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THE U.S. FOOD AND DRUG ADMINISTRATION

BEFORE THE

COMMITTEE ON OVERSIGHT AND GOVERNMENT REFORM

U.S. HOUSE OF REPRESENTATIVES

"Should FDA Drug and Medical Device Regulation Bar State Liability Claims?"

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RELEASE ONLY UPON DELIVERY

INTRODUCTION

Good morning, Chairman Waxman, Ranking Member Davis, and Members of the Committee. I am Dr. Randall Lutter, Deputy Commissioner for Policy at the U.S. Food and Drug Administration (FDA or the Agency) in the Department of Health and Human Services (HHS). Thank you for the opportunity to discuss issues relating to the safety of medical products regulated by FDA and the importance and accuracy of the information associated with those products.

Under the Federal Food, Drug & Cosmetic (FD&C) Act, FDA is the public health agency charged by Congress with ensuring that drugs, biologics, and devices are safe and effective, and that the labeling of drugs, biologics, and devices adequately informs users of the risks and benefits of the product. FDA considers not only complex clinical issues related to the use of the product in study populations, but also important and practical public health issues pertaining to the use of the product in day-to-day clinical practice, such as the nature of the disease or condition for which the product will be indicated, and the need for risk management measures to help assure in clinical practice that the product maintains its favorable benefit-risk balance. FDA believes, based on the authority that Congress has given it and the scientific expertise that resides in the Agency, that it is uniquely qualified to make important judgments about the safety, effectiveness and labeling of medical products.

FDA is concerned that state product liability lawsuits that challenge FDA's careful determination of safety, efficacy and appropriate labeling can have detrimental effects to

public health in a number of ways, including limiting patient and doctor choices and decreased patient access to beneficial products, and increased confusion over warnings or statements that can deter the use of beneficial medical products. Of course, if a plaintiff claims to have been harmed by a sponsor's *failure* to meet the conditions of FDA's approval for a drug, biologic, or device, then state-law liability on that basis would not interfere with Federal law and manufacturers would get no protection from such claims. But to both protect the public health and as a matter of law, state law claims are preempted if they challenge a design or labeling that FDA approved, after being informed of the relevant health risk, based on its expert weighing of the risks and benefits of requiring additional or different warnings.

FDA'S ROLE IN ENSURING THE SAFETY AND EFFICACY AND APPROPRIATE LABELING OF MEDICAL PRODUCTS

FDA extensively reviews drugs for safety and efficacy using standards specified in statute, regulations and guidance.[i] FDA review teams consisting of medical doctors, chemists, statisticians, microbiologists, pharmacologists, and other experts evaluate whether the studies the sponsor submitted show that the drug is safe and effective for its proposed use. FDA reviewers analyze study results and look for issues with the application, such as weaknesses of the study design or analyses. Reviewers determine whether they agree with the sponsor's results and conclusions, or whether they need any additional information to decide whether benefits outweigh risks for intended uses. The process for pre-market approval of medical devices is similarly rigorous.[ii]

A critical part of FDA's mission is its review of the adequacy of labeling. FDA carefully controls the content and labeling of medical products, because such labeling is FDA's principal tool for educating health care professionals and consumers about the risks and benefits of the approved products to help ensure safe and effective use. FDA employs scientists and other experts to review the information submitted by the manufacturer on a product's risk and carefully calibrate warnings and other information that should be placed on the labeling. FDA continually evaluates the latest available scientific information to monitor the safety of products and to incorporate new information into product labeling when appropriate.

FDA takes care that labeling neither underwarns nor overwarns. FDA works to ensure that approved labeling not omit important risk information that patients and physicians should consider in making healthcare decisions. FDA further works to ensure that less important risks not be presented in a way that detracts from important risk information, and that risk information not adequately supported by scientific information not be presented in labeling, as such unsupported information could deter beneficial use of medical products.

In addition to its comprehensive pre-market review of medical product safety and efficacy, FDA engages in post-market surveillance to detect and respond to emerging information about approved products after they have been on the market. After a drug has been approved and marketed, the manufacturer must investigate and report to FDA any adverse events associated with use of the drug in humans, Title 21, *Code of Federal Regulations* (CFR), 314.80, and must periodically submit any new information that may affect FDA's previous

conclusions about the safety, effectiveness, or labeling of the drug, 21 CFR 314.81. (See 21 *United States Code* (U.S.C.), 355(k) (post-approval reporting and record-keeping requirements). Device sponsors similarly have obligations to report certain adverse events, see 21 CFR 803.10(c)(1), 803.50(a)(1)-(2), and to file annual reports. 21 CFR 803.55(b), 814.84.

FDA receives signals of post-marketing problems from individual adverse event reporting, surveillance networks, inspections, and various other resources. FDA directs internal and external data analysis, laboratory research, post approval studies and problem assessment groups in order to assess post-marketing problems. FDA's response includes communication of important risk information to the public and enforcement action where appropriate. FDA is currently in the process of modernizing its post-marketing surveillance and risk communication efforts through its implementation of the Food and Drug Administration Amendments Act of 2007 and other major initiatives.[iii] FDA believes its teams of scientists are unsurpassed in ensuring that labeling meets patients' needs.

FEDERAL PREEMPTION

Congress authorized FDA to apply its scientific expertise to determine, in the first instance, whether a medical product is safe and effective and what labeling, including warnings, is appropriate and necessary for a particular product. Therefore, FDA's determinations about safety, efficacy and labeling are paramount. The legal basis for Federal preemption of state law is the Supremacy Clause of the United States Constitution (U.S. Constitution Article VI,

clause 2). One form of preemption is express preemption, where Congress explicitly states in statute that Federal law supersedes state law in a particular area. For example, Congress has expressly preempted state lawsuits concerning certain medical devices. The Supreme Court recently ruled that an express preemption provision of the FD&C Act was properly interpreted to preempt state-law tort claims premised on allegations that a medical device that has received FDA pre-market approval is unsafe or ineffective.[iv] Even in the absence of an express preemption provision, however, implied conflict preemption principles still function to preempt state law in some circumstances. This type of preemption arises when there is conflict between Federal and state law, and the preemptive effect can occur with any Federal regulation. Under implied preemption doctrine, a state may not force a manufacturer to choose between compliance with Federal law and state law; Federal law prevails. State laws are also impliedly preempted if they stand as an obstacle to the accomplishment of Federal objectives [v] Where state law would force a drug sponsor to pay damages for failing to include a warning in labeling that FDA had rejected, for example, the state-law claim would be preempted. More generally, state law claims are preempted if they challenge a design or labeling that FDA approved, after being informed of the relevant health risk, based on its expert weighing of the risks and benefits of requiring additional or different warnings. [vi]

FDA believes that the important decisions it makes about the safety, efficacy, and labeling of medical products should not be second guessed by state courts. As the Supreme Court has stated with regard to medical devices,

> State tort law that requires a manufacturer's catheters to be safer, but hence less effective, than the model the FDA has approved disrupts the federal scheme no less than state regulatory law to the same effect. Indeed, one would think that tort law, applied by juries under a negligence or strict-liability standard, is less deserving of

> preservation. A state statute, or a regulation adopted by a state agency, could at least be expected to apply cost-benefit analysis similar to that applied by the experts at the FDA: How many more lives will be saved by a device which, along with its greater effectiveness, brings a greater risk of harm? A jury, on the other hand, sees only the cost of a more dangerous design, and is not concerned with its benefits; the patients who reaped those benefits are not represented in court.[vii]

FDA abides by standards set forth in regulations and guidance documents that are issued through a public process. FDA is the scientific regulatory body that is publicly accountable for effectively executing its mission of protecting and promoting the public health. FDA also believes, as explained in more detail below, that state court actions that undermine FDA decisions may have the consequence of serving to hinder, rather than help, public health.

Recent documents clarify FDA's longstanding position that it has primary responsibility to review the safety, efficacy, and labeling of medical products. In particular, FDA has reiterated the bases for this position in its Supreme Court brief in Wyeth v. Levine, No. 06-1259, and before that in the preamble to the physician labeling rule.

Physician Labeling Rule

The FD&C Act gives FDA the authority to determine when drug products are misbranded[viii]. FDA, therefore, is the appropriate arbiter of whether a drug's labeling is considered false and misleading. The Department of Justice (DOJ) has participated on behalf of FDA in preemption cases, and FDA has advanced this position in rulemakings. FDA rules dating back to 1979 reflect the Agency's view that the ultimate decision whether to require a warning on a drug label rests with FDA.

In the preamble to the final Physician Labeling Rule, FDA described some examples of instances in which it believes preemption is appropriate, for example, where there are claims that a sponsor breached an obligation to warn, but where FDA had considered the substance of the warning and decided that it should not be required. FDA also expressly recognized that FDA's regulation of drug labeling would not always preempt state law actions, noting that the Supreme Court has held that certain state law requirements that parallel FDA requirements may not be preempted.

The 2006 preamble sets out FDA's understanding of some of the ways in which a state tort judgment can interfere with FDA's implementation of Federal law. FDA's regulation of prescription drugs and biologics labeling and Federal preemption over conflicting state requirements are important to FDA's ability to protect the public health. The Agency's regulation of drugs and biologics is designed to ensure the optimal use of medical products by requiring scientifically substantiated warnings.

Changes Being Effected—CBE Proposed Rule

On January 16, 2008, the Agency published a proposed rule titled, "Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices." These supplemental applications are commonly referred to as "changes being effected supplements" or "CBE supplements." This document proposes to amend the regulations on CBE supplements to reflect FDA's longstanding policy to allow CBE changes only (1) when a sponsor has new evidence not previously submitted to FDA; and (2) when there is sufficient evidence supporting the change. This policy dates back as far as 1982,

when the Agency stated with regard to the proposal to implement the CBE rule: "[S]ome information, although still the subject of a supplement, would no longer require agency preclearance. These supplements would describe changes placed into effect to correct concerns about *newly discovered* risks from the use of the drug." (47 *Federal Register* (FR) 46622, 46623, October 19, 1982) (emphasis added).

This proposed rule, if finalized, would not alter the Agency's existing practices with respect to accepting or rejecting labeling changes proposed by a CBE supplement. The proposed rule was drafted so it would avoid inhibiting appropriate and timely submissions of new safety information, or the Agency's ability to review supplements in a prompt manner.

In several products liability cases, FDA/DOJ have taken the position that state law claims for failure to warn are preempted by Federal regulation of drug or device labeling. In those cases, FDA/DOJ have taken the position that CBE supplements are appropriate only in situations when a sponsor has new evidence and there is sufficient evidence supporting the change. This proposed rule, if finalized after FDA's review of the public comments, would simply codify that position.

To be clear, the proposed rule, if finalized, would not affect a sponsor's obligation to amend product labeling under FDA regulations (for instance, drug manufacturers are required to include "a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not be established.").[ix]

Further, the proposed rule would not affect this responsibility to bring appropriate safety information to FDA's attention – through a CBE supplement or other mechanism.

STATE PRODUCT LIABILITY LAWSUITS THAT UNDERMINE FDA'S EXPERT DETERMINATIONS MAY THREATEN PUBLIC HEALTH

Medical products are inherently risky. FDA evaluates evidence of a medical product's risks and benefits in the prevention or treatment of disease *across populations*. An FDA approval means that, on average and across the target population, the benefits of the product outweigh the risks for the intended uses. However, this does not mean that for each *individual* who uses the product the benefits of using a medical product will always outweigh the risks, and any system of regulation that required the benefits to outweigh the risks for every individual who might use the product would result in few or no medical products for the public. The use of the product is a decision that each patient must make in consultation with his or her doctor, who must apply the known risks and benefits of the product to their patient's particular situation. In some cases, even with the best information and judgment, a patient may still be hurt. Even so, because of the product's benefits to users as a whole, in FDA's judgment the product should be available with the appropriate labeling in order to best improve public health.

FDA is concerned that state product liability lawsuits that challenge FDA's careful determination of safety, efficacy and appropriate labeling can have detrimental effects to public health. Such effects include (1) decreased consumer access to beneficial products

through decreases in availability or even the removal of beneficial products from the market, limiting patient and doctor choices; and (2) the requirement for additional and conflicting warnings or statements that can cause confusion or deter the use of beneficial medical products. Of course, if a plaintiff claims to have been harmed by a sponsor's failure to use the specific design or labeling approved by FDA, then state liability would not interfere with Federal requirements and preemption would not apply.

Decreased Consumer Access

The public health is not served if tort litigation has the unintended consequence of decreasing or eliminating access to a beneficial product. In the case of childhood vaccines in the 1980's, tort liability contributed to a threat to public health that compelled Congress to act.[x] After a series of lawsuits were filed against vaccine manufacturers and administrators in the 1970's, the number of manufacturers of the DTP (diphtheria and tetanous toxinoids and pertussis) vaccine fell from seven to two, the manufacturers of OPV (Sabin oral poliovirus vaccine) from three to one, and the manufacturers of the measles vaccine from six to one.[xi] Prices of the DTP vaccine rose from 19 cents to $12 in six years. Rising prices, uncertainty about the results of vaccine research and development and the possibility of disease outbreaks were the impetus for the National Childhood Vaccine Injury Act, which shielded individual vaccine manufacturers from liability while compensating individuals from vaccine-related injuries.[xii]

Some commentators have observed the relationship between tort liability and the lack of available types of birth control in the U.S., and suggested it is in part causal.[xiii] For instance, Dalkon shield lawsuits led to the removal of other IUDs (intrauterine devices) on the market

by manufacturers, even though FDA had not raised questions about their safety. Randall reported in the Journal of the American Medical Association (JAMA) in 1992 that all but one major U.S. pharmaceutical company (Ortho Pharmaceutical Corporation) had withdrawn from the field of contraceptive research and development and that the U.S. was lagging behind other countries in the availability of modern contraceptives.

Confusion and Deterrence Due to Conflicting Labeling Requirements

FDA is also concerned that state tort actions would create requirements on manufacturers to seek to amend labeling to include warnings of speculative risks or warnings that do not accurately communicate FDA's careful evaluation of the risks and benefits of the product. Including warnings in the labeling without a determination by FDA that they are well-grounded in science can have the effect of overwarning and confusion as well as deterring use of a beneficial drug. Thus, FDA interprets and implements its responsibility under the act as establishing both a "floor" and a "ceiling" for risk information. Additional disclosures of risk information by the manufacturer can violate the act if the statement is unsubstantiated or otherwise false or misleading.

An example of such a state law requirement was in *Dowhal v. Smithkline Beecham Consumer Healthcare*. In *Dowhal*, the plaintiffs argued that a nicotine replacement therapy was required to bear a warning under California's Proposition 65 for pregnant women. FDA believed that the warning label required by Proposition 65 did not properly communicate the benefits of the product, and might deter women from using the product in lieu of smoking, an

activity that would be far less healthy than using the product. The California Supreme Court ultimately agreed with FDA that the state requirement was preempted.[xiv]

In the recent case of *Colacicco v. Apotex*,[xv] plaintiffs brought a state tort action alleging that the manufacturers of a class of antidepressant medications known as selective serotonin reuptake inhibitors (SSRIs) failed to appropriately warn about risks of suicidality associated with the drugs. FDA had extensively considered and adjusted the warnings regarding suicidality for these drugs, balancing the information about risk suicidality with the benefits of these products of lowering rates of suicide overall. FDA had considered and rejected certain warnings regarding suicidality; a state tort suit sought to punish a drug sponsor for failing to include such a warning that FDA had rejected. T he Court of Appeals for the Third Circuit Court found such claims preempted.

Another case about SSRIs involved labeling for the drug PAXIL. Though FDA had reviewed advertisements claiming PAXIL was "non-habit forming" and had concluded they were not false or misleading, a Federal district court applying California law enjoined GlaxoSmithKline (GSK) from running advertisements that had this language.[xvi] Though the parties ultimately settled out of court, this serves as an illustration of where states have attempted to undermine FDA's careful assessment of risk-benefit medical product information.

As FDA articulated in the Physician Labeling Final Rule, the public health risks associated with over-warning can be as great as the health risks associated with under-warning. Over-

warning can cause patients not to use beneficial medical products and doctors not to prescribe them. Under-utilization of a product based on dissemination of scientifically unsubstantiated warnings, so as to deter patients from undertaking beneficial, possibly lifesaving treatment, could well frustrate the purposes of Federal regulation as much as over-utilization resulting from a failure to disclose a drug's scientifically demonstrable adverse effects. Further, allowing unsubstantiated warnings may also diminish the impact of valid warnings by creating an unnecessary distraction and making even valid warnings less credible.

CONCLUSION

Mr. Chairman, Congress has given FDA the responsibility for ensuring the safety, effectiveness, and proper labeling of medical products, and Federal preemption of state standards that are different from the design or labeling approved by FDA is the inevitable consequence of our carrying out that important mission. FDA is committed to helping ensure the safety and efficacy of drug products in the U.S. marketplace and the communication of appropriate risk information to the public.

Thank you for the opportunity to discuss this very important topic. I am happy to answer any questions.

ENDNOTES

[i] Under the FD&C Act, 21 U.S.C. 301 *et seq.*, a drug manufacturer may not market a new drug unless it has submitted a new drug application to the Food and Drug Administration (FDA) and received the Agency's approval. 21 U.S.C. 355(a). An application must contain, among other things, "the labeling proposed to be used for such drug," 2 21 U.S.C. 355(b)(1)(F) (Supp. V 2005); see 21 CFR 314.50(c)(2)(i) and (e)(2)(ii); "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is * * effective in use," 21 U.S.C. 355(b)(1)(A) (Supp. V 2005); and "a discussion of why the benefits exceed the risks [of the drug] under the conditions stated in the labeling," 21 CFR 314.50(d)(5)(viii); see 21 CFR 314.50(c)(2)(ix). The FD&C Act also requires that drugs not be misbranded. 21 U.S.C. 331(a) and (b). A drug is misbranded if, among other things, the drug's "labeling is false or misleading in any particular;" the labeling does not provide "adequate directions for use" or certain "adequate warnings;" the drug "is dangerous to health when used in the dosage or manner, or with the frequency or duration prescribed, recommended, or suggested in the labeling thereof;" or the labeling does not comply with certain FDA regulations. 21 U.S.C. 352(a), (f) and (j). FDA has established specific requirements for prescription drug labeling. 21 CFR Pt. 201. FDA will approve a new drug application if it finds, among other things, that (i) the drug is "safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof," (ii) there is "substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof," and (iii) the proposed labeling is not "false or misleading in any particular." 21 U.S.C. 355(d). After a drug has been approved and marketed, the manufacturer must investigate and report to FDA any adverse events associated with use of the drug in humans, 21 CFR 314.80, and must periodically submit any new information that may affect FDA's previous conclusions about the safety, effectiveness, or labeling of the drug, 21 CFR 314.81. See 21 U.S.C. 355(k) (post-approval reporting and record-keeping requirements); Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, § 901 *et seq.*, 121 Stat. 922 (enhancing FDA's authority to require post-market studies and surveillance). FDA "shall" withdraw its approval of an application if it finds, among other things, that the drug is not safe or effective under the conditions of use specified in the drug's labeling. 21 U.S.C. 355(e). Following FDA's approval of an application, the manufacturer generally may not make changes to the drug, including "[c]hanges in labeling," without first submitting a supplemental application to FDA and securing the agency's prior approval for the change. 21 CFR 314.70(b)(2)(v)(A). A manufacturer must submit such a supplemental application "to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug." 21 CFR 201.57(c)(6). "An applicant may ask FDA to expedite its review of a supplement for public health reasons." 21 CFR 314.70(b)(4). In addition, a manufacturer may change a drug's labeling after FDA has received the supplemental application, without waiting for the agency's approval of the change, if, among other things, the change "add[s] or strengthen[s]" a warning or a statement about administration of the drug in order to promote safety. 21 CFR 314.70(c)(6)(iii)(A) and (C). FDA interprets that regulation to permit changes without prior approval only to address "newly discovered risks." 47 FR. 46,623 (1982). If a manufacturer makes a change before receiving FDA's approval, the Agency may later reject the change and order the manufacturer to cease distribution of the changed product. 21 CFR 314.70(c)(7).

[ii] Class III devices are subject to premarket review. The Medical Device Amendments of 1976 (MDA), 21 U.S.C. 360c *et seq.*, to the FD&C Act, 21 U.S.C. 301 *et seq.*, sort medical devices into three classes. See 21 U.S.C. 360c(a)(1). Class I and II devices are subject to regulatory controls or standards, but do not require pre-market approval. See 21 U.S.C. 360c(a)(1)(A) and (B); *Medtronic, Inc.* v. *Lohr*, 518 U.S. 470, 476-477 (1996). A device falls within Class III if (i) it "presents a potential unreasonable risk of illness or injury," or is purported to be used to sustain or support human life or to have substantial importance in preventing impairment of human health, and (ii) there is inadequate evidence for FDA to determine that controls or standards authorized for Class I or II devices would provide reasonable assurance of safety and effectiveness. 21 U.S.C. 360c(a)(1)(C). In general, a Class III device requires pre-market approval (PMA) by FDA unless it was marketed for use before the MDA's enactment or it is "substantially equivalent" to a device that is already lawfully on the market. 21 U.S.C. 360e(a) and (b)(1)(A) and (B), 360(k). Fewer than 1% of new devices require pre-market approval. FDA's PMA process for the relatively few devices that require it is "rigorous." *Lohr*, 518 U.S. at 477. A manufacturer must submit: full reports of all studies and investigations, including clinical investigations, of the device's safety and effectiveness; a full statement of the components, ingredients, properties,

and principles of operation of the device; a full description of the methods used in, and facilities and controls used for, the manufacture, processing, packing, and installation of the device; a reference to any performance standard that would apply if the device were a Class II device, and information showing that the device satisfies that standard or justifying any deviation from it; any sample of the device or its components requested by FDA; and the proposed labeling. See 21 U.S.C. 360e(c)(1); 21 CFR 814.20. FDA may request additional information from the manufacturer, and may also consult with a scientific advisory committee made up of outside experts. See 21 CFR 814.44, 814.20(b)(13). The Agency conducts an in-depth review of requests for pre-market approval, devoting an average of 1,200 hours to each application. See *Lohr*, 518 U.S. at 477.

FDA may grant pre-market approval for a Class III device only if it finds, among other things, that (i) there is "reasonable assurance" of the device's "safety and effectiveness" under the conditions of use included in the proposed labeling, and (ii) the proposed labeling is neither false nor misleading. 21 U.S.C. 360e(d)(1)(A), (2)(A), (B) and (D). In determining safety and effectiveness, FDA must "weigh[] any probable benefit to health from the use of the device against any probable risk of injury or illness from such use." 21 U.S.C. 360c(a)(2)(C). FDA may impose restrictions on the sale or distribution of the device as a condition of pre-market approval, see 21 U.S.C. 360e(d)(1)(B)(ii); 21 CFR 814.82(a)(1), and it may also impose device-specific restrictions by regulation, see 21 U.S.C. 360j(e)(1). Following FDA's pre-market approval, a manufacturer must submit a supplemental application to FDA and receive its approval before making any changes to a device that affect its safety or effectiveness. See 21 U.S.C. 360e(d)(6)(A)(i); 21 CFR 814.39(a). The same process that applies to an original PMA application generally applies to a supplemental application. See 21 U.S.C. 360e(d)(6)(B); 21 CFR 814.39(c). With only narrow exceptions, the manufacturer also must receive FDA's approval before making any changes to the labeling of a device. See 21 CFR 814.39(a) and (d)(1). Manufacturers are also required to collect and report to FDA information on certain adverse events related to the device after it has been approved. See 21 U.S.C. 360i(a); 21 CFR Pt. 803.

The manufacturer must report within 30 days any incident in which a device may have caused or contributed to a death or serious injury, or in which the device malfunctioned in a manner that would likely cause or contribute to serious injury if the malfunction recurred. See 21 CFR 803.10(c)(1), 803.50(a)(1)-(2). The manufacturer must report such an incident within five days if remedial action is required "to prevent an unreasonable risk of substantial harm to the public health." See 21 CFR 803.10(c)(2)(i). A device manufacturer is also required to provide annual reports to FDA. See 21 CFR 803.55(b), 814.84. Among other things, an annual report must identify any reports in the scientific literature about the device, as well as any unpublished reports of data from clinical investigations or nonclinical laboratory studies involving the device about which the manufacturer knows or reasonably should know. See 21 CFR 814.84(b)(2).

Based on new information reported to FDA or other information known to the agency, FDA may withdraw premarket approval of a Class III medical device if it finds, among other things, that the device no longer satisfies the standards for premarket approval. 21 U.S.C. 360e(e)(1).

[iii] *See* FDAAA, Public Law 110-85, sec. 901-921; The Future of Drug Safety — Promoting and Protecting the Health of the Public, *available at* http://www.fda.gov/oc/reports/iom013007.html; Ensuring the Safety of Marketed Medical Devices: CDRH's Medical Device Post-market Safety Program, available at *http://www.fda.gov/cdrh/postmarket/mdpi-report.pdf*

[iv] Riegel v. Medtronic, 128 S.Ct. 999 (2008).

[v] Federal preemption would affect a state requirement that, for example, a sponsor of a medical product include in labeling a statement not supported by the level of evidence required by Federal labeling regulations, or a requirement that a sponsor include a statement in labeling that FDA has rejected. 71 FR. 3922, 3936. Preemption would not block a claim against a sponsor for an injury alleged to be caused by a product's noncompliance with a design or labeling requirement of FDA's approval (for example, a claim that a patient was injured by a sponsor's non-compliance with the ingredient requirements of FDA's drug approval).

[vi] Colacicco v. Apotex, 521 F.3d 253 (3d Cir. April 8, 2008) ("we agree that the FDA's rejection of the warning plaintiffs proffer preempts a state-law action premising liability on a drug manufacturer's failure to include such a warning in the drug labeling"); compare Riegel v. Medtronic, 128 S.Ct. 999, 1008 (2008) ("Absent other indication, reference to a State's 'requirements' includes its common-law duties.").

[vii] Riegel v. Medtronic, 128 S.Ct. 999, 1008 (2008).

[viii]See 21 U.S.C. 352

[ix] 21 CFR 201.57(c)(6).

[x] Evans, Geoffrey. Update on vaccine liability in the United States: presentation at the National Vaccine Program Office Workshop on strengthening the supply of routinely recommended vaccines in the United States, 12 February 2002. Clin Infect Dis. 2006 Mar 1;42 Suppl 3:S130-7.

[xi] Evans G, Harris, D. and Levine, E, Legal Issues in Plotkin SA, Orenstein WA, eds. Vaccines. 4th ed. Philadelphia: WB Saunders, 2003:1591-617.

[xii.] Pub. L. No. 99-660 sec. 311 et seq., 100 Stat. 3755, codified at 42 U.S.C.A. sec. 300aa-1 et seq. (1989).

[xiii] Randall, Terri, *United States Loses Lead in Contraceptive Choices, R&D; Changes in Tort Liability, FDA Review Urged.* JAMA, 268(2):176-179.

[xiv] Dowhal v. Smithkline Beecham Consumer Healthcare, 32 Cal. 4th 910 (Cal. 2004).

[xv] Colacicco v. Apotex, 521 F.3d 253, (3d Cir. 2008)

[xvi] In re PAXIL Litigation, Case No. CV01-07037 MRP (C.D. 2002).