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MEMO

FDA: the first 60 days under President Obama

To: President-Elect Obama HHS Transition Team
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Thank you for the opportunity to submit ideas on immediate steps the Obama Administration should take at FDA. First and foremost, it is essential that the Administration appoint a credible leader who signals that he (or she) will protect scientific integrity and re-invigorate the FDA's mission of protecting public health. Beyond the crucial public policy implications, this will send an essential message to staff at the Agency.

Some of the items on this list can be implemented quickly using existing authority. Others, we feel, are part of a longer-term agenda for change that the new Administration and Commissioner should set out during the first days.

First 60 Days

1. **Warning letters.** FDA should discontinue the practice in place since March 2002 that required all Warning Letters and 'untitled letters' be reviewed by FDA's Office of Chief Counsel before release². FDA should return to their former practice of allowing Warning Letters to be released, as soon as possible, after their preparation by appropriate agency staff.
2. **Oversight of promotion.** FDA should adopt a much more rigorous posture concerning the requirement that all drug promotion (ads, sales rep behavior, DTCA) represent a fair balance of risks vs. benefits, and announce that it will promptly act to stop promotional activities that violate this requirement. (This is the inverse of an announcement that former FDA Chief Counsel Daniel Troy made immediately after his appointment under President Bush.)
3. **Appropriate use of the pediatric exclusivity extension.** The FDA should announce that it will extend the additional exclusivity only to manufacturers whose studies are useful to pediatric prescribing, which should include being published in peer-reviewed journals (one market of a valid addition to the literature). The FDA could also commit to gathering data on the cost effectiveness of the exclusivity extension in anticipation of the next renewal in 2012.
4. **Pre-emption.** FDA should return to the agency's long-standing position, held from 1938 to 2002, that FDA approval of prescription drug labeling does not preempt a drug manufacturer's duty to warn consumers of known risks, or otherwise preempt state law based common-law claims.³ This should be done to ensure that any consumer, injured by a prescription drug, shall have their full access to any legal remedies for their injuries that the

¹ Bruce Psaty, MD PhD, at the University of Washington; Jerry Avorn, MD and Aaron Kesselheim MD, of Harvard Medical School; and Alastair Wood, MD, of Symphony Capital, contributed to this memo.

² <http://oversight.house.gov/documents/20040818103905-16991.pdf>

³ If the Supreme Court decides, in the pending *Wyeth v. Levine* case, that FDA approval of a prescription drug's label does preempt such a consumer's right, FDA's return to their former stand on 'non-preemption' may help limit a preemption defense by industry to the time period of 2002 to 2009.

relevant law of their state will allow.⁴ (Later in this memo, we discuss the related 'Changes Being Effectuated' rule.)

5. **Empower OSE to make post-market safety determinations.** Currently, final post-marketing safety decisions are made by the Office of New Drugs (OND), which is also responsible for drug approvals. Authority for decisions about post-marketing safety should sit with the Office of Safety and Epidemiology, which has the appropriate scientific qualifications and which has no investment in the initial approval decision. Where appropriate, a review group with joint authority (e.g. OSE together with the Drug Safety Advisory Board) should make the decision. It may not be possible to effect this change within 60 days, but the Commissioner could signal intent to substantially increase the authority and scientific capacity of this office, a process that began, in a limited way, through implementation of the FDAAA.
6. **Off-label reprint guidance.** A recent draft guidance⁵ clarifies (and seems to expand) the circumstances under which industry sales representatives may provide physicians with published studies of drugs used for unapproved indications. We recognize the difficult legal environment created by the Washington Legal Foundation decision, but within the limited scope available, the Commissioner should take steps to see that no final guidance is issued that increases the industry scope to market its products for unapproved uses. It may be appropriate to re-open the existing draft guidance for public comment, with a view to ensuring that the Agency's right to regulate marketing is fully exerted.
7. **Signal commitment to a new Safety and Effectiveness Agenda.** Major changes in the Agency's approach may not be possible within the first 60 days, but the Commissioner should re-commit the Agency to its public health mission and initiate a process of meaningful improvements in the approvals and safety system (see below). As outlined in the IOM "Future of Drug Safety" report, the authority to make much-needed changes already exists.

Approvals, Safety and Effectiveness Agenda

It is less clear whether these are attainable in the first days of the Administration, but they are steps toward the agenda we propose in 7, above.

8. **Open the FDA database.** The Commissioner should commit to full public access to FDA drug safety database. Any safety or efficacy data submitted to the Agency during an approvals process is a matter of public interest, with no justification for trade secret exemptions.⁶ Currently, only limited data are available. Full public access should include safety data for drugs that are not approved. For example, at least half a dozen glitizars (for diabetes) did not come on the market. Knowing the adverse events caused by these agents would be an important tool for the drug safety community to evaluate potential toxicities of related drugs that are approved (such as Avandia). Some, though not all, experts believe the Commissioner has the authority to make this change without new legislation.
9. **Approvals for clinical benefit.** Announce that consistent with the FDA mission to promote public health, drugs will be approved based on health outcomes, not surrogate endpoints that may not accurately predict clinical benefits. Where approval based on surrogate endpoints is judged to be in the interest of public health, the FDA should require further trials to demonstrate actual health benefits.
10. **Proactive safety assessment in approvals.** The FDA should take a more proactive stand concerning relative safety in the approval process itself, by considering the availability of other therapeutic alternatives. Demonstrating the authority to consider relative safety was

⁴ Note that the US Government filed an amicus brief for the petitioner (Wyeth) in Wyeth v Levine. To the extent possible, the new administration, through the Solicitor General, should amend the government position to be consistent with those of former Commissioners David Kessler and Donald Kennedy, that failure-to-warn litigation does not conflict with FDA authority over labeling.

⁵ "Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices" [Docket No. FDA-2008.D.0053]

⁶ Kesselheim AS and Mello MM. Confidentiality Laws And Secrecy In Medical Research: Improving Public Access To Data On Drug Safety. Health Affairs. 2007. 26 (2483) DOI 10.1377/hlthaff.26.2.483

the Agency's recent rejection of Merck's latest Cox-2 inhibitor on the grounds that it wasn't demonstrated to be safe enough -- an important departure from prior practice.

11. **Evaluate benefits relative to available treatments.** While recognizing FDA's statutory ability to simply approve or not approve a drug, the agency should announce that it will begin issuing a qualitative summary of all approved drugs at the time of approval (or within a defined period thereafter) presenting an evidence-based overview of their comparative efficacy and safety in the context of other drugs currently on the market. This would not be connected to the approval process, but would be an 'ex cathedra' evaluation issued by the Commissioner, based on an additional assessment by either the Advisory Committee, FDA staff, or an outside body such as AHRQ or the IOM. Such information should also be included in Medguides, online and in other consumer-oriented communications.
12. **Require OSE to implement directed phase 4 review** at time of approval to identify, design and plan phase 4 clinical trials or safety studies that may be necessary to address key questions (historically, approval has often been the end of evaluation and the beginning of marketing; not all drugs will require major phase 4 studies, but all drugs should have this question posed). The design and evaluation of phase 4 safety studies should include external peer review to ensure appropriate study design and analysis.

In particular, FDA should **require long-term safety data** consistent with real-world patterns of clinical use. Drugs prescribed for indefinite periods should not be approved on the basis of a safety profile established in 8-week trials.

To address capacity issues within the OSE, the Commissioner will need to work over the long term to add qualified staff. In the short term, the Agency could develop and announce a set of affiliation agreements with major university pharmacoepidemiology programs to establish training and research interchange programs to provide FDA scientists with additional drug safety expertise.

13. **Develop a mechanism to identify and organize trials of public health importance.** This is a major unimplemented recommendation of the IOM Drug Safety panel.⁷ Note that the FDAAA (2007) created the Reagan-Udall Foundation, a public-private partnership, for which funding was never appropriated. In any case, Reagan-Udall did not have the mission envisioned in the IOM report. An FDA Commissioner could put the structures recommended by IOM in place without any requirement for new legislation.

Additional steps

14. **Address off-label CME.** FDA should strengthen its guidance to limit, as much as legally possible, the role of industry funding for CME on off-label indications. An emerging consensus in medicine recognizes that industry funding of continuing medical education (CME) introduces inappropriate bias – content bias and topic bias – into physician education.⁸ Industry funding of CME for unapproved (off-label) indications is especially concerning. A current FDA guidance does not permit industry to use scientific or educational activities to promote products for unapproved uses, but does allow “independent” CME, provided it meets a number of tests related to content, speakers, focus, etc. However, more than half of all CME activities are now industry-funded, and it is clear that industry funding of CME has become a major avenue for the promotion of unapproved uses. Notwithstanding existing accreditation standards, the CME industry depends on the financial assistance from manufacturers. The new guidance should recognize that any such activity constitutes marketing and is subject to regulation.
15. **Changes Being Effected (CBE) rule.** FDA should act to repeal or nullify any restrictions created by a recently enacted rule⁹ regarding changes to existing labeling for prescription

⁷ IOM The Future of Drug Safety (2006) Recommendation 4.3

⁸ Josiah H Macy Foundation report http://www.josiahmacyfoundation.org/documents/Macy_ContEd_1_7_08.pdf; Stanford University Medical School http://deansnewsletter.stanford.edu/archive/08_25_08.html#1; AMA Council on Ethical and Judicial Affairs www.ama-assn.org/ama1/pub/upload/mm/471/ceja1.doc

⁹ 73 FR 49603-49610 (08-19-2008)

drugs, approved biologics, or medical devices. The new CBE ('changes being effected') rule requires that such changes must now be based on "newly acquired information" beyond that already provided to FDA.¹⁰

The effect of the rule is to create a conflict between a manufacturer's common-law-based duty to warn consumers of known risks associated with a product, and their ability to revise the product's label to warn of such risks. This conflict strengthens industry claims to an implied conflict 'preemption defense.'¹¹

Repeal of the rule would remove this confusing obstacle to label changes, and return to the prior system that requires a manufacturer to add warning information to a label "as soon as" the manufacturer had "*reasonable evidence* of a causal association with a drug" or where they have "*some basis to believe there is a causal relationship* between the drug and . . . the adverse event." [See 21 CFR 201.57(c)(6) and 21 CFR 201.57(c)(7).]

A few proposed mechanisms to repeal this rule in the short term include

-- FDA issuing a regulation immediately repealing the CBE rule change, based upon FDA's finding of "good cause" that such a repeal without notice or comment is within the public interest, and/or unnecessary in that the repeal merely resolves an existing conflict, created by the recent CBE change, between the new 21 CFR 314.70 (c)(6)(iii) regulations, and the continuing regulations regarding required disclosures of warnings and precautions under 21 CFR 201.57(c)(6) and of adverse event profiles under 21 CFR 201.57(c)(7).

--Alternatively, while FDA repeals the rule under usual notice and comment procedures, FDA should immediately issue a guidance or interpretive rule articulating that a) FDA's threshold determination on the sufficiency of new information to allow a label change will be guided by the principle that any reinterpretation of new or existing data that reveals any greater level of risk than was previously known, is sufficient, and b) that label changes to add any warnings, precautions, or adverse reactions will be freely permitted.

Longer-term

16. **Quality of overseas manufacturing.** The Agency recently an additional appropriation to increase its ability to conduct inspections of overseas manufacturing facilities, including opening a new office office in China. However, the scale and logistics of production in China, India and elsewhere mean that inspections alone will never guarantee quality. FDA must create a system that puts the onus on top pharmaceutical executives to ensure supply chain integrity, including being able to account for quality standards at every step of the supply chain for both API and excipient ingredients. To ensure and incentivize compliance, Congress will need to provide for criminal penalties for executives who fail to adequately ensure that drugs and API are manufactured appropriately.

¹⁰ Because this rule still allows that a manufacturer's subsequent reanalysis of existing data already submitted to FDA is such 'newly acquired information' the process may provide manufacturers with too much discretion as to when to update a label to describe of known risks, side-effects, or contraindications.

¹¹ This new CBE rule, effective as of Sept. 22, 2008, may even allow this preemption issue to return to the courts should the Supreme Court find no preemption in the pending case *Wyeth v. Levine*, which is based upon facts before the new CBE rule was implemented. Its hasty repeal may help prevent the 'preemption defense' issue lingering for several more years of legal appeals.