changes being made and include

necessary supporting data. Under the proposed rule, the changes identified in Sec. 601.12(e)(2) could be implemented prior to agency approval. FDA could, however, deny approval of a supplement for a labeling change that has already been disseminated with the product. In assessing an applicant's plans to correct a problem, FDA would consider the applicant's reasons for making the change and the alternatives available to the applicant. If the circumstances warranted, FDA could require the labeling change to be immediately discontinued. However, when circumstances permit, the agency would allow the applicant to correct a problem with minimal expense and without unnecessary waste. -

Under proposed Sec. 601.12(e)(3), an applicant making editorial or other minor changes, or a change in the information on how the biologic is supplied that does not involve a change in the dosage strength or dosage form, would be required to submit a description of the changes and all final printed labeling incorporating the changes in an annual report to be submitted to the Director, CBER. For all changes in the package insert, package label, and container label that would not fall under Sec. 601.12(e)(2) or (e)(3), an applicant would be required to submit a supplement supporting the proposed change and await FDA approval prior to distribution.

Under proposed Sec. 601.12(e)(4), promotional labeling and advertising would be submitted in accordance with 21 CFR 314.81(b)(3)(i), which requires that an applicant submit specimens of mailing pieces and any other labeling or advertising devised for promotion of the product at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription product.

e. Failure to comply. FDA is proposing in Sec. 601.12(f) that in the event of repeated failure of the applicant to comply with Sec. 601.12, the Director, CBER, may require that the applicant submit a supplement for any proposed change and obtain CBER approval prior to distributing the product made using the change. This measure would be in addition to other remedies available in applicable laws and regulations, including suspension or revocation of licenses, seizure of products, and injunction, among others. With this proposed rule, FDA is undertaking to significantly reduce the number of changes that are reported, reviewed, and approved by the agency. Continued protection of the public from products with compromised safety, purity, potency, or effectiveness will depend on applicants' adherence to the proposed requirements to conduct validation and/or other studies to document the lack of adverse effect on the product and utilization of the appropriate mechanism to inform the agency of such changes. In determining repeated failure to comply with the Sec. 601.12 and whether an applicant would be required to file future submissions as supplements, the agency would consider, among other things, the applicant's compliance history and the significance of the deficiencies.

f. Administrative review. Proposed Sec. 601.12(g) provides that an applicant may request a review of FDA employee decisions made pursuant to section Sec. 601.12 in accordance with Sec. 10.75 (21 CFR 10.75). Section 10.75 provides a mechanism for internal agency review of decisions. FDA proposes to include the reference to Sec. 10.75 in Sec. 601.12(g) so that applicants who wish agency review of a decision made under the provisions of the rule are made aware of the mechanism for such review. The internal agency review of a decision would be based on the information in the administrative file. FDA believes that it is important for the agency to apply regulations affecting regulated products consistently and fairly, and believes that agency review should be available to resolve a disputed issue.

II. Analysis of Impacts

A. Method of Analysis

To determine the impact of the proposed rule, CBER undertook an analysis of changes approved as supplements during the 9-month period between October 1, 1994, and June 1, 1995. CBER has determined that the proposed rule as currently written would result in an overall 32 percent reduction in submissions requiring prior agency approval before an applicant could commence distributing product made using the change. The extent of the reduction would be greater for certain products. Under the proposed regulation, 88 of 175 submissions reviewed as supplements under the current regulation (for changes to biological products other than blood products and blood component products) would be supplements requiring prior approval, 62 would be notifications to CBER not requiring FDA approval, and 25 would be described in an annual report. For blood and blood components, of 177 supplements approved in a 2-month portion of the 9-month period, 128 would be supplements requiring prior approval under the proposed rule, 36 would be notifications, and 13 would be described in an annual report.

B. Review Under Executive Order 12866 and the Regulatory Flexibility Act

FDA has examined the impact of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96-354). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select the regulatory

[[Page 2745]]

approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in the Executive Order. The proposed rule is a significant regulatory action as defined by the Executive Order and is subject to review under the Executive Order because it deals with a novel policy issue.

In accordance with the principles of Executive Order 12866, the overall result of the proposed rule would be a substantial reduction in reporting burden for applicants and in review burden for the agency. In addition, FDA anticipates that the proposed rule would encourage applicants to improve their licensed products and methods of manufacture.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because, as stated above, the overall result of the proposed rule would be a substantial reduction of the regulatory and reporting burden, the agency certifies that the proposed rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

C. Review under the Paperwork Reduction Act of 1995

This proposed rule contains information collections which are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995. The title, description, and respondent description of the information collection are shown below with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing instructions, gathering and maintaining the data needed, and completing and reviewing the collection of information.

With respect to the following collection of information, FDA invites comments on: (1) Whether the proposed collection of information

is necessary to for proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: 21 CFR 601.12--Changes to an Approved Application and 21 CFR 314.70(g) Exception.

Description: This proposed rule would change the requirements for respondents to report to FDA changes in the product, labeling, production process, equipment, facilities, or responsible personnel established in an approved application for a biological product or for a well-characterized biotechnology product. The respondent would report the change to FDA in one of the three following ways depending on the potential for the change to have an adverse effect on the safety, purity, potency or effectiveness of the product: (1) Changes that have a significant potential to have an adverse effect on the product would be submitted in a supplement requiring prior approval by FDA before distribution of a product made using the change; (2) changes that have a moderate potential to have an adverse effect on the product would be submitted to FDA in a notification not less than thirty days prior to distribution of the product made using the change; and (3) Changes that have a minimal potential to have an adverse effect on the product would be submitted by the respondent in an annual report.

Labeling changes for a biological product would also be submitted in one of the following ways: (1) A supplement requiring FDA approval prior to distribution of product with the revised labeling; (2) a supplement requiring FDA approval but permitting the distribution of product with the accompanying revised labeling prior to such approval; or (3) submission of final printed labeling in an annual report.

Promotional labeling and advertising would be submitted in accordance with 314.81(b)(3)(i). Labeling changes for well-characterized biotechnology products would not be affected by this proposed rule.

Description of Respondents: All manufacturers and applicants holding a biological license approved under section 351 of the Public Health Services Act and all manufacturers and applicants of well-characterized biotechnology products holding an approved NDA would report (Business or other for-profit). -

These estimates are an approximation of the average time expected to be necessary for a collection of information. They are based on such information as is available to FDA. There are no capital costs associated with this information collection. It is estimated that 20 percent of all reports required under these proposed regulations are being prepared by contractors. The burden hours in the chart below therefore reflect a 20 percent reduction per regulation because these burden hours will not be expended by the affected industry rather they will be expended by the contractors. It is estimated that a contractor will charge \$40 per hour for the service of preparing these reports. The 20 percent burden hours multiplied by \$40 per hour are reflected in the column labeled "Operating and Maintenance Costs."

The agency seeks comments on these estimates, particularly the industry's view of the number of firms and products affected by the collections of information contained in this proposed rule.

Regulation (21 CFR)	Number of Respondents	Hours Per Response	Number of Responses
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601.12(b)	391	80	610
601.12(c)	391	40	280
601.12(d)	391	10	110
601.12(e)(1)	391	40	200
601.12(e)(2)	391	20	20
601.12(e)(3)	391	10	220
601.12(e)(4)	391	10	110

[[Page 2746]]

314.70(g)(1)	4	80	50
314.70(g)(2)	2	40	3
314.70(g)(3)	6	10	20

Totals

The agency has submitted a copy of this proposed rule to OMB for its review and approval of these information collections. Interested persons are requested to send comments regarding this information collection, including suggestions for reducing this burden to the Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, Attn: Desk Officer for FDA. Submit written comments on the information collection by February 28, 1996, but not later than March 29, 1996.

D. Review Under the National Environmental Policy Act

The agency has determined under 21 CFR 25.24(a)(8) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Interested persons may, on or before April 29, 1996, submit to the Dockets Management Branch (address above) written comments regarding the proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Submit comments on the information collection requirements to the Office of Information and Regulatory Affairs, OMB, (address above).

As stated previously, FDA plans to hold an open public meeting during the comment period to facilitate public comment on this proposed rule. The time and location of this meeting will be announced in a future issue of the Federal Register.

List of Subjects

21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

21 CFR Part 600

Biologics, Reporting and recordkeeping requirements.

21 CFR Part 601

Administrative practice and procedure, Biologics, Confidential

business information.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, and under the authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR parts 314, 600, and 601 be amended as follows:

PART 314--APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG OR AN ANTIBIOTIC DRUG

1. The authority citation for 21 CFR part 314 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701, 704, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371, 374, 379e).

2. Section 314.70 is amended by adding new paragraph (g) as follows:

Sec. 314.70 Supplements and other changes to an approved application.

* * * * *

(g) Exception. An applicant proposing to make a change in a well-characterized biotechnology product of the type described in Sec. 314.70(a), (b)(1), (b)(2), (c)(1), (c)(3), (d)(1), and (d)(4) through (d)(9) shall comply with the following:

(1) Changes requiring supplement submission and approval prior to distribution of product made using the change. (i) A supplement shall be submitted for any proposed change in the product, production process, equipment, or facilities that has substantial potential to have an adverse effect on the safety, purity, potency, or effectiveness of the product. These changes include but are not limited to:

(A) A new indication, route of administration, dosage form, dosing schedule or formulation;

(B) Addition, removal, or reordering of the step(s) of the production process; and

(C) Change from production of a single product to production of multiple products at a facility.

(ii) The applicant shall obtain FDA approval of the supplement prior to distribution of the product made using the change. The following information shall be contained in the supplement:

(A) A detailed description of the proposed change;

(B) The product(s) involved;

(C) The manufacturing site(s) or area(s) affected;

(D) A description of the methods used and studies performed to evaluate the effect of the change on the product's safety, purity, potency, and effectiveness;

(E) The data derived from such studies;

(F) Relevant validation protocols and data; and

(G) A reference list of relevant standard operating procedures (SOP's).

(2) Changes requiring notification not less than 30 days prior to distributing product made using the change. (i) An applicant shall inform FDA, in a written notification labeled "Notification--Changes being effected in 30 days," of any change in the product, production process, equipment, facilities, or responsible personnel that has moderate potential to have an adverse effect on the safety, purity, potency, or effectiveness of the product. Distribution of the product manufactured after the change was instituted may not begin until 30 days after FDA notification. The following information shall be contained in the notification:

(A) A clear, brief description of the change;

(B) The products(s) involved;

(C) The manufacturing site(s) or area(s) involved;

(D) A brief description of the validation and/or other studies

[[Page 2747]]

conducted to analyze the effect of the change on the safety, purity, potency, and effectiveness of the product;

(E) The dates of the studies;

(F) Reference to relevant SOP's used to complete the studies; and

(G) A summary of the relevant data or information.

(ii) If within 30 days following FDA's receipt of the notification FDA informs the applicant that either:

(A) The change requires supplement submission in accordance with paragraph (g)(1) of this section; or

(B) Any of the information required under paragraph (g)(2)(i) of this section is missing, the applicant shall not distribute the product made with the change until FDA determines that compliance with this section is achieved.

(3) Changes to be described in an annual report. Changes in the product, production process, equipment, facilities, or responsible personnel that have minimal potential to have an adverse effect on the product's safety, purity, potency, or effectiveness, shall be documented by the applicant in an annual report submitted each year within 60 days of the anniversary date of approval of the application. The annual report shall contain the following information for each change:

(i) A list of all products involved;

(ii) A brief description of and reason(s) for the change; -

(iii) The manufacturing sites or areas involved;

(iv) The date each change was made; and

(v) A cross-reference to relevant validation protocol(s) and/or

SOP's.

* * * * *

PART 600--BIOLOGICAL PRODUCTS: GENERAL

3. The authority citation for 21 CFR Part 600 continues to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 519, 701, 704 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 360i, 371, 374); secs. 215, 351, 352, 353, 361, 2125 of the Public Health Service Act (42 U.S.C. 216, 262, 263, 263a, 264, 300aa-25).

4. Section 600.3 is amended by adding new paragraphs (ff) and (gg) to read as follows:

Sec. 600.3 Definitions.

(ff) Amendment is the submission of information to a pending license application or supplement, to revise or modify the application as originally submitted.

(gg) Supplement is a request to the Director, Center for Biologics Evaluation and Research, to approve a change in an approved license application.

PART 601--LICENSING

5. The authority citation for 21 CFR part 601 continues to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 513-516, 518-520, 701, 704, 721, 801, of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 360c-360f, 360h-360j, 371, 374, 379e, 381); secs. 215, 301, 351, 352, of the Public Health Service Act (42 U.S.C. 216, 241, 262, 263); secs. 2-12 of the Fair Packaging and Labeling Act (15 U.S.C. 1451-1461).--

6. Section 601.12 is revised to read as follows:

Sec. 601.12 Changes to an approved application.-

(a) General. As provided in this section, an applicant shall inform the Director, Center for Biologics Evaluation and Research (CBER), about each change in the product, labeling, production process, equipment, facilities, or responsible personnel established in the approved license application(s). Before distributing a product made using a change, an applicant shall demonstrate through appropriate validation and/or other clinical and/or nonclinical laboratory studies the lack of adverse effect of the change on the safety, purity, potency, and effectiveness of the product. Single copies of Food and Drug Administration (FDA) guidance describing FDA's current interpretation of this regulation may be obtained from the Congressional and Consumer Affairs Branch (HFM-12), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448.

(b) Changes requiring supplement submission and approval prior to distribution of product made using the change.

(1) A supplement shall be submitted to the Director, CBER, for any proposed change in the product, production process, equipment, or facilities that has substantial potential to have an adverse effect on the safety, purity, potency, or effectiveness of the product. These changes include but are not limited to the following:

(i) A new indication, route of administration, dosage form, dosing schedule or formulation;

(ii) Addition, removal, or reordering of the step(s) of the licensed production process; and

(iii) Change from production of a single product to production of multiple products at a licensed facility;

(2) The applicant shall obtain approval of the supplement from the Director, CBER, prior to distribution of the product made using the change. The following information shall be contained in the supplement:

(i) A detailed description of the proposed change;

(ii) The product(s) involved;

(iii) The manufacturing site(s) or area(s) affected;

(iv) A description of the methods used and studies performed to evaluate the effect of the change on the product's safety, purity, potency, and effectiveness;

(v) The data derived from such studies;

(vi) Relevant validation protocols and data; and

(vii) A reference list of relevant standard operating procedures (SOP's).

(c) Changes requiring notification not less than 30 days prior to distributing product made using the change. (1) An applicant shall inform the Director, CBER, in a written notification labeled "Changes being effected in 30 days," of any change in the product, production process, equipment, facilities, or responsible personnel that has moderate potential to have an adverse effect on the safety, purity, potency, or effectiveness of the product. Distribution of the product manufactured after the change was instituted may not begin until 30 days after receipt of the notification by CBER. The following information shall be contained in the notification:

(i) A clear, brief description of the change;

(ii) The product(s) involved;

(iii) The manufacturing site(s) or area(s) involved;

(iv) A brief description of the validation and/or other studies conducted to analyze the effect of the change on the safety, purity, potency, or effectiveness of the product;

(v) The dates of the studies;

(vi) Reference to relevant SOP's used to complete the studies; and

(vii) A summary of the relevant data or information.

(2) If within 30 days following FDA receipt of the notification, the Director, CBER informs the applicant that either:

(i) The change requires supplement submission in accordance with paragraph (b) of this section; or

(ii) Any of the information required under paragraph (c)(1) of this section is missing, the applicant shall not distribute the product made with the change until compliance with this section is achieved.

(d) Changes to be described in an annual report. (1) Changes in the product, production process, equipment, facilities, or responsible personnel that have minimal potential

[[Page 2748]]

to have an adverse effect on the product's safety, purity, potency, or effectiveness, shall be documented by the applicant in an annual report submitted each year within 60 days of the anniversary date of approval of the application. The annual report shall contain the following information for each change: -

(i) A list of all products involved;

(ii) A brief description of and reason(s) for the change; -

(iii) The manufacturing sites or areas involved;

(iv) The date each change was made; and

(v) A cross-reference to relevant validation protocol(s) and/or SOP's.

(2) The applicant shall submit the report to the FDA office responsible for reviewing the application. The report shall include all the information required under this section obtained for each change made during the annual reporting interval which ends on the anniversary date.

(e) Labeling changes--(1) Label changes requiring supplement submission--distribution of a product with a label change must await FDA approval. An applicant shall submit to CBER a supplement describing a proposed change in the package insert, package label, or container label, except those described in paragraphs (e)(2) and (e)(3) of this section, and include the information necessary to support the proposed change. The supplement shall clearly highlight the proposed change in the label. The applicant shall obtain approval from the Director, CBER, prior to distributing a product with the label change. -

(2) Label changes requiring supplement submission; product with a label change may be distributed before FDA approval. (i) An applicant shall submit to CBER, at the time such change is made, a supplement for any change in the package insert, package label, or container label to accomplish any of the following:

(A) To add or strengthen a contraindication, warning, precaution, or adverse reaction;

(B) To add or strengthen a statement about abuse, dependence, psychological effect, overdosage;

(C) To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the product; or

(D) To delete false, misleading, or unsupported indications for use or claims for effectiveness.

(ii) The applicant may distribute a product with a package insert, package label, or container label bearing such change at the time the supplement is submitted. The supplement shall clearly identify the change being made and include necessary supporting data. The supplement and its mailing cover should be plainly marked: "Special Labeling Supplement--Changes Being Effectuated."

(3) Label changes requiring submission in an annual report. (i) An applicant shall submit any final printed package insert, package label, or container label incorporating the following changes to CBER in an annual report submitted each year within 60 days of the anniversary date of approval of the application:

(A) Editorial or similar minor changes; or

(B) A change in the information on how the drug is supplied that does not involve a change in the dosage strength or dosage form.

(ii) The applicant may distribute a product with a package insert, package label, or container label bearing such change at the time the change is made.

(4) Advertisements and promotional labeling.

Advertisements and promotional labeling shall be submitted in accordance with the requirements set forth in Sec. 314.81(b)(3)(i) of this chapter, except that Form FDA-2567 shall be used in lieu of Form FDA-2253.

(f) Failure to comply. In addition to other remedies available in law and regulations, in the event of repeated failure of the applicant to comply with this section, the Director, CBER, may require that the applicant submit a supplement for any proposed change to, and obtain approval of the supplement from, the Director, CBER, prior to distributing a product made using the change. -

(g) Administrative review. Under Sec. 10.75 of this chapter, an applicant may request internal FDA review of CBER employee decisions under this section.

Dated: January 16, 1996.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 96-1580 Filed 1-25-96; 10:41 am]

BILLING CODE 4160-01-F

For
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FDA REFORM – KASSEBAUM BILL
SERIOUS CONCERNS ABOUT S. 1477 AND POSSIBLE COMPROMISE POSITIONS

Device modifications. Section 702(d) would eliminate FDA's role in assuring that changes made to a product do not adversely affect its safety and effectiveness. Under the bill, unless the manufacturer's own data shows the safety and effectiveness were to diminish, FDA could not require data on the modified product. The provision raises serious safety concerns.

Compromise language could ensure that FDA is not prevented from seeking a 510(k) when a change or modification could affect the safety or effectiveness of the device - regardless of whether the effect is adverse.

Substantial equivalence determinations. Section 702(c) would recognize any use "included within a general use for a predicate device" as an approved use for 510(k) devices. This would allow a device originally marketed for one clinical indication to later be marketed for other indications, with only the submission of an abbreviated application (510(k)) that would not document the product's effectiveness for the new indication. The provision's effect is to virtually eliminate approval of devices for specific uses and thus, eliminate the requirement to show that these uses are safe and effective.

Compromise language could allow a new use of a device that is substantially similar to the use of the predicate device to be deemed a legally marketed use of the predicate device for purposes of section 510(k) premarket notifications. Such language would have to be drafted in a way that would not permit devices with significantly different uses to be marketed without first submitting safety and efficacy data.

Automatic exemption of all class I devices. Section 702(a) exempts all class I devices from premarket notification. FDA has already exempted 572 class I devices. Many of the 216 devices that FDA has not exempted, were not exempted for public health reasons.

Compromise language could permit FDA to not exempt certain class I devices that have serious public health concerns. Alternatively, compromise language could simplify and expedite reclassification of the most problematic class I device into Class II.

The Device Approval Standard. Section 703 would require the agency to accept retrospective or historical clinical data as a control or for determining the effectiveness of a device if sufficient valid data are available and the effects of the device are clearly defined and well understood. The provision indicates a preference for a lower quality of evidence.

Compromise language could set forth the concept that retrospective or historical clinical data are acceptable if they are sufficient to demonstrate an assurance of effectiveness and that FDA can require concurrent clinical trials when the effects of the device are not clearly defined or well understood, when the retrospective or historical clinical data do not meet the statutes standards, or when there is a compelling health reason.

Device Performance Standards. Section 708 requires FDA to recognize performance standards of certain standard setting organizations.

The concept of greater regulatory use of consensus standards is supportable. However, FDA should have the authority to decertify any standard setting organization and to decide which standards it will recognize. FDA also should have authority to decide whether it is appropriate for companies to self-certify compliance with recognized standards.

Sound medical practice. Section 407 would establish a procedure for approving new uses of previously approved drugs and devices based on sound medical practice (i.e., a use that has existed for five years, is "common" among experienced clinicians, and is reasonably based on experience and other confirmatory evidence). This provision, which would create a standard for permitting new uses that completely bypasses the approval process and could result in marketing for unsafe or ineffective uses, is not acceptable.

As an alternative to this provision, legislative concepts designed to improve FDA's performance in reviewing and approving efficacy supplements could be adopted. The concepts would require FDA:

- (1) to have performance goals for efficacy supplements;**
- (2) to create a small office that would be responsible for working with companies and the centers on expediting efficacy supplements, working to identify off label uses/studies that might be the basis for efficacy supplements, and working with outside scientific experts to identify new indications that might be studied; and**
- (3) to issue guidance to industry that reflects the presumption that the safety data required for efficacy supplements is often not as extensive as that required for NDAs and that if the new indication is related to an approved indication, developing the protocol should be easier.**

The concepts further suggest that FDA could be required to report back to Congress after a reasonable period on the success of these efforts.

Off-label promotion. Section 407 would allow companies to distribute journal articles and other types of information (such as textbooks, continuing medical education materials, etc.) to promote unapproved uses. This provision allows manufacturers to promote uses that have not been proven safe and effective. Moreover, it reduces the incentive for companies to do the scientific research and have the new uses reviewed by FDA (in fact, there would be a disincentive because FDA might determine that the new use is not supported by the evidence).

A proposed compromise would be to tie the distribution of articles to the submission of efficacy supplements. Under this approach, a manufacturer would be permitted to disseminate journal articles etc. (as set forth in section 407) 90 days after an efficacy supplement has been submitted to FDA for review. FDA should be allowed to disclose information in its possession about the safety or efficacy of a product regardless of the source. This compromise approach addresses FDA's concern that the safety and efficacy of these off label uses will never be known and gives FDA the opportunity to prevent the dissemination of articles, etc. if such dissemination raises public health concerns. There also could be a provision directing an IOM study on the issue of whether there are specific areas where the compromise position does not go far enough.

Shortened Review Times Without Additional Resources. Without providing new resources, S.1477 would require FDA to meet extremely short deadlines (e.g., 4-6 months for drugs). Moreover, it imposes a substantial number of burdensome requirements (e.g., FDA must meet with sponsors at defined time periods and prior to such meeting must provide the sponsor written information regarding application deficiencies and steps towards approval (see sections 404 and 707)). The requirements would have the effect of further shortening the time periods (e.g., in order to provide the written information FDA would have to substantially complete its review of the application prior to the meetings). As a result of the shortened timeframes, reviewers may have to approve drugs, devices, or food additives based on less information, with fewer analyses and much greater uncertainty about the products' safety and efficacy. The agency also may have to strip away all work other than product approval reviews. This will adversely impact other programs (e.g., blood safety, product tampering, mammography).

As to timeframes, a compromise should include the Prescription Drug Use Fee Act (PDUFA) times for drugs and biologics. Anything else undercuts the progress FDA has made under PDUFA. Other statutory timeframes should be changed so that they are realistic. A compromise to sections 404 and 707 could require one pre-submission meeting, one post submission meeting (to be held at a time that is meaningful) and consultation throughout the time period for application review. The compromise language should also make the requirements for FDA's "deficiency" letters more reasonable -- e.g., letters would include deficiencies identified to date (thus not cutting the short deadlines even further).

Third Party Reviews Section 403(a) permits FDA to contract for outside review to evaluate parts or all of applications or petitions. Section 403(b) appears to require FDA to contract out all applications, notifications, and conditions if certain (quite loose) conditions are met.

A proposed compromise would be to add language to ensure that the section 403(b) language is discretionary. Alternatively, the language could be revised to limit and tighten the conditions under which contracting out would be required.

The Drug Approval Standard. Section 602 states that substantial evidence may consist of data from one well-controlled clinical investigation and confirmatory evidence. This may lower the effectiveness requirement from two adequate and well-controlled studies to, at most, one. Although FDA often accepts data from one adequate and well-controlled trial, this should not be the standard. Section 410 provides that for efficacy supplements, the data may consist entirely of information published in medical literature if the proposed condition of use relates to treatment of a life-threatening disease. This suggests that information other than from adequate and well-controlled studies would be acceptable. Moreover, although FDA has, on occasion, relied on reports of adequate and well-controlled studies published in journal articles to approve an efficacy supplement, this is not and should not be the general rule.

Re: section 602: A compromise position could include minor changes to the provision that would (1) add the phrase "adequate and" before the term "well-controlled" (to make the term consistent with its prior use in the statute) and (2) add the phrase "if appropriate" to ensure that while FDA may accept one trial, one trial is not the presumption.

Re: section 410: The concerns regarding efficacy supplements that this provision is trying to address are dealt with in the concepts being proposed as a compromise to the sound medical practice provision. If it is felt, however, that this provision needs to stay in the bill, it should be clarified to provide that the information in the literature is about one or more adequate and well controlled studies.

Limits FDA's Review of Safety and Efficacy. Section 408 provides that the review of an application cannot include the evaluation of any use not included in the labeling. Section 408 appears to prohibit FDA from including, in the labeling, warnings concerning indications for which a product is known not to be effective.

A proposed compromise would be to change section 408 so that it would not permit FDA to deny an application based on any potential use not included in the labeling. This change would permit FDA, where appropriate, to include in the labeling a warning that the product is not effective for a certain use.

Animal Drug Approval Standard. Section 802(a) amends the Act to redefine the "substantial evidence" criteria that currently must be met to establish effectiveness. The requirement for adequate and well controlled studies would be changed to "scientifically sound studies." Section 802 also replaces the requirement that the studies fairly and reasonably show effectiveness to a requirement that there is a reasonable assurance of effectiveness.

A compromise position would be to revise the current standard to clarify that one study may be enough to establish effectiveness and that field investigations will only be required where appropriate.

Pediatric Studies Marketing Exclusivity. Section 411 provides a 6 month marketing exclusivity for approved applications with pediatric studies submitted by an applicant.

It is important to provide incentives for conducting pediatric studies. However, there are concerns about whether the provision is sufficiently tailored so that it applies to important new uses and as to whether the incentive is too generous in light of the fact that these trials often are very inexpensive.

Statutory Hammers. The bill includes a number of statutory hammers. Section 404 requires FDA to contract for outside review if in any fiscal year it fails to meet the statutory time frame for 95% of the applications in a particular category. It also requires FDA to give special priority to applications, notifications, or petitions for products that have been approved in the EU or UK if by July 1, 1998, FDA fails to meet a time period for action on an application, notification, or petition for approval or clearance of a new drug, biologic, device, or animal drug that is a significant improvement over existing products or of a food additive that has the potential to make foods more wholesome and contribute to a healthier diet.

The understanding is that these hammer provisions will be deleted from the bill. If left in the bill, however, they would present serious concerns in that they undermine the statute's primary objective that FDA find that drugs and devices be proven safe and effective and that food additives be proven safe before they can be marketed.

There are a number of additional technical and substantive changes throughout the bill that are important, but in general, are not likely to be controversial.

Walk through

- Post-approval manufac changes

Consistency

[Statutory provisions? Breadth of ^{discretion} ~~discretion~~ now?
Establishment License Applications req'd for drugs and biologics

- largely governed by regulation?

- What type of validation

- then ongoing testing, right

See 604 - Constraining amendments?

- monograph / non-monograph

terms: "validation" (ln. 26) ^{p. 81}

^{p. 82}
"appropriate study" (ln. 10)

Discretion as to whether the ^{biological} product can be "adequately characterized" for purposes of this subsection
p. 83, ln. 16.

FDA Reform - brainstorming

- Members voted for Coats

Want something in btw

- DK doesn't have much sympathy for that

- Pilot - enough?

- deadlines

- manufacturing change

→ off-label use?

Scope of IAP

May 1st