



Wampole Laboratories

DIVISION OF CARTER-WALLACE, INC.

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September 8, 2000

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

Re: Docket No. 00N-1394
Medical Devices; CLIA Waiver
Criteria; Public Workshop

To Whom It May Concern:

Wampole Laboratories, Inc. is herein submitting comments in response to the FDA's request for public comment regarding the CLIA Waiver Criteria, as published in the *Federal Register* of July 21, 2000 (Volume 65, Number 141). These written comments and accompanying slides represent the contents of an oral presentation given Mr. Glenn Neuman, Director of Product Development, Wampole Laboratories, at the FDA Public Workshop held on August 14 and 15, 2000.

Wampole Laboratories, Inc. a division of Carter-Wallace, Inc., is a manufacturer and supplier of professional use diagnostic test kits for infectious diseases, autoimmune conditions, and pregnancy. Wampole Laboratories offers a broad range of testing options, ranging from ELISA kits to point-of-care rapid membrane tests.

Sincerely yours,

Maureen Garner
Manager, Regulatory Affairs

Attachment

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Presentation by Wampole Laboratories
Division of Clinical Laboratory Devices Public Workshop
August 14 – 15, 2000.

Slide 1 – Title

My name is Glenn Neuman, and I am the Director of Product Development at Wampole Laboratories. The title of my presentation is “The Proposed Rule: Salvaging the Good Work.” I borrowed this concept from Clara Sliva, whose past presentations appear on her CLIA website. In her talk entitled “What’s News at FDA,” slide 34, she referred to FDA’s challenge of “keeping up the good work by CDC” in reference to FDA’s assuming responsibility for waived test categorization. I’d like to expand on that theme today.

Slide 2 – Facts

The Proposed Rule was established in 1995 in response to 1,100 comments on categorization of waived tests. Many of the comments were in reference to the apparent subjectiveness used in granting waivers. The 1995 Proposed Rule was created to eliminate subjectiveness through proposed guidelines. These guidelines were endorsed by the Clinical Laboratory Improvement Act Committee, or CLIAC.

Slide 3 – Facts

CLIAC members came from diverse backgrounds and included some of the best minds in their fields. A great deal of time, effort and tax dollars have already been invested in establishing the Proposed Rule. Remember all those CLIAC meetings, and subcommittee meetings? We have established a valuable precedent through the criteria set forth in the Proposed Rule, and this precedent is supported by years of cumulative historical field performance data. If you add up the number of waived products and multiply by the number of years they have been waived, there are literally centuries of data. We can use these data to support the validity of the criteria in the Proposed Rule.

Slide 4 – Revisiting the Proposed Rule - Terminology

Recently, there has been debate over some of the terms that are used to describe the attributes of a waived test, particularly “simple,” “accurate,” and “reference material.” But there should be no debate about these terms, because they are already unambiguously defined in the CDC guidelines to manufacturers, presented in the Proposed Rule as Test System Characteristics and Field Studies, and no further interpretation of these terms is necessary or warranted.

Slide 5 – Simple

Let’s see how the Proposed Rule defines “simple.” I will be addressing only qualitative tests. There are other criteria listed for quantitative tests, but my comments will be limited exclusively to qualitative tests. I have referenced the Proposed Rule where it states that for qualitative tests, are to be limited to simple reagent impregnated devices that produce only a positive or negative result, “simple” or “easy to use” test systems must use only direct unprocessed specimens, require no specimen manipulation before or during the testing procedure, produce a well-defined distinct positive or negative endpoint, and contain fail-safe mechanisms that render no result when the test system malfunctions. How can we prove a test is simple? The Proposed Rule has established how to prove “simple” through Field Studies.

Slide 6 – Accuracy

The guidelines in the Proposed Rule also provide the means to demonstrate that the test meets the statutory criteria for “accuracy.” The guidelines use “accuracy” to define the statutory phrase “have an insignificant risk of an erroneous result”. They further state, “We believe that test systems must ... demonstrate a level of accuracy and precision that would ensure the correct test result is generated regardless of the user’s level of expertise.” It does not say the “correct result,” but specifically states “the correct test result... regardless of the user’s level of expertise.” So the test must perform the same in the hands of any group of users.

Slide 7 – Accuracy

The Proposed Rule defines “accuracy” to determine whether there is an insignificant risk of different results between professional and untrained users. An insignificant risk means an insignificant difference in accuracy when the test is performed by different groups of users. In the Proposed Rule, “simple” and “accurate” are established by field studies, using “reference materials.” Nowhere does the Proposed Rule mandate establishing “accuracy” against a gold standard or other reference method. In fact, if you download the Proposed Rule and search for the text phrase “reference method” you will find that it does not appear at all, nor does the term “gold standard.”

Slide 8 – Reference Materials

What does appear in the Proposed Rule is the phrase “reference material.” There are two usages of “reference material” in the Proposed Rule. One usage refers to printed material, such as home use protocols and NCCLS guidelines. The other usage refers to experimental reference material, which is aliquoted and used in method accuracy studies. Method accuracy studies include field studies, which demonstrate that there is no statistically significant difference between observed values and expected values at the cutoff point when the test values are compared to the known value of a “reference material,” or to the presence or absence of a particular biologic component, and it states once again here, “when comparing results between laboratory professionals and study participants...”

The cutoff point is the best place to compare the accuracy of a qualitative test between two groups of users, because it is where differences in reading the test are most likely to be observed. Since there are any number of analyte concentrations that will give a positive test result, these studies are best conducted at the cutoff, where a qualitative test will give a positive result less than 100% of the time. Wampole uses the NCCLS guidelines for positive “cutoff” as defined for an hCG test, which is the analyte concentration that will give a positive result 95% of the time. Testing slightly below the positive cutoff, where a positive result is expected between 80 and 90% of the time, is an even better level of reference material to use in field studies, as 95% is too close to 100%. One may not be able to distinguish differences in accuracy between groups of users when the sample gives a positive result 95 to 100% of the time.

Slide 9 – Summarizing the Terminology

So, in summary, we find that the Proposed Rules specifies how “simple” and “accurate” are verified in field studies using a “reference material” with a known value, which confirm that study participants, at nonlaboratory sites, who have no previous laboratory experience or

training, are able to read the test endpoint with the same precision as laboratory professionals, and will perform essentially the same as laboratory professionals when testing samples at, above and just below the cutoff.

Slide 10 – Conclusions from the Proposed Rule

In conclusion, in the Proposed Rule, all references to “simple,” “accuracy” and “reference material” are intended to establish the comparative performance of the test system in the hands of untrained users versus laboratory professionals. This appropriate application of the Proposed Rule has led to the waiver of many tests by both CDC and FDA.

Slide 11 – Industry Concerns

Industry is concerned with the agency’s interpretation of the statutory criteria that are so clearly defined in the Proposed Rule, because while some tests meeting these criteria as defined have been granted waived status, other tests that meet the same criteria have not been granted waiver (yet). Since the only difference between these tests is the analyte, I wonder if we are suffering from “analyte anxiety.”

Slide 12 – PreVue Lyme Waiver Submission, background

Let’s look at the pending waiver of our PreVue Lyme test as an example. As the first Lyme test 510(k) cleared for POL use, PreVue Lyme was featured in an FDA Talk Paper on 2/16/99, stating that, “The test provides results ... at the point of care, compared to the standard laboratory tests which have to be performed in a lab, delaying test results. This means doctors will be able to make a probable diagnosis quicker...” The paper also referred to the accuracy of the test that was demonstrated in the 510(k) submission, stating, “The new test... uses antigenic proteins developed by recombinant DNA techniques rather than the whole cell *B. burgdorferi* preparations used in current laboratory tests. Antigenic proteins developed by recombinant DNA techniques allow for more accuracy.” I was encouraged by the FDA’s view of the test. To allow the test to be used in a point of care setting, we knew that a waiver was needed, and we immediately began the process to obtain waived status for PreVue Lyme.

Slide 13 – PreVue Lyme background

Wampole submitted a “transition” waiver petition to the CDC on December 23, 1999. By “transition” I mean that we knew this submission would be among those to be transferred from CDC to FDA, since FDA was going to take over waived classification in January. We submitted a protocol to CDC about one week after the Talk Paper appeared, and we designed the studies to mirror exactly the Wampole Mono-plus Whole Blood Test, which was previously waived by CDC. CDC recommended one minor change to the protocol, which I will describe in a moment. Since Mono-plus was the first test for heterophile antibodies given waived status, I was encouraged that a parallel study for PreVue Lyme, which also represents a new analyte for waived status, should have the same outcome.

Slide 14 – CDC Precedent

Let’s compare the results of the Wampole PreVue Lyme test with the Wampole Mono-plus Whole Blood Test, a precedent test waived by CDC. As is outlined for field studies in the Proposed Rule, we ran studies at three sites, with a minimum of 20 participants per site. When we compare the results for accuracy between PreVue Lyme and the CDC precedent, we see

identical overall accuracy between the two tests. Note that CDC recommended each participant run three samples in PreVue Lyme, while only two samples were required for Mono-plus, so we have more data points for the PreVue Lyme studies. To make samples below the positive cutoff, we diluted the reference material to target an analyte level that will give a positive result about 85% of the time, as determined by laboratory professionals. We then compared the laboratory precision with field precision, using untrained participants testing double-blinded aliquots of the same sample. We found that the comparative accuracy of lab professional and field participants was 100% for Mono-plus, and was the same for PreVue Lyme. Furthermore, the test procedure is the same for both tests. PreVue Lyme and Mono-plus equally met “simple,” “accurate,” and all other proposed regulatory criteria.

Slide 15 – FDA Precedent

Now I would like to compare PreVue Lyme against a test recently waived by FDA, a Strep A test. Again, the results for both tests were equivalent. Since the Strep A test is not in Wampole labeling, I cannot share the specific data with you, but since I prepared both submissions, I know the results were the same. So, using an FDA precedent, we find that PreVue Lyme and the Strep A test equally met “accurate” and other proposed regulatory criteria. However, there were notable differences in “simplicity” between the two tests.

Slide 16 – Simple Criteria, PreVue Lyme versus FDA Precedent

Both tests use unprocessed specimens. However, the whole blood sample for the PreVue Lyme test is added directly to the test, while the swab for the Strep A test must be extracted. The extraction process takes six steps, while the PreVue Lyme test can be read after only two steps; those being: adding sample, adding buffer, and then reading the test result. The waived Strep A test requires the separate addition of two reagents, mixing, a timed waiting step, squeezing out and discarding the swab, and adding the test strip to the extracted sample. Note that for Strep A tests, if one extracts the sample and adds the sample to the test, that is considered an outboard preparation of sample and is not waiveable. However, if one extracts the sample and adds the test to the sample, that is a waiveable configuration. So, adding the test to the sample is OK, but adding the sample to the test is not. It is evident, however, that the PreVue Lyme test is simpler to perform than is the Strep A test waived by FDA. The accuracy of PreVue is also a little better than the Strep A test, but I did not disclose those data.

Slide 17 – New Suggested Requirements – Supplemental Testing

During discussions with Wampole, CDC and FDA personnel have suggested new requirements for waiver, that in our view are not supported in the Proposed Rule, namely: since positive test results require supplemental testing, waiver cannot be granted. However, a precedent already exists that defeats this argument. Using an analyte waived by both CDC and FDA, let’s compare the recommendation for second-tier testing between a Strep A test and PreVue Lyme. The package inserts for both tests recommend that second-tier testing be performed. For the Strep test, negatives should be cultures, and for the PreVue Lyme test, positives should be immunoblotted. So waived tests that require second-tier testing already exist.

Slide 18 – Supplemental Testing

Additionally, second-tier testing is required regardless of whether the initial test result is generated by an untrained user or a laboratory professional. Therefore, this is not a factor that

should affect waiver status. The waiver simply allows that decision to be made at the point of care.

Slide 19 – New Requirements – Gold Standard

A second argument we encountered was the issue of testing versus a gold standard, without which a waiver could not be granted. In the case of Lyme disease, we suggested using sera from patients with biopsy-confirmed infection. FDA accepted biopsy as a gold standard, and requested the data, even though the Proposed Rule does not mandate establishing Accuracy against a gold standard or other Reference Method. Nevertheless, we submitted data that compared the sensitivity of PreVue Lyme to other first-tier tests using biopsy-confirmed samples as a Reference Material. The sensitivity of PreVue Lyme was equal or better than other first-tier tests. A statistically significant improvement could not be demonstrated with the number of samples we ran, but since we were claiming a substantial equivalence to a predicate device in the 510(k), we were not interested in establishing a claim for improved sensitivity.

Slide 20 – Gold standard

However, we should keep in mind that the *Wampole PreVue B. burgdorferi* Antibody Detection Assay, and that is the official name for the test, is intended to presumptively detect antibodies to *B. burgdorferi*, not to diagnose Lyme disease. The most troubling aspect of using biopsy confirmed samples as a reference method is that the accuracy of detecting Lyme Disease is not consistent with the Intended Use of the PreVue Lyme test. Therefore, one cannot deny waiver because a test did not perform in a manner for which it was not intended.

Slide 21 – Newest Requirements

The addition of new requirements was not over, and even newer arguments surfaced more recently. The lack of an administrative procedure for handling waiver requests has plagued the system from the beginning. Therefore, we encourage FDA to “provide guidance on how categorizations will be administratively processed before manufacturers begin to send their requests to CDRH” as was published in the Federal Register last December. We do applaud FDA for being accessible and verbally responsive throughout this process, but we believe the newest requirements suggested by FDA are not supported by the proposed regulatory criteria.

Slide 22 – Newest Requirements – Capillary

These newest requirements include: the foolproof capillary is not simple. The same capillary was selected and approved by CDC for use in the Mono-plus Whole Blood test, to satisfy concerns that the sample may have bubbles or may drip out before being applied to the test. The capillary we use does not allow for bubbles or sample loss to occur, and it cannot be over-filled. The plunger ensures delivery of the entire sample onto the test. The simplicity of this capillary can be demonstrated by historical data from Mono-plus. This capillary was also validated in field studies for both Mono-plus and PreVue Lyme, as untrained users were required to run the tests with this capillary. Finally, there are several capillary devices from other waived products that can be substituted.

Slide 23 – Newest Requirements – Test Time

Another new argument was that a 20 minute test is not simple. This suggests that whole grain brown rice is not suitable for home use, because it takes 35 minutes to prepare, but Uncle Ben’s

minute rice is OK, because it takes only five minutes. Or a potato can only be cooked in a microwave, which takes eight minutes, but not in a conventional oven, which takes 45 minutes. The Strep A test, which has two separate timed steps, is considered simpler to perform than a test with single 20-minute timed step. We do not believe that test time is a factor for waiver, and there is no limit on test time in the proposed regulatory criteria.

Slide 24 – Newest Requirements – Supplemental Testing

Another new argument against waiver is that the CDC is concerned that waived labs will not wait for supplemental testing results. When you are issued a driver's license, imagine the person refusing to give it to you because they are concerned that you might violate a traffic law. Enforcement of the statute is provided for in the Proposed Rule, through labeling, and through HCFA. Actually, if you have enough points on your license they won't issue it to you, and perhaps a similar system could be useful for certificate of waiver labs.

Slide 25 – Newest Requirements – Non-endemic Performance

Another new concern is one that the CDC has over the performance of the test in a non-endemic setting. By 510(k) clearance, every non-endemic patient can already be tested with PreVue Lyme in moderately complex labs. And we have shown that untrained users will get the same result as those labs. In fact, the high specificity demonstrated for PreVue Lyme should help reduce the incidence of misdiagnosis. The increased specificity for PreVue Lyme over other first-tier tests was shown to be statistically significant when potentially cross-reactive samples were tested.

Slide 26 – Statutory Intent

According to the Regulatory Impact Statement in the Proposed Rule, the waived categorization was intended to, and I quote: "expand the universe of waived tests, to the benefit of patients, laboratories, manufacturers, and producers, drive the technology toward simpler tests that would then be widely available (because of waived status), benefit laboratories by reducing the regulatory burden, provide an expanded test menu without incurring the higher fees associated with a regular CLIA certificate and increase access to health care, particularly in underserved and rural areas." Waiver of new analytes was clearly intended.

Slide 27 – Statutory Intent

PreVue Lyme achieves the statutory intent for waived classification, by introducing new accurate technology that will broaden the menu of waived analytes. PreVue Lyme offers improved accuracy through recombinant antigens. In an independent study performed by CDC in Fort Collins, the sensitivity of PreVue Lyme was equal to or better than other first-tier tests, and superior to two-tier system. Additionally, the specificity was significantly superior to other first-tier tests when potentially cross-reactive samples were tested. The Wampole PreVue Lyme test satisfies all the proposed regulatory criteria for waiver, as demonstrated both by CDC and by FDA precedents.

Slide 28 – Conclusions

We conclude that waived classification was intended to put a result in the hands of the physician at the point of care. Since reducing time in Lyme Disease diagnosis is critical to outcome, a waived test for Lyme Disease is desperately needed. In a waived laboratory, PreVue Lyme will

deliver results that are at least as accurate as can be generated in a reference laboratory. And waived classification for PreVue Lyme, which outperformed all other available test methods, will benefit the public health.

Slide 29 – Final Remarks

In closing, I would like to add that using the Proposed Rule and the guidelines CDC sent to manufacturers, industry has invested substantial scientific resources into the development of new simple and accurate technologies designed to achieve the Congressional vision of a Waived Test Categorization. Industry is prepared to make these technological advances available to the public. We do not believe that undoing the “good work” and starting from scratch will benefit the public health.

Slide 30 – Thank you

The Proposed Rule Salvaging the "Good Work**"

Presented by,
Glenn Neuman
Director of Product Development
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Cranbury, NJ

*Reference: "What's News at the FDA 2000" presented by Clara
Sliva, DCLD, Slide 34."Challenges: Keep up the good work by CDC."

The Proposed Rule: Salvaging the Good Work

FACTS

- The 1995 Proposed Rule (60 FR 47534) responded to 1,100 comments on categorization of waived tests.
- Specific guidelines proposed to eliminate subjectiveness.
- The guidelines were endorsed by Clinical Laboratory Improvement Act Committee (CLIAC).

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The Proposed Rule: Salvaging the Good Work

FACTS, cont'd

- Lots of talented effort, time and tax dollars have gone into the Proposed Rule and its guidelines.
- A valuable precedent has been established.
- The precedent is supported by many years of cumulative historical performance data for waived products.

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Revisiting the Proposed Rule

- There should be no debate about the terminology in the Proposed Rule, specifically:

- 1) *Simple*
- 2) *Accuracy*
- 3) *Reference Material.*

- These terms are unambiguously defined in the CDC guidelines to manufacturers, presented in the Proposed Rule as Test System Characteristics and Field Studies.
- No further interpretation of these terms is necessary or warranted.

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Revisiting the Proposed Rule

Example 1: Simple

- *Simple* is defined in 60 FR 47534, at 47541, §493.7 Waived tests (b) Criteria (2), and includes:
"For qualitative tests [limited to simple reagent impregnated devices that produce only a positive or negative result]... *simple* (easy to use) ... (i) test systems..."
 - ✓ Use only direct unprocessed specimens.
 - ✓ Require no specimen manipulation before or during the testing procedure.
 - ✓ Require a well-defined distinct positive or negative endpoint.
 - ✓ Contain fail-safe mechanisms that render no result when the test system malfunctions.
- *Simple* is ensured through (iii) *Field Studies*.

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Revisiting the Proposed Rule

Example 2: Accuracy

- "... guidelines ... verify the *accuracy* and ... demonstrate that the test *meets the statutory criteria for waiver*."**
- The guidelines use *accuracy*,
"... to define the statutory phrase 'have an insignificant risk of an erroneous result'. We believe that test systems must ... demonstrate a level of *accuracy* and precision that would ensure the *correct test result* is generated *regardless of the user's level of expertise*.'"**

* 60 FR 47534, at 47535, I. Background
** 60 FR 47534, at 47536, III. Proposed Revisions, Clarified criteria.

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Revisiting the Proposed Rule

Example 2: *Accuracy, cont'd*

- *Accuracy* means insignificant risk of different results between professional and untrained users.

Insignificant Risk = Insignificant Difference in Accuracy.

- In the Proposed Rule, *Simple* and *Accurate* are established by field studies, using *Reference Materials*.
- Nowhere does the Proposed Rule mandate establishing *Accuracy* against a gold standard or other *Reference Method*.

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Revisiting the Proposed Rule

Example 3: *Reference Materials*

Two usages appear in the Proposed Rule:

1. *Printed* -- Home Use protocols and NCCLS guidelines.
2. *Experimental* -- Testing material used in method accuracy studies, which demonstrate

"...that there is no statistically significant difference between observed values and expected values at the cutoff point when ... the test values are compared to ... the value of a *reference material* or presence or absence of a particular biologic component ... comparing results between laboratory professionals and study participants ... at the cutoff..."

*60 FR 47534, at 47541 §493.7 Waived tests (b) Criteria (2) Qualitative tests (v) Method accuracy studies

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Summarizing the Terminology

Simple and *Accurate* are verified in *field studies* using a *Reference Material* with known value, which confirm that study participants, at nonlaboratory sites, who have no previous laboratory experience or training,

- ✓ are able to read the test endpoint with the same precision as laboratory professionals.
- ✓ perform essentially the same as laboratory professionals when testing samples at, above and below the cutoff.

60 FR 47534, at 47541 §493.7 Waived tests (b) Criteria (2) Qualitative tests (iv) Data from field studies

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Conclusions from the Proposed Rule

- All references to *Simple*, *Accurate* and *Reference Material* are intended to establish the comparative performance of the test system in the hands of *untrained users versus laboratory professionals*.
- This appropriate application of the Proposed Rule has led to the waiver of many tests by both CDC and FDA.

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Industry Concerns: Agency Interpretation of the Statutory Criteria

- Other tests that meet the same statutory criteria have not been granted waiver (yet).
- Are we suffering from...

ANALYTE ANXIETY?

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Pending Waiver Submission: Wampole PreVue™ "Lyme"

Background

As the first Lyme test 510(k)-cleared for POL use, PreVue Lyme was featured in an FDA Talk Paper on 2/16/99:

"The test provides results ... at the point of care, compared to the standard laboratory tests which have to be performed in a lab, delaying test results. This means doctors will be able to make a probable diagnosis quicker..."

"The new test ... uses antigenic proteins developed by recombinant DNA techniques rather than the whole cell *B. burgdorferi* preparations used in current laboratory tests. Antigenic proteins developed by recombinant DNA techniques allow for more accuracy."

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Pending Waiver Submission: Wampole PreVue Lyme

Background cont'd

A "transition" waiver petition was submitted to CDC on December 23, 1999, following 10 months of communications with CDC.

The waiver studies mirrored, with minor modifications recommended by CDC, the Wampole Mono-plus Whole Blood Test, which was previously waived by CDC.

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Waiver Under The Proposed Rule Using a CDC Precedent:

Field Studies	Mono-plus	PreVue Lyme
Sites, Participants	3 sites, 82 participants	3 sites, 69 participants
Samples Run	2 samples each	*3 samples each
Overall Accuracy	154/163 = 94%	195/207 = 94%
		*Recommended by CDC
<u>Below Positive Cutoff</u>		
Lab Accuracy	17/19 = 89%	17/20 = 85%
Field Accuracy	62/70 = 89%	78/90 = 87%
Comparative Accuracy	89%/89% = 100%	87%/85% = 102%

✓ PreVue Lyme and Mono-plus equally met *simple, accurate*, and all other proposed regulatory criteria.

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Waiver Under The Proposed Rule Using an FDA Precedent:

Strep A PreVue Lyme

Data were equivalent in both submissions.

✓ PreVue Lyme and the Strep A test equally met *accurate* and other proposed regulatory criteria.

However, there are notable differences in *simplicity*...

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"Simple" Waiver Criteria PreVue Lyme versus FDA Precedent

"Simple" Criteria	Strep A	PreVue Lyme
Unprocessed specimens?	Yes, throat swab	Yes, whole blood
Specimen manipulation?	Yes, extract	No, add sample
Multiple Steps?	Yes, six	Yes, two:
	1) add Reagent A	1) add sample,
	2) add Reagent B	2) add Diluent
	3) mix	Read in 20' - 60'
	4) wait 2' - 5'	
	5) Squeeze swab and discard	
	6) add test strip	
	Read in 5' - 10'	

✓ PreVue Lyme is *simpler* to perform than the Strep A test waived by FDA.

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New Suggested Requirements Raised During the Lyme Waiver Review:

During discussion, CDC and FDA personnel have suggested new requirements for waiver, that in our view are not supported in the Proposed Rule, namely:

1) *Since positive test results require supplemental testing, waiver cannot be granted.*

A precedent exists that defeats this argument:

Criteria	Strep A	PreVue Lyme
2nd tier testing?	yes, culture negatives	yes, blot positives

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New Suggested Requirements Raised During the Lyme Waiver Review:

1) *Since positive test results require supplemental testing, waiver cannot be granted, cont'd.*

2nd tier testing is required regardless of whether the initial test result is generated by an untrained user or a laboratory professional. Therefore, it is not a factor that should affect waiver status.

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**New Suggested Requirements
Raised During the Lyme Waiver Review:**

2) *In the absence of an appropriate gold standard, waiver cannot be granted.*

FDA requested accuracy data compared with biopsy-confirmed Lyme Disease.

- The Proposed Rule does not mandate establishing *Accuracy* against a gold standard or other *Reference Method*.
- Data with biopsy-confirmed samples as a *Reference Material* were submitted.
- The *sensitivity* of PreVue Lyme was equal or better than other 1st-tier tests.

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**New Suggested Requirements
Raised During the Lyme Waiver Review:**

2) *In the absence of an appropriate gold standard, waiver cannot be granted, cont'd.*

- The *Wampole PreVue B. burgdorferi* Antibody Detection Assay is intended to (presumptively) detect antibodies to *B. burgdorferi*, not to diagnose Lyme disease.
- Accuracy of detecting Lyme Disease is not consistent with the Intended Use of the PreVue Lyme test, and cannot be used to deny waiver.

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**Newest Suggested Requirements
Raised During the Lyme Waiver Review:**

- We encourage FDA to "provide guidance on how categorizations will be administratively processed before manufacturers begin to send their requests to CDRH." (64 FR 73561, December 30, 1999)
- In the meanwhile, we applaud FDA for being accessible and verbally responsive throughout this process.
- However, we believe the newest requirements suggested by FDA are not supported by the proposed regulatory criteria.

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**Newest Suggested Requirements
Raised During the Lyme Waiver Review:**

The newest requirements include:

1) *The fool-proof capillary is not simple.*

- Simplicity of the capillary is validated by historical data from Mono-plus, and by field studies for Mono-plus and PreVue Lyme.
- Capillary devices from other waived products can be substituted.

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**Newest Suggested Requirements
Raised During the Lyme Waiver Review:**

2) *A 20-minute test is not simple.*

- The proposed regulatory criteria do not limit test time.

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**Newest Suggested Requirements
Raised During the Lyme Waiver Review:**

3) *CDC is concerned that waived labs will not wait for supplemental testing results.*

- Enforcement of the statute is provided for in the Proposed Rule, through labeling, and through HCFA.

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Newest Suggested Requirements Raised During the Lyme Waiver Review:

- 4) *CDC is concerned with the performance of the test in a non-endemic setting.*
- By 510(k) clearance, every non-endemic patient can already be tested with PreVue Lyme.
 - The high specificity demonstrated for PreVue Lyme will help reduce the incidence of misdiagnosis.

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Statutory Intent of CLIA Waiver

According to 60 FR 47534, at 47539, Regulatory Impact Statement, the waived categorization was intended to:

- ✓ "... expand the universe of waived tests, to the benefit of patients, laboratories, manufacturers, and producers",
- ✓ "... drive the technology toward simpler tests that would then be widely available (because of waived status)",
- ✓ "... benefit laboratories by reducing the regulatory burden",
- ✓ "... provide an expanded test menu without incurring the higher fees associated with a regular CLIA certificate" and
- ✓ "... increas[e] access to health care, particularly in underserved and rural areas."

Waiver of new analytes was clearly intended.

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Statutory Intent of CLIA Waiver

- PreVue Lyme achieves the statutory intent for waived classification, by introducing new accurate technology that will broaden the menu of waived analytes.
 - PreVue Lyme offers improved accuracy through recombinant antigens.
- As determined in an independent CDC study,
 - Sensitivity was equal or better than other 1st tier tests, and superior to two-tier system.
 - Specificity was significantly superior to other first tier tests.
- PreVue Lyme satisfies all proposed regulatory criteria for waiver, as demonstrated by CDC and FDA precedents.

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Conclusions

- Waived classification was intended to put a result in the hands of the physician at the point of care.
- Since reducing time in Lyme Disease diagnosis is critical to outcome,
- A waived test for Lyme Disease is desperately needed.
- In a waived laboratory, PreVue Lyme will deliver results that are at least as accurate as can be generated in a reference laboratory.
- Waived classification for PreVue Lyme, which outperformed all other available test methods, will benefit the public health.

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Final Remarks

- Using the Proposed Rule and the guidelines CDC sent to manufacturers, industry has invested substantial scientific resources into the development of new simple and accurate technologies designed to achieve the Congressional vision of a Waived Test Categorization.
- Industry is prepared to make these technological advances available to the public.
- We do not believe that undoing the "good work" and starting from scratch will benefit the public health.

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Thank You.

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Align top

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