

# Appendix B

In Depth Review<sup>B1</sup> Of:

*“Influenza: Vaccination Still the Best Protection”*

by Linda Bren, FDA Writer-Editor

Online *“September-October 2006”* FDA Consumer magazine

[http://www.fda.gov/fdac/features/2006/506\\_influenza.html](http://www.fda.gov/fdac/features/2006/506_influenza.html)

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<sup>B1</sup> 27 September 27 2006 Article Review by CoMed's Science Advisor

## Review of “Influenza: Vaccination Still the Best Protection” Article by “Linda Bren” as published in the September–October 2006 Issue of FDA Consumer magazine

*“Seasonal influenza is among America’s most lethal killers, according to the Centers for Disease Control and Prevention (CDC), because the virus infects so many people—5 percent to 20 percent of the U.S. population every year. Most people who get this contagious respiratory illness caused by the influenza virus recover in a week or two without complications. But each year, more than 200,000 people have complications severe enough to send them to the hospital. And another 36,000 die each year from seasonal influenza.”*

As a recent paper<sup>1</sup> reviewing the government’s own data on influenza vaccine effectiveness reported, the influenza vaccines do *not* appear to be effective<sup>2</sup> in:

- Preventing the person inoculated from contracting influenza or
- Stopping the spread of influenza from person to person.

Moreover, based on the data the governmental health agencies generated, that paper found that the reported annual deaths were in the range from 604 to 3,006 “*seasonal influenza*” deaths with an average of 1,269 “*seasonal influenza*” deaths indicating that this article’s reports “*36,000 die each year*” is a gross exaggeration (12-fold to 60-fold [with an average 28-fold] exaggeration). [See Table 1, column 5.]

Similarly, this article reports “*each year, more than 200,000 people have complications severe enough to send them to the hospital,*” while the reported discharges seem to indicate that the number admitted to the hospital each year is in the range of 13,000 to 44,000 with an average of 25,667 persons – indicating this article’s “*200,000 people*” is a significant exaggeration (4.5-fold to 15-fold [with an average 7.8-fold] exaggeration). [See Table 1, column 7.]

Ironically, this reviewer finds the writer has apparently grossly underestimated the percentage of the population annually infected (“*the virus infects so many people—5 percent to 20 percent of the U.S. population every year*”) when the data indicates that the percentage range for those infected ranges from “33”% to “52”%. [See Table 1, column 6.]

Therefore, based on the federal government’s reported influenza cases’ data for the period 1979 to 2001, seasonal influenza is *not* “*among America’s most lethal killers.*”

Hopefully, after reading the article in **Footnote 1** as well as the papers referenced therein, the writer will appropriately correct the erroneous values reported and the conclusions drawn from them.

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<sup>1</sup> Geier DA, King PG, Geier MR. Influenza Vaccine: Review of effectiveness of the U.S. immunization program, and policy considerations. *J Am Phys Surg* 2006; **11**(3): 69-74.

<sup>2</sup> **Effective**, for a vaccine, should mean that: **a)**, for those properly inoculated with the vaccine, greater than 90% of those vaccinated are protected from getting the diseases against which the vaccine is supposed to provide immunity and **b)**, for the general population, inoculation of a significant portion of any local population segment should prevent the spread of the disease in that local population. Based on the government’s available published data on: **a)** estimated US population, **b)** net influenza doses distributed, population coverage, influenza deaths, influenza cases, and hospital discharges examined by this reviewer for the period 1979–2000, the influenza vaccines are *not effective* vaccines.

**Table 1.** A summary of the raw data employed for analysis in the present study

Year	Estimated United States Population <sup>1</sup>	Total Net Number of Influenza Vaccine Doses Distributed <sup>2</sup>	Influenza Vaccine Percent Population Coverage [IVPPC]	Influenza Death Rate <sup>3</sup> (per 100,000 people) [Total Number]	Influenza Case Rate <sup>3</sup> (per 100 people) [Total Number]	Influenza First-Listed Hospital Discharge Rate <sup>3</sup> (per 10,000 people) [Total Number]
1979 <sup>4</sup>	225,055,487	18,270,794	8.1	0.3 [604]	-	-
1980	227,224,681	12,425,890	5.5	-	-	-
1981	229,465,714	19,829,170	8.6	1.3 [3,006]	-	-
1982	231,664,458	16,959,690	7.3	-	33 [74,925,000]	-
1983	233,791,994	17,877,970	7.6	0.6 [1,431]	38 [87,299,000]	-
1984	235,824,902	19,179,060	8.1	-	45 [103,440,000]	-
1985	237,923,795	20,700,761	8.7	0.9 [2,054]	40 [94,409,000]	-
1990	249,464,396	27,076,206	11	-	43 [106,807,000]	1.8 [44,000]
1991	252,153,092	32,809,662	13	0.4 [1,137]	52 [129,583,000]	1.0 [26,000]
1992	255,029,699	40,352,367	16	-	43 [107,309,000]	0.5 [13,000]
1993	257,782,608	42,980,814	17	0.4 [1,044]	52 [132,633,000]	1 [25,000]
1994	260,327,021	60,084,728	23	-	35 [90,447,000]	1.2 [31,000]
1995	262,803,276	36,512,538	14	0.2 [606]	41 [108,009,000]	0.7 [19,000]
1996	265,228,572	38,915,520	15	0.3 [745]	36 [95,049,000]	0.8 [21,000]
1997	267,783,607	40,996,883	15	0.3 [720]	-	0.7 [19,000]
1998	270,248,003	48,080,122	18	0.6 [1,724]	-	1.3 [34,000]
1999 <sup>5</sup>	272,690,813	60,468,427	22	0.6 [1,665]	-	1.4 [37,000]
2000	281,421,906	65,582,650	23	0.6 [1,765]	-	1.4 [39,000]
			Mean ± std	0.5 ± 0.3 [1,269 ± 786]	38 ± 13 [94 ± 3.4 million]	1 ± 0.5 [25,667 ± 12,323]

<sup>1</sup> Data obtained from the United States’ Census Bureau

<sup>2</sup> Data obtained from the Biologic Surveillance Summaries of the Centers for Disease Control and Prevention

<sup>3</sup> Data obtained from the National Center for Health Statistics

<sup>4</sup> Estimates for 1979 through 1998 use International Classification of Diseases, 9<sup>th</sup> Revision (ICD-9) coding

<sup>5</sup> Estimates for 1999 through 2000 use International Classification of Disease, 10<sup>th</sup> Revision (ICD-10) coding

“Ninety percent of the deaths occur in those ages 65 and older, but the highest rates of infection occur in children.”

While this reviewer does *not* dispute the writer’s “*Ninety percent of the deaths occur in those ages 65 and older,*” he notes that, *as reported in 2005 by Simonsen et al. from the National Institute of Allergy and Infectious Disease, who studied influenza-related mortality in the US over the past three decades,*<sup>3</sup> the estimated influenza-related mortality rates in the 65-and-over age group did *not* decrease in spite of a concurrent “4”-fold increase in the vaccination rates in this age group (from 15% in 1980 to 65% in 2001).

Their studies led Simonsen *et al.* to conclude:

“We could not correlate increasing vaccination coverage after 1980 with declining mortality rates in any age group. Because fewer than 10% of all winter deaths were attributable to influenza in any season, we conclude that observational studies substantially overestimate vaccination benefit.”

These findings clearly indicate that the influenza vaccines are *not* effective in preventing the “elderly” segment of the population from getting or spreading the influenza virus.

In addition, a study by Cohen<sup>4</sup> has also questioned the benefits of vaccinating the elderly with the current influenza vaccines.

Moreover, though “*the highest rates of infection*” may occur in children, the mortality rates for children, *as obtained from the National Center for Health Statistics,* indicate average annual mortality rates for the period from 1979–2000 range from less than 0.5 deaths per million for children 1–4 years of age to 2.5 deaths per million children less than 1 year of age (**see Table 2**).

In spite of the preceding factual realities (which clearly show that a “universal vaccination program” for influenza is clearly *not* cost effective for young children), the CDC has recommended the influenza vaccines for “universal” administration to children six months of age to “two” years of age since December 2003 and have increased the age range so that, in 2006, the recommended age range is from six months to eight years.

In addition, recent published studies have clearly established that influenza vaccines are *not* effective in preventing young children from getting influenza.<sup>5,6</sup>

“And healthy children younger than 2 years are as likely to land in the hospital because of influenza as those over 65.”

Even if the writer’s statement were statistically valid, the reality is that the risk of an “*influenza*” death in “*children younger than 2 years*” is low (**see Table 2**) and, based on studies by Maeda *et al.*<sup>5</sup> and Jefferson *et al.*<sup>6</sup>, the current human influenza vaccines are *not* effective in protecting those 2 years of age and under from getting influenza when

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<sup>3</sup> Simonsen L, Reichert TA, Viboud C, Blackwelder WC, Taylor RJ, Miller MA. Impact of influenza vaccination on seasonal mortality in the US elderly population. *Arch Intern Med* 2005; **165**: 265-272.

<sup>4</sup> Cohen J. Study questions the benefits of vaccinating the elderly. *Science* 2005; **307**: 1026.

<sup>5</sup> Maeda T, Shintani Y, Nakano K, Terashima K, Yamada Y. Failure of inactivated influenza A vaccine to protect healthy children aged 6-24 months. *Pediatr Int* 2004; **46**: 122-125.

<sup>6</sup> Jefferson T, Smith S, Demicheli V, Harnden A, Rivetti A, Di Pietrantonj C. Assessment of the efficacy and effectiveness of influenza vaccines in healthy children: systematic review. *Lancet* 2005; **365**: 773-780.

exposed to the human influenza viruses.

Therefore, this reviewer is at a loss to understand why the writer included this statement in this article.

Since:

- Vaccination is truly *not* effective in protecting “*children younger than 2 years*” (or, for that matter, the elderly) from getting influenza and
- The majority of the available influenza vaccine doses that are administered to these children contain Thimerosal, a “50”%-mercury compound (whose safe level has *not* been established), at levels more than 100,000 times the level that has been found to adversely impact developing human neurons (Parran *et al.* Effects of Thimerosal on NGF signal transduction and cell death in neuroblastoma cells. *Tox Sci* 2005; 86(1): 130-140) when the influenza vaccine is “Thimerosal preserved,” or about 2,000 times that developing-human-neuron adverse level when the Thimerosal-containing vaccine is a “trace Thimerosal” vaccine,

it is apparent that all the Thimerosal-containing influenza vaccines are effective in doing is mercury poisoning, to some degree, all of those injected with a Thimerosal-containing influenza vaccine.

Based on the preceding realities, the government should stop recommending that the human influenza vaccines be used in any general population and ban the administration of any Thimerosal-containing human influenza vaccine to:

- Pregnant women (to protect the fetus),
- Children under the age of “24” (since brain development continues into the early 20s), and

**Table 2.** Number of influenza deaths<sup>1</sup> per year in children

<b>Year</b>	<b>&lt;1 year-old</b>	<b>1-4 years-old</b>	<b>5-14 years-old</b>	<b>0-14 years-old</b>
1979	9	8	8	25
1981	13	8	12	33
1983	6	8	3	17
1985	7	6	7	20
1987	8	6	1	15
1989	12	8	14	34
1991	16	15	11	42
1993	10	14	13	37
1995	7	7	7	21
1996	15	3	8	26
1997	12	10	13	35
1998	6	3	14	23
1999	13	12	11	36
2000	9	10	11	30
2001	7	6	12	25
Mean ± Std	10.0 ± 3.2	8.3 ± 3.5	9.7 ± 3.7	27.9 ± 8.0 <sup>2</sup>
Median	9.0	8.0	11.0	26

<sup>1</sup> Data obtained from the National Center for Health Statistics

<sup>2</sup> Mean-based death rate for children aged “0”–14 of about 0.5 deaths per million children

- Adults over the age of 55.

“Vaccination remains the single most effective preventive measure available against influenza, and can prevent many illnesses and deaths,” says Jesse Goodman, M.D., director of the Food and Drug Administration’s Center for Biologics Evaluation and Research (CBER). Yet each year, millions of Americans choose to take a chance and forgo influenza vaccination.”

Based on the recent peer-reviewed published scientific studies cited, it is clear to this reviewer that Dr. Goodman is simply wrong because vaccination with the current influenza vaccines is *not* effective against influenza.

“Public health officials urge those eligible for vaccination to receive it and remind people that although influenza vaccination begins in September or October each year, vaccine continues to be available in November, December, and later, and immunization during those months is still beneficial.”

Since vaccination is *not* effective against influenza, this reviewer would urge the “(p)ublic health officials” to tell the truth and urge everyone “eligible for vaccination to”:

- Avoid vaccination for influenza,
- Practice sound personal hygiene (e.g., frequent hand and face washing, and the wearing of a suitable mask if you contract the flu),
- Get 8 to 10 hours of sleep, and
- Increase their dietary intake of vitamins A and E, and zinc and magnesium, during the influenza season.

“The CBER regulates vaccines for use in the United States and is responsible for their safety and effectiveness.”

IF, as the author asserts, “CBER regulates vaccines for use in the United States and is responsible for their safety and effectiveness,”

THEN, this reviewer respectfully requests CBER explain:

- Why, without the requisite proof of safety (which has been a minimum requirement under **21 CFR § 610.15(a)**<sup>7</sup> since 1973), does CBER continue to illegally license Thimerosal-preserved vaccines – vaccines that are clearly adulterated under **21 U.S.C. Sec. 351(a)(2)(B)**<sup>8</sup> since **21 CFR § 610.15(a)** clearly falls within the legally binding requirement minimums for “current good manufacturing practice” as set forth in **21 CFR § 211.1**?

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<sup>7</sup> “§ 610.15 Constituent materials.

(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. 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 recipient, ...”

<sup>8</sup> “Sec. 351. Adulterated drugs and devices

A drug or device shall be deemed to be adulterated -

(a) Poisonous, insanitary, etc., ingredients; adequate controls in manufacture

(1) If it consists in whole or in part of any filthy, putrid, or decomposed substance; or

(2) (A) ...; or

(B) if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this chapter as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess; or ...”

- Why, since it has been clearly established that the influenza vaccines are *not* effective in preventing the person vaccinated from getting influenza or in stopping the spread of influenza, does CBER continue to illegally license any influenza vaccine?

**“Who should get vaccinated?”**

*Vaccine is available to anyone who wants to reduce his or her chances of getting influenza, with a few exceptions, but the CDC strongly recommends it for the following groups of people:*

- *All children 6 months to 59 months of age—a new recommendation for this influenza season*
- *Women who will be pregnant during the influenza season*
- *People ages 50 years and older*
- *Children and teen-agers (ages 6 months to 18 years) who must take aspirin regularly and therefore might be at risk for developing Reye syndrome if they get influenza*
- *Adults and children ages 6 months and older with chronic heart or lung conditions, including asthma*
- *Adults and children who have required hospitalization or regular doctor visits during the past year because of chronic metabolic diseases, including diabetes, kidney disease, hemoglobin abnormalities, or weakened immune system*
- *People with any condition that makes it hard to breathe or swallow, such as brain injury or disease, spinal cord injuries, seizure disorders, or other nerve or muscle disorders*
- *Residents of nursing homes and other facilities that provide care for people with chronic medical conditions*
- *Healthy household contacts and caregivers of children up to 5 years old and people at high risk for severe complications from influenza*
- *Health care workers.”*

Since influenza vaccines have been proven to be less-than effective, then the CDC should immediately stop recommending that any person be inoculated with any influenza vaccine until truly independent scientifically sound and appropriate studies can establish that each influenza vaccine is:

- Safe to the extent that:
  - A single dose is nontoxic to all who may be directly or indirectly (in the case of the fetus) administered a given vaccine and
  - That dose is safe enough that it does *not* put others who have *not* been inoculated at risk of contracting influenza from the person inoculated, and
- Effective to the extent that:
  - A single dose or, *at most*, two doses can effectively prevent more than 90% of the population from contracting almost any influenza virus, and
  - After dosing, the protection conferred provides protection against almost all influenza viruses for not less than ten (10) years after the date of inoculation.

Because today’s vaccines fail to meet the preceding clear minimum requirements for safety and/or effectiveness, this reviewer respectfully requests the CDC abandon its current immunization program because all of today’s influenza vaccines have clearly *not* been proven safe and/or effective.

“Since no influenza vaccine is approved for children younger than 6 months of age, families should use a strategy known as “cocooning,” says William Schaffner, M.D., professor and chairman of the Department of Preventive Medicine at Vanderbilt University School of Medicine in Nashville, Tenn. ‘They should provide a cocoon, or zone of protection, around that very vulnerable young child by vaccinating all the other people in the family, including grandma and granddad who come in for visits, and out-of-home caregivers.’”

Since the human influenza vaccines have clearly been shown to be less-than effective, Dr. Schaffner’s “well-intentioned” advice, “... *provide a cocoon, or zone of protection, around that very vulnerable young child by vaccinating all the other people in the family, including grandma and granddad who come in for visits, and out-of-home caregivers,*” should be ignored.

### “How well does influenza vaccine work?”

Infection-fighting antibodies develop about two weeks after vaccination.

Studies have shown that influenza vaccine is 70 percent to 90 percent effective in healthy adults younger than 65. In older people, children, and those with chronic illnesses, the vaccine may not necessarily prevent influenza, but it can reduce the severity of the symptoms and the risk of complications if they do get sick.

Vaccination in people older than 65 reduces the likelihood of hospitalization for influenza-related complications by 30 percent to 70 percent. And for those living in nursing homes or other long-term care facilities, the vaccine is up to 80 percent effective in preventing death from influenza.”

Since:

- Studies of the outcomes experienced by all populations over periods of 20 or more years have clearly established that influenza vaccines are *not* effective,
- Developing antibodies is *not* proof of effective protection,
- The studies used to claim effectiveness have been based on antibody titer and/or “flawed” clinical studies, and
- There is no scientifically sound proof of which this reviewer is aware that:
  - Inoculation with a human influenza vaccine can universally “*reduce the severity of the symptoms and the risk of complications if they do get sick,*” or
  - While *not* effective in preventing those over 65 who are vaccinated from getting influenza, “*the vaccine is up to 80 percent effective in preventing death from influenza*” (especially since most of the elderly infected with influenza die from pneumonia or, if affected, one of their other chronic disease conditions),

this reviewer is again compelled to state:

- The influenza vaccines are *not* effective, and
- The article’s rhetoric here appears to be simply empty hyperbole.

### “Two types of influenza vaccine

The FDA has licensed two types of influenza vaccine for use in the United States: the ‘shot’ and the inhaled vaccine.

The shot contains inactivated, or killed, viruses and is given with a needle in the arm. The inhaled vaccine contains live viruses that are weakened and is administered into the nose with a

sprayer. The influenza shot can be given to those 6 months of age and older, including healthy people and those with medical conditions.”

Here, the writer fails to mention, much less delineate, the documented general risks associated with the inactivated influenza vaccines including severe immune system reactions (e.g., severe skin allergy, anaphylaxis and Guillian-Barré syndrome) as well as the significant mercury toxicity associated with the “Thimerosal preserved” vaccine formulations.

In addition, the writer fails to mention that:

- No reproductive toxicity studies have been conducted to establish the safety of giving any inactivated influenza vaccine to pregnant women,
- These vaccines are therefore labeled “Pregnancy C” to warn of the unknown risk to the fetus, and,
- *Since the majority of the doses of these vaccines are Thimerosal-preserved,*
  - These inactivated vaccines present an actual risk to the fetus for mercury poisoning and
  - Evidence of the damage such Thimerosal-preserved shots can produce has been documented (as a recent article<sup>9</sup> by Ayoub and Yazbak has clearly established).

Based on the preceding and the proven toxicity of Thimerosal-preserved vaccines to children and the elderly, *at a minimum*, this reviewer must again recommend Thimerosal-preserved flu shots be banned for pregnant women, children up to age 24, and those over 55.

“The inhaled vaccine is approved only for healthy people between the ages of 5 years and 49 years, excluding pregnant women.”

Again, the writer fails to warn the reader that:

- Everyone inoculated with the “inhaled vaccine” actually contracts the three strains of “weakened” live influenza virus that are present in the vaccine, which can lead to a serious viral infection in people who appear to be healthy but are *not*,
- Each person inoculated becomes a “Typhoid Mary” who, *because they can infect others for up to 21 days after being given this vaccine*, should rigorously quarantine themselves from close contact to others for at least 21 days (3 weeks) after being inoculated, and
- Because this is a live-virus vaccine and there is a 21-day shedding period, this vaccine:
  - Actually spreads influenza and
  - Risks, through genetic exchange with other influenza strains, the creation of a virulent pandemic influenza strain from such genetic exchanges.

Moreover, this reviewer again asks:

“Why do influenza vaccines that have been proven ineffective (based on the outcomes observed from decades of their usage) continue to be ‘licensed/approved’ for any use in humans?”

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<sup>9</sup> Ayoub DM, Yazbak FE. Influenza vaccination during pregnancy: A critical assessment of the recommendations of the Advisory Committee on Immunization Practices (ACIP). *J Am Phys Surg* 2006; **11**(1): 41-47.

### “Can the influenza vaccine cause influenza?”

Some people may get a mild fever, body aches, and fatigue for a few days, but you can't get influenza from the influenza shot, says Karen Midthun, M.D., the deputy director for medicine in the FDA's Center for Biologics Evaluation and Research. ‘No vaccine is 100 percent effective. So you may get the flu soon after you received the vaccine, before it could be expected to protect you. It does not mean the shot gave you the flu.’”

This reviewer notes that Dr Midthun’s statement is an admission that the inactivated influenza vaccine is *not* effective in preventing some of the persons vaccinated from getting influenza.

Moreover, her “*No vaccine is 100 percent effective*” statement is interesting because the experiential data indicate that, *at best*, the inactivated influenza vaccines are between 0% and less than 50% effective in a given year in preventing adults from 18 to 55 from getting a clinical influenza infection.

Based on the preceding, this reviewer again asks,

- Why has CBER continued to license these less-than-effective vaccines?
- Why does the CDC continue to approve the use of these less-than-effective vaccines in a general vaccination program?
- Why, *other than to risk mercury poisoning those vaccinated with such vaccines*, have both agencies failed to ban the use of Thimerosal-preserved vaccines?

“In addition to the influenza shot, an inhaled influenza vaccine is approved by the FDA. The inhaled vaccine does not cause influenza in healthy people, the only group for which it's approved.

Technically, no “*influenza vaccine is approved by the FDA*” – the FDA (CBER) licenses each vaccine formulation.

However, in conjunction with the NIH and the CDC, the FDA does approve the labeling, including the package inserts, for all drugs, including vaccines.

### “Working year-round to prepare for influenza season

Preparing for the influenza season each year is a time-critical, highly orchestrated, collaborative effort between the FDA, the CDC, the National Institutes of Health (NIH), the World Health Organization (WHO), vaccine manufacturers, and the health care community.”

Since the vaccine manufacturers have apparently acquired and exert considerable influence over the decisions made by CBER (the branch of the FDA that oversees vaccine issues), the CDC, the NIH, and the WHO, the effort appears, *to this reviewer today*, to be more of a process whereby the vaccine manufacturers *essentially* dictate to the others what they are willing to do with respect to the strain make-up of each year’s “new” vaccine and the others are virtually compelled to go along the vaccine manufacturers’ proposals.

This is one of the major reasons that, *in some years, like the 2003–2004 flu season*, there is nearly “no” match or a “poor” match between the predominate strains circulating in the United States and the strains in the vaccines.

“One of the biggest challenges in the process is to produce a new vaccine every year, says Jesse Goodman, M.D., director of the CBER. ‘Because the virus mutates, each year's vaccine may be different from the preceding year.’”

Here, this reviewer agrees with Dr. Goodman’s observation concerning the varying nature of each year’s trivalent influenza vaccine formulation.

However, this reviewer must note that one of the tenets in the decision process for the choice of a “vaccine” as the control approach for a given viral disease is that the virus that causes the disease should *not* rapidly mutate – and the influenza viruses clearly violate this tenet.

“The process begins in late January or early February when an FDA advisory committee meets to recommend which three strains of the virus should be included in the vaccine, based on data from WHO laboratories in more than 80 countries. The FDA makes the final decision on which strains will be included in the vaccine for the U.S. population.”

Drawing from similarly structured relationships that this reviewer has observed, it appears that the vaccine manufacturers present the choices of strains of the virus from which the FDA can choose.

Then, from that “pool” of the strains the vaccine manufacturers present to the committee, the FDA committee selects the three of the strains in that pool that it thinks should be included in the influenza vaccine for the upcoming U.S. influenza season.

“Once the strains are selected, the FDA, CDC, or other WHO collaborating centers can produce reference influenza viruses that are adapted to high growth in eggs.

The reference influenza viruses are provided to the licensed vaccine manufacturers to generate the ‘seed virus’ for further manufacturing influenza vaccine.

Manufacturers inject the seed viruses into fertilized chicken eggs, which contain a nutrient in which the virus multiplies.

The manufacturer harvests and purifies the virus from the egg and applies chemical treatments to kill (inactivate) the virus so that it cannot transmit infection.

These treatments are done for each of the three strains, which are tested and retested by both the manufacturer and the CBER before being blended into the three-virus strain vaccine.

The CBER produces and provides manufacturers with antiserum, which they use to test vaccine potency for each influenza strain.

Manufacturers ship sample vials of vaccine from each lot, along with their test results, to the CBER for ‘lot release.’

The CBER reviews the test results as well as performs its own tests to ensure the accuracy of the manufacturers’ tests and the vaccine’s safety and effectiveness before releasing each lot for distribution.

Some lots of vaccine may be released as early as July, but manufacturing usually continues until October or later in order to produce and test the large volume of vaccine required for the U.S. population.

It takes about six months to complete influenza vaccine production—from egg to vial—each season.

Throughout the process, the FDA discusses technical and manufacturing issues with the companies and inspects each company’s facility and manufacturing processes while it is making vaccine.”

In general, this reviewer finds this narrative presents an idealized scenario of the process by which each year’s supply of influenza vaccines is generated.

Moreover, the narrative fails to mention:

- The recent (2000–2004) problems Chiron (now merged with Novartis) had with non-sterility – problems that the US FDA “overlooked” until the British ministry of health (and *not* the FDA who was well aware of the problem and “working with” Chiron to “resolve” the non-sterility issues) inspected the facility and, *seeing the on-going sterility problems*, suspended the plant’s operating license, and/or
- Sanofi-Aventis’ recent (2006) problems with sterility in certain batches of one of the individual strains that were to be blended to form the vaccine formulation.

Moreover, since the influenza vaccines have been recently (2005) added to the list of vaccines covered by the National Vaccine Injury Compensation Act (codified in **42 U.S.C. Sec 300aa**), the vaccine manufacturers no longer even have to worry about being sued for the harm their vaccines may cause thus increasing their incentive to make the cheapest vaccine they can get away with producing so as to maximize their per-dose profit – increasing their incentive to take risks and decreasing whatever incentive they may, *at one time*, have had to produce a safe and truly effective influenza vaccine.

Hopefully, the American people will soon realize once and for all that the influenza vaccines are *not* effective and demand that the appropriate actions be taken against those responsible in FDA, CDC and NIH for perpetrating this fraud on the American public as well as those firms who have and are knowingly manufacturing human influenza vaccines that are not truly effective and thus defrauding the people.

Since, *as this writer has clearly outlined*, this *knowing* fraud has occurred and is occurring through collusive actions between the federal government and the vaccine manufacturers, it seems clear to this reviewer that this apparent influenza vaccines’ racket falls within the scope of the criminal provisions of the Racketeering, Influencing, and Corrupt Organizations (RICO) statutes and should, therefore, be vigorously prosecuted for the fraud that it so obviously is.

### **“Why are there vaccine shortages?”**

Selecting the influenza virus strains each year, preparing the vaccine, and manufacturing and distributing millions of doses all must be precisely timed to make the vaccine available for the influenza season.

Any problems encountered during the process may cause delays or shortages.

In addition, because the number of companies that make influenza vaccine for the United States is small, a production problem with any company can substantially affect the overall supply.

Since the influenza vaccines are *not* effective in preventing those inoculated from getting the flu (and, in the case of the live vaccines, actually give people the flu), all of the “*vaccine shortages*,” real and imagined, are but part of the marketing strategy used by the CDC to drum up more business for their friends who make the vaccines and the business strategy used by the vaccine makers to get increasing federal protections, subsidies, and guaranteed purchases for a less-than-effective product to fatten their bottom lines in an apparent “snake oil” swindle of the American people.

### **“How much vaccine is available for this influenza season?”**

Manufacturers have projected making about 100 million doses of influenza vaccine for the 2006–2007 season in the United States, but these projections could change as manufacturing continues.

The projected supply is 16 percent more than the 2005–2006 season's 86 million doses and 40 percent more than the 2004–2005 season's 61 million doses.

Demand has usually been around 70 million to 75 million doses.”

If the “demand” is protected to be “70 million to 75 million doses,” then this reviewer asks:

“Why are the now four major players (Sanofi-Aventis [SA], Chiron [CH, now part of Novartis], GlaxoSmithKline [GSK], who make US-licensed inactivated-influenza vaccines, and MedImmune [MI], who makes US-licensed live-influenza vaccines) in the US influenza vaccine market planning to make “*about 100 million doses of influenza vaccine for the 2006–2007 season in the United States*”?

In addition, this reviewer notes that the writer has failed to disclose how many of the doses of these influenza vaccines for children and pregnant women will be:

- “Thimerosal Free” (part of SA’s doses) – suitable for children 6-months and up and pregnant women and presenting “no” mercury poisoning risk;
- “Reduced Thimerosal” (all of GSK’s doses) – suitable only for pregnant women 18 and over, and presenting “some” mercury-poisoning risk to the fetuses of pregnant women; or
- “Trace Thimerosal” doses (part of CH’s production) – suitable for children 4 and over and for pregnant women, and presenting “some” mercury-poisoning risk to the fetuses of pregnant women (but less than GSK’s vaccine) and to children 4 years and older (in the US, GSK’s vaccine [Fluarix®] is only approved for use in adults 18 and over, even though it is approved for use in children as young as 6 months of age in other countries since before 2004).

Given the joint 1999 commitment on the part of the government and the vaccine makers to remove Thimerosal from all vaccines as soon as possible, this reviewer notes:

- For the 2006 – 2007 US influenza season, probably 80-plus percent of the doses of these less-than-effective influenza vaccines will still be “Thimerosal preserved,” and
- These “Thimerosal-Preserved” doses will, to some degree, mercury poison every person injected with them.

When is this “mercury poisoning by Thimerosal in vaccines” madness going to be stopped?

Why does the CDC continue to promote and the FDA continue to allow adulterated vaccines containing a preservative level of Thimerosal without the required proofs of safety?

Hopefully, the American people will soon wake up and stridently demand answers for these questions.

### **“Why doesn't my doctor have influenza vaccine?”**

Government agencies monitor the vaccine market, but do not control it.

Distributing and administering influenza vaccine is mostly a private sector enterprise.

The CDC and state and local health departments work to influence distribution through collaborations and recommendations so that vaccine reaches the people most at risk, including older people, health care workers, nursing homes residents, young children, and expectant mothers.

Vaccine distribution is a complex process involving manufacturers, wholesalers, distributors, purchasers, and providers.

Some manufacturers sell directly to providers, others work exclusively with wholesalers, and some use both methods of distribution.

Since there is no coordinated system that manufacturers and distributors use to deliver vaccines, some health care providers receive their vaccine before others.”

Accepting the validity of the explanation provided by the writer, it seems to this reviewer that the answers to the question posed, “*Why doesn't my doctor have influenza vaccine,*” are simply that “*my doctor*” did *not* order the vaccine soon enough, did *not* order enough of the vaccine you want, or wasn't willing to pay top dollar to ensure he or she received the vaccine you want soon enough.

#### “Getting vaccinated later still beneficial

Sometimes, vaccine is in short supply early in the season, but there is leftover vaccine at season's end.

How much vaccine is produced and distributed plays a role, but so does timing, says Christine Layton, Ph.D., M.P.H., of RTI International, a nonprofit firm in Research Triangle Park, N.C. ‘The peak demand for flu vaccine is in October and November, when only about 50 percent of the vaccine has been delivered. But it's not until January, generally speaking, that all the vaccine has been available to providers.’

And it's usually not until January or later that the influenza disease season peaks in the United States, according to the CDC.

The FDA and the CDC support extending vaccination throughout the influenza season, into January and February.

Since the influenza inoculations are less than effective, the question that needs to be asked is, “**Beneficial to whom?**”

Obviously, the vaccine makers' benefit increases as the number of doses sold of their vaccine increases.

Thus, the writer's “*FDA and the CDC support extending vaccination throughout the influenza season, into January and February,*” indicates that both agencies are acting as marketing agents for the vaccine makers and, *as such agents do for seasonal items,* are doing what they can to extend the sales season for the benefit of the vaccine makers, because, *as this reviewer has repeatedly noted,* the influenza vaccines are less than effective: **a)** in preventing those inoculated from getting influenza or **b), in general,** in stopping the spread of influenza.

#### “New vaccines and faster production

Scientists and public health experts are looking for ways to boost the production of influenza vaccine and make it available more quickly to more people.

And researchers are looking at new technologies that could be used to produce vaccine, not just for seasonal influenza, but **also** for a pandemic—a worldwide outbreak of serious illness.

One of the technologies researchers are using is cell culture production, which allows a virus to grow and multiply in living animal cells instead of eggs. Cell-based vaccines could help meet surge capacity—making a lot of vaccine in a short time period—in the event of a shortage or a pandemic.

With cell culture production, cells can be frozen and stored, and then thawed out and used to produce more vaccine as needed—a speedier process than acquiring millions more fertilized eggs.

Like the current method of influenza vaccine production, the safety of vaccines produced in cell culture would be thoroughly evaluated by the FDA.

In May 2006, Health and Human Services Secretary Mike Leavitt announced the department's investment of more than \$1 billion in contracts with five companies to develop influenza vaccine made from cell culture.”

First, this reviewer notes that this article fails to mention, much less address, the issue of improving the effectiveness of vaccines.

The issues addressed are faster production and more doses for more people.

However, this reviewer and, hopefully, the American people want influenza vaccines that are truly effective.

Given the historical record, effectiveness is *not* a top priority for either the governmental agencies or the vaccine makers.

Second, given the FDA’s abysmal track record in the area of safety for “Thimerosal Containing” vaccines, in general, and for “Thimerosal Preserved” influenza vaccines in specific as well as their less-than-stellar record with Chiron in making sure microbially contaminated influenza doses were *not* released into distribution, this reviewer has no confidence that “*the safety of vaccines produced in cell culture would be thoroughly evaluated by the FDA*” as the writer asserts.

Finally, since the current influenza vaccines are, *at best*, less than effective and, *for some*, present serious health risks, this reviewer finds that “*the department's investment of more than \$1 billion in contracts with five companies to develop influenza vaccine made from cell culture*” is but another corporate giveaway of American taxpayer dollars that will produce little or no benefit to the American people.

“Researchers also are looking at recombinant vaccines, made by genetic engineering, for influenza prevention.

The gene from a specific influenza protein is isolated from the influenza virus, cloned, and grown in yeast or other cells to create large amounts of the protein.

The protein produced is purified and then used to make vaccine.

When the vaccine is injected into a person, the body's immune response to the recombinant protein protects against infection by the naturally occurring virus.”

Since the current influenza vaccines are, *at best*, less than effective, this reviewer has little confidence that the genetically engineered vaccines that the vaccine makers will produce will be any more effective than the current ineffective virus-based vaccines.

In addition, though the “*recombinant protein*” injected may produce an immune system response, there is no assurance that it will truly protect against “*against infection by the naturally occurring virus.*”

In addition, there is even less assurance that the “*recombinant protein*” injected will enable the immune system to respond to other strains of the influenza virus.

Finally, this reviewer notes that the issue of the long-term safety for these, or any other, “*recombinant protein*” vaccines is a serious concern that the article does *not* even mention, much less address.

“Researchers also are experimenting with substances that enhance vaccine effectiveness (adjuvants) to make current vaccines more potent.

‘If you could double the potency, the current technology could make twice as many doses, which would make 50 percent of the doses available sooner,’ says George Curlin, M.D., M.P.H., an infectious diseases researcher and adviser on vaccine clinical trials at the National Institute of Allergy and Infectious Diseases. Studies supported by the NIH are under way using adjuvants as a ‘dose-sparing’ technology.”

Though most vaccines currently contain “*substances that enhance vaccine effectiveness (adjuvants)*,” there is a growing body of evidence that such “*adjuvants*” cause more harm than good to the human immune system and, thereby, increase the risk of inducing long-term adverse autoimmune responses by the inoculees’ immune systems and/or increase the risk of induced allergies.

This is one area of research that, *hopefully*, will, *in light of the long-term negatives*, be abandoned and, *recognizing the dangers inherent in adjuvants*, the FDA will ban the use of all such unless and until long-term (10-year-plus) safety studies prove that a given vaccine formulation containing any adjuvant has near-zero (< 1 in 100,000,000) risk of inducing autoimmune disease or allergy in those inoculated with such vaccines.

“Another area of research is a universal vaccine.

This one-shot-fits-all vaccine would protect people for years against all strains of influenza anywhere in the world.

Although universal vaccine research has been going on for decades, says Curlin, ‘nothing seems like it’s available right around the corner, but there are clinical trials starting.’”

Provided such were truly proven to be safe in both the short term and the long term and more than 90% effective for at least 10 years, this reviewer sees these “*universal*” vaccines as a viable alternative to today’s influenza vaccine formulations, which have:

- *Not* been proven to be truly safe in either the short term or long term and
- Been found to be, *at best*, less than effective.

However, since these “*universal*” vaccines would “slay” the vaccine makers’ annual multi-billion cash cow, this reviewer sees no impetus upon the current makers’ part to undertake making such vaccines unless the price for “complete” protection was at least \$ 300.00.

Moreover, should some start-up company have some success in a clinical trial, this reviewer understands that some of the current vaccine makers would be inclined to simply buy up the company and bury the product to preserve their current revenue stream.

Given the preceding problems and realities, this reviewer currently does *not* foresee any such “*universal*” influenza vaccines being licensed and marketed in the current regulatory and healthcare establishment environments.

### “The FDA stimulates vaccine development

The FDA has worked to streamline the vaccine approval and licensing process to encourage new vaccine development and to make vaccines available for use sooner.

In March 2006, the agency published recommendations, in the form of two draft guidelines, to aid manufacturers in developing vaccines for both seasonal and pandemic influenza.

The guidelines give specific approaches that vaccine developers can follow to show the safety and effectiveness of new vaccines, and they provide flexible, regulatory pathways for getting vaccines on the market.”

This reviewer finds that, as these statements clearly indicate, the FDA has become an industry supporter at the expense of its role in assuring the safety of all drugs especially the safety of drugs that are given to “healthy” people for diseases that they do *not* have and may *not* ever contract even if *not* vaccinated.

Thus, the FDA is apparently abandoning its role as the protector of the interests of the American public in favor of its role as a facilitator for, and protector of, the general interests of the healthcare establishment and, *in this case*, the vaccine makers in specific.

Though the writer refers to these draft guidance documents as “*guidelines*” to “*aid manufacturers in developing vaccines*” and characterizes them as providing “*flexible, regulatory pathways for getting vaccines on the market,*” this reviewer recognizes them as providing the manufacturers easier access to the market by unnecessarily increasing the health risk to the American public.

“One of these pathways is the accelerated approval process, which can reduce the development time for a new vaccine.

For an application that does not use the accelerated approval pathway, a company must show that a vaccine actually prevents influenza, which requires waiting to see whether people in studies get sick or not.

For accelerated approval, if the manufacturer demonstrates that within weeks after vaccination, adequate levels of protective antibodies are made in the blood that the FDA believes may prevent influenza, then this approach may be acceptable.

If the accelerated approval approach is used, further studies are required after approval to make sure that the vaccine actually prevents influenza.”

This reviewer must first note that the March 2006 draft guidance, “**Guidance for Industry Clinical Data Needed to Support the Licensure of Trivalent Inactivated Influenza Vaccines,**” states (on “page 6” in the Adobe “pdf” file with **bolding** added for emphasis), when discussing the criteria for the clinical proof of influenza vaccine effectiveness:

“c. Study sample size calculations should be based on estimates of vaccine effectiveness and influenza attack rates. The study should be powered to assess the lower bound of the 95% confidence interval (CI) of vaccine effectiveness, anticipated to be substantially above zero (**e.g., in the range of 40 to 45%**).”

Given the low bar (“40 to 45%”) set for vaccine effectiveness in this draft guidance, it should be clear that this guidance does *not* expect the clinical trials of influenza vaccines to be truly effective or they would have set the “effectiveness” bar’s lower-bound 95%-confidence-interval expectation at a minimum of 75 to 80%.

So that all can see, this reviewer first notes that, for the “*accelerated approval pathway*,” the draft guidance states (with **bolding** added for emphasis):

**“B. Accelerated Approval of a BLA for a New Trivalent Inactivated Influenza Vaccine**

Accelerated approval may be granted for certain biological products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments. (See Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses (21 CFR Part 601 Subpart E)).

Such an approval will be based on adequate and well-controlled clinical trials establishing that the product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit (21 CFR 601.41). Approval under this section will be subject to the requirement that the sponsor study the biological product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit (21 CFR 601.41). Post-marketing studies must also be adequate and well-controlled and should be conducted with due diligence (21 CFR 601.41). The protocols for these studies should be submitted with the original BLA. Marketing approval for products approved under these regulations may be withdrawn, for example, if the clinical study fails to verify the clinical benefit or the sponsor fails to perform the required post-marketing study with due diligence (21 CFR 601.43(a)(2)).

The option to pursue an accelerated approval pathway for trivalent inactivated influenza vaccines is available to sponsors if a shortage of influenza vaccine exists for the U.S. market at the time the new vaccine is approved. **We interpret the accelerated approval regulation, 21 CFR 601.40, as allowing accelerated approval of an influenza vaccine during a shortage because influenza is a serious and sometimes life-threatening illness.** Providing prophylaxis to those who would not otherwise be immunized during a shortage does certainly provide a meaningful benefit over the then-existing treatments, which are in short supply at that time. **We understand a shortage to exist when the supply of influenza vaccine is inadequate to immunize all persons for whom the CDC recommends annual vaccination. The CDC estimates that there are 185 million individuals in the United States for whom influenza vaccination is recommended annually** (Ref. 12).

For influenza vaccines, evaluation of an immune response elicited following receipt of the vaccine may serve as a surrogate endpoint that is likely to predict clinical benefit, that is, prevention of influenza illness and its complications. Influenza virus hemagglutinins, present on the viral surface, are important for cell-receptor binding. The immune response to the hemagglutinin as measured by the presence of serum HI antibodies is an important protective component following vaccination and/or infection. However, considerable variability can be introduced into the laboratory assay used to measure HI antibodies as a result of a number of factors including differences in viral strains, red blood cell types, and the presence of non-specific inhibitors in the assay medium. Thus, suitable controls and assay validation are important for interpreting HI antibody results.

To date, prospectively designed studies to evaluate the effectiveness of influenza vaccines have not identified a specific HI antibody titer associated with protection against culture confirmed influenza illness. Some studies of influenza infection, including human challenge studies following vaccination, have suggested that HI antibody titers ranging from 1:15 to 1:65 may be associated with protection from illness in 50% of subjects and protection from illness is increased with higher titers (Refs. 13 and 14). Seroconversion and GMT have been used as measures of vaccine activity (Refs. 15 and 16).

For the purposes of accelerated approval of trivalent inactivated influenza vaccines, the HI antibody response may be an acceptable surrogate marker of activity that is reasonably likely to predict clinical benefit.

To be considered for accelerated approval, a BLA for a new trivalent inactivated influenza vaccine should include results from one or more well-controlled studies designed to meet immunogenicity endpoints and a commitment to conduct confirmatory post-marketing studies during the next influenza season. Since each vaccine candidate is unique (e.g., particular product characteristics, manufacturing process, etc.), we recommend that you discuss with CBER early in development the adequacy of the manufacturing methods and product testing and the extent of the clinical data needed to license your candidate vaccine.

### 1. Effectiveness

This section describes possible approaches for establishing effectiveness based on immune responses under an accelerated approval.

a. A non-inferiority immunogenicity trial of HI antibody responses to the new vaccine as compared to a U.S. licensed trivalent inactivated influenza vaccine may support an accelerated approval. The study should be adequately powered to assess the co-primary endpoints for HI antibodies to each viral strain contained in the vaccine (i.e., a total of six co-primary endpoints): 1) GMT, and 2) seroconversion rates. **Recommendations for the co-primary endpoints include the following:**

- **The upper bound of the two-sided 95% CI on the ratio of the GMTs (GMT<sub>U.S. licensed vaccine</sub>/GMT<sub>new vaccine</sub>) should not exceed 1.5.** A proposal for use of a different GMT ratio should be based upon the characteristics of the assay that will be used to assess antibody responses.
- **The upper bound of the two-sided 95% CI on the difference between the seroconversion rates (Seroconversion<sub>U.S. licensed vaccine</sub> – Seroconversion<sub>new vaccine</sub>) should not exceed 10%.”**

b. Alternatively, a placebo-controlled immunogenicity trial in which HI antibody responses to the new vaccine are assessed may be supportive of accelerated approval if the study was adequately powered to assess the co-primary endpoints for HI antibodies to each viral strain contained in the vaccine: **1) seroconversion rates, and 2) percent of subjects achieving an HI antibody titer ≥ 1:40.** A saline placebo may be an acceptable control if the population studied is not at increased risk of complications from influenza illness or if the study is conducted off-season.

If a study is conducted just prior to the influenza season in populations who are at increased risk from influenza illness, use of a U.S. licensed influenza vaccine as a control may be appropriate. The purpose of the control arm in this type of study design, whether it is a saline-placebo or a U.S. licensed influenza vaccine, is primarily to provide a comparative assessment of safety, not effectiveness.

For example, the following recommendations, which have been modified from guidelines by the currently-titled, “Committee for Medicinal Products for Human Use of the European Medicines Agency” (Ref. 15), may support an accelerated approval.

**For adults < 65 years of age and for the pediatric population:**

- **The lower bound of the 95% CI for the percent of subjects achieving seroconversion for HI antibody should meet or exceed 40%.**
- **The lower bound of the 95% CI for the percent of subjects achieving an HI antibody titer ≥ 1:40 should meet or exceed 70%.**

**For adults ≥ 65 years of age:**

- The lower bound of the 95% CI for the percent of subjects achieving seroconversion for HI antibody should meet or exceed 30%.
- The lower bound of the 95% CI for the percent of subjects achieving an HI antibody titer  $\geq$  1:40 should meet or exceed 60%.

c. Alternative study designs that assess different endpoints and/or other immune responses will be reviewed by CBER and may be accepted in support of an accelerated approval. CBER would need to determine that the study design is acceptable and the proposed surrogate endpoint(s) is reasonably likely to predict clinical benefit.”

Reviewing this section of the guidance and **21 CFR 601 Subpart E<sup>10</sup>**, the first item that the readers should notice is the FDA’s “We interpret the accelerated approval regulation, 21

<sup>10</sup> **21 CFR 601 Subpart E, “Subpart E—Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses**

Source: 57 FR 58959, Dec. 11, 1992, unless otherwise noted.

**§ 601.40 Scope.**

This subpart applies to certain biological products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy).

**§ 601.41 Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.**

FDA may grant marketing approval for a biological product on the basis of adequate and well-controlled clinical trials establishing that the biological product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the biological product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Postmarketing studies would usually be studies already underway. When required to be conducted, such studies must also be adequate and well-controlled. The applicant shall carry out any such studies with due diligence.

**§ 601.42 Approval with restrictions to assure safe use.**

(a) If FDA concludes that a biological product shown to be effective can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to assure safe use of the biological product, such as:

- (1) Distribution restricted to certain facilities or physicians with special training or experience; or
- (2) Distribution conditioned on the performance of specified medical procedures.

(b) The limitations imposed will be commensurate with the specific safety concerns presented by the biological product.

**§ 601.43 Withdrawal procedures.**

(a) For biological products approved under §601.41 or §601.42, FDA may withdraw approval, following a hearing as provided in part 15 of this chapter, as modified by this section, if:

- (1) A postmarketing clinical study fails to verify clinical benefit;
- (2) The applicant fails to perform the required postmarketing study with due diligence;
- (3) Use after marketing demonstrates that postmarketing restrictions are inadequate to ensure safe use of the biological product;
- (4) The applicant fails to adhere to the postmarketing restrictions agreed upon;
- (5) The promotional materials are false or misleading; or
- (6) Other evidence demonstrates that the biological product is not shown to be safe or effective under its conditions of use.

(b) Notice of opportunity for a hearing. The Director of the Center for Biologics Evaluation and Research or the Director of the Center for Drug Evaluation and Research will give the applicant notice of an opportunity for a hearing on the Center’s proposal to withdraw the approval of an application approved under §601.41 or §601.42. The notice, which will ordinarily be a letter, will state generally the reasons for the action and the proposed grounds for the order.

(c) Submission of data and information.

- (1) If the applicant fails to file a written request for a hearing within 15 days of receipt of the notice, the applicant waives the opportunity for a hearing.
- (2) If the applicant files a timely request for a hearing, the agency will publish a notice of hearing in the Federal Register in accordance with §§12.32(e) and 15.20 of this chapter.
- (3) An applicant who requests a hearing under this section must, within 30 days of receipt of the notice of opportunity for a hearing, submit the data and information upon which the applicant intends to rely at the hearing.

(d) Separation of functions. Separation of functions (as specified in §10.55 of this chapter) will not apply at any point in withdrawal proceedings under this section.

(e) Procedures for hearings. Hearings held under this section will be conducted in accordance with the provisions of part 15 of this chapter, with the following modifications:

- (1) An advisory committee duly constituted under part 14 of this chapter will be present at the hearing. The committee will be asked to review the issues involved and to provide advice and recommendations to the Commissioner of Food and Drugs.
- (2) The presiding officer, the advisory committee members, up to three representatives of the applicant, and up to three representatives of the Center may question any person during or at the conclusion of the person’s presentation. No other person attending the hearing may question a person making a presentation. The presiding officer may, as a matter of discretion, permit questions to be submitted to the presiding officer for response by a person making a presentation.

(f) Judicial review. The Commissioner’s decision constitutes final agency action from which the applicant may petition for judicial review. Before requesting an order from a court for a stay of action pending review, an applicant must first submit a petition for a stay of action under §10.35 of this chapter.

[57 FR 58959, Dec. 11, 1992, as amended at 68 FR 34797, June 11, 2003; 70 FR 14984, Mar. 24, 2005]

CFR 601.40, as allowing accelerated approval of an influenza vaccine during a shortage because influenza is a serious and sometimes life-threatening illness.”

Though the language of 21 CFR 601.40 clearly only provides for accelerated approval of biological products when they “provide meaningful therapeutic benefit to patients over existing treatments,” the FDA has chosen to ignore the clear language of this regulation in order to justify allowing the manufacturers of influenza vaccines that, based on the guidance recommendations, do *not* “provide meaningful therapeutic benefit to patients over existing treatments.”

As such, it is clear to this reviewer that the FDA is:

- *Knowingly* (as that term is defined in **21 U.S.C. Sec. 321(bb)**<sup>11</sup>) operating outside of the latitude provided in this clear regulation (**21 CFR § 601.40**) and
- Therefore, apparently knowingly violating the restrictions on its administrative discretion as set forth in the unanimous 1998 Supreme Court decision *Berkovitz v. US*<sup>12</sup>.

Second, the readers should note the FDA’s statement, “We understand a shortage to exist when the supply of influenza vaccine is inadequate to immunize all persons for whom the CDC recommends annual vaccination. The CDC estimates that there are 185 million individuals in the United States for whom influenza vaccination is recommended annually,” flies in face of the reality that the current vaccination level is 70–75 million doses annually and the estimated production for the 2006–2007 influenza season is 100 million doses – indicating a real surplus of 25–30-million doses.

Since the current influenza vaccines have been proven to be less-than effective, this reviewer, *who is over 60 years of age*, does *not* accept that 185 million individuals need to be vaccinated for influenza and rejects the validity of the FDA’s obviously twisted definition of a vaccine “*shortage*,” although *neither* the clear language in **21 CFR § 601.40**, *the cited regulation*, *nor* the clear language in **21 CFR Part 601 Subpart E** contain the word “*shortage*” so that the FDA’s assertions here are *not* actually germane to the regulations being used to *improperly* justify use of the “*FDA’s accelerated approval process*” for “*new*” influenza vaccines that not only do *not* “provide meaningful therapeutic benefit to patients over existing treatments,” but also, *based on the guidance provided*, can

**§ 601.44 Postmarketing safety reporting.**

Biological products approved under this program are subject to the postmarketing recordkeeping and safety reporting applicable to all approved biological products.

**§ 601.45 Promotional materials.**

For biological products being considered for approval under this subpart, unless otherwise informed by the agency, applicants must submit to the agency for consideration during the preapproval review period copies of all promotional materials, including promotional labeling as well as advertisements, intended for dissemination or publication within 120 days following marketing approval. After 120 days following marketing approval, unless otherwise informed by the agency, the applicant must submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

**§ 601.46 Termination of requirements.**

If FDA determines after approval that the requirements established in §601.42, §601.43, or §601.45 are no longer necessary for the safe and effective use of a biological product, it will so notify the applicant. Ordinarily, for biological products approved under §601.41, these requirements will no longer apply when FDA determines that the required postmarketing study verifies and describes the biological product’s clinical benefit and the biological product would be appropriate for approval under traditional procedures. For biological products approved under §601.42, the restrictions would no longer apply when FDA determines that safe use of the biological product can be assured through appropriate labeling. FDA also retains the discretion to remove specific postapproval requirements upon review of a petition submitted by the sponsor in accordance with §10.30.”

<sup>11</sup> **21 CFR Sec. 321(bb)** The term “knowingly” or “knew” means that a person, with respect to information –  
 (1) has actual knowledge of the information, or  
 (2) acts in deliberate ignorance or reckless disregard of the truth or falsity of the information.

<sup>12</sup> Kevan BERKOVITZ, a Minor by his Parents and Natural Guardians Arthur BERKOVITZ, et ux., et al., Petitioners, v. UNITED STATES, 108 S.Ct. 1954, 100 L.Ed.2d 531, 56 USL W 4549, (Cite as: 486 U.S. 531, 108 S.Ct. 1954)

actually be less therapeutically beneficial than one or more of the current influenza vaccines.

Given the guidance recommendations provided concerning the co-primary endpoints, the guidance provides:

- The upper bound of the two-sided 95% CI on the ratio of the GMTs ( $\text{GMT}_{\text{U.S. licensed vaccine}} / \text{GMT}_{\text{new vaccine}}$ ) should not exceed 1.5. A proposal for use of a different GMT ratio should be based upon the characteristics of the assay that will be used to assess antibody responses.
- The upper bound of the two-sided 95% CI on the difference between the seroconversion rates ( $\text{Seroconversion}_{\text{U.S. licensed vaccine}} - \text{Seroconversion}_{\text{new vaccine}}$ ) should not exceed 10%,”

it is clear that vaccines that are less therapeutically beneficial can meet these criteria and that, therefore, this guidance does *not* conform to the clear “and that provide meaningful therapeutic benefit to patients over existing treatments” **CGMP** (current good manufacturing practice) *minimum* established under **21 PART 211—CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS** (as the regulations set forth in **21 CFR § 211.1**<sup>13</sup> clearly establish) as set forth in **21 CFR § 601.40**.

Third, the guidance further suggests in the “FDA’s accelerated approval pathway,” that the following recommendations may be acceptable for effectiveness to support accelerated approval:

“For adults < 65 years of age and for the pediatric population:

- The lower bound of the 95% CI for the percent of subjects achieving seroconversion for HI antibody should meet or exceed 40%.
- The lower bound of the 95% CI for the percent of subjects achieving an HI antibody titer  $\geq 1:40$  should meet or exceed 70%.

For adults  $\geq 65$  years of age:

- The lower bound of the 95% CI for the percent of subjects achieving seroconversion for HI antibody should meet or exceed 30%.
- The lower bound of the 95% CI for the percent of subjects achieving an HI antibody titer  $\geq 1:40$  should meet or exceed 60%.”

Again, it is clear to this reviewer that, *even if there is a relationship between titer and effectiveness (though none has been clearly proven)*, the guidance provided will allow the FDA to continue approving vaccines that are less than 50% effective.

“The accelerated approval pathway was critical in allowing the rapid approval in 2005 of Fluarix, a new influenza vaccine and the first vaccine of any kind approved using the FDA's accelerated approval process.”

Since the basic vaccine formulation for GSK’s “Fluarix” had been approved and used for years (since at least 1998) in other countries (*e.g.*, Germany and New Zealand) having safety and effectiveness standards similar to those of the United States, citing Fluarix as:

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<sup>13</sup> “§ 211.1 Scope.

(a) The regulations in this part contain the minimum current good manufacturing practice for preparation of drug products for administration to humans or animals.

(b) The current good manufacturing practice regulations in this chapter as they pertain to drug products; in parts 600 through 680 of this chapter, as they pertain to drugs that are also biological products for human use; and in part 127 I of this chapter, as they are applicable to drugs that are also human cells, tissues, and cellular and tissue-based products (HCT/Ps) and 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 35 I of the Public Health Service Act); supplement and do not supersede the regulations in this part unless the regulations explicitly provide otherwise. . . .”

- “a new influenza vaccine” and
- “the first vaccine of any kind approved using the FDA’s accelerated approval process,” seems to be, at best, disingenuous.

“The FDA has corresponded with the major manufacturers of influenza vaccine in the world to stimulate interest in producing vaccine for the U.S. market.

This outreach resulted in one additional vaccine product approval for the 2005–2006 season, and the possibility for others in future influenza seasons.”

Here, this reviewer would simply note that the “additional vaccine product approval” is the same Fluarix vaccine discussed in the previously under the “FDA’s accelerated approval process.”

“The FDA is also undertaking efforts to aid development of influenza vaccines using new technologies.

To accomplish this goal, the CBER is using various approaches to reach a broad audience, such as convening an advisory committee meeting to discuss the use of novel cell substrates for making influenza vaccine, and having frequent interactions with vaccine manufacturers to provide both scientific and regulatory guidance.

In addition, the CBER is participating in and leading meetings with industry, regulatory authorities of other nations, and stakeholders concerning the development of influenza vaccine.”

Here, this reviewer notes that the FDA, through CBER, is again obviously emphasizing its mission to assist the vaccine makers and deemphasizing, or forgetting about, its mission to protect the American people from unsafe and ineffective drugs.

In addition, this reviewer notes that CBER is *not* “participating in or leading meetings with” the American people, the stakeholders in having the government ensure that their influenza vaccines are *truly* safe and effective – characteristics that the current body of evidence indicates today’s influenza vaccines have been proven *not* to possess.

### “Drugs to prevent or treat influenza

Getting an annual influenza vaccination continues to be the first line of defense against seasonal influenza. But antiviral drugs—started within the first two days of experiencing influenza symptoms—can shorten the time influenza lasts.

The FDA has approved four antiviral prescription drugs to treat influenza: Tamiflu (oseltamivir), Relenza (zanamivir), Symmetrel and generics (amantadine), and Flumadine and generics (rimantadine).

All of these drugs also are approved to prevent influenza, but they are not substitutes for influenza vaccine.

The CDC recommends that the drugs be used in specific circumstances, for example, in combination with the vaccine to help control influenza outbreaks in institutions such as nursing homes where people at high risk for complications from influenza are in close contact with each other.

The antiviral drugs should not be used, however, in people who receive inhaled influenza vaccine until at least two weeks after vaccination.

In addition, people should not get vaccinated within two days of stopping the use of antiviral drugs.

The drugs may be prescribed by a doctor to prevent influenza in place of vaccine in certain people, such as those who are allergic to eggs, the medium used to grow the virus for the vaccine.

Influenza viruses can rapidly develop resistance to certain drugs.

Because of recent evidence that many circulating influenza viruses are resistant to amantadine and rimantadine, the CDC has recommended that these drugs not be used to treat or prevent influenza in the United States at this time.”

All that this reviewer would note here is that, *although the antiviral are not free of significant adverse side effects*, it would be better, *from the point of view of effectiveness and overall cost*, to confirm influenza (using a simple direct test) and then prescribe an effective antiviral to those having influenza than it is to inoculate a population with the current less-than-effective influenza vaccines when many in that population will never get the flu for which they have been vaccinated and to which some of those inoculated will have severe adverse reactions and, *when the vaccines are Thimerosal-preserved*, some degree of mercury poisoning.

Thus, this reviewer must disagree with the writer’s “*All of these drugs also are approved to prevent influenza, but they are not substitutes for influenza vaccine*,” because the effective ones, “*Tamiflu (oseltamivir)*” and “*Relenza (zanamivir)*,” are not only substitutes for influenza but, based on their history, are also more effective when used as directed and more cost-effective than vaccinating the entire population with the current less-than-effective influenza vaccines.

Moreover, to date, those strains of the influenza virus that have developed partial resistance to the current generation of antiviral drugs have all been strains that had weak infectivity and poor transmissibility.

Finally, *given the adverse findings by the Japanese when Tamiflu and Relenza are used prophylactically*, this reviewer must recommend that these only be prescribed to persons testing positive for influenza when they are tested by a rapid screening test.

### “Tips to help prevent influenza

The Centers for Disease Control and Prevention recommends the following good health habits to help prevent getting influenza:

- *Avoid close contact. Keep your distance from people who are sick.*
- *Stay home from work, school, and errands, if possible, when you are sick.*
- *Use a tissue to cover **your mouth and nose** when coughing or sneezing.*
- *Wash your hands frequently with warm, soapy water for about 15 seconds to help protect you from germs.*
- *Avoid touching your eyes, nose, or mouth.”*

This reviewer agrees with the writer’s recommendations.

In addition, he also recommends that all who are inoculated with a live-virus influenza vaccine, currently MedImmune’s FluMist®, should rigorously adhere to the first two recommendations for not less than 21 days **after** they are inoculated with a live-virus influenza vaccine.

### “Where to get influenza vaccination

- Contact your personal health care provider.
- Check the American Lung Association's locator at [www.flucliniclocator.org](http://www.flucliniclocator.org) for influenza clinics in your area.

- Call your local public health clinic or state health department immunization program. Or call the Centers for Disease Control and Prevention at (800) CDC-INFO (232-4636).
- Check newspapers, radio stations, or other public information sources for specific clinics in your community.
- Check with your county medical society.”

Since the influenza vaccines were added to the vaccines covered by the National Vaccine Injury Compensation Act (NVICA) in 2005, you should only go to your personal healthcare provider or other healthcare agency who holds your health records and who will follow up some weeks after your inoculation to ensure that you have *not* had a bad reaction or, if you have had a bad reaction, to document it in your permanent health records and appropriately notify the government.

Those wishing to receive healthcare in a manner that complies with the NVICA’s statutes should avoid being inoculated in any clinic or other setting that does not:

- Require them to provide a copy of their health records for review before inoculation,
- Update that record after inoculation,
- Promise to call or otherwise follow up to see if they had any problems, and
- After some weeks:
  - Call them to follow up,
  - Make the appropriate entry in their health records,
  - Appropriately maintain their health records, and,
  - In the case of an adverse reaction of any kind, take the appropriate action to:
    - Accurately enter it into their healthcare records and
    - Promptly file an appropriate “vaccine adverse event” report with CBER for inclusion in the VAERS database so that the adverse effects they have are available and a more-accurate picture of the adverse effects of influenza vaccines may be made available for appropriate scientific assessment.

**“For More Information**

[www.fda.gov/oc/opacom/hottopics/flu.html](http://www.fda.gov/oc/opacom/hottopics/flu.html)  
[www.cdc.gov/flu/](http://www.cdc.gov/flu/)  
[www.pandemicflu.gov](http://www.pandemicflu.gov)”

In addition to, or in lieu of, the sites provided by the government, this reviewer would recommend that the concerned reader consult:

- National Vaccine Information Center, <http://www.909shot.com/>
- Vaccination News, <http://www.vaccinationnews.com/default.htm>
- Institute for Vaccine Safety, <http://www.vaccinesafety.edu/>

“This article has been condensed from the original article as it appears in *FDA Consumer* magazine and edited for the FDA Web site. The print version of *FDA Consumer* is available by [subscription. </fdac/orderform/fdap.html>](http://fdac/orderform/fdap.html)”

This review is based on studies published in peer-reviewed journals, including those cited in this review, and data published by the federal government.