

CoMeD Inc.

14 Redgate Court,
Silver Spring, MD 20905-5726

Friday, 25 June 2010

To: Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

**Re: Docket No. FDA-2010-N-0099 [RIN 0910-AG15]
"Revision of the Requirements for Constituent Materials"**

FORMAL COMED COMMENTS

After having read just the "**SUMMARY**"¹ of this proposal by the U.S. Food and Drug Administration (FDA), which supposedly is an agent of the Secretary of Health and Human Services (henceforth and in the applicable statutes, the Secretary) to which it reports, this commenter was struck by the following:

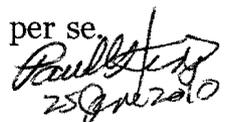
1. The FDA is again ignoring its mandate to safen vaccines by any and all means at its disposal (as set forth in 42 U.S.C. § 300aa-27(a)(2)²) and
2. It is proposing to change the regulations that govern vaccines in a manner that will not ensure that vaccines, which are biological drug products, will be even as safe, much less safer, than they currently are.

In fact, despite the repeated use of the phrase "*safety, purity, and potency*" (nine [9] times) and pro forma language that includes the words "*safe*"³ and "*safeguards*"⁴, or phrases such as "*safety or potency*"⁵, and "*public health and safety*"⁶, this proposed change does nothing to make vaccines safer, as 42 U.S.C. § 300aa-27(a)(2) clearly mandates that the FDA, an agency reporting to the Secretary, must do whenever it proposes changes to any regulation impacting the "manufacturing" and/or "processing" of vaccines, which this proposed change clearly does.

Neither the "**SUMMARY**" nor the "**SUPPLEMENTARY INFORMATION**" addresses making biological drug products safer or the FDA's clear statutory mandate to make vaccines safer – a legal mandate and an ethical responsibility which is again being ignored by the Agency.

Furthermore, *by removing the certainty as to what are some of the minimum standards that a biological product must meet*, this proposed change:

- ❖ Increases the potential that the "*exception or alternative*" granted for a given vaccine will actually make that vaccine less safe and
- ❖ Further undermines the public trust in the safety of vaccines per se.


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Given the recent action by the FDA to allow a vaccine manufacturer to conceal all of information about the nature and amounts of the components (ingredients) in each dose of vaccine except for the level of formaldehyde and the active antigens, and the active antigens' composition in the recently FDA-approved MenVeo^{®7} from the public and healthcare providers⁸, it appears to this commenter and CoMeD that the Agency is not only knowingly ignoring its statutory mandate to make vaccines safer but is also undermining the confidence of the American public in the safety of vaccines in general.

Therefore, seeking:

- a. The Agency's compliance with 42 U.S.C. S 300aa-27(a)(2),
- b. Safer vaccines,
- c. Improved minimum safety standards for biological drug products,
- d. Greater Agency and manufacturer transparency for all aspects of drugs that are also biologics, and
- e. The protection of both the health of the individual and the public's health,

this commenter and CoMeD must oppose this proposed change because it is:

- Neither in keeping with the governing statutory requirement set forth in 42 U.S.C. § 300aa-27(a)(2) (which currently applies to all vaccines recommended for national use except the 2009-A-H1N1 [pandemic swine flu] influenza vaccines),
- Nor in the public interest.

In addition, *as proposed*, it fundamentally weakens the public's certainty about the minimum current good manufacturing practice (CGMP) standards that apply to biological products, including vaccines.

The apparent impetus for this proposed change comes from the manufacturers' desire for more amorphous regulatory "flexibility" without any apparent consideration of the FDA's mandate to safen vaccines, which raises serious questions about the FDA's understanding of the safety mandates that should be considered above all else in proposed regulations that impact vaccines.

As proposed, this change clearly favors the interests of the manufacturers and ignores the interests, concerns and demands of the American public, whose members are increasingly demanding:

- Safer vaccines,
- More certainty about the validity of the proof of safety for vaccines,
- Full disclosure concerning the ingredients in each dose of vaccine and their long-term safety in component susceptible/sensitive populations, and

- The right of “informed consent” with regard to the risks and the theoretical benefits of each vaccine to the persons receiving each vaccine.

Since the proposed regulation:

“§ 610.15 Constituent materials.

* * * * *

(d) The Director of the Center for Biologics Evaluation and Research or the Director of the Center for Drug Evaluation and Research may approve an exception or alternative to any requirement in this section. Requests for such exceptions or alternatives must be in writing.”

does not:

- Establish any *minimum* requirements for proof of safety upon which any interested party may rely or by which the appropriateness of any safety decision may be judged, and
- Require that the written “(r)quests for such exemptions or alternatives” include the appropriate proofs (toxicological and immunological) of the short-term and long-term safety to the most susceptible humans to which the biological product may be given,

this commenter and CoMeD must oppose this regulation as a contrivance that, based on one FDA administrator’s flawed or compromised judgment, could have catastrophic consequences for an untold portion of the population.

We are compelled to take this stance because the historical record clearly demonstrates that neither the “*Director of the Center for Biologics Evaluation and Research*” nor “*the Director of the Center for Drug Evaluation and Research*” can be trusted to make such decisions based on their continual documented failure, since 1977, to comply with 21 CFR § 601.4(a),

“(a) A biologics license shall be issued upon a determination by the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research that the establishment(s) and the product meet the applicable requirements established in this chapter. A biologics license shall be valid until suspended or revoked” [with emphasis added]

with respect to the required toxicological proofs of safety for:

- a. The use of Thimerosal as a preservative in vaccines and/or
- b. The use of polymeric hydroxyaluminum or other adjuvants.

As documented in an official congressional report issued in 2003⁹ and as confirmed in official agency correspondence to CoMeD from the Food and Drug Administration (FDA)¹⁰, these self-same designated FDA officials, or their surrogates, have repeatedly issued biological licenses for Thimerosal-preserved vaccines without the required proof that the preservative is toxicologically safe to the clear standard established in the applicable CGMP regulations, “*sufficiently nontoxic ...*”, which clearly, as the FDA’s response on page 19 of the 2008 letter in

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endnote 9 admits, requires “*toxicity*” studies that have not been done before the licensing of the vaccine formulation in question can be issued or, if already issued, and not conducted, “*revoked or suspended*”.

Further, in all of the FDA’s correspondence to CoMeD, dating back to 2004, concerning proof of safety, the agency has repeatedly failed to provide or cite any documents that have clearly established that the level of Thimerosal in any Thimerosal-preserved vaccine has been proven to be “*sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the recipient*” by the vaccine makers, as required by 21 CFR § 610.15(a), an absolute, nondischargeable safety standard (an applicable current good manufacturing practice [CGMP] minimum) with which the producers of biological drug products are explicitly required to comply¹¹.

With respect to the foregoing CGMP requirement minimum, this commenter and CoMeD must again note that, for the amount of Thimerosal in a dose of a Thimerosal-preserved vaccine to be “*nontoxic*”, the appropriate toxicity studies (not epidemiological studies that cannot prove toxicity or the lack thereof) must establish that the dose of Thimerosal is below the lowest applicable “no observed adverse-effect level” (NOAEL) in the most susceptible “*recipient*” group to which that vaccine may be given.

In addition, to be “*sufficiently nontoxic*”, the requisite toxicity studies must establish (prove) that the dose of Thimerosal is more than an order of magnitude below Thimerosal’s NOAEL because Thimerosal has been established to be a highly toxic bioaccumulative mercury poison, teratogen, mutagen, carcinogen, immune-system toxin and reproductive toxin in humans at levels below 1 part-per-million.

Clearly, these self-same FDA officials have been knowingly approving vaccine formulations since 1977 without the requisite manufacturer-supplied¹² proof that the level of Thimerosal in aforesaid Thimerosal-preserved vaccines met the applicable CGMP “*sufficiently nontoxic ...*” minimum.

Given the preceding realities, clearly this commenter and CoMeD must oppose the transfer of any additional “discretionary” authority to the “*Director of the Center for Biologics Evaluation and Research or the Director of the Center for Drug Evaluation and Research*”, particularly when the FDA’s failure, since 1977¹³, to:

- Require vaccine manufactures to comply with these specific CGMP requirement minimums since 1977 before approving a Thimerosal-preserved vaccine formulation or,
- For then-approved vaccine formulations, suspend or revoke the licenses of all Thimerosal-preserved vaccines lacking the requisite proofs of safety required by this regulation

is the subject of on-going litigation¹⁴.

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When: **a)** there is a genuine scientifically sound and appropriate need for additional flexibility in some aspect of the regulations set forth in 21 CFR § 610.15 and **b)** it is demonstrated that this flexibility will not compromise the health of individuals or the public's health, then each such proposed flexibility should be explicitly added as it was in 1983.

Since the issues that the FDA raises in its attempt to render the CGMP minimums set forth in 21 CFR § 610.15 more flexible are purportedly issues involving:

- a. The safe manufacture, and use, of multi-dose vials of vaccines without a preservative,
- b. Allowing a higher per-dose level of a polymeric hydroxyaluminum adjuvant in a given vaccine,
- c. The level of extraneous protein in certain vaccines, and
- d. The level of antibiotics in certain vaccines

then, the Agency should propose revisions to the language of regulations in each part of 21 CFR § 610.15 that would:

1. Provide the needed "flexibility" and
2. Actually safen vaccines (as 42 U.S.C. § 300aa-27(a)¹⁵ requires the FDA to do).

On that basis, CoMeD, having studied these issues for years and having documented that it represents the interests of millions of U.S. citizens who are seeking safer vaccines, would propose the following alternative revisions to 21 CFR § 610.15 to improve the safety of vaccines as 42 U.S.C. § 300aa-27 seemingly requires the FDA, an agent of the Secretary, to do while providing the increased "flexibility" that is being sought by the Agency and apparently the manufacturers of vaccines for "*Constituent materials*" in biological drug products [note: the suggested revisions are in **bold text**]:

(a) Ingredients, preservatives, diluents, adjuvants. All ingredients used in a licensed product, and any diluent provided as an aid in the administration of the product, shall meet generally accepted standards of purity and quality. **Appropriate mammalian and primate toxicity studies must show that any preservative used shall be sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the most susceptible recipients, and in the combination used it shall not denature the specific substances in the product to result in a decrease below the minimum acceptable potency within the dating period when stored at the recommended temperature. Unless the packaging incorporates a proven dispensing mechanism that unequivocally prevents contamination of the contents of a multiple-dose container, products in multiple-dose containers shall contain a non-mercury-containing preservative, except that a preservative need not be added to**

Yellow Fever Vaccine; Poliovirus Vaccine Live Oral; **live** viral vaccines labeled for use with the jet injector; dried vaccines when the accompanying diluent contains a preservative; or to an Allergenic Product in 50 percent or more volume in volume (v/v) glycerin. An adjuvant shall not be introduced into a product unless **the manufacturer proves that neither a single dose of the adjuvanted product nor the maximum lifetime dose of the adjuvanted product, in combination with all other currently approved adjuvanted products that may be administered to the population for whom the product is intended, significantly increases the lifetime risk of adverse immune and/or autoimmune outcomes as compared to a comparable formulation without the adjuvant.**

(b) Extraneous **substances**; cell culture produced vaccines. **Unless proven to be incapable of producing allergenic effects in susceptible human subjects at 10 times the calculated concentration in the final medium,** extraneous **substances** shall not be added to **the** virus medium of cell culture produced vaccines intended for injection.

(c) Antibiotics. **Provided that studies in susceptible populations establish no reactions other than localized reddening at the injection site in appropriately sized test groups that are allergic to the added antibiotics at 10 times their calculated final concentration in the vaccines,** a minimum concentration of antibiotics may be added to the production substrate of viral vaccines.

(d) **Alternatives. Except for the generally accepted standards of purity and quality, in keeping with the vaccine safening mandates set forth in 42 U.S.C. 300aa-27,** the Director of the Center for Biologics Evaluation and Research or the Director of the Center for Drug Evaluation and Research may approve an exception or alternative to any requirement in this section **provided the manufacturer proves that the exception or alternative would improve the safety of the biological drug product or, failing that, improves the effectiveness, not efficacy, or reduces the per dose cost, of the biological drug product without reducing the safety of said product.** Requests for such exceptions or alternatives must be in writing **and include the findings, pro and con, of and the data from all of the studies conducted to support the request.**

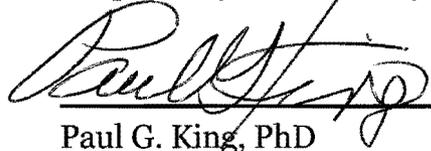
Hopefully, after carefully considering these comments, the FDA will, *at a minimum:*

- ❖ Withdraw this proposed regulation change, and
- ❖ Begin requiring the manufacturers of Thimerosal-preserved drug products, including vaccines, to conduct and submit all of the

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applicable toxicity studies required to prove that their Thimerosal-preserved products meet the “*sufficiently nontoxic ...*” standard set forth in 21 CFR § 610.15(a).

Respectfully submitted by

A handwritten signature in black ink, appearing to read "Paul G. King", is written over a horizontal line. To the right of the signature, the date "25 June 2010" is handwritten.

Paul G. King, PhD
CoMeD Science Advisor and Secretary

END NOTES

- ¹ **“SUMMARY:** The Food and Drug Administration (FDA) is proposing to amend the biologics regulations to permit the Director of the Center for Biologics Evaluation and Research (CBER) or the Director of the Center for Drug Evaluation and Research (CDER), as appropriate, to approve exceptions or alternatives to the regulation for constituent materials. FDA is taking this action due to advances in developing and manufacturing safe, pure, and potent biological products licensed under a section of the Public Health Service Act (the PHS Act) that, in some instances, render the existing constituent materials regulation too prescriptive and unnecessarily restrictive. This rule provides manufacturers of licensed biological products with flexibility, as appropriate, to employ advances in science and technology as they become available, without diminishing public health protections”.
- ² **“Sec. 300aa-27. Mandate for safer childhood vaccines**

 - (a) General rule

In the administration of this part and other pertinent laws under the jurisdiction of the Secretary, the Secretary shall -

 - (1) promote the development of childhood vaccines that result in fewer and less serious adverse reactions than those vaccines on the market on December 22, 1987, and promote the refinement of such vaccines, and
 - (2) **make or assure improvements in, and otherwise use the authorities of the Secretary with respect to, the licensing, manufacturing, processing, testing, labeling, warning, use instructions, distribution, storage, administration, field surveillance, adverse reaction reporting, and recall of reactogenic lots or batches, of vaccines, and research on vaccines, in order to reduce the risks of adverse reactions to vaccines**”. [Emphasis added.]
- ³ **a. FR; 75(70): 15639, col. 1, “Summary”, line 12, “and manufacturing safe, pure, and”**
b. FR; 75(70): 15640, col. 1, 3rd bullet, line 4, “safe and necessary to produce the”
c. FR; 75(70): 15640, col. 2, line 5, “containers have a long record of safe”
d. FR; 75(70): 15640, col. 3, footnote 4, line 4, “amount of aluminum used is safe and necessary to”
e. FR; 75(70): 15641, col. 1, “III. Legal Authority”, line 15, “products are safe, pure, and potent; and”
- ⁴ **FR; 75(70): 15640, col. 2, par. 2, line 14, “safeguards, such as adequate storage,”**
- ⁵ **FR; 75(70): 15639, “I. Background”, col. 3, par. 2, line 32, “adversely the safety or potency of the”**
- ⁶ **FR; 75(70): 15641, col. 2, line 11, “environmental, public health and safety”**
- ⁷ A meningococcal meningitis vaccine licensed to Novartis Vaccines and Diagnostics, Inc, 4560 Horton St Emeryville, CA 94608-2916, License 1751.
- ⁸ On February 9, 2010, the FDA approved the MenVeo meningococcal vaccine with a package insert [see: <http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM201349.pdf>] that does not state the level of the ingredients (components) in each dose other than the active antigens and formaldehyde. Moreover, both the FDA and Novartis (private communications) has refused to release this information to this commenter, who was told by a Novartis official that the information about the names and amounts of the

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other ingredients are “trade secrets” – preventing the public from knowing even the names of the undisclosed components that the public is supposed to all to be injected into themselves and their children.

- ⁹ May 2003, Subcommittee on Human Rights & Wellness of the Government Reform Committee, US House of Representatives, report titled, “Mercury in Medicine – Taking Unnecessary Risks”, pages 1-80.
- ¹⁰ FDA Letter to Paul G. King, Ph.D., and Other Representatives for CoMeD, Coalition for Mercury-free Drugs, 33A Hoffman Avenue, Lake Hiawatha, NJ 07034-1922, Re: Docket Number 2007P-0331/CP1, date-stamped “NOV 21 2008”, page 19, paragraph 2, lines 12 and 13: “Also, and contrary to your assumption, **all recently licensed influenza vaccines have been or are being evaluated in reproduction toxicity studies.**” [With emphasis added.]
- ¹¹ “21 CFR § 210.1 **Status of current good manufacturing practice regulations.**
- (a) **The regulations set forth in this part and in parts 211 through 226 of this chapter contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.**
- (b) **The failure to comply with any regulation set forth in this part and in parts 211 through 226 of this chapter in the manufacture, processing, packing, or holding of a drug shall render such drug to be adulterated under section 501(a)(2)(B) of the act and such drug, as well as the person who is responsible for the failure to comply, shall be subject to regulatory action.**
- (c) Owners and operators of establishments engaged in the recovery, donor screening, testing (including donor testing), processing, storage, labeling, packaging, or distribution of human cells, tissues, and cellular and tissue-based products (HCT/Ps), as defined in §1271.3(d) of this chapter, that are drugs (subject to review under an application submitted under section 505 of the act or under a biological product license application under section 351 of the Public Health Service Act), are subject to the donor-eligibility and applicable current good tissue practice procedures set forth in part 1271 subparts C and D of this chapter, in addition to the regulations in this part and in parts 211 through 226 of this chapter. Failure to comply with any applicable regulation set forth in this part, in parts 211 through 226 of this chapter, in part 1271 subpart C of this chapter, or in part 1271 subpart D of this chapter with respect to the manufacture, processing, packing or holding of a drug, renders an HCT/P adulterated under section 501(a)(2)(B) of the act. Such HCT/P, as well as the person who is responsible for the failure to comply, is subject to regulatory action. ...” [Emphasis added.]
- ¹² Since the manufacturers of all drugs and drug products, including all vaccines and other biological drug products, have an absolute nondischargeable duty to prove the safety of their products, the FDA currently has neither the administrative discretion nor the authority to interpose itself between the manufacturers of drugs and their absolute nondischargeable duty to prove that the manufacturers’ drugs, including biological drug products like vaccines, are “safe” to whatsoever are the established standards for that proof of safety.
- ¹³ 21 CFR § 601.4(a):
- “§ 601.4 Issuance and denial of license.
- (a) A biologics license shall be issued upon a determination by the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research that the

establishment(s) and the product meet the applicable requirements established in this chapter. A biologics license shall be valid until suspended or revoked”.

¹⁴ Currently, in the UNITED STATES DISTRICT COURT FOR THE DISTRICT OF COLUMBIA as case: 1:2009-cv-00015-RBW.

¹⁵ **42 U.S.C. Sec. 300aa-27. Mandate for safer childhood vaccines** [see Note 1.]

“(a) **General rule**

In the administration of this part and other pertinent laws under the jurisdiction of the Secretary, the Secretary shall -

(1) promote the development of childhood vaccines that result in fewer and less serious adverse reactions than those vaccines on the market on December 22, 1987, and promote the refinement of such vaccines, and

(2) **make or assure improvements in, and otherwise use the authorities of the Secretary with respect to, the licensing, manufacturing, processing, testing, labeling, warning, use instructions, distribution, storage, administration, field surveillance, adverse reaction reporting, and recall of reactogenic lots or batches, of vaccines, and research on vaccines, in order to reduce the risks of adverse reactions to vaccines**”. [Emphasis added]

Note 1: Since adult vaccines have been added to the National Vaccine Injury Compensation Program, the mandate in 42 U.S.C. § 300aa-27 for safer vaccines now applies to childhood and other vaccines recommended for ongoing general, non-pandemic use in the US in all of the population groups for which it is approved.

Paul [Signature]
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