

# CHOLESTECH

September 14, 2000

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Dockets Management Branch (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20850

Dear Sir or Madam:

I am submitting written comments related to topics presented or discussed at the Public Workshop on CLIA waiver Criteria held on August 14 and 15 in Gaithersburg, MD.

Cholestech Corporation is an in vitro diagnostics company located in Hayward, CA with annual revenues of approximately 28 million dollars that manufactures and markets a portable desktop analyzer and reagent cassettes for the point of care market. The Cholestech LDX® was the first system to be granted waived status by the CDC in early 1996. We currently have 4 tests that have been granted waived status: Total Cholesterol, High Density Lipoprotein Cholesterol, Triglycerides and Glucose. We have a new test, Alanine Aminotransferase that is currently being reviewed for waived status. Two additional tests, BUN and Creatinine, received 510(k) clearance but were not granted waived status.

Based on the description of Cholestech in the preceding paragraph, it is clear that we have had extensive experience with the waived process and have significant interest in the regulatory processes that affect waived status. Our experience has been quite varied: on the one hand, Cholestech worked with the CDC to help develop the criteria by which tests would be judged for waived status; on the other hand we have seen the process require inordinately long review times that ultimately resulted in denial of waived status. The issues that we have experienced can be classified into several different categories; test standards, pre-submission communications, undefined review durations and lack of a formal appeal process for tests that have been denied waived status.

## **Test Standards:**

**Issue:** We are concerned that the criteria for automatically waiving over the counter (OTC) cleared tests are less stringent than those used to assess the appropriateness of waived status for those tests meant for professional use. While the use of these waived OTC products may appear different, in fact some OTC CLIA waived tests are inappropriately used in professional use situations. This places the professional use test at a significant disadvantage in that these tests must meet a higher standard of performance as well as be subjected to a lengthy review cycle.

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**Solution:** Clarify the wording for Indications for Use on the OTC cleared tests to preclude the off-label use of OTC tests in professional use settings.

**Pre-Submission Communications:**

**Issue:** In our experience, the CDC did not encourage or support any discussion between the manufacturer and the CDC during the pre-submission process. While the CDC has published “guidance” documents describing the studies required for either a quantitative or qualitative test to be considered for waiver status, they failed to define how the acceptance criteria that would be applied during the review process. Two examples will illustrate the problem: in the guidance document for quantitative tests, the CDC describes the use of the Tonk’s test to estimate total error. They failed to define the acceptance criteria for the Tonk’s test. The denial of waived status for the Cholestech BUN and Creatinine tests were attributed to a failure to meet the total error defined by the Tonk’s test. When the petitions for these tests were submitted, it was believed by the Cholestech personnel at that time, that if the individual sites met the Tonk’s limit for each of the three samples that the test would meet the acceptance criteria based on the Tonk’s test. Over a year after the petitions were submitted and only after specific questions were posed during a teleconference was it revealed that the CDC did not assess the total error site by site but rather grouped all results from the three sites into a single group. The Tonk’s test was then applied. While this may seem like a minor difference in analysis, in the case of BUN and Creatinine the difference was significant. The two tests met the Tonk’s test when assessed site by site, but failed when they were grouped. This was a significant issue for the company; if the personnel had known how the Tonk’s test was, in actuality used by the CDC, the same assessment would have been made when the data was generated by the sites and given the failure of the Tonk’s test, we would have made changes to the product to assure that the tests would meet that requirement.

In the case of the waiver petition for ALT, six months after submission of the waiver petition, the CDC first brought up the requirement for a reference method to assess accuracy. They used a vague reference to the proposed rule as their justification. When asked what type of reference method would meet their requirements, they refused to say. Their only response was “make a proposal and we will review it”. Ultimately, we had conversations with the FDA that agreed with our proposal for a reference method. Studies were then performed and the results submitted after our request for the acceptance criteria for the study was received from the FDA.

**Solution:** The FDA should clearly define the studies needed to meet the requirements for waived status along with the acceptance criteria for each study. This approach would satisfy the majority of manufacturers. Exceptions to these requirements, perhaps due to technological idiosyncrasies, could then be handled on an individual basis by the FDA and the manufacturer.

Recently, there have been quotations attributed to FDA officials who apparently defined the criteria for waived status as requiring a product be “damned near perfect”. Rather than being a clarification of an issue it appears to further institutionalize “regulation by

personality”. A product that has already been found by the FDA to be “safe and effective” should not then be required to be “damned near perfect”. More complex tests with greater import to the diagnostic process are not held to a standard beyond “safe and effective”. For example, a parathyroid hormone (PTH) test is one of a few tests where a physician will make a medical decision to schedule surgery based on that test result (along with a serum Calcium test) since the combination of the two tests in the appropriate algorithm defines primary hyperparathyroidism. Here a single result could cause a serious medical procedure to occur. Yet this test does not have to meet the criteria applied to a waived test. The PTH test only needs to be deemed “safe and effective”.

The critical issue is to move away from “regulation by personality” which is an appropriate description of the way the CDC addressed CLIA waiver petitions and install clear and predictable requirements (with acceptance criteria) that will allow manufacturer’s to only submit products for waived status that have a high likelihood of success. This makes the process clearer for the manufacturer and easier on the FDA since it is unlikely that a manufacturer will expend time and money submitting waiver petitions on products that do not meet the known acceptance criteria.

**Undefined Petition Review Duration:**

**Issue:** Unlike the FDA for 510(k)’s, the CDC does not have a metric for the duration of the review process. While this probably causes some consternation at the FDA to constantly have the duration of the review process measured, it does have significant ramifications to the manufacturer when there is no metric in place. For a manufacturer that focuses on the waived point of care market, the absence of any metric or goal for the review process means that the manufacturer cannot make any plans to launch the new product since there is no way to know when the review process will be completed.

In the case of the original submission for the LDX system, Cholestech had to wait several years before the CDC developed the criteria for waiver and then used those criteria to assess the system. Ultimately, it required intervention by Representative Pete Stark and Senator Barbara Boxer before the waiver was granted.

In the case of BUN and Creatinine, the petition for waiver was submitted in September 1997. Formal correspondence from the CDC denying waived status was received in March of 1999 – eighteen months after the petitions were submitted. I did not become involved in the BUN and Creatinine issue until fall of 1998. When I inquired by telephone about the status of the petitions I was required to submit by request for status in writing. About two months later, during an unrelated call to the CDC, I was given a verbal update and told that the CDC response would not be sent by letter – a casual telephone conversation was sufficient. Almost six months later, we finally received a letter-denying waiver. The letter did not have adequate feedback on the reasons for denial.

For ALT, it took approximately six months before there was an initial teleconference with the CDC. This teleconference call, in late January 2000, was so frustrating that the FDA was immediately called to request that they take over the review of the waiver

petition. Since then, we have had a number of teleconference calls with the FDA. The communications have improved significantly; the duration, though, is still unknown.

**Solution:** A modification of the pre-market notification process could be used to define the CLIA waiver process and timelines.

- Manufacturer submits 510(k) and CLIA waiver as a single package.
- FDA assigns a K number.
- FDA begins review of submission and waiver petition.
- Initial teleconference between FDA reviewer and Manufacturer. Approximately 45-60 days after assignment of K number.
- Additional information/experimental data requested.
- Information/experimental data submitted.
- Additional teleconference(s) if required.
- 510(k) clearance and waiver granted.

**Lack of a Formal Appeal Process:**

**Issue:** When a test is denied waived status, there is no formal appeal process by which the manufacturer can contest the decision. Some companies badgered the CDC until a resolution is reached; other companies accept the decision and either shelve the product or return it to R & D for additional work. It is not possible to know how much unneeded re-development of products denied waived status has occurred and whether it was even necessary. The availability of a formal appeal process would have reduced the re-development to those products that really had performance issues that were clearly identified and agreed to by both parties.

**Solution:** Define an appeal process (preferably with industry support) and implement.

As the FDA moves forward with the transfer of test categorization and the waiver process, we feel that it is important to have a clear understanding of the processes involved and to develop processes that satisfy regulatory requirements while, at the same time, provide the clearances in a timely and well understood way. While the experiences described above may help improve the processes currently in place, I would like to suggest an approach to the waiver process that would be helpful to both the FDA and manufacturers.

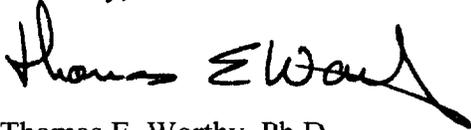
For new products that are seeking pre-market notification at the same time that they are preparing a waiver petition, expand the 510(k) submission to permit the inclusion of the data to support the waiver petition and then review the entire submission at the same time. This approach would permit both the FDA and the manufacturer to work more efficiently and in a much more timely manner. The FDA could then review all of the data at the same time and reduce their total review time significantly. The manufacturer could then plan for the 510(k) submission and CLIA waiver studies at the beginning of the project and take advantage of the simultaneous submission in increased efficiency in the product development cycle. This would especially be the case if the review process for the waiver petition was a reasonably short increment in time attached to the typical 90 day review time for a pre-market notification. A review process as suggested above

would permit predictability to the review cycle and would permit the manufacturers to plan their product development process more accurately. As indicated above the current duration of review for a waiver petition is typically over a year in length and not close to average of 90 days for a pre-market notification clearance.

Cholestech Corporation currently has a test under consideration for waived status by the FDA. The waiver petition was submitted to the CDC on September 30, 1999 and as of September 14, 2000 the petition is still outstanding. Additional data had been requested and the response was submitted on July 20, 2000. In the intervening two months, no action has been taken. Several requests have been made for resolution since the data submitted met the acceptance criteria defined by the statistician assigned to the petition. It should be a straight forward decision: Did the data submitted meet the stated acceptance criteria? If so, then the petition should be granted. We are hopeful that the petition will be acted on in the next couple of weeks and since the requested data meets the acceptance criteria, a CLIA waiver will be granted.

Cholestech Corporation is pleased that we have been provided an opportunity to provide comments in response to the recent Public Workshop on CLIA waiver held on August 14-15, 2000. We look forward to working the FDA is developing criteria for CLIA waiver that will best address the needs of the patient. Please contact me at (510) 293-8002 or by email at [tworthy@cholesteck.com](mailto:tworthy@cholesteck.com) if you have any questions or would like more information

Sincerely,

A handwritten signature in black ink, appearing to read "Thomas E. Worthy". The signature is fluid and cursive, with a long, sweeping underline that extends to the right.

Thomas E. Worthy, Ph.D.

Vice President, Development and Regulatory Affairs

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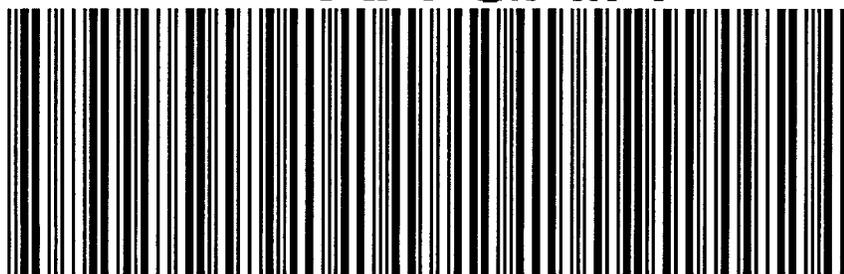
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