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21 June 1999 5717 '99 JUN 30 P1:44

Jane E. Henney, M.D.
Commissioner
Food and Drug Administration (HF1)
Room 14-71 Parklawn Bldg.
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Henney:

As your assistant suggested when I called on Friday, 18 June 1999, I am writing to you to express my dismay with the inaccurate "summary" that CDER made of the remarks presented to them in my formal presentation at the FDAMA Stakeholders Meeting held in Philadelphia, PA on 28 April 1999.

In order for you to see my concern, CDER's summary of that presentation, my summary thereof, and a copy of the transcript of said remarks have been included for your review. As you will see when you review the presentation transcript, the presentation parallels the letter I sent to you back in May of 1999.

Though I understand that no Agency likes criticism, any summary of any formal criticism should, nonetheless, accurately reflect the comments made.

As you can see from my concerns are also being submitted to the appropriate docket (99N-386). In addition, copies are being sent to my congressman and senators.

Should you wish to discuss any of this matters further with me or need more specifics in any area, then, I would be glad to arrange a time where we could meet (along with any others you felt would be needed) and discuss the issues that have been raised in more detail.

Finally, let me thank you in advance for taking the time to read and reflect upon this letter that I trust you will take.

Sincerely yours

Paul G. King, Ph.D. 21 June 1999

c.: Congressman Rodney P. Frelinghuysen, Senator Frank R. Lautenberg and Senator Robert G. Torricelli with all enclosures

Enclosures (The CDER Summary, my summary in docket submission form, and a partial transcript of my formal remarks at the CDER FDAMA Stakeholders meeting on 28 April 1999 in Philadelphia, PA)

Dr. King v 33 Hoffman Avenue v Lake Hiawatha, NJ 07034-1922

99N-0386

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U.S. Food and Drug Administration Center for Drug Evaluation and Research Conversation with Stakeholders Temple University School of Pharmacy Philadelphia, April 28, 1999

Center Director's Report

Center Director Janet Woodcock, M.D., opened the session by reviewing the state of drug regulation and CDER's current level of performance for the 96 attendees. She reported that CDER's core programs, especially in the area of premarket review, are performing efficiently and effectively. She referred the audience to statistical information contained in the CDER 1998 Report to the Nation: Improving Public Health Through Human Drugs (http://www.fda.gov/cder/reports/rptntn98.pdf). User fees have resulted in more new drug approvals with the peak in 1996. She noted that approvals for new uses of existing drugs have doubled in the last three years compared with the previous three years, indicating that firms are continuing to conduct studies on drugs once they are marketed. The generic drug program helps improve the affordability of medicines through competition. This program area does not receive support from user fees; but, through streamlining processes, it has reduced approval times from three and a half years to 18 months.

Dr. Woodcock also reviewed the Center's performance in the post-market surveillance programs for prescription drug advertising and promotion, adverse events involving drugs and product quality. Efforts at international harmonization are an important step to setting up a worldwide safety system. Consumers can be assured that drug product quality is very high in United States.

In the area of drug safety, she rejected the notion that shorter approval times have compromised review standards and led to an increase in drug withdrawals. There is evidence that CDER currently performs a higher quality review than previously when it was accused of taking too long to review drugs. For example, the number of patients studied has grown, drug recalls are down, and withdrawals are fewer than in previous decades. In other areas, she reported on the transition to an electronic review environment, noting that the equivalent of 12 million pages of paper were submitted last year electronically. One area for improvement is making better use of regulatory research. The Center met its deadlines related to the FDA Modernization Act of 1997.

Stakeholder Presentations

Paul G. King, Ph.D., a consultant, expressed his views on FDA inspections of current good manufacturing (CGMP) practices. He disagreed with current FDA practices and called for strict enforcement of all CGMP regulations, continual training of FDA inspectors and batch release testing.

Lorna Totman, Ph.D., director of scientific affairs, Consumer Healthcare Products Association, pointed to the "remarkable success story" of switching about 80 drugs from prescription only sales to over-the-counter sales. The law doesn't say how FDA should make the decision if a drug can be sold over the counter. Consequently, each decision is made on a case-by case-basis, with the FDA demanding more complex data to justify each switch. She called for the Center to identify in advance the kinds of high quality safety studies needed to switch a drug's status. For example, she said that CDER's guidance on hypercholesterolemia effectively blocks OTC switches of cholesterol-lowering drugs. She called on the Center to amend its guidance by identifying specific questions that could be investigated scientifically and would provide evidence for safely switching cholesterol-lowering drugs to OTC status. She encouraged joint workshops with associations and industry with the goal of addressing current problems. Jointly developed meetings help FDA benefit from scientific expertise in industry.

CDER/FDA Panel Discussion

Ways to improve communications about the risks and benefits of drugs were the top issues raised during the audience participation portion. Issues were discussed by a CDER/FDA panel consisting of Dr. Woodcock; Susan Setterberg, Mid-Atlantic Regional Director; Douglas Ellsworth, New Jersey District Director; and Nancy Smith, Ph.D., Director, CDER Office of Training and Communications (OTCOM). Linda Brophy, OTCOM Associate Director, moderated the question and answer session. Issues raised in open discussion included the pros and cons of direct-to-consumer advertising, improving communications for consumers and health care professions about the risks and benefits of drug therapy, and setting priorities for the FDA's limited inspection resources that most effectively meet public health and safety needs.

FDA/Center for Drug Evaluation and Research Last Updated: May 19, 1999 Originator: OTCOM/DCM HTML by NJ

Paul G. King Consulting

SUPPORT IN CHEMICALS & PHARMACEUTICS

Friday, 18 June 1999

Documents Management Branch [**HFA-305**]
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RE: Docket No. 99N-0386

FORMAL COMMENTS TO:

Docket Number : 99N-0386

Comments: **Speaker's Response To The Summary Miss-characterization Of My Comments As Made In the FDAMA Stakeholders Meeting Held On 28 April 1999 On The Campus Of Temple University In Philadelphia, Pennsylvania.**

On "5/21/99," CDER published a "Summary for CDER" in the FDAMA Docket 99N-0386.

In spite of the fact that both of the "stakeholder" speakers spoke for about the same time, the summary document "summarized" my comments in one-fourth the space given to the comments made by the other presenter, Dr. Lorna Trotman.

Moreover, while the summary of Dr. Trotman's presentation accurately reflected her comments, the summary of my comments was, to say the least, not accurate.

The following page contains my summary of my comments. In order to be fair, I have restricted them to the same "space" as given to Dr. Trotman's comments.

Please post the following document to the docket with the title "Dr. King's CDER FDAMA Remarks Summary."

Thank you.

Respectfully,

Paul G. King 21 June 1999

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SUPPORT IN CHEMICALS & PHARMACEUTICS

Dr. King's Summary Of His FDAMA Remarks At PA Meeting

Paul G. King, Ph.D., a consultant, expressed his views on the FDA and the drug industry that it regulates. He began by stating that it is both wrong and illegal for CDER not to comply with the FDC Act's "must" that all drug establishments be inspected by CDER at least biannually. He then noted that an Agency that disregards the law should not be surprised that the drug industry does the same and worse. Next, he observed that CDER lacks any metric-based proof of the competency of its inspection, review and management personnel. He then outlined a training- and assessment- based approach to correcting that deficiency so that their requisite competencies could be established in both the requirements of the statutes and regulations they administer and the basics of inspection science and statistics appertaining thereto. He then suggested that all approved and pending drug applications should be audited and shown to provide scientifically sound proof that they meet the strictures of CGMP regulations because his experience is that this is often not the case.

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with the outside world, we're doing them, but we certainly aren't doing them at a high level. So, I think our report card is mixed but for our core, we 're performing very well. We face numerous challenges as the world changes and as our job is somewhat redefined and we invite your suggestions and comments, and that is really one of the purposes of this meeting. So, I thank you for your attention.

LINDA BROPHY: Thank you, Janet. She certainly has given us a context to have a conversation. The next section of our discussion this afternoon, we'll hear from two of our stakeholders. We have two stakeholder presentations. The first is Dr. King, who is a consultant from Paul G. King Consulting, and he has come to speak to us for about ten minutes.

PAUL G. KING: Well, I want to thank everyone for letting me have the

chance to say a few words. I guess I'm a contrarian in many respects.

Let me just start off by saying I'm not speaking for myself, I'm not speaking for industry and I'm not speaking for the agency. I'm speaking for the people who watch their children, parents and friends suffer from the side effects of the agency's failure to protect the public from those in the pharmaceutical industry, whose greed outweighs their concerns for the public health. That's who I'm speaking to.

As a consultant, time and time again, I have witnessed FDA-regulated companies, large and small, deliberately not comply with a law or regulation simply so they could make more money. They have done this because their management was, and is, confident that they will get away with their noncompliance — or, if caught, profit more than their overall cost. Though my heart goes out to the FDA in many

respects, its decision not to inspect every drug establishment as often as required by law is not only wrong, it's illegal.

Beset by priorities, loss of many knowledgeable personnel under REGO, and underfunded, the agency has attempted to balance conflicting priorities instead of holding fast and protecting public health by strictly enforcing all of the current CGMP regulations for drugs.

Emboldened by an FDA that holds itself above the law and overlooks the industry's deliberate noncompliance with certain regulations, many firms, under the same cost and manpower pressures imposed on the FDA, have likewise reduced their compliance program.

Given their agency's lead, why should anyone be surprised that many of the firms it regulates currently not only ignore applicable laws and

regulations, but are also pushing for even more concessions?

For example, emboldened by their success in getting the FDA to ignore enforcement of key parts of the drug CGMP's, the industry is now pressuring the agency to allow skip-lot testing, although they know full well that the CGMP regulations explicitly require the testing of each batch.

Instead of wasting time considering such initiatives, the agency again needs to begin rigorously enforcing compliance with all of the drug CGMP regulations.

This bring the public face-to-face with a major flaw in the science-based questions posed to the stakeholders.

As Dr. Henney has recognized, without knowledgeable personnel who understand the true minimum requirements of both the sciences and regulations involved, the agency will continue to

accept the pseudo science that some firms submit as "valid science", and the non-compliant or violative practices that some firms are using.

Yet the reality today is that agency personnel often lack the education, training and/or experience in the regulations they are supposed to be administering or the fundamental sciences that they're supposed to understand, or both, required for them to properly discharge their duties.

Beyond hiring people that have the expertise it lacks and simply "providing training", what should the agency's course of action be today to address these recognized deficiencies?

First, the agency needs to initially and continually establish the fundamental metric-based competency of its management, review, inspection and testing personnel in the applicable requirements of the statutes and regulations as well as the fundamentals

of all aspects of inspection science and statistics.

To do this, the agency needs to provide continual training and metric-based assessments of all such personnel to assure that said personnel, "A", understand the requirements of all applicable regulations, "B", properly assess the science submitted or applied and, "C" determine that the science submitted or applied is valid science that truly meets the minimum requirements of the current good manufacturing practices regulations.

Second, before attempting to expand its use of science, the agency needs to ensure that all firms incorporate fundamentally sound science in all areas of their submission.

Minimally, all existing and pending drug establishments submissions need to be audited and shown to provide scientific proof that, "A", their in-process and batch-release

specifications are such that they assure, with a high level of confidence, that every article in each releasable batch will, if tested, comply with the USP'S lifetime standards, but the law requires that; "('B')" All critical control points in each process step of each batch of every product need to be identified and properly controlled using valid inspection plans, — most of the inspection plans that I see are just nonsense; "C", all samples tested are of appropriate size and representative of the batch from which they were taken; and "D", the number of representative samples tested is sufficient to satisfy the statistical minimums required under 21 CFR 211.165(d) for validly predicting the lifetime quality of each batch — not just the present values for the samples tested.

Third, until the agency can provide the requisite in-depth ongoing metric-based training of and establish

the competency of each such employee, the agency needs to seek out, learn from, and rely upon written advice and instruction but only from those outside the agency who can prove that their advice has applied sound science in determining the true minimum requirements for compliance with a given drug CGMP as based supposedly on science. It's amazing. I understand, as a scientist, why the public in general doesn't trust scientists. It's amazing how cheaply some of us sell science to make a buck.

The preceding is but a short overview of some issues that this agency must truly address if it wishes to expand the agency's capability to incorporate state-of-the-art science or any science into its risk-based decision-making and to facilitate the exchange and integration of scientific information to better enable the FDA to meet its public health responsibilities

throughout a product's life cycle if it truly wants to protect the public.

In closing, let me thank the agency for allowing me to speak to these issues today. For those interested, my formal response to all five stakeholder questions is available on-line in the docket, and also, there are 25 copies of what I presented today, more or less, for anyone who would like to have a written copy. Thank you.