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September 13, 2002

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

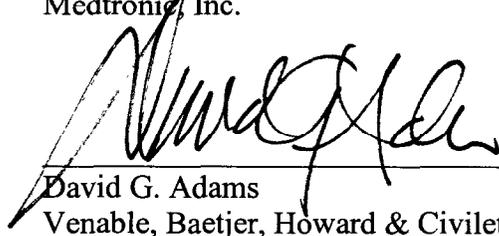
Re: Docket No. 02N-0209 (First Amendment Issue)

Dear Sir or Madam:

The attached comments are submitted on behalf of Medtronic, Inc. regarding the constitutional limitations on FDA regulation of dissemination of information on device and drug product candidates that are not cleared for marketing by the agency.

Respectfully submitted,

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02N-0209

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September 13, 2002

Dockets Management Branch
Food and Drug Administration
Room 1-23
12420 Parklawn Drive
Rockville, Maryland 20857

Re: Docket No. 02N-0209 (First Amendment Issues)

Dear Sir or Madam:

On May 13, 2002, FDA requested comments on certain issues raised by governing First Amendment case law. Medtronic, Inc., offers the following comments regarding constitutional limitations on FDA regulation of dissemination of information on device and drug product candidates that are not cleared for marketing by the agency.

I. FDA's Ban on Speech Related to Unapproved Product Candidates

FDA strictly regulates dissemination of information on device and drug products that require FDA clearance under the PMA, 510(k), and new drug provisions of the act. In the case of products that are candidates for approval, the agency broadly prohibits manufacturers from disseminating information about the products to health-care professionals and patients, even though the products are not being marketed and regardless whether the information is truthful and non-misleading.

This restraint on speech prior to the approval of a product has evolved largely through agency policy rather than law. The Food, Drug, and Cosmetic Act (FDCA) contains no prohibition against dissemination of truthful and non-misleading information in advance of product approval. The only regulations addressing information on unapproved products are those governing investigational devices and drugs. These regulations do not apply to non-investigational products and limit only "commercialization," "promotion," and "represent[at]ions] in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation..." See 21 C.F.R. 312.7(a), 812.7(a). The regulations do not define "commercialization" or "promotion," and agency pronouncements appear to take the position that any information related to the possible safety or effectiveness of a product is considered promotion, with certain limited exceptions.¹

¹ See, e.g., 62 Fed. Reg. 64074, 64083 (1997) ("This final guidance seeks to clarify the distinction between the concepts of promotion/commercialization and industry-supported scientific exchange... Programs supported by companies that are not otherwise independent, scientific or educational activities are subject to regulation as product promotion/commercialization."). See also *id.* at 64075 ("The agency, thus, regulates products based not only on information provided 'with' the product (approved professional

In the case of devices, Medtronic has observed the establishment of a de facto ban on pre-approval information through compliance actions and public speeches. This ban extends even to the display of the device unless the device is the subject of a pending 510(k).²

These policies preclude manufacturers from providing truthful and non-misleading information to health-care professionals and patients. Examples of banned information include the following:

1. Copies of scientific investigations published in peer-reviewed journals.
2. Reference texts discussing unapproved therapies.
3. Information presented to health-care professionals at scientific meetings or to interested patient groups concerning applications submitted to FDA for approval or clearance.
4. Displays at meetings of health-care professionals of devices for which approval is being or will be sought.

II. The Harmful and Unwarranted Effects of FDA's Ban on Speech

The agency's broad ban on disseminating information prior to approval thus extends to valuable information on potential new products – information that health-care professionals and patients clearly and increasingly desire. Medtronic has observed FDA officials comment publicly on the growing interest among patients regarding therapies. Dr. David Feigal, CDRH Director, commented at the Advamed 2001 Annual Meeting that research involving hits on websites demonstrated that searches for medical device information were increasing. Dr. Feigal suggested that this was part of a growing trend toward patients desiring to have a part in their medical care.

labeling), but also based on information disseminated by or on behalf of manufacturers in other contexts, such as scientific and educational meetings and symposia, books, reprints of articles from scientific journals, in part because all of these activities/materials can create new intended uses for the products, which must be reflected in the approved labeling of the products”).

Virtually any information disseminated by the manufacturer that “explains” a product is deemed by the agency to labeling or an advertisement. *See, e.g.*, 59 Fed. Reg. 59820, 59822 (1994). Moreover, as noted above, any discussion related to the potential use of a product can be deemed to create a new intended use. This effectively prohibits disseminating any substantive information on a potential new therapy prior to its approval, with only limited exceptions such as independent scientific and educational activities, submission of scientific studies for publication, responses to unsolicited requests for information, and notices to investigators and potential subjects regarding clinical investigations.

² Section 300.600: Commercial Distribution with regard to Premarket Notification (Section 510(k)) (Compliance Policy Guide 7124.19) (reissued on September 24, 1987) (“Although a firm may advertise or display a device that is the subject of a pending 510(k)--in the hope that FDA will conclude that the device is substantially equivalent to a pre-amendments device--a firm may not take orders, or be prepared to take orders, that might result in contracts of sale for the device unless limited to research or investigational use.”). Prior to submission of the 510(k), the device cannot be placed on display

This trend is illustrated by the growth of disease-oriented patient support groups that gather and disseminate information on current and potential new therapies. Medtronic witnessed this form of patient involvement with regard to a clinical device designed to treat life-threatening reflux by stimulating the stomach. After initial studies, it did not appear to Medtronic that there were sufficient data to support the filing of a PMA. Patient advocates began a campaign to gain access to the product, lobbying FDA and Congress. . Eventually FDA and Medtronic provided access under a Humanitarian Device Exemption. Medtronic has observed a steady increase in this sort of patient activism.

Patients not only *want* to know, but may in fact *need* to know, about potential new therapies. Many Medtronic devices are intended for patients who suffer from long-term, chronic conditions and who have tried numerous unsuccessful therapies. Many of these patients have diseases that involve slow degradation of the body or body function. They search for information on possible new therapies, and often consider enrolling in clinical studies. In some cases they face a choice between undergoing a high-risk and irreversible surgical procedure or waiting for approval of a safer and reversible device therapy. They must have, and are clearly entitled to have, accurate and complete information on possible future treatments to make these important decisions.

Similarly, health-care professionals want and need information on possible future therapies in order to advise their patients. When these professionals attend conferences or meet with device company representatives, they rarely seek information on currently available treatment options. In Medtronic's experience, they want information on the new technologies being developed to help their patients.

Generally, neither professionals nor patients seek representations of safety and efficacy of unapproved products. They instead seek information on products that are being developed for approval and what those products are intended to do. They want facts and data, not promotional claims.

Manufacturers of devices and drugs have a right to provide information to professionals and patients about products they are developing for agency approval. They have a right to tell professionals and patients how a device or drug product candidate is intended to work, what the product is being studied for, and the uses for which approval is being sought, as long as the information is truthful and non-misleading

The needs of health-care professionals, patients, and manufacturers are being thwarted under current FDA policy. FDA policy focuses on the genesis and route of transmission of the information from the manufacturer to the public rather than on whether the information is truthful and non-misleading. Medtronic believes the policy imputes improper motives to the manufacturer, presuming that the manufacturer is circumventing the agency's review and approval of its products. Medtronic believes that the policy does not reflect consideration of (1) the true need for information by health-care professionals and patients and (2) the legitimate interests of manufacturers in

providing truthful and non-misleading information on their efforts to demonstrate safety and effectiveness and obtain approval of its products.

The American public is left in the ironic position being able to obtain more information about possible new consumer products, such as DVD players, than it can obtain about possible new treatments for life-threatening diseases. Americans can hear from DVD manufacturers about the latest technologies under development for DVD players but cannot hear truthful information from device manufacturers about the latest technologies under development for pacemakers. Medtronic believes this outcome is not in the interests of physicians and patients and cannot pass constitutional muster.

III. The Constitutional Does Not Permit a Ban on Speech Regarding Products that Are Candidates for Approval.

As noted by the agency in its announcement soliciting comments on constitutional issues raised by restrictions on labeling and advertising, the Supreme Court has held that the government has only limited authority to prohibit truthful and non-misleading commercial speech. For such a prohibition, the government's must demonstrate, *inter alia*, (1) that the restriction on speech directly advances a substantial governmental interest and (2) that there is no other means for advancing that interest that is less restrictive on speech. The government cannot sustain this burden in the case of FDA's prohibition of truthful speech related to unapproved products.

A. The Prohibition on Speech Does Not Directly Advance the Government's Asserted Interests.

1. Truthful Information Does Not Undermine the Integrity of the Investigational Process.

As authority for prohibiting dissemination on unapproved products, the agency has generally relied upon its regulations forbidding "commercialization" and "promotion" of investigational drugs and devices.

In the case of an investigational device, the regulation provides as follows:

A sponsor . . . shall not . . . [p]romote or test market an investigational device, until after FDA has approved the device for commercial distribution.

21 C.F.R. 812.7(a).

In the case of an investigational drug, the regulation provides as follows:

A sponsor . . . shall not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug. This provision is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination

of scientific findings in scientific or lay media. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.

21 C.F.R. 312.7(a).

The intent behind the regulations is stated in section 312.7 -- “to *restrict promotional claims* of safety and effectiveness . . . and to *preclude commercialization* of the drug before it is approved.” (Emphasis added.) These regulations are obviously designed to protect the integrity of the investigational process from influences that might turn the process into a scheme for marketing prior to approval. Other provisions of the regulations further the same objective by directly prohibiting commercial distribution and test marketing, 21 C.F.R. 312.7(b), 812.7(a), by prohibiting sponsors from prolonging investigations, 21 C.F.R. 312.7(c), 812.7(c), and by prohibiting sponsors from charging for investigational drugs or devices except under unusual circumstances, 21 C.F.R. 312.7(d), 812.7(b).

Although neither the regulations nor their preambles explain how the regulations relate to the integrity of the investigational process,³ the intent behind these provisions was explained by a commentator in 1964 as a “[p]rohibition of the dissemination, for promotional purposes, of investigational drugs, a form of pre-marketing sampling.” Gibson, “The Effect of the Investigational Drug Regulations on Drug Research and Development,” 19 *Food and Drug Law Journal* 153, 154 (March 1964).” The author explains FDA’s concern as related to the possibility of drugs being supplied to “marginal investigators whose chief function is to make the investigational drug better known to the medical profession prior to marketing.” *Id.* at 158-9.

Because the regulations are designed to protect the integrity of the investigational process from becoming a means for commercial distribution, the prohibition can be enforced only through a termination or withdrawal of the IND or IDE. *See* 21 C.F.R. 312.44(b)(1)(v) (termination where “drug is being promoted or distributed for commercial purposes not justified by the requirements of the investigation or permitted by § 312.7”); 21 C.F.R. 812.30(b)(1) (withdrawal where “[t]here has been a failure to comply with any requirement of this part”). There is no statutory prohibition on making promotional claims regarding an investigational drug or device.

There is no evidence or reason to believe that allowing manufacturers to show their products and provide truthful and non-misleading information about their products to health-care professionals and patients will transform clinical investigations into marketing schemes. Clinical investigations are expensive and manufacturers are generally precluded from charging for their products.

³ Both regulations are based on a regulation that was promulgated in 1963, 21 Fed. Reg. 179, for which there is no preamble.

There is no record that FDA considered the needs of patients of health-care professionals in promulgating these regulations. There is no record suggesting that the agency made any effort to find a less restrictive way of controlling promotional activity that would preserve the public's right to receive information on potential therapies.

In sum, the agency has no substantial interest in the IND or IDE process that is directly advanced by the agency's prohibition of truthful and non-misleading speech about products prior to their approval.

2. Truthful Information Does Not Undermine the Government's Interest in Prohibiting False and Misleading Claims.

FDA's ban on dissemination of information on product candidates for approval extends to all products, regardless whether the products are subject to an IND or IDE. This suggests that the agency's real interest is unrelated to the integrity of the investigational process. The agency's real interest appears to be in preventing the dissemination of information prior to approval that may be inconsistent with the labeling that is ultimately approved by the agency. Although this is a legitimate concern, it cannot justify a ban on truthful and non-misleading speech.

If a manufacturer promotes an unapproved product in a manner that is false or misleading, the agency can take appropriate corrective action. As discussed above, if the product is subject to an IDE or IND, the agency can terminate the investigational exemption. The agency can also deem the investigational product misbranded under section 502(a) of the act. If there is no IND or IDE and, thus, no product in commerce within the meaning of the act, obviously there can be no violation until a product is actually approved and brought to market. After approval, however, the agency can take action against the product under section 502(a) of the act if the pre-approval information causes consumers to be misled about the product that is introduced onto the market.⁴ If

⁴ The agency has, in the past, asserted a second significant interest in prohibiting unapproved claims of safety or efficacy based on the theory that such claims are inherently misleading. In *Washington Legal Foundation v. Friedman*, 13 F.Supp.2d 51, 67-68 (D.D.C. 1998), a district court firmly rejected FDA's arguments that certain forms of manufacturer promotion of off-label uses for drugs were inherently misleading and thus not subject to First Amendment protection. The court explained that the speech was not inherently misleading because, *inter alia*, the court found that the availability of many less restrictive controls that could be used by FDA to make the activities less likely to be even potentially misleading suggested that the activities were not inherently misleading. Similarly, in the dietary supplement context, The D.C. Circuit rejected FDA's argument that health claims lacking "significant scientific agreement" were inherently misleading and thus entirely outside the protection of the First Amendment. *Pearson v. Shalala*, 164 F.3d 650, 655 (D.C. Cir. 1999).

At the district court level in the *Western States* case, FDA argued that advertising of pharmacy compounding beyond that allowed by Section 503A of the Food and Drug Modernization Act of 1997, 21 U.S.C. § 353a, was inherently misleading. The district court rejected this argument for two main reasons. First, the court found that there was no evidence that the prohibited statements contain any information that is actually false. Second, the district court explained that the targeted speech was not inherently misleading when it appears that a narrower restriction, such as a disclaimer, may reduce or eliminate its misleading nature. *Western States Medical Center v. Shalala*, 69 F.Supp.2d 1288, 1298-1300 (D.Nev. 1999). On appeal at the circuit court, FDA did not contend that the speech at issue was unlawful or misleading. *Western States Medical Center v. Shalala*, 238 F.3d 1090, 1093 (9th Cir. 2001).

the agency cannot demonstrate that the pre-approval information caused consumers to be misled, the pre-approval information has no regulatory significance and should be of no concern to the agency.

In sum, agency's interest in prohibiting false and misleading claims about approved products is not directly advanced by a general prohibition against truthful and non-misleading information prior to approval.

3. The Ability to Speak Prior to Approval Does Not Eliminate the Incentive for Approval.

The agency's policies on promotion of unapproved products are, of course, related to the agency's policies on promotion of approved products for unapproved uses. *See, e.g.*, 62 Fed. Reg. at 64081 ("Consistent with this statutory scheme, FDA has consistently prohibited the promotion of unapproved products and unapproved uses of approved products").⁵

The only substantial governmental interest recognized by the courts in the context of FDA's approval processes is the government's interest in providing incentives for manufacturers to demonstrate their products safe and effective, through studies or equivalence to other safe and effective products, in the drug and device approval and clearance processes. *See Washington Legal Foundation v. Friedman*, 13 F.Supp.2d at 69-71 (unapproved uses of approved products), *Thompson v. Western States Medical Center*, 535 U.S. ___, 122 S.Ct. 1497, 1504 (2002) (unapproved products).

In the case of products that are candidates for approval, prohibitions on truthful and non-misleading information simply do not advance the government's interest. This is because the products are not being marketed and cannot be marketed until they are approved. No matter what a manufacturer says about a product candidate, the manufacturer cannot make any money off of the product until it is approved and marketed. There can be no greater incentive to go through the approval process than to have a product candidate can produce no revenue until it is approved. Prohibitions on truthful and non-misleading speech do not affect this incentive.

Here, in the case of pre-approval speech, the agency's prohibition goes beyond claims of safety and effectiveness. Even the display of a medical device with only a statement that the device is being studied is prohibited under the agency's policy. In such a circumstance, where it is clearly communicated that the device is not approved and has not been demonstrated safe and effective for any use, the agency could hardly demonstrate that it is protecting the public from misleading claims of safety and effectiveness.

⁵ In fact, the agency, under the agency's interpretation of the FDCA, the promotion of an unapproved use for an approved product results in a new, unapproved product. The agency's position is that a new intended use for a product results in a new product, which must be approved by the agency in a new, supplemental application.

In sum, the agency's interest in preserving incentives for the drug and device approval processes is not directly advanced by prohibiting truthful and non-misleading speech about a product prior to its approval.

B. The Government Has Other Means for Advancing Its Interests.

Even if the agency's restrictions on truthful and non-misleading speech directly advanced a substantial governmental interest, which they do not, the restrictions would not pass muster because the government has other, less restrictive means for advancing those interests. In the *Western States* case, the majority opinion restates the strict requirement of First Amendment analysis: "In previous cases addressing this final prong of the *Central Hudson* test [*Central Hudson Gas & Electric Corp. v. Public Service Commission of New York*, 447 U.S. 557, 566 (1980)], we have made clear that if the Government could achieve its interests in a manner that does not restrict speech, or that restricts less speech, the Government must do so." 122 S.Ct. at 1506.

The government must demonstrate under this test that there are no non-speech-related means of advancing its interests. In *Western States*, the government failed to meet its burden because "[s]everal non-speech-related means of drawing a line between compounding and large-scale manufacturing *might* be possible here." *Id.* (emphasis added). The Court noted several possible legislative alternatives and held against the government because it "has not offered any reason why these *possibilities*, alone or in combination, would be insufficient to prevent compounding from occurring on such a scale as to undermine the new drug approval process." *Id.* at 1506-7 (emphasis added).

Here there is no evidence or reason to believe that prohibitions on truthful and non-misleading speech are required.

1. Preventing the Investigational Process from Becoming a Marketing Scheme

There is no reason to believe that the numerous protections provided in FDA's IND and IDE regulations would not suffice to prevent investigations from being corrupted into marketing activities without a ban on truthful and non-misleading speech. As discussed above, various provisions of the regulations further this objective by directly prohibiting commercial distribution and test marketing, 21 C.F.R. 312.7(b), 812.7(a), prohibiting sponsors from prolonging investigations, 21 C.F.R. 312.7(c), 812.7(c), and prohibiting sponsors from charging for investigational drugs or devices except under unusual circumstances, 21 C.F.R. 312.7(d), 812.7(b).

Moreover, there is no evidence that FDA has considered the needs of patients or health-care professionals in banning this speech. It does not appear that the agency made any attempt to find a less restrictive way of controlling promotional activity that would preserve the public's right to receive information on potential new therapies.

Should the government nevertheless believe that further measures are necessary to protect the integrity of the investigational process, Congress could require greater oversight and monitoring by FDA over the process of recruiting patients and investigators and provide FDA with greater resources for this task. There is no evidence or reason to believe that prohibitions on truthful and non-misleading speech are necessary to preserve the integrity of the investigational process.

2. Preventing False and Misleading Claims Related to Approved Products

There is no evidence or reason to believe that the protections provided under the misbranding provisions of the act are inadequate to address concerns over false and misleading information disseminated prior to approval. In the event of such dissemination, the agency has ample authority to require correction of the misinformation or to keep the product off the market. In fact, the dissemination of problematic information prior to approval, rather than after approval, is far easier for the agency to address and control. Corrective measures can be taken prior to approval. If such measures were inadequate, the agency could refuse to approve the product or seek judicial relief immediately upon approval.

Should the government nevertheless believe that greater controls are necessary, Congress could provide the agency with greater statutory authority and resources to scrutinize and correct problematic claims before the agency allows the product onto the market.

3. Providing Incentives for Manufacturers to Seek Approval for Their Products

Prior to approval, manufacturers cannot sell their products and earn revenues. There is no evidence or reason to believe that this incentive is inadequate to induce manufacturers to seek approval of their products. Should the government deem this incentive inadequate, Congress has ample authority to provide greater incentives, such as grants and tax breaks, to further encourage manufacturers to seek approval for their products. There is no evidence or reason to believe that the only way to convince a manufacturer to seek approval and market a product is to prevent truthful and non-misleading speech prior to approval.

IV. The Need for a Safe Harbor

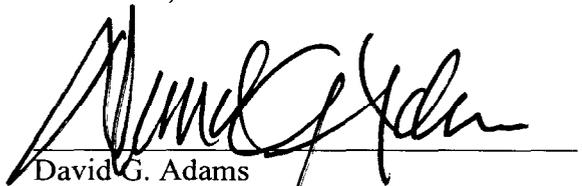
Medtronic does not propose that FDA react to these constitutional infirmities by ignoring discussions of a product prior to approval. Such a policy is not required and may be unwise. Medtronic does believe, however, that the agency should acknowledge a clear safe harbor for providing truthful and non-misleading speech related to these product candidates. This safe harbor should allow, at a minimum, the following activities:

1. Dissemination of truthful factual information about the structure, composition, intended therapeutic use, and regulatory status of the product.
2. In the case of devices, presentation (display) of the device and dissemination of information about the intended operation of the device.
3. Dissemination of truthful information about planned, ongoing, or completed clinical trials, including information on a trial's purpose, inclusion criteria, clinical endpoints, risks, and currently available results.
4. Dissemination of information about the status of applications for clearance or approval, about the estimated time for FDA action on the application, and, assuming the application is approved, the expected release date for the product.
5. Dissemination of information on the approval and availability of the product in other countries.

It is important to note that Medtronic does not seek to make claims of safety or effectiveness for any unapproved products. Medtronic supports concepts expressed in CDRH guidelines for disseminating this type of information. *See* "Preparing Notices of Availability of Investigational Medical Devices and for Recruiting Study Subjects" (March 19, 1999). This guidance document addresses the dissemination of factual information on investigational devices to clinical investigators and precludes claims of safety or effectiveness. Medtronic believes these concepts may be useful for the agency to consider in moving quickly towards creating a safe harbor for providing health-care professionals and patients with information on potential new therapies.

Respectfully submitted,

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The Effect of the Investigational Drug Regulations on Drug Research and Development

By AUGUSTUS GIBSON, M.D.

Dr. Gibson is Director of the Medical Research Division, Schering Corporation; Bloomfield, New Jersey. This Paper Concluded the Nineteenth Annual Meeting of the New York Bar Association Section on Food, Drug and Cosmetic Law, Which Was Held on January 28, 1964.

AS WITH MOST LAWS, no one can oppose the intent of the drug law of 1962 and its implementing regulations. As Hoover said of the 18th Amendment, it is "noble in motive." We are all in favor of safe and efficacious drugs. However, no law or regulation is self-enforcing and few are completely predictable in their ultimate effect. I hope, therefore, that an examination of the effects to date of the new law and regulations will not be construed as opposition to their intent.

Intent of New Regulations

Perhaps, however, this intent should be outlined more specifically so that we can consider in detail the extent to which it has been achieved. As I understand it, it was as follows:

(A) To insure efficacious as well as safe drugs. Others have been assigned this topic for discussion.

(B) To insure the safety, not only of the purchaser of the marketed drug, as was provided for in the New Drug Law of 1938, but also of the patient on whom its effects in man are initially determined. Specific measures designed to accomplish this end include: (1) Requirements for animal studies before any drug is given to man; (2) Administration only by qualified clinical investigators; (3) The formulation of adequate plans of investigation; (4) Notification of the subject that he is receiving an investigational drug unless, an

important proviso, the investigator believes it not to be in the best interest of the patient to so inform him; (5) Prohibition of the dissemination, for promotional purposes, of investigational drugs, a form of pre-marketing sampling; and (6) Requirements that adequate records be kept of distribution of the drug and the detailed effects thereof in each patient who has received it.

The new regulations have not been in effect very long. It is premature to assume that the present environment in which drug research is conducted will persist indefinitely into the future. Furthermore, I doubt if anyone really knows just what is now going on. However, for what it may be worth, I will present my own opinion on the present state of affairs. Even if it may be somewhat valid as of today, the situation is changing, hopefully for the better, and my comments on this occasion may be badly outdated within a year. One thing, however, may be said with some degree of assurance. The new regulations were not designed to expedite the marketing of new drugs, to increase their number, or to decrease the cost of their development. None of these objectives were intended. They have not come to pass.

How the New Regulations Are Faring

Have the other intentions been fulfilled? Taking them one at a time, the situation seems to be like this:

(1) The better companies have always carried out appropriate animal studies before going to the clinic. Now all companies must do so. Whether this has provided significant additional protection to the public is impossible to say. We don't know about the bad things that haven't happened since the new regulations have been in force and, even in the bad old days, few patients were harmed by investigational drugs. However, the value of animal studies depends on their ability to predict effects in man. There is a high degree of predictability for certain types of toxicity, such as acute lethal effect. There is much less for others almost equally important, such as teratogenicity. A great deal has been said on this subject; there are many opinions but not much research and few facts. We badly need better correlation of animal and human data and research on better methods of experimentation. This, it seems to me, is too big a job for the individual company. It is one on which government, the universities and foundations, and the industry should collaborate. The new regulations have resulted in very high mortality among experi-

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mental animals. However, if such testing is considered an end in itself and is done in a routine fashion without thoughtful consideration of its significance and without efforts to improve techniques and understanding, these animals die in vain.

(2) The regulations provide that only qualified investigators take part in clinical investigation. This obviously is desirable. However, regulations do not train, provide, or reward investigators so that the supply has not increased to meet the demand. Drug investigation has never been considered a glamorous field and has been made even less attractive by the restrictive provisions which inhibit the initiative of the scientist and increase the number of forms which he must fill out. In spite of this, it is gratifying and slightly surprising that a larger number of investigators have not discontinued drug evaluation. There have been many statements to the effect that this has happened, and I can only speak from my own experience but, in general, it is still possible to find qualified investigators to study drugs with some promise of usefulness. On the other hand, the cost of drug investigation has gone up appreciably, since we are requiring more laboratory work, more secretarial assistance, and more of the time of the investigator himself. It is only to be expected that the average cost to the pharmaceutical company of a clinical study has increased and is continuing to rise.

Question of Qualifications of Investigators for Drug Testing

The regulations do not give us an answer to one of the most difficult questions which they pose: Who is qualified to do drug testing; what are the criteria for determining this; and by whom are these questions decided? The FDA has given us little guidance. Certification in a specialty, academic rank, and hospital staff positions are all factors which enter into the judgment of qualification, but I know of many people with eminent names in medicine who are poor investigators, and there are many young men just starting a career in clinical investigation who have not yet become known but who by native intelligence, diligence, and good basic training are well-qualified. As in every other field, an investigator is best judged by his performance. As you know from reading the daily papers, there probably have been rare instances of falsification of clinical records. It is, nevertheless, very easy to tell on examining an investigator's plan for research and the case reports and analysis which follow its conclusion whether he is truly qualified. The FDA has

always used these criteria in an informal way and has weighed drug research reports according to the internal evidence of their quality. This, no doubt, will continue to be the practice, and we who arrange clinical studies for the industry have used very much the same criteria. We are, however, tightening up our requirements and sharpening our critique in order to be able to present clinical data in our applications which will be acceptable to the physicians in the FDA.

One interesting by-product of the regulations is that a number of commercial organizations have sprung up throughout the country, offering to provide drug research for the pharmaceutical companies all the way from screening to toxicity studies to clinical evaluation. These are often well-staffed, and although I doubt if the large companies avail themselves of this service, these research institutes may be of help to the small firms which cannot afford large, full-time staffs.

Advance Protocols of Research Required

(3) The new regulations require that protocols of research be prepared in advance both by the drug company which sponsors the drug and by each individual clinician. Planning is always desirable, and probably has often not been as thorough in the past as it should have been. The chief objection to this provision is the fear that it will lead to loss of flexibility and that the clinician may be forced to carry out a study which experience proves unworkable or undesirable. We have been assured, however, by the FDA that reasonable flexibility will be permitted, and it goes without saying that a plan of investigation which proves to be hazardous may be abandoned. Changes in protocol, however, require further notification of the FDA.

Although our plans for investigation must be submitted to the FDA at the time that the clinical investigation is initiated, thus far we have received little or no comment on them, probably because the overworked staff in Washington has not gotten around to reading them. This is unfortunate, since it deprives us of the benefit of the judgment of the FDA on the suitability of our studies until we finally submit a New Drug Application. It is only then that we learn that they were inadequate in some respect. It is to be hoped that the prolonged period from the start of a clinical drug investigation to the submission of an NDA will be made more fruitful by an interchange of information and opinion between the physicians in the industry and those in the agency; otherwise, there will inevitably be great loss of time and delay in the availability of new drugs.

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(4) The new discussion and that he is receiving of the clinician patient. Some routinely notified additional problems handicap to accept large subjective and side effects. evidence which

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The FDA has divided clinical drug evaluation into three parts: Stage I, the initial trial in a few normal people to determine the probable dose and the immediate effects; Stage II, the first limited trials in ill patients to obtain some hint of efficacy; and Stage III, the prolonged and extensive studies in depth to delineate more accurately the dose, the efficacy in various indications, and the nature and incidence of side effects. It has for many years been the custom in a rather informal way to follow similar sequence of events, but there has been a tendency to pass gradually from one stage to another. The new regulations have emphasized Stage I studies in normal persons, since these require less preliminary data. The increase in such studies has resulted in much wider utilization of prisoners and student volunteers as subjects. This may, at times, present unusual ethical and medico-legal problems.

Notification of Patient

(4) The next provision is one which has caused a great deal of discussion and debate—the requirement that the patient be notified that he is receiving an investigational drug unless in the judgment of the clinician such notification is contrary to the best interest of the patient. Some investigators even prior to passage of the present law routinely notified their patients and, of course, now encounter no additional problems. Others have found this requirement a great handicap to accurate drug evaluation, since it is bound to introduce a large subjective element into the reporting of both relief of symptoms and side effects. This makes it more difficult to provide the objective evidence which the FDA requires.

A particularly difficult problem is raised in double-blind studies, where neither the physician nor the patient knows what drug is being administered. How can the patient give informed consent if the doctor cannot tell him whether he is getting an investigational drug, an old drug made up to look like it, or a placebo? Of course, the patient could be told that he is going to get one or another of these. In this case he might reasonably object to the possibility of receiving a placebo which could not possibly have any real effect on his illness. However, the placebo controlled double-blind technique has received a great deal of emphasis by the FDA. This in turn has created conflict with the legal requirement that drugs shipped in interstate commerce be labeled in such a way as to indicate their composition. Such a provision has been in the law for many years and, in spite of

it, double-blind studies have been carried out. However, the problem has been brought into sharp relief during recent months. There are, nevertheless, ways of complying with the regulations on labeling and at the same time providing for truly double-blind studies. However, they are both tedious and cumbersome.

Burden of Record Keeping

(5) Record keeping both as to the effects of an investigational drug and of its disposition is now required. In other words, if we send a doctor one hundred doses, at the conclusion of his investigation he should have a record indicating how many of these have been used, he should return to us the unused portion, and should report fully the effects in each patient. Such provisions are a useful measure of protection in case a drug is found harmful, since it is then possible to trace all outstanding supplies and to retrieve or destroy them. It does, however, provide an added burden of record keeping which the physicians do not always take to kindly. Most important is the requirement that there be adequate records of the effects of the drug on each patient. If a doctor fails repeatedly to furnish adequate reports, he may be declared unacceptable as an investigator and no longer eligible to receive investigational drugs. It has always been difficult to get adequate, complete reports from physicians, since their secretarial facilities are usually overtaxed and their own records are often in a sort of illegible medical shorthand. However, I welcome this provision of the law, since it aids us as well as the FDA in making an accurate evaluation of a drug. We no longer have to rely on impressions which may not be backed by data, and we have the authority of the federal government in demanding complete reports from each clinician on each patient he has treated.

(6) The regulations prohibit the use of investigational drugs except for bona fide investigational purposes. A tacit exception to this is made for emergency cases where a patient may be dying of a disease for which a drug still in the investigational stage is the best treatment. In such a case we are permitted to make immediate shipment and to fill out the paper work later. Furthermore, the treatment of such an individual case is obviously not part of a planned investigation. Yet we will not be criticized for making a drug available to possibly save a life. However, the FDA does frown on supplying investigational drugs to marginal investigators whose chief function is to make the investigational drug better known to the medical

<profession prior to marketing. There have, no doubt, been abuses in this respect, but the FDA regulations also make it far more difficult to carry out a legitimate, broad-scale drug evaluation, since this may be misinterpreted as semi-promotional distribution. Yet such broad-scale investigations often have a great value. A few cases carefully studied will, it is true, provide certain types of information more effectively than a large number observed more casually. Nevertheless, the true incidence of beneficial and harmful effects can only be determined on a broad statistical basis. The wider use of investigational drugs, once they are proved safe and probably effective should not be hindered, provided the results of such use are reported. Once a drug is on the market, we lose contact with the physicians using it and rarely learn about their experiences. There is, therefore, a real place for broad-scale studies which may point out the existence of unusual side effects or establish the degree of efficacy.

Having indicated certain specific areas in which the new regulations have altered the conduct of drug research, I should like to point out what I consider to be their more general effects.

More General Effects of New Regulations

First, there is little doubt that there is some inconvenience to investigators. This has made a few clinicians with borderline interest in the field of drug evaluation drop out of it and may well have kept others from entering it.

Secondly, the new regulations require paper filing and record keeping even in investigating an old drug for a new use or in altering a study of a new one just as they do for initiating the evaluation of an entirely new compound. As a rule these requirements are not difficult to fulfill but, nevertheless, this does prevent the independent investigator from lightly following up some educated hunch, new line of reasoning, or chance observation which may open up an entirely new area of medical usefulness. For instance, a drug introduced some years ago as an adjunct to the use of penicillin was found to be much more valuable in the treatment of gout. It is entirely possible that under the present regulations this use might not have been considered probable enough to justify even a modest amount of paper work. Thus, we may lose the important fruits of serendipity found by following faint leads or intuitions. Also, there are certain products which are of interest to only a few people either for academic purposes or the treatment of rare conditions. The average pharmaceutical com-

pany now does not find it possible to cater to such interests, since the effort required is almost as great as that for a large volume, highly profitable product.

Investment of Time and Money Increased

Above all, the regulations do increase the length of time necessary to introduce a drug. I doubt if many people realize how long this takes, even under the most favorable circumstances. From the time a new chemical structure is envisaged to its actual synthesis may take several months or even occasionally years. The first quantity produced is usually so small that it is only sufficient to provide the faintest hint of medicinal activity. Then comes the problem of producing enough for fuller evaluation in animals of possible usefulness and acute toxicity. This may take another three or four months. If the data up to this point are favorable, larger amounts are needed for chronic toxicity testing and for early clinical experiments. Fairly large amounts of material at high cost may be required and another six months or more may ensue in its preparation. One might ask "Why not make all of this in the first place?" The answer is that the cost would be prohibitive and the gamble not justified until we have some indication we are on the right track. The subacute toxicity prior to giving a drug even to the first human being requires six weeks or more of administration to animals and then several weeks for evaluation of results. After the first clinical pharmacology, which takes two or three months to complete, one must do additional animal studies prior to final clinical evaluation. The average drug is then in the clinic for anywhere from a year and a half to three or four years before a new drug application can be filed.

From the time of filing the new drug application until the first reply from the FDA is another six months, and it is the rare exception for a drug to be accepted on first submission. Refiling with correction of original deficiencies may occur in three to six months, and we may then get a final approval from four to six months later. After approval of the new drug application, preparation for full-scale production frequently takes another two or three months. It is only then that one begins to get some return on the successive investments of time and money. From the initial conception in the scientist's mind to appearance of a product on the market may easily take five years and often longer. The substantial investments of time and money make it more and more difficult for small companies to enter the pharmaceutical field

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or to stay in it unless they have been so fortunate as to hit on a major successful product early in their career. The legislation bearing Senator Kefauver's name has not lowered drug costs nor helped the small manufacturer.

Even more important, the public may on occasion be denied the use of valuable agents for the prevention, alleviation, and cure of disease for many months or years by the serial time-consuming process of drug development. Much of the delay is quite unavoidable, but we should not unnecessarily add to that which is inherent in the discovery and adequate testing of valuable new drugs. The FDA, I am sure, does not wish to do this. The opportunities and temptations to procrastination and indecision, however, are great. A reasonable pace can only be maintained by insistence on the most rapid evaluation and decision consistent with safety. This present period of adjustment is difficult and exasperating for the manufacturer, the clinical investigator, and the FDA officials. By communication and cooperation in all phases of the drug development and testing process, we can keep it from also being costly to the health of the public.

[The End]

WIDE RANGE OF SOCIAL SERVICES AVAILABLE TO PREVENT ALCOHOLISM

Public welfare departments have been urged to provide a wide range of social services to help prevent alcoholism or to minimize its damaging effects on the family. Commissioner Ellen Winston, Welfare Administration, Department of Health, Education and Welfare, pointed out in a recent letter to state welfare directors that the federal government may pay 75 per cent of the cost of furnishing rehabilitative and preventive services to families and individuals whose social and economic conditions may contribute to alcoholism.

Commissioner Winston called attention to a new leaflet which suggests the kinds of specialized services that local public welfare departments can provide under the 75 per cent matching arrangement authorized in the Social Security Amendments of 1962. These services have "particular relevance to families in which alcoholism is, or is likely to become, a problem," she said.

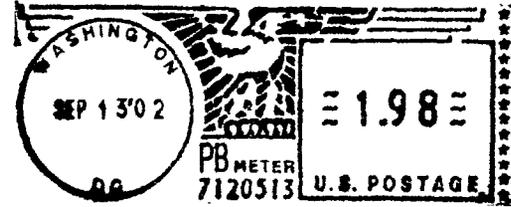
The leaflet, "Alcoholism—A Preventive Approach Through Programs of the Welfare Administration," points out that the problem of alcoholism affects rich and poor alike, that it wastes family earnings, adds to the numbers receiving public assistance, and is responsible for a number of cases of abuse and neglect of children. It also notes that alcoholism among parents contributes to family breakdown and to juvenile delinquency and that it complicates the problems of caring for and protecting older persons.

The leaflet may be purchased for 5 cents per copy from the Superintendent of Documents, United States Government Printing Office, Washington 25, D. C.

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