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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Medicare & Medicaid Services

42 CFR Part 493

[CMS-3355-P]

RIN 0938-AT55

Clinical Laboratory Improvement Amendments of 1988 (CLIA) Proficiency Testing Regulations Related to Analytes and Acceptable Performance

AGENCY: Centers for Medicare & Medicaid Services (CMS), HHS; Centers for Disease Control and Prevention (CDC), HHS.

ACTION: Proposed rule.

SUMMARY: This proposed rule would update proficiency testing (PT) regulations under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) to address current analytes (that is, substances or constituents for which the laboratory conducts testing) and newer technologies. This proposed rule would also make additional technical changes to PT referral regulations to more closely align them with the CLIA statute.

DATES: To be assured consideration, comments must be received at one of the addresses provided below, no later than 5 p.m. on **[**insert date 60 days after date of publication in the **Federal Register]**.

ADDRESSES: In commenting, please refer to file code CMS-3355-P. Because of staff and resource limitations, we cannot accept comments by facsimile (FAX) transmission.

Comments, including mass comment submissions, must be submitted in one of the following three ways (please choose only one of the ways listed):

1. Electronically. You may submit electronic comments on this regulation to http://www.regulations.gov. Follow the "Submit a comment" instructions.

2. By regular mail. You may mail written comments to the following address ONLY:

Centers for Medicare & Medicaid Services,

Department of Health and Human Services,

Attention: CMS-3355-P,

P.O. Box 8016,

Baltimore, MD 21244-8016.

Please allow sufficient time for mailed comments to be received before the close of the comment period.

3. By express or overnight mail. You may send written comments to the following address ONLY:

Centers for Medicare & Medicaid Services,

Department of Health and Human Services,

Attention: CMS-3355-P,

Mail Stop C4-26-05,

7500 Security Boulevard,

Baltimore, MD 21244-1850.

For information on viewing public comments, see the beginning of the "SUPPLEMENTARY INFORMATION" section.

FOR FURTHER INFORMATION CONTACT:

Sarah Bennett, CMS, (410)786-3531; Caecilia Blondiaux, CMS, (410)786-2190; or Nancy Anderson, CDC, (404)498-2741

SUPPLEMENTARY INFORMATION:

Inspection of Public Comments: All comments received before the close of the comment period are available for viewing by the public, including any personally identifiable or confidential business information that is included in a comment. We post all comments received before the close of the comment period on the following website as soon as possible after they have been received: http://www.regulations.gov. Follow the search instructions on that Web site to view public comments.

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I. Background

On October 31, 1988, Congress enacted the Clinical Laboratory Improvement Amendments of 1988 (Pub. L. 100-578) (CLIA'88), codified at 42 U.S.C. 263a, to ensure the accuracy and reliability of testing in all laboratories, including, but not limited to, those that participate in Medicare and Medicaid, that test human specimens for purpose of providing information for the diagnosis, prevention, or treatment of any disease or impairment, or the assessment of health, of human beings. The Secretary established the initial regulations implementing CLIA on February 28, 1992 at 42 CFR part 493 (57 FR 7002). Those regulations required, among other things, for laboratories conducting moderate or high-complexity testing to enroll in an approved proficiency testing (PT) program for each specialty, subspecialty, and analyte or test for which the laboratory is certified under CLIA. PT referral was further addressed by enactment of the Taking Essential Steps for Testing Act of 2012 (Pub. L. 112-202, December 4, 2012) (TEST Act) and our implementing regulations (79 FR 25435 and 79 FR 27105). As of January 2017, there were 246,143 CLIA-certified laboratories, of which 36,777 Certificate of Compliance and Certificate of Accreditation laboratories were required to enroll in a U.S. Department of Health and Human Services (HHS)-approved PT program and comply with the PT regulations.

Testing has evolved significantly since 1992, and technology is now more accurate and precise than the methods in use at the time the PT regulations became effective for all laboratories in 1994. In addition, many tests for analytes for which PT was not initially required are now in routine clinical use. For example, tests for cardiac markers, such as troponins, and the hemoglobin A1c test commonly used to monitor glycemic control in persons with diabetes, were not routinely performed prior to 1992. Recognizing these changes, we are proposing

revisions to our existing PT regulations in this proposed rule.

As part of the process for developing our proposals to revise the PT regulations, HHS requested input from the Clinical Laboratory Improvement Advisory Committee (CLIAC) regarding appropriate revisions to the regulations. CLIAC is the official federal advisory committee charged with advising HHS regarding appropriate regulatory standards for ensuring accuracy, reliability and timeliness of laboratory testing. Questions posed to CLIAC at the September 2008 CLIAC meeting and their recommendations are documented in the meeting summary on the CLIAC website at https://ftp.cdc.gov/pub/CLIAC_meeting_presentations/pdf/CLIAC_Summary/cliac0908_summary.pdf.

In response to our request for input, CLIAC established a PT Workgroup that included laboratory experts, representatives from accreditation organizations, state surveyors, and PT program officials. The CLIAC PT Workgroup provided information and data to CLIAC for their deliberation in making recommendations to HHS regarding appropriate revisions to subparts H and I of the CLIA regulations. These recommendations addressed updating the list of required PT analytes; revising the scoring criteria for acceptable performance for current and proposed analytes; changes to specialties or subspecialties, including microbiology, that do not have required PT analytes; and clarification of the PT referral requirements. The questions posed to CLIAC at the September 2010 CLIAC meeting and their recommendations are documented in the meeting summary on the CLIAC website at http://wwwn.cdc.gov/cliac/pdf/cliac0910.pdf.

After the September 2010 CLIAC meeting, CMS and CDC met to review and consider the recommendations. Following this, the two agencies collaborated to develop a process to revise the list of required PT analytes. That is, CMS and CDC reviewed current analytes listed

in subpart I to determine which analytes should be retained in the regulations and which should be deleted. In addition, CMS and CDC examined analytes not currently listed in subpart I to determine if any additional analytes should be added to subpart I.

As discussed in section II of this proposed rule, a systematic approach was taken in order to update the required PT analytes, using various factors in selecting candidate analytes. A variety of PT-related and test volume data were subsequently collected from HHS-approved PT programs and various sources as described below, and analyzed by CMS and CDC.

As discussed in section II.B.2. of this proposed rule, CMS and CDC used those data and applied the criteria in a step-wise approach to determine the analytes included in this proposed rule. Following selection of those candidate analytes, CMS and CDC sought feedback from PT programs on the following topics: current PT program practices using "peer grouping" to determine target values; the potential to include new analytes as required PT; mechanism for grading current of analytes; possible changes to the criteria for acceptable performance; and potential changes to microbiology subspecialties, including the replacement of the types of service as outlined currently at §§493.911(a), 493.913(a), 493.915(a), 493.917(a) and 493.919(a), with the candidate analytes and the replacement of the list of specific organisms for each microbiology subspecialty at the above citations with our proposal to adopt a general list of types of microorganisms for each microbiology subspecialty.

Specifically, with CDC's expertise and assistance, we then developed an approach and rationale, as discussed in section II.B.10. of this proposed rule, for revising PT acceptance limits based upon empirical data, including clinical relevance. CMS and CDC worked to determine the acceptance limits, that is, the symmetrical tolerance (plus and minus) around the target value (as defined in §493.2), to propose for both new and existing required analytes. As a result of this

work, we ultimately decided to propose stating acceptance limits as percentages whenever possible.

We then again sought industry input. For each analyte, we requested that PT programs consider our potential new acceptance limits and provide data simulations using real PT data as a means of pilot testing our potential acceptance limits. We received simulation data from several PT programs, which facilitated the development of the acceptance limits proposed in this rule. We note that acceptance limits are intended to be used for scoring PT performance by PT programs and are not intended to be used by individual laboratories to satisfy the requirement at §493.1253(b) to establish performance specifications.

II. Provisions of the Proposed Regulations

This section provides an overview of our proposed revisions to the CLIA definitions and PT requirements in subpart A − General Provisions, §493.2 Definitions; subpart H − Participation in Proficiency Testing for Laboratories Performing Nonwaived Testing; and subpart I − Proficiency Testing Programs for Nonwaived Testing.

A. Proposed Changes to Microbiology PT

1. Categories of Testing

Subpart I of the CLIA regulations includes PT requirements for each subspecialty of microbiology, §§493.911 through 493.919, which describe "Types of services offered by laboratories" for each subspecialty. In addition, since the regulations do not specify required analytes for microbiology as they do for other specialties, they include descriptions of levels or extents (for example, identification to the genus level only, identification to the genus and species level) used to determine the type of laboratory for PT purposes. CLIAC discussed the usefulness and limitations of the types of services listed in subpart I in helping laboratories enroll

properly or in helping surveyors conduct laboratory inspections. It was noted that the types of services listed in subpart I do not allow for reporting growth or no growth, presence or absence, or presumptive identification of microorganisms on PT samples, which are common ways that physician office laboratories report patient results. Based on input from the PT Workgroup, CLIAC suggested revision of the regulations to include broad categories for the types of PT required for each microbiology subspecialty to allow flexibility for inclusion of new technologies.

After deliberation, CLIAC made the following recommendations:

- A system for categorizing types of service should be maintained in the regulations to help laboratories determine what PT they need to perform and assist surveyors in monitoring PT performance and patient testing.
- The regulations should include four categories of testing for each microbiology subspecialty, as applicable: stain(s), susceptibility and resistance testing, antigen and/or toxin detection, and microbial identification or detection.

Based on these recommendations, we conducted a review of the PT modules offered by HHS-approved PT programs and consulted with CDC microbiology subject matter experts who concurred that not all four recommended categories above are applicable to each microbiology subspecialty nor do PT programs have PT available for each category. If at some point in the future PT becomes available, we may propose to include additional categories of testing to microbiology subspecialties in future rulemaking. Based on these recommendations and our review, we are proposing to modify §§493.911 through 493.919 to remove the types of services listed for each microbiology subspecialty and to add the recommended categories of testing for

each microbiology subspecialty as described in the bullets below. We believe that the revised microbiology PT regulations would better reflect current practices in microbiology.

- Section 493.911(a): For bacteriology, we are proposing that the categories required include, as applicable: Gram stain including bacterial morphology; direct bacterial antigen detection; bacterial toxin detection; detection and identification of bacteria which includes one of the following: detection of growth or no growth in culture media or identification of bacteria to the highest level that the laboratory reports results on patient specimens; and antimicrobial susceptibility or resistance testing on select bacteria.

- Section 493.913(a): For mycobacteriology, we are proposing that the categories for which PT is required include, as applicable: acid-fast stain; detection and identification of mycobacteria which includes one of the following: detection of growth or no growth in culture media or identification of mycobacteria; and antimycobacterial susceptibility or resistance testing.

- Section 493.915(a): For mycology, we are proposing that the categories for which PT is required include, as applicable: direct fungal antigen detection; detection and identification of fungi and aerobic actinomycetes which includes one of the following - detection of growth or no growth in culture media or identification of fungi and aerobic actinomycetes; and antifungal susceptibility or resistance testing.

- Section 493.917(a): For parasitology, we are proposing that the categories for which PT is required include, as applicable: direct parasite antigen detection; and detection and identification of parasites which includes one of the following - detection of the presence or absence of parasites or identification of parasites.

- Section 493.919(a): For virology, we are proposing that the categories for which PT is required include, as applicable: viral antigen detection; detection and identification of viruses; and antiviral susceptibility or resistance testing.

In all of these subspecialties, as outlined in sections II.B.5., II.B.7., and II.B.8. of this proposed rule, we are also proposing to revise the requirements for evaluation of a laboratory's performance at §§493.911(b) through 493.919(b) to be consistent with these categories.

We are not proposing to include antigen and toxin detection in the mycobacteriology subspecialty because no PT program currently offers applicable PT modules. We are not proposing to include stains and antiparasitic susceptibility or resistance testing in the subspecialty of parasitology because no PT program offers applicable PT modules. We invite the public to comment on these proposals and specifically on the proposed categories of testing for the subspecialties listed above. If public comments indicate that applicable PT modules are available for antigen and toxin detection or for stains and antiparasitic susceptibility or resistance testing, we may finalize their inclusion in the final rule, as applicable. If at some point in the future, PT becomes available for mycobacteriology antigen and toxin detection testing, and stains and antiparasitic susceptibility or resistance testing, we may propose to include this category of testing for PT in future rulemaking.

2. Major Groups of Microorganisms

Each subspecialty of microbiology, §§493.911 through 493.919, currently includes a list of the types of microorganisms that might be included in an HHS approved PT program over time. Several PT programs have suggested to HHS that the regulations should include a more general list of types of organisms that must be included in required PT instead of a specific list. CLIAC considered whether there needs to be a more general list of organisms in the regulations

to assure a variety of challenges are offered over the course of the year. Following their deliberation, CLIAC made the following recommendation:

- Require PT for a general list of types of organisms in each subspecialty. For example, in bacteriology, the groups listed should include gram-negative bacilli, gram-positive bacilli, gram-negative cocci, and gram-positive cocci.

Generally, we have found that PT programs include only those organisms listed in the current regulations, and do not include additional organisms outside of the current regulatory list. By restructuring to a more general list of organisms, it will be clearer that PT programs are able to be flexible in selecting which samples to provide to laboratories for PT, especially as new organisms are identified as being clinically important. Therefore, we are proposing to remove the lists of specific example organisms from each microbiology subspecialty, §§493.911 through 493.919, and to add the following list of types of organisms to each.

- §493.911(a)(3): For bacteriology, we are proposing that the annual program content must include representatives of the following major groups of medically important aerobic and anaerobic bacteria if appropriate for the sample sources: gram-negative bacilli; gram-positive bacilli; gram-negative cocci; and gram-positive cocci. The more general list of types of organisms will continue to cover the six major groups of bacteria currently listed in the regulations.

- §493.913(a)(3): For mycobacteriology, we are proposing that the annual program content must include Mycobacterium tuberculosis complex and Mycobacterium other than tuberculosis (MOTT), if appropriate for the sample sources.

- §493.915(a)(3): For mycology, we are proposing that annual program content must include the following major groups of medically important fungi and aerobic actinomycetes if

appropriate for the sample sources: yeast or yeast-like organisms; molds that include dematiaceous fungi, dermatophytes, dimorphic fungi, hyaline hyphomycetes, and mucormycetes; and aerobic actinomycetes.

- §493.917(a)(3): For parasitology, we are proposing that the annual program content must include intestinal parasites and blood and tissue parasites, if appropriate for the sample sources.

- §493.919(a)(3): For virology, we are proposing that the annual program content must include respiratory viruses, herpes viruses, enterovirus, and intestinal viruses, if appropriate for the sample sources.

3. Declaration of Patient Reporting Practices

The PT requirements at §493.801(b) specify that laboratories must examine or test, as applicable, the proficiency testing samples it receives from the proficiency testing program in the same manner as it tests patient specimens. CLIAC considered this requirement as applied to microbiology and agreed that PT programs should instruct laboratories to perform all testing as they normally would on patient specimens, including reporting PT results for microorganism identification to the same level that would be reported on patient specimens. CLIAC deliberated on this issue and made the following recommendation:

- Laboratories should declare their patient reporting practices for organisms included in each PT challenge. However, PT programs should only gather this information as it is the inspecting agency's responsibility to review and take action if necessary.

We believe that laboratories should be instructed to report PT results for microbiology organism identification to the "highest" level that they report results on patient specimens to ensure that they do so to the "same" level that they report results on patient specimens. As a

result, we are proposing to amend §§493.801(b), 493.911(b), 493.913(b), 493.915(b), 493.917(b), and 493.919(b), to state that laboratories must report PT results for microbiology organism identification to the highest level that they report results on patient specimens. If finalized, this proposal should address an issue we identified during the PT program reapproval process in which we found laboratories inappropriately deciding whether to participate in a PT event based on the reporting criteria required by the PT program.

4. Gram stain PT

CLIAC considered whether required PT for Gram stains should include both stain reaction and morphology. CLIAC concluded it should and recommended:

- PT results for Gram stains should include both stain reaction and morphology.

We agree with this recommendation because knowing the bacterial morphology is essential for accurate identification of specific groups of bacteria. Therefore, we are proposing the following in §493.911:

- Section 493.911(a): The addition of required morphology for Gram stains.
- Section 493.911(b): The evaluation of a laboratory's performance would be modified to include bacterial morphology as one part of the performance criterion for scoring the Gram stain.

5. Mixed Culture Requirement

The current CLIA requirements for bacteriology §493.911(b)(1), mycobacteriology §493.913(b)(1), and mycology §493.915(b)(1) specify that at least 50 percent of the PT samples in an annual program must be mixtures of the principal organism and appropriate normal flora. The purpose of this requirement is to simulate the findings that would occur with actual patient specimens. In bacteriology, this 50 percent mixed culture requirement must be met for two

required sample types, those that require laboratories to report only organisms that the testing laboratory considers to be a principal pathogen that is clearly responsible for a described illness (excluding immuno-compromised patients) and those that require laboratories to report all organisms present. The CLIA requirements for mycobacteriology and mycology PT do not specify two sample types, but include the 50 percent requirement for cultures containing a mixture of the principal organism and appropriate normal flora. None of the 50 percent mixed culture requirements in these subspecialties applies to samples that would only contain normal flora and no reportable organisms.

CLIAC considered whether PT should include mixed cultures, and discussed the difficulties of having mixed cultures in challenges for antimicrobial susceptibility testing. CLIAC considered lowering the mixed culture requirement to 25 percent for all subspecialties in microbiology. Upon deliberation, CLIAC made the following recommendation:

- Lower the mixed culture requirement from 50 percent to 25 percent for PT challenges of both sample types (those that require laboratories to report only the principal pathogen and those that require laboratories to report all organisms present).

We agree it is appropriate to lower the mixed culture requirement from 50 percent to 25 percent for bacteriology, mycobacteriology, and mycology to better reflect actual patient samples. As a result, we are proposing changes as follows:

- Section 493.911(a)(2): In bacteriology, we are proposing to decrease the required mixed cultures from 50 percent to 25 percent for culture challenges that require laboratories to report only the principal pathogen and those that require laboratories to report all organisms present.

- Sections 493.913(a)(2) and 493.915(a)(2): In mycobacteriology and mycology, respectively, we are proposing to decrease the mixed culture requirement from 50 percent to 25 percent.

Since the requirements for parasitology and virology do not currently include requirements for mixed cultures (or mixed PT challenges), we do not propose to make any changes to these subspecialties.

6. Antimicrobial Susceptibility Testing

PT for antimicrobial susceptibility testing is currently required for bacteriology at §493.911(b)(1) and mycobacteriology at §493.913(b)(1), but it is not required for mycology, parasitology, or virology. For antimicrobial susceptibility testing in bacteriology at §493.911(b)(3), at least one sample per testing event must include one gram-positive or gram-negative sample and for mycobacteriology at §493.913(b)(3), at least one sample per testing event must include a strain of Mycobacterium tuberculosis with a predetermined pattern of susceptibility or resistance to the common antimycobacterial agents. In some instances, laboratories appreciate the opportunity to participate in additional susceptibility testing challenges as educational tools. Under the current regulations, some laboratories may perform the minimum required susceptibility testing on some organisms such as gram-positive cocci. When CLIAC discussed this issue, the point was made that by increasing the frequency and number of required susceptibility testing PT challenges for different groups of organisms, potential issues with patient testing in a laboratory may be detected sooner. CLIAC considered recommending increasing the susceptibility testing challenges to two per event and requiring one gram-positive and one gram-negative organism in each bacteriology testing event. CLIAC also considered whether PT should be required for resistance as well as susceptibility testing and

whether these requirements should be extended to other microbiology subspecialties. Following this deliberation, CLIAC made the following recommendations:

- Required PT for antimicrobial susceptibility and/or resistance testing should be increased to two challenges per event for a total of six challenges per year in bacteriology and should include one gram-positive and one gram-negative organism in each event.
- PT should be required for laboratories that perform susceptibility and/or resistance testing in all microbiology subspecialties. It should include two challenges per event and should include resistant organisms.

In considering these recommendations, we reviewed the modules currently offered by PT programs that include susceptibility testing and noted that there is a limited number of applicable PT modules currently available for resistance testing. Also, no PT program currently offers applicable PT modules for antiparasitic susceptibility or resistance testing in the subspecialty of parasitology. We believe it could be beneficial to increase the number of challenges per event from one to two for each microbiology subspecialty to increase the likelihood of detection of a problem in a laboratory. Antiparasitic susceptibility or resistance testing is not included in the subspecialty of parasitology because no PT program currently offers applicable PT modules. Therefore, we are proposing the following:

- Section 493.911(a)(4): For bacteriology, we are proposing to require at least two PT samples per event for susceptibility or resistance testing, including one gram-positive and one gram-negative organism with a predetermined pattern of susceptibility or resistance to common antimicrobial agents.

- Section 493.913(a)(5): For mycobacteriology, we are proposing to require at least two PT samples per event for susceptibility or resistance testing, including mycobacteria that have a predetermined pattern of susceptibility or resistance to common antimycobacterial agents.

- Section 493.915(a)(4): For mycology, we are proposing to require at least two PT samples per event for susceptibility or resistance testing, including fungi that have a predetermined pattern of susceptibility or resistance to common antifungal agents.

- Section 493.919(a)(4): For virology, we are proposing to require at least two PT samples per event for susceptibility or resistance testing, including viruses that have a predetermined pattern of susceptibility or resistance to common antiviral agents.

In each of these subspecialties, we are also proposing to revise the requirements for evaluation of a laboratory's performance at §§493.911(b), 493.913(b), 493.915(b), and 493.919(b) to account for the fact that PT would be required for susceptibility or resistance testing and that the scoring should be consistent with the testing performed.

7. Direct Antigen Testing

PT for direct antigen testing is only required for bacteriology and virology under §§493.911(a) and 493.919(a), respectively, not for the other microbiology subspecialties of mycobacteriology, mycology, and parasitology. Since this type of testing is commonly used for testing patient specimens especially in mycology and parasitology, CLIAC considered whether PT for direct antigen testing should be part of all of the microbiology subspecialty requirements. CLIAC indicated that direct antigen PT should be required in subspecialties where these methods are used and PT is available and made the following recommendation:

- PT for direct antigen testing should be required for all microbiology subspecialties.

We reviewed the modules currently offered by PT programs and determined there are a number of modules that include direct antigen testing for all microbiology subspecialties except mycobacteriology, for which this technology is not commonly used for testing patient specimens. In addition, we recognized that in bacteriology, PT for direct antigen testing to detect toxins produced by organisms such as *Clostridioides* (formerly *Clostridium*) *difficile* is also commonly available. Based on the information collected from the PT programs, availability of the modules, and importance to the health and safety of the public, we are proposing:

- To retain the requirement for direct antigen detection for:

++ Section 493.911(a)(1)(ii): Bacteriology.

++ Section 493.919(a)(1)(i): Virology.

And add the requirement for direct antigen testing detection for:

++ Section 493.915(a)(1)(i): Mycology.

++ Section 493.917(a)(1)(i): Parasitology.

- To require PT for bacterial toxin detection under §493.911(a)(1)(iii). No changes are proposed for mycobacteriology.

- To add the evaluation criteria of a laboratory's performance for two of the affected subspecialties under §§493.911(b) and 493.917(b) to include performance and scoring criteria that address direct antigen and toxin detection. Evaluation of a laboratory's performance for direct antigen testing at §493.917(b) would align with the other microbiology subspecialties and reflect current microbiology practices in reporting patient results. Evaluation of a laboratory's performance for bacterial toxin detection at §493.911(b) would reflect the current practice of reporting patient test results (that is, absence or presence of bacterial toxin).

B. Proposed Changes to PT for Non-Microbiology Specialties and Subspecialties

1. Analytes Proposed for Addition to Subpart I

The CLIA statute requires the PT standards established by the Secretary to require PT for each examination and procedure for which the laboratory is certified "except for examinations and procedures for which the Secretary has determined that a proficiency test cannot reasonably be developed" (42 U.S.C. 263a(f)(3)(A)). In determining whether PT can reasonably be developed for a given analyte, we considered whether the estimated cost of PT is reasonable in comparison to the expected benefit. Considering CLIAC's recommendations regarding possible changes to the analytes for which PT is required, we attempted to maximize improvements to the effectiveness of PT to improve accuracy, reliability and timeliness of testing while minimizing costs to the laboratories. In addition, we recognize that it is not necessary to require PT for every analyte to derive benefits generalizable to all test methods. For example, systematic analytical problems on a multichannel analyzer might be detected by participation in PT for any of the analytes tested. Further, laboratories are already required under §493.1236(c)(1) to verify the accuracy of any test or procedure they perform that is not included in subpart I at least twice annually. Also, based on the results of the national PT survey[1] conducted by CDC and the Association of Public Health Laboratories (APHL) in 2013, a large number of laboratories voluntarily purchased PT materials for many nonrequired analytes.[2] Keeping this in mind, as discussed in section II.B.2. of this proposed rule, we are proposing to add the most crucial analytes based upon the following criteria:

(1) Current availability of PT materials and the number of PT programs offering PT.

(2) Volume of patient testing performed nationwide.

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1 Office of Management and Budget control number 0920-0961. Expiration date 4/30/2015.
2 Earley, Marie C., J. Rex Astles, and Karen Breckenridge. Practices and Perceived Value of Proficiency Testing in Clinical Laboratories. Journal of Applied Laboratory Medicine 1, 4 (2017), pp. 415 - 420.

(3) Impact on patient health and/or public health.

(4) Cost and feasibility of implementation.

2. Process for Ranking Analytes Proposed for Addition to Subpart I

We used a sequential process to narrow the list of eligible analytes for addition based on each of the four criteria listed above.

a. Current availability of PT materials and the number of PT programs already offering PT

We believe that the availability of these PT samples for a particular analyte is an appropriate criterion for narrowing the list of eligible analytes and that scaling up a program would be relatively less difficult than creating a PT sample for a particular analyte that had not previously been offered. For the reasons noted below, we believe that at least three PT programs offering PT samples for a particular analyte under consideration would provide a sufficient number of programs to offer immediate access to PT by laboratories and a reasonable starting point for the analytes under consideration. CMS and CDC want to ensure that the laboratories could choose the best PT program for the services that their laboratories offered as well as not create a market advantage for a small number of PT programs. To evaluate the current availability of PT materials and PT programs offering PT samples for a particular analyte, we analyzed the distribution of available PT programs for analytes for which PT is currently not required by subpart I of the CLIA regulations. The supporting data were collected from available sources, including data from PT program catalogs, and data routinely reported by PT programs, including enrollment data. We examined the number of PT programs offering these analytes at any number of events per year and any number of challenges per event. We initially determined the number of analytes under consideration for which PT was offered by at least two, three, or four of the eleven existing PT programs. We determined that limiting the analytes

under consideration to those for which PT was offered by at least three PT programs allowed a sufficient number of programs to offer immediate access to PT by laboratories and provided a reasonable starting point of 199 for the number of analytes under consideration (96 in routine chemistry, 27 in endocrinology, 28 in toxicology, 25 in general immunology, 21 in hematology, two for antibody identification). Expected impact on laboratories and PT programs was also taken into account (for example, minimizing the cost of purchasing and providing samples) when determining the minimum number of PT programs. Decreasing the minimum PT programs to two rather than three would increase the number of analytes under consideration to 303, but presumably decrease PT program availability and access for a given analyte. Conversely, increasing the minimum number of PT programs to four, while presumably increasing PT program availability and access for a given analyte, decreased the number of analytes under consideration to 164. This was the first cut, based upon available PT modules.

b. Volume of patient testing being performed nationwide

For the second cut, we prioritized the remaining 199 analytes under consideration based upon estimated national testing volumes. We decided that an estimated national test volume of 500,000 per analyte annually was an appropriate threshold as it was based upon testing volumes of the majority (68 out of 81) of analytes currently listed in subpart I. For comparison, of the analytes that are currently required under subpart I, 63 had a total national test volume above 1,000,000; five had national test volumes between 500,000 and 1,000,000; and 13 had national test volumes below 500,000. We used 500,000 annual tests as a preliminary cut-off for retention on the list of analytes under consideration. We also retained analytes that were below the 500,000 threshold that we determined to be clinically important based on literature already footnoted in section II.B.2.b. of this proposed rule and consultation with CDC health experts.

The following analytes with test volumes less than 500,000 that were retained are: carbamazepine, alpha-1-antitrypsin, phenobarbital, hepatitis Be antigen, antibody identification, theophylline, gentamicin, and tobramycin.

In estimating national testing volumes to rank the remaining 199 analytes under consideration in this proposed rule, we were unable to identify a single source of available data for all patient testing being performed nationwide. We had complete data for Medicare reimbursements, as well as the most current MarketScan Commercial Claims and Encounters (CCAE) and MarketScan Medicaid Multi-state data sets (2009 Truven Health MarketScan® data, https://truvenhealth.com/your-healthcare-focus/life-sciences/data_databases_and_online_toolsMarkets/Life-Sciences/Products/Data-Tools/MarketScan-Databases) and extrapolated accordingly. We used data provided by an HHS-approved accreditation organization, specifically a list of the number of their accredited laboratories offering each tests we considered for addition to, or deletion from, subpart I in order to determine how many laboratories were performing testing for the proposed analytes. We also considered smaller representative data sets, including data sets obtained from a large healthcare network, a large reference laboratory, and a university hospital network in order to evaluate the trends in performing testing for the proposed analytes. We analyzed national trends in testing based upon Medicare Part B reimbursement data (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4698806/) to determine the analytes in each specialty that are increasingly used for patient diagnosis and/or management. We concluded that the trends revealed in the data could continue to show increases in reimbursement for the proposed analytes.

We estimated the 2009 national test volumes based upon two data sets: (1) Medicare Part B reimbursement statistics (excluding waived testing); and (2) CCAE. For all analytes under consideration for the addition to subpart I, we used Current Procedural Terminology (CPT) codes from claims data. We identified all possible occurrences of a particular analyte and combined them into one count. For example, if bicarbonate could be performed in a panel and by itself, we included all possible occurrences.

A complete count was available for the Medicare Part B data, and for this sector no estimation of total counts was necessary. MarketScan data, which is a sample of approximately 40 million covered individuals, was necessary to estimate CCAE data and approximately 6.5 million covered individuals for Medicaid data. Therefore, we estimated the total number of tests in both of these categories for the entire United States. The Agency for Healthcare Research and Quality (AHRQ)[3] data showed that an estimated total of 181.5 million covered individuals enrolled in CCAE healthcare insurance; from this we derived a factor of 4.5 (181.5 million individuals/40 million individuals) by which to multiply the MarketScan CCAE estimates to extrapolate estimates for the entire U.S. Similarly, for the Medicaid estimates, we knew from CMS data that there were approximately 52.5 million individuals covered by Medicaid, so we derived a factor of 8.0 (52.5 million individuals/6.5 million individuals) by which to multiply the MarketScan Medicaid estimates to extrapolate estimates for the entire United States.

We note that these estimates did not account for some inpatient testing that was paid through capitation arrangements for inpatient testing. Testing paid directly by patients was also not counted because, in these cases, CPT codes would not be captured in the data because there was no request for reimbursement. Even with this limitation, we believe that these estimates

3 https://meps.ahrq.gov/mepstrends/hc_ins/

provide a relative sense of the numbers of tests being performed annually per analyte. No other accurate data were available to us.

As noted above, for the second cut, based upon our estimates of national testing volumes, we decided that an estimated national test volume of 500,000 per analyte annually was an appropriate threshold as most of the analytes listed in subpart I had national testing volumes above this threshold. Together with the above-described analytes that were below the 500,000 threshold that we determined to be clinically important, this narrowed our list of potential analytes under consideration for addition to subpart I to 73, representing analytes in five specialties or subspecialties

c. Impact on patient and/or public health

For the third cut, we considered the evidence available as to patient and public impact for each analyte. There was no standardized, generally accepted way available to us to assess the relative impact of testing for particular analytes on clinical care and public health. Therefore, we used the following parameters to get a relative sense of the importance of the analytes under consideration: a review of published laboratory practice guidelines (LPGs); a review of critical values; and a review of the analyte's classification by the Food and Drug Administration (FDA) (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfClia/Search.cfm). We accessed several data sources, including tests listed in the CDC Guide to Community Preventive Services (https://www.thecommunityguide.org); National Healthcare Priorities/Disparities reports (https://www.ahrq.gov/research/findings/nhqrdr/index.html); clinical practice guidelines including the National Guideline Clearinghouse (NGC) database available from AHRQ (https://www.guideline.gov/)[4]; critical values available in publications;[5] and (CAP) Q-Probes.[6]

4 AHRQ's National Guideline Clearinghouse website accessed for this proposed rule, however, no longer exists on

In order to assess patient and public impact for each analyte, we considered the evidence available related to each analyte under consideration. To do so, our first parameter was a review of published LPGs. We hypothesized that if there was a relatively large number of LPGs available for a particular analyte, that analyte would be important for health testing. To estimate the number of LPGs, we used the AHRQ's NGC database. For example, there were 60 LPGs listed in the NGC for LDL cholesterol, 31 for hemoglobin A1c, and 27 for troponin, all of which are proposed for addition in Table 1. However, this approach did not differentiate analytes for which there were conflicting recommendations. For example, there are controversies about the value of screening men with prostate specific antigen (PSA) testing, and there is an ongoing debate about the prudence of testing vitamin D in asymptomatic adults (Kopes-Kerr, 2013).[789]

Our second parameter was a review of critical values. Critical values are pre-determined limits for specific analytes that when exceeded may suggest that immediate clinical intervention is required. We assessed analytes included on "critical values" lists to determine the analyte's relative importance in helping clinicians to make rapid life-altering decisions. This approach allowed us to gauge how important an accurate result could be because an incorrect result could lead to a life-threatening intervention or a failure to intervene. We reviewed published

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the internet effective July 16, 2018.

5 Burtis, C. A., Ashwood, E. R., & Bruns, D. E. (2012). Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. London: Elsevier Health Sciences

6 Laboratory critical values policies and procedures: a college of American Pathologists Q-Probes Study in 623 institutions. Howanitz PJ, Steindel SJ, Heard NV. Arch Pathol Lab Med. 2002 Jun;126(6):663-9

7 Barry, Micheael J. Screening for Prostate Cancer – The Controversy That Refuses to Die. New England Journal of Medicine 360;13 (March 2009.

8 Eck, Leigh M. Should family physicians screen for vitamin D deficiency? yes: targeted screening in at-risk populations is prudent. American Family Physician 87, 8 (2013), pp. 541b.Fr

9 Kopes-Kerr, Colin. Should family physicians screen for vitamin D deficiency? no: screening is unnecessary, and routine supplementation makes more sense. American Family Physician 87, 8 (2013), pp. 540b.

literature[10] and critical values posted online from 16 institutions including small hospitals, university hospitals, and reference laboratories[11].

Our final parameter for assessing the clinical impact of an analyte was reviewing its medical device classification (Class I, II, or III) as categorized by the Food and Drug Administration's risk classification list. In a similar way, we assessed the public health importance of the eligible analytes by counting the number of recommendations for testing the analytes from CDC's Morbidity and Mortality Weekly Report, the Infectious Disease Society of America, and the Council of State and Territorial Epidemiologists for surveillance of health conditions related to the particular analyte under consideration. We found supporting evidence for national prioritization in some of the following: the U.S. Preventive Services Task Force (https://www.uspreventiveservicestaskforce.org/Page/Name/recommendations), the National Healthcare Quality and Disparities Report (https://www.ahrq.gov/research/findings/nhqrdr/index.html), the CDC Hormone Standardization Program (https://www.cdc.gov/labstandards/hs.html). For some analytes that have important public health impact, such as blood lead, we consulted with subject matter experts in the CDC National Center for Environmental Health, which promotes national testing and/or has standardization programs for some priority analytes, specifically estradiol and testosterone. CMS and CDC used this information to help determine which analytes should be included in this proposed rule.

Therefore, we used those parameters in an attempt to get a relative sense of the patient and public health impact of the analytes under consideration, but, using the data available to us, we found no standardized, generally accepted way to assess the relative impact of testing for

10 Wagar, Friedberg, Souers, and Stankovic, 2007, https://www.ncbi.nlm.nih.gov/pubmed/18081434
11 www.mayomedicallaboratories.com/test-catalog/appendix/criticalvalues/index.html

particular analytes on clinical care and public health. After assessing patient and public health impact on a case-by-case basis for the third cut, we narrowed the analytes down to 34 for consideration of addition to the proposed list of analytes in subpart I.

d. Cost and feasibility of implementation

For the final analysis to determine whether an analyte would be proposed for inclusion in subpart I of the CLIA regulations, we focused upon feasibility and costs of conducting PT for each of the remaining 34 analytes under consideration. We provided each of the HHS-approved PT programs the opportunity to submit comments in writing related to: inclusion/deletion of analytes, grading schemes, method(s) for determining target values, evaluating data using peer groups, cost of including new analytes, and structure of microbiology PT. Analytes for which it would be difficult for the PT programs to scale up production to meet the CLIA required frequency of three events per year with five challenges per event were eliminated from consideration because we believe that the costs passed down to laboratories to purchase the PT would be overly burdensome. In other cases, the decisions were based on the difficulty of finding any suitable PT materials. Some potential analytes were eliminated because they were too unstable for product development or shipping or because the testing methodology was not sufficiently standardized to support PT, such as vitamin D testing. After assessing cost and feasibility of implementing PT on a case-by-case basis, we made the final cut, narrowing the analytes down to 29 potential analytes for the proposed list of analytes in subpart I.

3. Specific Analytes Proposed for Addition to Subpart I

Based upon the sequential process described above, information received from the PT programs and consultation between CDC and CMS, we narrowed the list down to 29 analytes that we are proposing to add to subpart I of the CLIA regulations (Table 1).

TABLE 1: Analytes Proposed for Addition to Subpart I

CLIA Regulation	Analytes
General Immunology §493.927	Anti-HBs Anti-HCV C-reactive protein (high sensitivity)
Routine Chemistry §493.931	B-natriuretic peptide (BNP) ProBNP Cancer antigen (CA) 125 Carbon dioxide Carcinoembryonic antigen Cholesterol, low density lipoprotein Ferritin Gamma glutamyl transferase Hemoglobin A1c Phosphorus Prostate specific antigen, total Total iron binding capacity Troponin I Troponin T
Endocrinology §493.933	Estradiol Folate, serum Follicle stimulating hormone Luteinizing hormone Progesterone Prolactin Parathyroid hormone Testosterone Vitamin B12
Toxicology §493.937	Acetaminophen, serum Salicylate Vancomycin

4. Analytes Proposed for Removal from Subpart I

Recognizing that changes in the practice of clinical medicine have resulted in less frequent use of certain analytes, we used the same process to review the existing list of analytes in subpart I to determine which should be retained. In addition to requesting CLIAC's recommendations, we generally used the same criteria for retention of an analyte in subpart I as those used for determining which PT analytes to propose adding, however, as such PT testing was already available on the market, we did not consider the availability of PT material or the feasibility of implementation; therefore, we believe that PT programs already have the mechanism(s) in place to manufacture and ship PT for these analytes.

5. Process for Ranking and Assessing Existing Analytes and Proposals for Removal from Subpart I

a. Estimating nationwide testing volume

We generally used the same rationale to select currently required analytes to propose for deletion. Specifically, we used the same threshold of 500,000 tests performed annually as an initial criterion for considering PT analytes. Those estimated to be lower than this threshold were considered for deletion from required PT. In particular, we focused on PT for several of the therapeutic drugs (ethosuximide, quinidine, primidone, and procainamide and its metabolite, N-acetyl procainamide). New drugs that are more effective or safer have entered the market since 1992, and may have replaced use of the therapeutic drugs that were included in the 1992 regulations. If so, we would expect to see a continued decline in the volume of testing for the use of such drugs. In addition to identifying decreases in testing for these drugs, we looked for probable causes of those decreases. These decreases in testing could be a result of new and emerging tests, including methodologies, replacing older tests, new technology, and changes to the way that the medical community orders laboratory testing. For example, the decrease in testing for LDH isoenzymes could be explained by the increased reliance on better alternative cardiac markers, especially troponin[12]. For some of the anticonvulsant drugs, there may have been changes in medical practice, including alternative drugs and other treatments, possibly decreasing the need to measure them[13]. We identified 13 currently required analytes with national test volumes that were less than our 500,000 annual test volume threshold.

b. Estimated impact on patient and public health

12 Shahangian, Alspach, Astles, Yesupriya, and Dettwyler, 2014, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4698806/

13 Krumholz, et al, 2015) (NICE, 2012, https://www.nice.org.uk/guidance/cg137)

For any analyte still under consideration for removal, we performed literature reviews to determine if testing for alternative analytes or other diagnostic strategies had begun to supplant testing for the considered analyte. We took into account testing trends over the past 10 years[14] and we attempted to project expected testing trends. We then assessed the critical importance of candidates for deletion from subpart I based upon the number of guidelines available in the AHRQ NGC and the same sources used for considering inclusion in subpart I, bearing in mind that for all analytes and tests that are not listed in subpart I, laboratories must demonstrate accuracy twice per year as specified at §493.1236(c)(1). . We also considered the potential impact on clinical medicine and public health of deleting these analytes. Based on our literature review and consultation with CDC health experts, we decided not to propose the elimination of eight analytes based upon their critical importance for patient testing: carbamazepine, alpha-1-antitrypsin, phenobarbital, hepatitis Be antigen (HBeAg), antibody identification, theophylline, gentamicin and tobramycin. These are used for making important health decisions, for example, diagnosing hepatitis B (HBeAg), performing crossmatching for blood transfusions (antibody identification), or assessing compliance with medication for critically ill asthmatic patients (theophylline).

6. Analytes Proposed for Deletion from Subpart I

Based upon the sequential process described above, we propose that the following analytes be deleted from subpart I: at §493.931 LDH isoenzymes and at §493.937 ethosuximide, quinidine, primidone, and procainamide (and its metabolite, N-acetyl procainamide).

7. Determining Criteria for Acceptable Performance

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14 Shahangian, Alspach, Astles, Yesupriya, and Dettwyler,2014 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4698806/

"Criteria for Acceptable Performance", as that term is used in §§493.923, 493.927, 493.931, 493.933, 493.937, 493.941, and 493.959, is defined by the target value and acceptance limits. Criteria for acceptable performance is meant for PT scoring only and not intended to be used to set acceptability criteria for a laboratory's verification or establishment of performance specifications.

8. Setting Target Values

Under §493.2, "target value" for quantitative tests are currently generally defined as either the mean of all participant responses after removal of outliers (those responses greater than 3 standard deviations from the original mean) or the mean established by definitive or reference methods acceptable for use in the National Reference System for the Clinical Laboratory (NRSCL) by the National Committee for the Clinical Laboratory Standards (NCCLS). However, in instances where definitive or reference methods are not available or a specific method's results demonstrate bias that is not observed with actual patient specimens, as determined by a defensible scientific protocol, a comparative method or a method group ("peer" group) may be used. If the method group is less than 10 participants "target value" means the overall mean after outlier removal (as defined above) unless acceptable scientific reasons are available to indicate that such an evaluation is not appropriate.

We recognize, based on input from PT programs, that peer grouping is generally the way that target values are set for most analytes. Therefore, in this rule, we are proposing to continue allowing PT programs to use peer grouping to set the target values. In addition, we propose removing the reference to the NRSCL and NCCLS, while retaining the other options for setting target values.

9. Changing Acceptance Limits

Because there have been improvements in technology resulting in better sensitivity, specificity, and precision, routinely using peer grouping to set target values means that the acceptance limits (AL) that were originally specified in each specialty and subspecialty of the CLIA'88 regulations in subpart I effectively allow for a more tolerant acceptance criteria for most analytes than would occur if targets were set by a reference method or overall mean. Based on feedback from several HHS-approved PT programs, we believe that it would be appropriate to update the ALs to reflect advancements in technology and analytical accuracy since the PT regulations were implemented in 1992. While narrowing limits may increase miss rates per challenge, we do not expect a high unsuccessful rate based on the data simulations provided by the PT programs. We expect the rates of unsatisfactory events would be low based on the simulation data, and that the rates of unsuccessful events (two consecutive or two out of three testing events being unsatisfactory) would be even lower; therefore, we believe it is reasonable to propose tighter limits given current analytic accuracy. We used all data available to us to minimize the negative consequences of the proposed changes (for example, too many unsuccessful performances) to acceptance limits, including simulations provided by PT programs.

10. Changes to Percentage Acceptance Limits (ALs)

a. Basis for Using Fixed Percentage PT ALs

Currently, the CLIA regulations at §§493.927(c)(2), 493.931(c)(2), 493.933(c)(2), 493.937(c)(2), and 493.941(c)(2) prescribe a variety of ALs, including: a multiple of the standard deviation (SD) of results from the mean of other participants in the peer group; fixed limit as a percentage of the assigned value; fixed limit in concentration units; and a mixture of percentage and concentration units, depending on the concentration of the analyte. For all new and

currently required non-microbiology analytes, we propose to use fixed ALs, preferably as percentage limits rather than concentration units.

There are 53 analytes (existing or proposed) for which we are proposing a percentage-based AL, for which biological variability data were published. For several analytes (for example, therapeutic drugs) there were no biological variability data because these analytes do not occur naturally in the body. Where there were such data, we used AL to get as close to, or below, an accuracy goal for the test that was based on biological variability data, and then we simulated several percentage-based ALs to see if their results would have passed or failed at each simulation. We wanted to get miss rates (that is, percent of laboratories that did not meet the criteria for acceptable performance per PT challenge) of somewhere in the 1 to 2 percent range as was observed in the data provided by the PT programs for current ALs. Of the 53 analytes, 34 of the proposed ALs were tighter than or equal to biological variability limits. For 19 analytes, the limits we are proposing are looser (greater) than the limits required to meet accuracy based upon biological variability. For these 19 analytes, using ALs based upon biological variability would be untenable because the current analytical accuracy for such testing would not be expected to be able to meet such limits. White blood cell differential is the only remaining analyte that would have ALs in SD. In this case there were no biological variability data available.

In general, fixed ALs, either in percentages or concentration units, are preferred to SDs for PT, for several important reasons: they can be tied directly to objective goals for performance, such as goals for analytical accuracy and technical expectations; they are constant in all PT events and do not vary because of statistical randomness, masked outliers, or small sample size; they assure the same evaluation criteria are used by all PT programs and discourage

opportunities for participants to "shop" for PT programs with less stringent criteria for which it is easier to achieve acceptable performance; they do not unfairly result in tighter effective ALs for peer groups that use analyzers that have tighter analytical precision; they can combine a fixed percentage and a fixed absolute concentration to allow for more robust evaluation while also fairly evaluating low analyte concentrations; and they are commonly used worldwide in other PT and external quality assessment programs.

Our analysis of existing PT and external quality assessment programs showed that ALs using two or three SDs have been used in PT in a wide variety of settings for several reasons, such as: limited experience with PT or matrix effects for a particular analyte; lack of consensus on criteria for acceptable performance; inertia with no compelling pressure for change; and analytical performance so poor that multiples of the overall SD are considered to be the only fair approach. In our opinion, all of these reasons to some extent contributed to initial reliance on SD limits for certain analytes when CLIA'88 was implemented. We also note that while regulations promulgated under CLIA'67 used ALs of three SD for several analytes, regulations finalized under CLIA'88 replaced these with fixed limits and PT programs were able to successfully make the transition. Therefore, we believe it is likely that the proposed changes from SD-based ALs to fixed ALs will not be problematic.

Therefore, as discussed in section II.B. of this proposed rule, we are proposing to amend certain analytes in §§493.927, 493.931, 493.933, 493.937, and 493.941 to include fixed ALs with or without percentages. Three analytes have only concentration-based ALs (that is, no percentage-based ALs): pH, potassium and sodium.

b. Adding Fixed Concentration Units to Fixed Percentage Units

A percentage-based criterion can be unnecessarily stringent at low concentrations – either because of technical feasibility or because medical needs at the low concentration do not require such tight precision[15.] Thus, when percentage-based fixed criteria are used for ALs, it may be necessary to place a minimum on the percentage as currently occurs with the criterion for acceptable performance for glucose (§493.931) for which the AL switches from 10 percent to 6 mg/dL below a concentration of 60 mg/dL. The combined ALs direct PT programs to score with whichever of the specifications is more tolerant; at lower limits of the analytical range this will be the fixed concentration limit. Therefore, to allow for more fair and realistic ALs, we propose to use combinations of percentage and concentration limits as appropriate. These combination limits are similar to limits that already exist in CLIA'88 regulations for glucose and other analytes.

Therefore, we are proposing to amend certain analytes in §§493.927, 493.931, 493.933, 493.937, 493.941 and 493.959 to include percentage-based ALs with or without additional fixed ALs.

c. Establishing ALs Based on Analytical Accuracy Goals for Proposed New and Several Current Analytes

For the newly proposed analytes and several current analytes for which current ALs are in units other than percentages such as three SDs or concentration units, we are proposing to change the ALs to percentages. Over the years, there have been many proposed criteria for establishing goals for analytical performance.[16],[17] The various possible approaches were

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[15] Thompson, Michael. Variation of precision with concentration in an analytical system. Analyst, 113, (1988), pp. 1579-1587.

16 Tonks, David B. A study of the accuracy and precision of clinical chemistry determinations in 170 Canadian laboratories. Clinical Chemistry 9, 2 (1963), pp. 217-233.

reviewed and a hierarchy was established based upon a 1999 consensus conference.[18] These strategies were reconsidered in the 2014 European Federation of Clinical Chemistry and Laboratory Medicine Strategic Conference in Milan. Participants in both conferences acknowledged that the ability of a test method to meet clinical needs is the highest priority and the most defensible approach would be clinical trials in which patient outcomes could be compared using different analytical accuracy goals. This approach was not feasible for many reasons. Although clinical outcomes studies would be the most rigorous basis for establishing analytical performance goals, these are seldom possible, leaving the natural dispersion of levels for each analyte (biological variability) as the next best scientifically defensible approach for establishing analytical accuracy goals.[19] The less the biological variability, the more stringent the analytical accuracy needs to be. This approach makes sense for two of the most important reasons to conduct patient testing: diagnosis of disease, that is, differentiating an abnormal result from a normal one, and monitoring a patient's progress during treatment. In the former case, we believe that the "within-group" biological variability is the important limiting factor defining an appropriate error goal for a test method. Furthermore, for monitoring progress, we believe the most important factor is the "within individual" variability. It was not possible for us to differentiate how analytes are being used or will be used clinically, with respect to diagnosis versus monitoring. Therefore, we accounted for both needs and used an approach that accounted for both kinds of biological variability to estimate analytical accuracy goals as the basis for our

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17 Cotlove, Ernest, Eugene K. Harris, and George Z. Williams. Biological and analytic components of variation in long-term studies of serum constituents in normal subjects. Clinical Chemistry 16, 12 (1970), pp. 1028-1032.
18 Fraser, Callum. The 1999 Stockholm consensus conference on quality specifications in laboratory medicine. Clinical Chemistry and Laboratory Medicine 53, 6 (2015), pp. 837-840.
19 Burtis, Carl A., Edward R. Ashwood, David E. Bruns, Ed. Tietz textbook of clinical chemistry and molecular diagnostics. (Chapter 2 Selection and analytical evaluation of methods with statistical techniques, pp. 17), Elsevier Saunders, Philadelphia, P.A., (2012).

proposals for acceptance limits in percentages.[20] The advantage of using analytical accuracy goals that are expressed in terms of percentages is that they can be directly related to ALs in a mathematical way expressed as percentages.

We have assumed that a laboratory that can meet the clinical needs for test accuracy based upon biological variability should perform successfully on PT most or all of the time. Therefore, whenever possible, we have used publically available estimates of allowed total error based upon estimates of biological variability[21] to approximate the proposed AL. CDC has shown in an a recent poster [22] that it is possible to design ALs based upon such accuracy goals, and it is possible to simulate the ability of a PT program to identify laboratories that cannot meet such goals, while minimizing the likelihood of misidentifying laboratories that are meeting analytical accuracy goals based upon biological variability.

Therefore, we are proposing to amend ALs for certain current analytes as well as establish ALs for analytes proposed for addition in §§493.927, 493.931, 493.933, 493.937, 493.941 and 493.959 based on analytical accuracy goals.

d. Tightening Existing Percentage ALs as Needed

There have been significant improvements in laboratories' performance in PT for the great majority of analytes[23] and PT unsatisfactory rates have dropped for all types of laboratories. The improvements are such that, for many analytes, laboratories that began to use PT to comply with CLIA'88 now perform as well as the hospital and independent laboratories

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20 Burtis, Carl A., Edward R. Ashwood, David E. Bruns, Ed. Tietz textbook of clinical chemistry and molecular diagnostics. (Chapter 17 Preanalytic variables and biological variation, pp. 470-471), Elsevier Saunders, Philadelphia, P.A., (2006).

21 https://www.westgard.com/biodatabase1.htm.

22 Astles, Tholen, and Mitchell, 2016, https://www.aacc.org/science-and-practice/annual-meeting-abstracts-archive

23 Howerton, Krolak, Manasterski, and Handsfield, 2010

which were previously required to perform PT under CLIA'67. Howerton, et al,[24] showed that for almost all analytes examined, PT performance improved somewhat after CLIA'88 was implemented, but the improvements were greater for laboratories that were not previously required to perform PT. The rates of unsatisfactory PT are now roughly the same for analytes listed in subpart I, regardless of the laboratory type, and this is consistent with CLIA's intent to ensure accurate clinical testing regardless of the setting where testing is performed. There are several factors contributing to the improvements in PT performance, including improved analytical methods being used in all settings; technological advances resulting in improved precision, sensitivity and specificity; and increased familiarity with handling preparation, and reporting of PT samples. Therefore, for the reasons above as well as supporting simulation data date from the PT programs, we are proposing to make criteria for acceptable performance for existing analytes listed in subpart I tighter so they are in closer agreement with analytical accuracy goals which are based upon biological variability and simulation data.

Therefore, based on the simulation data, we are proposing to tighten ALs for certain current analytes in §§493.927, 493.931, 493.933, 493.937, 493.941 and 493.959.

e. Simulating the Impact of New ALs on Unacceptable Scores for Challenges and Unsatisfactory Rates for Events

We evaluated a very specific PT data set to help CMS and CDC set appropriate limits. The total simulations reproduced PT that covered 2 years, representing 30 challenges (three events per year; five challenges per event; 2 years) of each proposed new analyte and for the analytes for which we propose to modify ALs. We reviewed the aggregated percentage of

24 Howerton D1, Krolak JM, Manasterski A, Handsfield JH. Arch Pathol Lab Med. 2010 May;134(5):751-8. Proficiency testing performance in US laboratories: results reported to the Centers for Medicare & Medicaid Services, 1994 through 2006.

unacceptable scores for each PT challenge using retrospective data. We then reviewed the simulation data which applied two or three new ALs for each of 84 analytes (consisting of 27 new analytes and 57 existing analytes). Based on the simulation data, we were able to make informed decisions to help us create or adjust the ALs.

Based upon our analysis of the simulation results, we further refined the proposed ALs and added potential absolute concentrations in lieu of percentage ALs, as was described previously. We then requested narrowly tailored data from PT programs as described above using retrospective PT data and peer group data for scoring, as they ordinarily would do. We focused on unsatisfactory scores with the data so that we could calculate the unsatisfactory rate per analyte among all participating laboratories that might occur with each proposed AL. The final simulations were conducted by several of the PT programs and this set of data was used to determine the ALs proposed in this rule.

We compared the unacceptable scores for each challenge and each proposed AL to determine at which concentrations it would be necessary to switch to a fixed concentration AL. Using this approach, we were able to identify an AL for each analyte and, in some cases, an additional concentration-based AL. This approach enabled us to identify an AL that would be sensitive enough to identify poor performing laboratories, yet not so sensitive that it will incorrectly identify laboratories that are likely meeting requirements for accuracy.

f. Limitation in our Ability to Predict the Number of New Unsatisfactory and Unsuccessful Scores

It is not possible for us to predict the precise effect of the proposed changes on the number of unsatisfactory and unsuccessful scores. The occurrence of an unsatisfactory score for a PT event depends upon at least two of five challenges being graded as unacceptable or outside

the criteria for acceptable for performance. PT programs select different combinations of samples for each event and it is impossible to predict how their selection could be modelled statistically. Finally, the distribution of unsatisfactory and unsuccessful PT scores is not randomly distributed across all participants.

C. Additional Proposed Changes

We are proposing to amend §493.2 to modify the definition of an existing term and define new terms as follows:

- Target value: We are removing the reference to NRSCL and NCCLS and retaining the other options for setting target values are retained in this proposed rule.

- Acceptance Limit: We are proposing to define this term to mean the symmetrical tolerance (plus and minus) around the target value.

- Unacceptable score: We are proposing to define this term to mean PT results that are outside the criteria for acceptable performance for a single challenge or sample.

- Peer group: We are proposing to define this term as a group of laboratories whose testing process utilizes similar instruments, methodologies, and/or reagent systems and is not to be assigned using the reagent lot number. PT programs should assign peer groups based on their own policies and procedures and not based on direction from any manufacturer.

We are also proposing the following revisions to the regulation text at subpart A:

- Sections 493.20 and 493.25: We are proposing to amend the regulations to reflect that if moderate and high complexity laboratories also perform waived tests, compliance with §493.801(a) and (b)(7) are not applicable. However, we propose to continue to require compliance with §493.801(b)(1) through (6) to align the regulations with the CLIA statute (42 U.S.C. 263a (i)(4)), which does not exclude waived tests from the ban on improper PT referral.

We are also proposing the following revision to the regulation text at subpart H:

- Section 493.861: We are amending the satisfactory performance criteria for failure to attain an overall testing event score for unexpected antibody detection from "at least 80 percent" to "100 percent." We are proposing this change because it is critical for laboratories to identify any unexpected antibody when crossmatching blood to protect the public health and not impact patient care.

We are also proposing the following revisions to the regulation text at subpart I:

- Section 493.901(a): We are proposing to require that each HHS-approved PT program have a minimum of ten laboratory participants before offering any PT analyte. We recognize that PT programs do not grade results when there are fewer than ten laboratory participants. This would require the laboratory to perform additional steps to verify the accuracy of their results. If at any time a PT program does not meet the minimum requirement of 10 participating laboratories for an analyte or module, HHS may withdraw approval for that analyte, specialty or subspecialty. This change reduces some burden on laboratories that have incurred the expense of enrolling in a PT program but do not receive a score or receive an artificial score requiring the laboratory to take additional steps to verify the accuracy of the analyte as required by §493.1236(b)(2).

- Section 493.901(c)(6): We are proposing to add the requirement that PT programs limit the participants' online submission of PT data to one submission or that a method be provided to track changes made to electronically reported results. Many PT programs currently allow laboratories an option to report PT results electronically while some other PT programs allow laboratories to only report PT results electronically with no other reporting option such as facsimile or mailed PT submission forms. However, at this time, the PT programs who do

participate in the online reporting have no mechanism to review an audit trail for the submitted result. In some cases of PT referral, it has been discovered that laboratories have sent PT samples to another CLIA certified laboratory for testing, received results from the other laboratory, and then changed their online reported results to the PT program since those results can be modified up until the PT event close date. In an effort to assist in PT referral investigations and determinations, an audit trail that includes all instances of reported results would aid in determining if a laboratory compared PT results obtained from another laboratory and changed their previously submitted results.

- Section 493.901(c)(8): We are proposing to add to the requirement previously found at §493.901 that contractors performing administrative responsibilities as described in §§493.901 and 493.903 must be a private nonprofit organization or a federal or state agency or nonprofit entity acting as a designated agent for the federal or state agency. Several PT programs have divided their administrative and technical responsibilities into separate entities or have had the administrative responsibilities performed by a contractor. We were made aware that administrative responsibilities were being performed by a for-profit entity. Because the CLIA statute (42 U.S.C. 263a(f)(3)(C)) requires PT programs to be administered by a private nonprofit organization or a state, we are proposing to amend §493.901 to state that all functions and activities related to administering the PT program must be performed by a private nonprofit organization or state.

- Section 493.901(e): We are proposing to add the requirement that HHS may perform on-site visits for all initial PT program applications for HHS approval and periodically for previously HHS-approved PT programs either during the reapproval process or as necessary to review and verify the policies and procedures represented in its application and other

information, including, but not limited to, review and examination of documents and interviews of staff.

- Section 493.901(f): We are proposing to add an additional requirement to the regulation that specifies CMS may require a PT program to reapply for approval using the process for initial applications if widespread or systemic problems are encountered during the reapproval process. The initial application for the approval as an HHS PT program requires more documentation in the application process than that which is required of PT programs seeking HHS reapproval.

- Section 493.903(a)(3): It has come to our attention that PT programs may have on occasion modified a laboratory's PT result submission by adding information such as the testing methodology which was inadvertently omitted by the laboratory. Therefore, we are proposing to add the requirement that PT programs must not change or add any information on the PT result submission for any reason including, but not limited to, the testing methodology, results, data, or units.

- Section 493.905: We are proposing to add that HHS may withdraw the approval of a PT program at any point in the calendar year if the PT program provides false or misleading information that is necessary to meet a requirement for program approval or if the PT program has failed to correct issues identified by HHS related to PT program requirements. We are also proposing to add a requirement that the PT program may request reconsideration should CMS determine that false or misleading information was provided of if the PT program has failed to correct issues identified by HHS related to PT program requirements.

- Sections 493.911 through 493.919: We are proposing, as discussed in section II.A.1. of this proposed rule, to modify the regulation by removing the types of services listed for each

microbiology subspecialty. We are also proposing to remove specific lists of example organisms from each microbiology subspecialty and replace the list with broader categories of organisms.

- Section 493.911(a): For bacteriology, as discussed in sections II.A.1. and V.C. of this proposed rule, we are proposing that the categories required include Gram stain including bacterial morphology; direct bacterial antigen detection; bacterial toxin detection; detection and identification of bacteria; and antimicrobial susceptibility or resistance testing on select bacteria.

- Section 493.911(a)(3): We are proposing that the bacteriology annual PT program content described must include representatives of the following major groups of medically important aerobic and anaerobic bacteria if appropriate for the sample sources: gram-negative bacilli; gram-positive bacilli; gram-negative cocci; and gram-positive cocci.

- Section 493.913(a): We are proposing to include required PT for acid-fast stain; detection and identification of mycobacteria; and antimycobacterial susceptibility or resistance testing.

- Section 493.913(a)(3): For mycobacteriology, we are proposing that the annual program content must include Mycobacterium tuberculosis complex and Mycobacterium other than tuberculosis (MOTT), if appropriate for the sample sources.

- Section 493.915(a): For mycology, we are proposing to require PT for direct fungal antigen detection; detection and identification of fungi and aerobic actinomycetes; and antifungal susceptibility or resistance testing.

- Section 915(a)(3): We are we are proposing that annual program content must include the following major groups of medically important fungi and aerobic actinomycetes if appropriate for the sample sources: yeast or yeast like organisms; molds that include dematiaceous fungi, dermatophytes, dimorphic fungi, hyaline hyphomycetes, and mucormycetes;

and aerobic actinomycetes.

- Section 493.917(a): For parasitology, we are proposing to require PT for direct parasite antigen detection and detection and identification of parasites.

- Section 493.917(a)(3): We are proposing that the annual program content must include intestinal parasites and blood and tissue parasites, if appropriate for the sample source.

- Section 493.919(a): For virology, we are proposing to require PT for viral antigen detection; detection and identification of viruses to the highest level that the laboratory reports results on patient specimens; and antiviral susceptibility or resistance testing.

- Section 493.919(a)(3): We are proposing that the annual program content must include respiratory viruses, herpes viruses, enterovirus, and intestinal viruses, if appropriate for the sample source.

- Sections 493.911(b)(1), 493.913(b)(1), 493.915(b)(1), 493.917(b)(1), 493.919(b)(1), 493.923(b)(1), 493.927(c)(1), 493.931(c)(1), 493.933(c)(1), 493.937(c)(1), 493.941(c)(1), and 493.959(d)(1): We are proposing to amend these provisions to clarify that for the purpose of achieving consensus, PT programs must attempt to grade using both participant and referee laboratories before determining that the sample is ungradable. We believe that this change will enhance consistency among the PT programs when grading samples. The current regulations noted above allow for scoring either with participants or with referees before calling a sample ungradable.

- Sections 493.923(a), 493.927(a), 493.931(a), 493.933(a), 493.937(a), 493.941(a), and 493.959(b): We are proposing to amend these provisions to remove the option that PT samples, "at HHS' option, may be provided to HHS or its designee for on-site testing".

- Section 493.927: We are proposing to amend, as discussed in sections II.B.8 through II.B.10. of this proposed rule, the criteria for acceptable PT performance to permit scoring of quantitative test results for the following immunology analytes: antinuclear antibody; antistreptolysin O; rheumatoid factor; and rubella. For these analytes, we have determined that there are one or more test systems that currently report results in quantitative units; therefore, we are adding ALs based on percentages or target values in addition to retaining the qualitative target values. We propose to make this allowance in CLIA for reporting PT which reflects current practice.

- Section 493.931(b): We are making a technical change to the description for creatine kinase isoenzymes to be CK-MB isoenzymes, which may be measured either by electrophoresis or by direct mass determination, for example using an immunoassay.

- Section 493.933: We propose to add the following analytes: estradiol, folate (serum), follicle stimulating hormone, luteinizing hormone, progesterone, prolactin, parathyroid hormone, testosterone, and vitamin B12.

- Section 493.937(a): We are proposing to revise this provision by including the requirement that annual PT programs must provide samples that cover the full range of values that could occur in patient specimens. We are proposing this amendment so that PT programs must provide samples across a toxicology sample's entire reportable range rather than just provide samples within a sample's therapeutic range.

- Section 493.941: We are differentiating the criteria for units of reporting of the analyte prothrombin time. Currently the analyte prothrombin time can be reported in seconds and/or INR (international normalized ratio), so we are proposing to amend the criteria for acceptable performance to reflect both units of reporting and proposing to add the requirement

that laboratories must report prothrombin time for PT the same way they report it for patient results; if patient results are reported in seconds or as INR results, they should report the same way to PT programs. If the laboratory reports patient results both in seconds and as INR, they should be reported the same way to the PT programs. We are also proposing to add criteria for acceptable performance for directly measured INR for prothrombin time. In addition, we propose to require laboratories that perform both cell counts and differentials to conduct PT for both (that is, the "or" would be changed to an "and"). Finally, we are proposing to change the criteria for acceptable performance for "cell identification" from 90 percent to 80 percent. We are proposing this change as the requirement of five samples per event does not allow for a score of 90 percent (that is, five samples would allow for scores of 0 percent, 20 percent, 40 percent, 60 percent, 80 percent, or 100 percent). PT for cell identification is currently required in §493.941. Further, §493.851(a) states that "failure to attain a score of at least 80 percent of acceptable responses for each analyte in each testing event is unsatisfactory performance for the testing event." If the requirement for acceptable performance remains at 90 percent, a laboratory can only have satisfactory performance if they receive 100 percent; however, §493.851(a) allows satisfactory performance for both 80 percent and 100 percent.

- Section 493.959: We are proposing to change the criteria for acceptable performance for unexpected antibody detection from 80 percent accuracy to 100 percent accuracy. We are proposing this change because it is critical for laboratories to identify any unexpected antibody when crossmatching blood in order to protect the public health and not impact patient care.

III. Collection of Information Requirements

Under the Paperwork Reduction Act of 1995 (PRA), we are required to publish a 60-day notice in the **Federal Register** and solicit public comment before a collection of information

requirement is submitted to the Office of Management and Budget (OMB) for review and approval.

To fairly evaluate whether an information collection should be approved by OMB, PRA section 3506(c)(2)(A) of the PRA requires that we solicit comment on the following issues:

- The need for the information collection and its usefulness in carrying out the proper functions of our agency.
- The accuracy of our burden estimates.
- The quality, utility, and clarity of the information to be collected.
- Our effort to minimize the information collection burden on the affected public, including the use of automated collection techniques.

We are soliciting public comment on each of the section 3506(c)(2)(A)-required issues for the following information collection requirements (ICRs).

The requirements and burden will be submitted to OMB under (OMB control number 0938-New).

A. Clarification for Reporting of Microbiology Organism Identification

We are proposing to clarify a requirement at §§493.801(b), 493.911(b), 493.913(b), 493.915(b), 493.917(b), and 493.919(b), to emphasize the point that, as currently required, laboratories must report PT results for microbiology organism identification to the highest level that they report results on patient specimens. In accordance with the implementing regulations of the PRA at 5 CFR 1320.3(b)(2), we believe the reporting of microbiology organism identification is a usual and customary practice when reporting PT results to PT programs. We are able to determine how many laboratories provide services in microbiology; however, we are unable to determine if the laboratories are enrolled in the appropriate PT outside of the survey

process, or if the microbiology PT samples for which the laboratory is enrolled are required under subpart I. There are no data systems that capture this information. We estimate the number of laboratories that are not currently reporting microbiology organisms to the highest level that they report results on patient specimens to be about 10 percent of 36,777 laboratories which is 368 laboratories. We estimate it would take 20 minutes for a laboratory to fill this information on the PT submission form. Each laboratory would report this information 3 times a year which would take approximately 1 hour. The total annual burden is 368 hours (368 laboratories X 1 hour). A Clinical Laboratory Technologists/Technicians would perform this task at an hourly wage of $25.59 as published in 2017 by the Bureau of Labor Statistics (https://www.bls.gov/oes/current/oes_nat.htm). The wage rate would be $51.18 to include overhead and fringe benefits. The total cost would be $18,834 (368 hours X $51.18).

B. Submission of PT Data by Laboratories

At §493.901(c)(6), we are proposing to add the requirement that PT programs limit the participants' online submission of PT data to one submission or that a method be provided to track changes made to electronically reported results. In an effort to assist in PT referral investigations and determinations, an audit trail that includes all instances of reported results would aid in determining if a laboratory compared PT results obtained from another laboratory and changed their previously submitted results. In accordance with the implementing regulations of the PRA at 5 CFR 1320.3(b)(2), we believe the ability for the PT programs to track this data already exists in their software; however, they may need to make minor modifications to their software in order to meet this requirement. If a PT program would need to update their software, we would estimate that the cost would be 15 hours for software modification. The total burden is 135 hours (9 PT programs X 15 hours). However, this would not be an annual burden, rather

it would only occur once when the requirement is implemented. A Software Developer, System Software would perform this task at an hourly wage of $107.48 as published in 2017 by the Bureau of Labor Statistics (https://www.bls.gov/oes/current/oes_nat.htm). The wage rate would be $107.48 to include overhead and fringe benefits. The total high estimated cost would be $14,510 (135 hours X $107.48). For those PT programs who already have this mechanism in place, there would be no additional burden or cost to meet this requirement.

C. Optional On-Site Visits to PT Programs

At §493.901(e), we propose to add the requirement that HHS may require on-site visits for all initial PT program applications for HHS approval and periodically for previously HHS-approved PT programs either during the reapproval process or as necessary to review and verify the policies and procedures represented in its application and other information, including, but not limited to, review and examination of documents and interviews of staff. There is no collection of information requirements associated with this proposed requirement because the documentation is already being collected and maintained by the PT program as normal course of business and is a usual and customary practice in accordance with implementing regulations at 42 CFR 493, subpart I.

D. PT Program Reapproval

At §493.901(f), we propose to specify that we may require a PT program to reapply for approval using the process for initial applications if widespread or systemic problems are encountered during the reapproval process. If a PT program would need to reapply for approval using the initial application process, we would estimate that the cost would be 10 hours for document collection. The total burden is 90 hours (9 PT programs X 10 hour). However, this would not be an annual burden, rather it would only occur under the circumstances outlined

above, and we believe that these would only occur rarely. An Office/Administrative Support Worker would perform this task at an hourly wage of $17.96 as published in 2017 by the Bureau of Labor Statistics (https://www.bls.gov/oes/current/oes_nat.htm). The wage rate would be $35.92 to include overhead and fringe benefits. The total cost would be $3,233 (90 hours X $35.92).

E. Withdrawal of Approval of a PT Program

At §493.905, we propose to add that HHS may withdraw the approval of a PT program at any point in the calendar year if the PT program provides false or misleading information that is necessary to meet a requirement for program approval or if the PT program has failed to correct issues identified by HHS related to PT program requirements. We are also proposing to add a requirement that the PT program may request reconsideration. We believe this is excepted because of it being an administrative action per 5 CFR 1320.4(a)(2).

IV. Response to Comments

Because of the large number of public comments we normally receive on **Federal Register** documents, we are not able to acknowledge or respond to them individually. We will consider all comments we receive by the date and time specified in the "DATES" section of this preamble, and, when we proceed with a subsequent document, we will respond to the comments in the preamble to that document.

V. Regulatory Impact Analysis

A. Statement of Need

Proficiency testing (PT) has long been recognized as a critical component of a quality management system. It was first required at a national level for some clinical laboratories under CLIA'67. When CLIA'88 was enacted, and its implementing regulations were finalized in 1992,

all clinical laboratories that perform nonwaived testing became subject to the CLIA PT requirements. Since that time, there have been many changes in the practice of laboratory medicine and improvements in the analytical accuracy of test methods, such that HHS decided to assess the need to revise the PT regulations. For example, a number of analytes and tests now used for making clinical decisions were not recognized or commonly used at the time the CLIA PT requirements were published on February 28, 1992 at 42 CFR part 493 (57 FR 7002). Improvements in analytical accuracy required revisions to the criteria for acceptable performance to reflect the current practices. We based our decision to update the regulations and incorporate the changes proposed in this rule upon advice from the CLIAC.

B. Overall Impact

We have examined the impacts of this rule as required by Executive Order 12866 on Regulatory Planning and Review (September 30, 1993), Executive Order 13563 on Improving Regulation and Regulatory Review (January 18, 2011), the Regulatory Flexibility Act (RFA) (September 19, 1980, Pub. L. 96-354), section 1102(b) of the Social Security Act, section 202 of the Unfunded Mandates Reform Act of 1995 (March 22, 1995; Pub. L. 104-4), Executive Order 13132 on Federalism (August 4, 1999) and the Congressional Review Act (5 U.S.C. 804(2)), and Executive Order 13771 on Reducing Regulation and Controlling Regulatory Costs (January 30, 2017).

Executive Orders 12866 and 13563 direct agencies to assess all costs and benefits of available regulatory alternatives and, if regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety effects, distributive impacts, and equity). Section 3(f) of Executive Order 12866 defines a "significant regulatory action" as an action that is likely to result in a rule: (1) having an annual

effect on the economy of $100 million or more in any one year, or adversely and materially affecting a sector of the economy, productivity, competition, jobs, the environment, public health or safety, or state, local or tribal governments or communities (also referred to as "economically significant"); (2) creating a serious inconsistency or otherwise interfering with an action taken or planned by another agency; (3) materially altering the budgetary impacts of entitlement grants, user fees, or loan programs or the rights and obligations of recipients thereof; or (4) raising novel legal or policy issues arising out of legal mandates, the President's priorities, or the principles set forth in the Executive Order. A regulatory impact analysis (RIA) is required for economically-significant regulatory actions that are likely to impose costs or benefits of $100 million or more in any given year.

This proposed regulation is economically significant within the meaning of section 3(f)(1) of the Executive Order since the estimated cost alone is likely to exceed the $150 million annual threshold. However, our upper limit of estimated impact is under the threshold of $150 million for the year of 2018 under Unfunded Mandates Reform Act (UMRA). The proposed rule, if finalized, would revise the CLIA PT requirements and would affect approximately 36,777 clinical laboratories now subject to participation in PT, resulting in some financial implications. In addition, this proposed rule, if finalized, would cause the seven existing CLIA-approved PT programs to incur some costs as they modify their programs to meet the requirements specified in this proposed rule. It may also have an effect on some state PT requirements. We prepared the RIA and found that it did not meet the UMRA threshold for a significant regulatory action.

The RFA requires agencies to analyze options for regulatory relief of small entities if a rule has a significant impact on a substantial number of small entities. For purposes of the RFA, we assume that the great majority of clinical laboratories and PT programs are small entities,

either by virtue of being nonprofit organizations or by meeting the Small Business Administration definition of a small business by having revenues of less than $7.5 million to $38.5 million in any one year. For purposes of the RFA, we believe that approximately 82 percent of clinical laboratories qualify as small entities based on their nonprofit status as reported in the American Hospital Association Fast Fact Sheet, updated January 2017 (https://www.aha.org/system/files/2018-01/fast-facts-us-hospitals-2017_0.pdf) and 100 percent of PT programs are nonprofit organizations. Individuals and states are not included in the definition of a small entity. We are voluntarily preparing a Regulatory Impact Analysis and are requesting public comments in this area to assist us in making this determination in the final rule.

In addition, section 1102(b) of the Social Security Act (the Act) requires us to prepare a regulatory impact analysis if a rule may have a significant impact on the operations of a substantial number of small rural hospitals. This analysis must conform to the provisions of section 603 of the RFA. For purposes of section 1102(b) of the Act, we define a small rural hospital as a hospital that is located outside of a metropolitan statistical area and has fewer than 100 beds. We do not expect this proposed rule, if finalized, would have a significant impact on small rural hospitals. Such hospitals often provide very limited laboratory services and may refer testing for the analytes we propose to add, to larger laboratories. For the small rural hospitals that have laboratories and perform testing for the analytes, we expect that our proposals will add minimal effort since they should already have PT policies and procedures in place. We are unable to estimate the number of laboratories that support small rural hospitals. We are requesting public comments in this area to assist us in making this determination in the final rule.

Section 202 of the Unfunded Mandates Reform Act of 1995 (UMRA) also requires that agencies assess anticipated costs and benefits before issuing any rule whose mandates require

spending in any one year of $100 million in 1995 dollars, updated annually for inflation. In 2018, that threshold is approximately $150 million.25 We do not anticipate this proposed rule would impose an unfunded mandate on states, tribal governments, or the private sector of more than $150 million annually. We request comments from states, tribal governments, and the private sector on this assumption.

Executive Order 13132 establishes certain requirements that an agency must meet when it promulgates a proposed rule (and subsequent final rule) that imposes substantial direct requirement costs on state and local governments, preempts state law, or otherwise has federalism implications. The proposed changes would not have a substantial direct effect on state and local governments, preempt state law, or otherwise have a federalism implication and there is no change in the distribution of power and responsibilities among the various levels of government. We do not believe that this rule would impose substantial direct compliance costs on state and local governments that are not required by statute. We do not believe that a significant number of laboratories affected by these proposals are operated by state or local governments. Therefore, the proposed modifications in these areas would not cause additional costs to state and local governments.

We are proposing to require that each HHS-approved PT program have a minimum of ten laboratory participants before offering any PT analyte. This change reduces some burden on laboratories that have incurred the expense of enrolling in a PT program but do not receive a score or receive an artificial score requiring the laboratory to take additional steps to verify the accuracy of the analyte as required by §493.1236(b)(2). PT programs will determine if it is economically feasible to offer those analytes or if they should market their products to

25 Bush, Laina. HHS Memo on Annual Update to the Unfunded Mandate Reform Act Threshold for 2017, March 24, 2017.

laboratories. Both of these activities are outside the scope of our authority.

C. Anticipated Effects.

This proposed rule, if finalized, would impact approximately 36,777 clinical laboratories (total of Certificate of Compliance and Certificate of Accreditation laboratories, as of January 2017) required to participate in PT under the CLIA regulations implemented by the February 28, 1992 final rule, seven current HHS-approved PT programs, and to a lesser extent, *in vitro* diagnostics (IVD) manufacturers, healthcare providers, laboratory surveyors, and patients. Although complete data are not available to calculate all estimated costs and benefits that would result from the changes proposed in this rule, we are providing an analysis of the potential impact based on available information and certain assumptions. Implementation of these proposed requirements in a final rule would result in changes that are anticipated to have quantifiable impacts on laboratories and non-quantifiable impacts on laboratories, PT programs, and others mentioned above. In estimating the quantifiable impacts, we separated the laboratory specialties into two broad categories that include: (1) proposed PT changes to the microbiology specialty; and (2) proposed PT changes to non-microbiology specialties. This was done because the PT requirements for microbiology differ from those than for other laboratory specialties, and laboratories that are certified to perform microbiology testing may be impacted differently than those that perform non-microbiology clinical testing. In each microbiology subspecialty PT participation is required based on the types of services offered by a laboratory and an overall score is given per that subspecialty. In the other specialties and subspecialties, PT participation is required and scores are given based on specific required analytes listed in the regulations.

For both the microbiology PT changes and addition of proposed analytes to subpart I, we anticipate minimal burden to laboratories as CLIA already requires that laboratories must verify

the accuracy of tests not currently listed in subpart I at least twice annually. We believe many laboratories meet this requirement by participating in proficiency testing voluntarily. However, we do not have a way of estimating how many of these participating laboratories actually meet the requirement through additional verification. Information on the costs of voluntary participation is also not reported. Although we cannot precisely predict how the proposed changes may qualitatively affect clinical laboratories, we do not expect there to be major changes in how they function. We have quantified the costs we expect laboratories to incur but there may be costs associated with other administrative functions related to PT ordering, result reporting, and record keeping that we are not able to estimate. As stated above, we are unable to estimate the number of laboratories voluntarily enrolled in PT which is not currently required in subpart I. Cost of adding a new analyte would range from $0.39 to $86.50; however, the majority of the costs/analyte are less than $5.00 per analyte.

1. Quantifiable Impacts for Laboratories

CDC receives catalogs from all CLIA-approved PT programs annually. We estimated material costs for purchasing PT based on the range of 2017 catalog prices from the seven CLIA-approved PT programs. In estimating the costs for performing PT for all laboratory specialties that would be affected by this regulatory change, we assumed that the average national CMS reimbursement rate for Part B Medicare (CMS Virtual Research Data Center: https://www.resdac.org/cms-data/request/cms-virtual-research-data-center) was a reasonable estimate of the cost the laboratory incurs when testing each sample (or challenge) because this amount represents the average reimbursement to laboratories performing patient testing for that analyte or test. We also assume the cost for testing patient samples is the same as the cost for testing PT samples.

We calculate that, on average, the impact would be between $721 and $3,218 per laboratory, with laboratories having fewer analytes bearing a smaller burden.

a. Impacts of Proposed PT Changes to the Microbiology Specialty

Proposed changes to the microbiology specialty include changes in each of the subspecialties (bacteriology, mycobacteriology, mycology, parasitology, and virology) that would replace the types of services offered and the examples of organisms to be included over time with a proposed list of categories of tests and groups of microorganisms for which PT is required. In addition, changes are being proposed for each individual subspecialty that would require specific PT for certain microbiology tests and procedures. These changes, if finalized, could have a cost impact on laboratories. However, as stated in §493.801(a)(2)(ii) and §493.1236(c)(1), for tests or procedures performed by the laboratory that are not listed in the CLIA regulations subpart I, Proficiency Testing Programs for Nonwaived Testing, a laboratory must verify the accuracy of that test or procedure at least twice annually. Although we can estimate how many microbiology laboratories voluntarily enroll in PT with HHS-approved PT programs to meet this requirement, we cannot estimate how many laboratories meet this requirement through other accuracy verification methods. The numbers of laboratories reported in Table 2 and Table 3 represent those laboratories the CDC was able to verify as voluntarily enrolled in PT for those types of microbiology tests not currently included in subpart I. The number of laboratories affected by this change as well as the cost can be estimated by adding the M1 (that is, laboratories already participating in required microbiology PT) and M2 (that is, laboratories not participating in a PT program for proposed microbiology PT) number in Table 2 and Table 3. For the 7,160 affected microbiology laboratories, the estimated cost of the proposed quantifiable changes to required PT for each microbiology subspecialty follows.

To estimate the costs that would be incurred by laboratories to purchase PT materials for the proposed changes to the microbiology specialty, if finalized, we compiled a range of PT material cost estimates per each challenge using 2017 catalog pricing for each PT program. For this analysis we refer to the PT catalog offerings as "modules". In microbiology, PT programs offer different types of modules. Independent modules such as stain(s), antigen detection, or toxin detection are intended for reporting a result for a single type of test. Many microbiology modules include challenges that address different types of testing. These modules, such as urine culture, may include individual PT challenges for Gram stain, bacterial identification, and antimicrobial susceptibility testing. In many cases, estimating the challenge cost was difficult because PT programs' pricing varies and in some cases the PT challenge cost per microbiology test depends upon whether the test is offered as an individual module or as part of a collection of multiple types of PT challenges in a module. In addition, to accurately estimate the challenge cost, we had to account for differences in the frequency at which the PT programs currently offer their modules and challenges. For example, one PT program may offer an antigen detection module at a frequency of two events per year, and three samples per event (six total samples per year); while another offers a similar module at three events per year, and five samples per event (15 total samples per year). Based upon the module type and frequency, we estimated the total low and high challenge cost for PT material using the range of 2017 catalog prices from the seven CLIA-approved PT programs. Details are explained under each subsection. We acknowledge that these estimated ranges may be higher than the actual costs of requiring additional PT since laboratories may already voluntarily purchase PT to meet the biannual CLIA requirement for verifying the accuracy of testing.

In estimating the number of microbiology laboratories that would be impacted by each of

the proposed changes, we determined the numbers of Certificate of Compliance (CoC) and Certificate of Accreditation (CoA) laboratories for each microbiology subspecialty using the CMS Online Survey Certification & Reporting System (OSCAR)/Quality Improvement and Evaluation System (QIES) database. To categorize the laboratories as described below, the OSCAR/QIES database was used to determine the accreditation organization for each CoA laboratory.

For the analysis of the impact on laboratories by the proposed microbiology PT changes, we used two laboratory categories:

- Laboratories participating in a PT program for already required microbiology PT (Category M1).
- Laboratories not participating in a PT program for proposed microbiology PT (Category M2).

Category M1: Laboratories already participating in required microbiology PT

For proposed changes or additions to required microbiology PT, we used data from the PT program event summaries provided to CDC by the PT programs to estimate the total number of laboratories performing the already required PT. We then used that number to estimate how many laboratories would be affected by proposed changes or additions to the required PT.

Category M2: Laboratories not participating in a PT program for proposed microbiology PT

As stated, we used Certificate of Accreditation data to facilitate the estimation of the number of laboratories that would be subject to proposed microbiology PT and are not already participating in a PT program. Of the seven CLIA-approved accreditation organizations, data were provided by COLA showing how many of the 7,414 COLA-accredited laboratories offer testing for four of the new microbiology tests we are proposing to add to the list for required PT.

We used these data to estimate the percentage of COLA-accredited laboratories that provide testing for these microbiology tests. We assumed that COLA-accredited laboratories are similar to CoC laboratories and laboratories accredited by accreditation organizations other than the College of American Pathologists (CAP). Therefore, we assumed that the percentage of COLA-accredited laboratories that perform a specific microbiology test could be used to approximate the total number of laboratories that perform the test using the OSCAR/QIES data. For the proposed microbiology PT changes, the number of CAP-accredited laboratories was considered negligible because they are already required to purchase PT for all testing performed and were not included in the total. We analyzed each proposed change for the microbiology specialty for each category and added our estimates to obtain the total projected impact to all affected laboratories.

(1) Effects of the Proposed PT Changes in the Bacteriology Subspecialty

In the bacteriology subspecialty, the proposed changes that may have a cost impact include the determination of bacterial morphology as part of the Gram stain module, the addition of bacterial toxin detection as required PT, and the addition of a second antimicrobial susceptibility or resistance testing challenge per year. Gram stain reaction is currently required in the PT regulations and all PT programs that offer a Gram stain PT module also offer the determination of bacterial morphology as part of the same module. We know the numbers of total laboratories enrolled in the PT program modules that require Gram stain reporting from the PT program event summaries. To determine the number of laboratories that would be impacted by this proposed change, if finalized, we calculated the number enrolled in Gram stain PT who do not report the bacterial morphology PT portion of the Gram stain module. Since this change would require that laboratories already performing PT report bacterial morphology in addition to

Gram stain reaction on each challenge, we estimate the cost impact would be minimal. Since laboratories are already participating in Gram stain PT and we know the numbers of laboratories not currently participating in the determination of bacterial morphology, the range of estimated costs was determined by using the number of category M1 laboratories that perform Gram stain; the estimate of the cost the laboratory incurs when testing each challenge, using the average national CMS reimbursement rate for Part B Medicare; the low price and high price per challenge for PT (based on PT program catalog variations); and the number of challenges required per year using one challenge for the low estimate and 15 challenges for the high estimate (Tables 2 and 3).

To evaluate the impact of requiring PT for bacterial toxin detection, we determined the total number of category M2 laboratories for bacteriology. Laboratories performing voluntary PT for bacterial toxin detection are already meeting the proposed PT requirements. Since CAP-accredited laboratories are already required to perform PT if they perform bacterial toxin detection, we assumed they are already meeting the proposed PT requirements and did not include them in our estimate. The range of estimated costs was determined by using the number of category M2 impacted laboratories that perform bacterial toxin detection; the estimate of the cost the laboratory incurs when testing each challenge, using the average national CMS reimbursement rate for Part B Medicare; the low price and high price per challenge for PT (based on PT program catalog variations); and the number of challenges required per year using one challenge for the low estimate and 15 challenges for the high estimate (Tables 2 and 3).

Currently, one sample or challenge per testing event is required for antimicrobial susceptibility testing in bacteriology. To evaluate the proposed impact of increasing the required antimicrobial susceptibility or resistance testing from currently required one challenge per year

to a proposed two challenges per year, we calculated the total number of category M1 laboratories already participating in PT for antimicrobial susceptibility testing. The range of estimated costs was determined by using the number of category M1 laboratories that currently perform antimicrobial susceptibility testing; the estimate of the cost the laboratory incurs when testing each challenge, using the average national CMS reimbursement rate for Part B Medicare; the low price and high price per challenge for PT (based on PT program catalog variations); and the number of challenges required per year using one challenge for the low estimate (Tables 2 and 3). Considering all of the potential cost impacts, the range of estimated impact for the proposed bacteriology subspecialty changes for the first year would be $101,785 to $2,599,552.

(2) Effects of the Proposed PT Changes in the Mycobacteriology Subspecialty

In the mycobacteriology subspecialty, the proposed changes that may have a cost impact include the addition of a second antimycobacterial susceptibility or resistance testing challenge per year. The same type of analysis that was performed to evaluate the proposed impact of increasing the required bacterial antimicrobial susceptibility or resistance testing from one challenge to two challenges per year was performed to evaluate the proposed impact of increasing the required antimycobacterial susceptibility or resistance testing from one challenge to two challenges per year (Tables 2 and 3). The range of estimated impact for the proposed mycobacteriology subspecialty changes for the first year would be $12,558 to $39,420.

(3) Effects of the Proposed PT Changes in the Mycology Subspecialty

In the mycology subspecialty, the proposed changes that may have a cost impact include the addition of required PT for direct fungal antigen detection, detection of growth or no growth in culture media, and the addition of two antifungal susceptibility or resistance testing challenges per year. To evaluate the impact of the proposed regulated PT for direct fungal antigen

detection, we determined the total number of category M2 laboratories for mycology. Laboratories performing voluntary PT for direct fungal antigen detection are already meeting the proposed PT requirements. Since CAP-accredited laboratories are already required to perform PT if they perform direct fungal antigen detection, we assumed they are already meeting the proposed PT requirements and did not include them in our estimate. The range of estimated costs was determined by using the number of category M2 impacted laboratories that perform direct fungal antigen detection; the estimate of the cost the laboratory incurs when testing each challenge, using the average national CMS reimbursement rate for Part B Medicare; the low price and high price per challenge for PT (based on PT program catalog variations); and the number of challenges required per year using one challenge for the low estimate and 15 challenges for the high estimate (Tables 2 and 3).

The proposal to add detection of growth or no growth in culture media to the mycology PT identification would impact laboratories that are currently performing dermatophyte identification using dermatophyte test medium to determine the presence or absence of dermatophytes in a patient specimen. We calculated the impact of this proposal using the same methodology as was performed to determine the impact of the proposal to include direct fungal antigen detection (Tables 2 and 3).

Because COLA did not indicate that any of their accredited laboratories participate in antifungal susceptibility or resistance testing, we assumed that no CoC or CoA laboratories other than those accredited by CAP would be required to participate in PT for antifungal susceptibility or resistance testing. Therefore, the cost impact of the proposed change to include two antifungal susceptibility or resistance testing challenges per year was calculated using the total number of category M1 laboratories that participate in CAP PT for antifungal susceptibility

testing, the only program that offers challenges, as the number of impacted laboratories. The range of estimated costs was determined by using the number of CAP category M1 impacted laboratories that perform antifungal susceptibility or resistance testing; the estimate of the cost the laboratory incurs when testing each challenge; based on the average national CMS reimbursement rate for Part B Medicare; the low price and high price per challenge for PT (based on PT program catalog variations); and the number of challenges required per year using one challenge for the low estimate (Tables 2 and 3). Considering all of the potential cost impacts, the range of estimated impact for the proposed mycology subspecialty changes for the first year would be $41,235 to $422,406.

(4) Effects of the Proposed PT Changes in the Parasitology Subspecialty

In the parasitology subspecialty, the proposed change that may have a cost impact is the addition of required PT for direct parasite antigen detection. To evaluate the potential impact of this addition, we determined the total number of category M2 laboratories for parasitology. Laboratories performing voluntary PT for direct parasite antigen detection are already meeting the proposed PT requirements. Since CAP-accredited laboratories are already required to perform PT if they perform direct parasite antigen detection, we assumed they are already meeting the proposed PT requirements and did not include them in our estimate. The range of estimated costs was determined by using the number of category M2 impacted laboratories that perform direct parasite antigen detection; the estimate of the cost the laboratory incurs when testing each challenge, using the average national CMS reimbursement rate for Part B Medicare; the low price and high price per challenge for PT (based on PT program catalog variations); and the number of challenges required per year using one challenge for the low estimate and 15 challenges for the high estimate (Tables 2 and 3). Considering all of the potential cost impacts,

the range of estimated impact for the proposed parasitology subspecialty changes for the first year would be $14,151 to $678,696.

(5) Effects of the Proposed PT Changes in the Virology Subspecialty

In the virology subspecialty, the proposed change that may have a cost impact includes the addition of two antiviral susceptibility or resistance testing challenges per year. Because COLA did not indicate that any of their accredited laboratories participate in antiviral susceptibility or resistance testing, we assumed that no CoC or CoA laboratories other than those accredited by CAP would be required to participate in PT for antiviral susceptibility or resistance testing. Therefore, the cost impact of the proposed change to include two antiviral susceptibility or resistance testing challenges per year was calculated using the total number of category M1 laboratories that participate in CAP PT for antiviral susceptibility or resistance testing, the only program that had subscribers to a PT module, as the number of impacted laboratories. The range of estimated costs was determined by using the number of CAP category M1 impacted laboratories that perform antiviral susceptibility or resistance testing; the estimate of the cost the laboratory incurs when testing each challenge, using the average national CMS reimbursement rate for Part B Medicare; the low price and high price per challenge for PT (based on PT program catalog variations); and the number of challenges required per year using one challenge for the low estimate (Tables 2 and 3). Considering all of the potential cost impacts, the range of estimated impact for the proposed virology subspecialty changes for the first year would be $216,318 to $314,145.

TABLE 2: Low Estimate for Proposed Microbiology PT Regulatory Changes

Proposed PT Regulation Change	Total Number of Affected M1 Laboratories	Total Number of Affected M2 Laboratories	Labor*	Supply/Material Cost**	TOTAL Low Impact for One Challenge	Total Low Impact for Microbiology Regulation Changes
Gram Stain including Morphology	26	0	$4.54	$4.67	$239.46	$386,047
Bacterial Toxin Detection	0	1542	$14.22	$11.44	$39,567.72	
Antimicrobial susceptibility and/or resistance testing	3281	0	$9.89	$9.00	$61,978.09	
Antimycobacterial susceptibility or resistance testing	454	0	$4.33	$23.33	$12,557.64	
Direct fungal antigen detection	0	96	$14.22	$16.00	$2,901.12	
Detection of growth or no growth in culture media - dermatophytes (DTM)	0	527	$8.16	$16.00	$12,732.32	
Antifungal susceptibility or resistance testing	0	369	$9.89	$24.80	$12,800.61***	
Direct parasite antigen detection	0	533	$14.22	$12.33	$14,151.15	
Antiviral susceptibility or resistance testing	332	0	$230.11	$95.67	$108,158.96[3]	

*Average national CMS reimbursement rate for Part B Medicare (CMS Virtual Research Data Center: https://www.resdac.org/cms-data/request/cms-virtual-research-data-center).

**Low 2017 PT catalog price per challenge.

***Total low impact is multiplied by two for the proposal to add two new susceptibility or resistance testing challenges.

TABLE 3: High Impact for Proposed Microbiology PT Regulations

Proposed PT Regulation Change	Total Number of Affected M1 Laboratories	Total Number of Affected M2 Laboratories	Labor[1]	Supply/Material Cost[2]	TOTAL High Impact/for one challenge	TOTAL High Impact/for 15 challenges	Total High Impact for Microbiology Regulation Changes
Gram Stain including Morphology	26	0	$4.54	$15.00	$508.04	$7,620.60	$4,054,219
Bacterial Toxin Detection	0	1542	$14.22	$91.50	$163,020.24	$2,445,303.60	
Antimicrobial susceptibility and/or resistance testing	3281	0	$9.89	$34.80	$146,627.89	N/A	
Antimycobacterial susceptibility or resistance testing	454	0	$4.33	$82.50	$39,420.82	N/A	
Direct fungal antigen detection	0	96	$14.22	$31.80	$4,417.92	$66,268.80	
Detection of growth or no growth in culture media - dermatophytes (DTM)	0	527	$8.16	$33.00	$21,691.32	$325,369.80	
Antifungal susceptibility or resistance testing	0	369	$9.89	$31.80	$15,383.61[3]	N/A	
Direct parasite antigen detection	0	533	$14.22	$70.67	$45,246.37	$678,695.55	
Antiviral susceptibility or resistance testing	332	0	$230.11	$243.00	$157,072.52[3]	N/A	

[1] Average national CMS reimbursement rate for Part B Medicare (CMS Virtual Research Data Center: https://www.resdac.org/cms-data/request/cms-virtual-research-data-center).

[2] High 2017 PT catalog price per challenge.

[3] Total low impact is multiplied by two for the proposal to add two new susceptibility or resistance testing challenges.

b. Impacts of Proposed PT Changes to the Non-microbiology Specialties/Subspecialties

The proposed changes in specialties and subspecialties other than microbiology include adding 29 new analytes at the frequency of three events per year and five challenges per event. According to CLIA, laboratories with Certificates of Compliance and Certificates of Accreditation are required to perform PT. There are 36,777 clinical laboratories that will be affected (19,287 Certificate of Compliance and 17,490 Certificate of Accreditation laboratories). This will be a new burden for some laboratories, but many laboratories are already paying for PT of these analytes. As previously mentioned, in §§493.801(a)(2)(ii) and 493.1236(c)(1), for tests or procedures performed by the laboratory that are not listed in the CLIA regulations subpart I, the laboratory must verify the accuracy of that test or procedure at least twice annually. Since laboratories may voluntarily enroll in PT as one way to meet this requirement, we assume the added burden would be minimal. We have evidence from laboratories that responded to our national PT survey (Earley, Astles, and Breckenridge, 2017) that of those who were not already required by the CAP to perform PT on more than the CLIA-required analytes, 39 percent purchased PT for 1 to 5 analytes, 17 percent for 6 to 10 analytes, 10 percent for 11 to 20 analytes, and 10 percent for more than 20 analytes. We estimated the costs for proposed analytes by grouping all affected laboratories into four categories, calculating the number of laboratories in each category and calculated the costs using the analyte price and test reimbursement rate. We also propose to tighten acceptance limits of several currently-required analytes, which may have an impact on laboratories, but the cost impact is not included in our estimate. In addition, we are proposing to delete five currently-required analytes (ethosuximide, LDH isoenzymes, primidone, procainamide/NAPA, and quinidine) that are infrequently performed. As such, we do not anticipate this being a substantial cost savings since laboratories may continue to use PT

voluntarily as a way of meeting the biannual accuracy verification requirement.

Three issues had to be considered to estimate the costs for PT materials for proposed analytes: PT programs may offer analytes as an individual analyte or as part of a module that combines multiple analytes; some of the proposed analytes may already be offered but at a frequency other than the CLIA-required frequency (3 X 5 = 15 samples per year); and the extent to which laboratories already use PT varies – that is, laboratories accredited by the CAP are required to enroll in PT for each test they perform. For all these reasons, laboratories enrolled in different PT programs will be impacted differently. Based on this observation and our inability to make estimates at the level of individual laboratories, we accounted for each of these variations when calculating the costs incurred.

To account for the different prices each PT program charges for different analytes, either alone or in different combinations, we used a range of estimates based upon the programs' unit costs for PT currently offered. We used two approaches to estimate the cost of individual PT analytes. If the analyte was offered individually by the PT program, we used that price. However, if the analyte was not offered individually, we divided the panel price by the total number of analytes in the panel to estimate the cost per analyte, which is used as individual analyte price. For the lower cost estimate, we selected the lowest individual analyte price among all PT programs. For the higher cost estimate, we used the highest individual analyte price. In some cases, PT programs offer PT for the proposed analytes at different frequencies, that is, different numbers of events per year and different numbers of challenges per event. Therefore, to accurately estimate the future unit costs, we had to calculate the increased frequency for each analyte in order to achieve three events/year with five challenges per event.

The proposed rule will have different impacts on CoA laboratories mainly because the

CAP has strict requirements for PT participation that exceed CLIA minimal requirements, while other accreditation organizations may not. Therefore, our analysis starts with CAP-accredited laboratories as CAP is not only a large accreditation organization but also the largest PT program. In estimating the number of affected laboratories resulting from the proposed PT changes, if finalized, we acknowledged that any CAP-accredited laboratory that offers patient testing for one of the CAP PT program analytes must enroll in the relevant program for that analyte. However, CAP-accredited laboratories are permitted to enroll in PT from other CAP-approved PT programs for certain analytes and only for specific programs. Laboratories not accredited by the CAP may purchase PT materials from any CMS-approved PT program, including the CAP PT program. Therefore, we have designated four categories to estimate the cost impact, if the proposed changes are finalized:

- Category 1: Laboratories accredited by the CAP that purchase material from the CAP PT program: The CAP provided us with the number of their accredited laboratories that are enrolled in their PT program for each proposed analyte. The cost increase was calculated on a per analyte basis by multiplying the cost per sample (PT material + CMS reimbursement amount) by the increase in frequency of samples and the number of laboratories that purchase PT from the CAP PT program.

- Category 2: CAP-accredited laboratories that purchase PT materials from other PT programs: For the analytes we considered adding, CAP-accredited laboratories are already required by CAP to enroll in a CAP-approved PT program. Ordinarily CAP-accredited laboratories enroll in the CAP PT program but they are permitted to enroll in PT from other CAP-approved PT programs. Using the data the CAP provided, we calculated the total number of CAP-accredited laboratories enrolled in one of the other PT programs provided through PT

Program A, PT Program D, PT Program E, or PT Program G. The cost increase in this category was calculated on a per analyte basis. We were able to obtain the enrollment distribution of the CAP-accredited laboratories in each of the non-CAP PT programs. The enrollment of laboratories not accredited by the CAP in each of the non-CAP PT programs (Category 4) was also available. Because the methodology to calculate Category 2 is the same as Category 4, we combine these two categories by using the enrollment of all laboratories (CAP-accredited laboratories and laboratories not accredited by the CAP) in each of the non-CAP PT program in the calculation.

- Category 3: Laboratories not already enrolled in a PT program: To derive the minimum and maximum number of laboratories not already enrolled in a PT program that may provide testing for the proposed analytes, we began by estimating that there are 29,927 laboratories that perform nonwaived testing and are not accredited by the CAP in the United States. To facilitate the calculations, we presumed that laboratories not accredited by the CAP will not purchase CAP PT. From the OSCAR/QIES database, we derived the number of laboratories not accredited by the CAP that provide testing in each specialty and reasoned that this was the maximum number of laboratories not accredited by the CAP that might provide testing for each analyte.

COLA provided us with the percentages of the approximately 7,414 COLA-accredited laboratories that perform testing for each proposed analyte. We determined that COLA-accredited laboratories are similar to CoC laboratories in terms of their annual test volumes. Therefore, we assumed that the percentage of COLA-accredited laboratories that test each proposed analyte could be used to estimate the number of CoC and CoA (other than CAP- or COLA-accredited) laboratories that test each analyte.

We used the percentage of CAP-accredited laboratories that participate in PT for each proposed analyte to estimate the maximum number of CoC and CoA (other than CAP and COLA) laboratories that test each analyte. This percentage was much higher for many of the analytes when compared to the laboratories accredited by organizations other than the CAP. Since CAP-accredited laboratories are often either hospital-based or commercial laboratories that already participate in PT for the additional analytes, approximations for high estimates may substantially overestimate the number of laboratories impacted.

Using the above information, we calculated low and high estimates for the total number of non-CAP-accredited, CoC and CoA laboratories that may provide testing for each proposed analyte.

For each proposed analyte, we calculated the number of CAP-accredited laboratories that buy from non-CAP PT programs by subtracting the CAP-accredited laboratories enrolled in CAP PT from the total number of CAP-accredited laboratories.

We derived a low estimate of the total number of laboratories not accredited by the CAP and not enrolled in one of the non-CAP PT programs for each analyte. Negative estimates were taken as "0". This represents our low estimate of the number of laboratories that will need to purchase PT for each analyte.

To obtain the high estimate for the number of laboratories not accredited by the CAP and not enrolled in one of the non-CAP PT programs, we took the high estimate of CoA laboratories not accredited by the CAP and CoC laboratories and subtracted the number of this subset of CoA laboratories already known to be enrolled in PT. For the high estimate of the number of laboratories not accredited by CAP and not enrolled in one of the non-CAP PT programs, we also used an additional criterion of the number of laboratories in the respective specialty from

OSCAR/QIES to limit the estimate at the number of laboratories in the specialty. If this number was less than the high estimate of CoC laboratories and CoA laboratories accredited by a program other than the CAP, then the high estimate was calculated by subtracting the number of laboratories not accredited by CAP and not enrolled in one of the non-CAP PT programs from the total number of laboratories in the specialty.

The cost increase in this category was calculated on a per analyte basis. The minimum cost per sample that was the lowest across all eight non-CAP PT programs and the maximum cost per sample that was the highest across all eight non-CAP PT programs were used for these calculations. The minimum cost increase was calculated by multiplying the minimum cost per sample, including the CMS reimbursement amount, by the number of laboratories that are not purchasing PT from any PT program. The same calculation was made using the maximum cost per sample for the maximum cost increase.

- Category 4: Laboratories not accredited by the CAP and enrolled in PT programs other than the CAP PT program: We obtained the number of laboratories enrolled in PT programs other than the CAP PT program and subtracted the number of CAP-accredited laboratories enrolled in a non-CAP PT program per analyte for this category. The cost increase in this category was calculated on a per analyte basis. The estimated cost increases were calculated for each of the non-CAP PT programs for which information was available. The minimum increase was calculated for each of the PT programs by multiplying the cost per sample, including the CMS reimbursement amount, by the increase in frequency of samples and the number of laboratories that purchase PT from that individual program. To determine the maximum increase, the same calculation was made using the highest cost per analyte including the CMS reimbursement amount.

c. Results

We estimate that the overall impact of adding requirements for the proposed analytes in the specialties and subspecialties other than microbiology will range from $26 to $114 million for the first year (Table 4), if these proposed changed are finalized. Because of their larger number, and the fact that non-CAP accredited laboratories tend not to enroll in non-required PT as frequently as CAP-accredited laboratories do, we estimate that non-CAP accredited laboratories that are not enrolled in any PT program will have an impact between $16 and $100 million for the first year. We also estimate that laboratories that are enrolled in PT programs other than CAP will have a relatively minor impact, $5.4 million for the first year (Table 4).

TABLE 4: Estimated Impact for Proposed Non-Microbiology PT Regulations for the First Year in 2017 Dollars

Category	Low Estimate	High Estimate
1. Laboratories accredited by CAP that purchase material from the CAP PT program	4,516,673	4,516,673
2. Laboratories accredited by CAP that purchase PT materials from other PT programs	Included in Category 4	Included in Category 4
3. Laboratories not accredited by CAP that not already enrolled in other PT programs	16,248,746	100,303,499
4. Laboratories not accredited by CAP enrolled in other PT programs (category 2 and 4 combined)	5,351,565	4,103,686
Total increased cost	**$26,116,984**	**$114,275,423**

For each of the four categories of affected laboratories previously described, Table 5 shows the total estimated range of annual cost for the proposed changes (including both microbiology and non-microbiology) in undiscounted 2017 dollars and discounted at 3 percent and 7 percent to translate expected costs in any given future years into present value terms. The base year is 2017 for the calculations displayed in Table 5 and we assume inflation-adjusted costs in future years to be the same as costs in the base year.

TABLE 5: Total Estimated Annual Costs for Proposed PT Regulations
(All Specialties in Both Microbiology and Non-microbiology)

	Undiscounted (2017 $)			Discounted at 3 percent			Discounted at 7 percent		
	Primary	Low[#]	High[&]	Primary	Low	High	Primary	Low	High
2019	$72,416,336	$26,503,031	$118,329,642	$68,259,342	$24,981,649	$111,537,036	$63,251,232	$23,148,774	$103,353,692
2020	$72,416,336	$26,503,031	$118,329,642	$66,271,206	$24,254,028	$108,288,385	$59,113,301	$21,634,368	$96,592,236
2021	$72,416,336	$26,503,031	$118,329,642	$64,340,977	$23,547,600	$105,134,354	$55,246,076	$20,219,035	$90,273,117
2022	$72,416,336	$26,503,031	$118,329,642	$62,466,968	$22,861,748	$102,072,188	$51,631,847	$18,896,294	$84,367,399
2023	$72,416,336	$26,503,031	$118,329,642	$60,647,542	$22,195,871	$99,099,212	$48,254,062	$17,660,088	$78,848,037

[#] Total low cost is the sum of Table 2 (microbiology) and Table 4 (non-microbiology).

[&] Total high cost is the sum of Table 3 (microbiology) and Table 4 (non-microbiology).

2. Non-quantifiable Impacts

If the changes proposed in this rule are finalized, a number of non-quantifiable impacts will also result for PT programs and laboratories. We solicit comments and data to facilitate the determination of quantifiable estimates in the final rule.

As with any currently required PT, if finalized, the proposed regulation would not require approved PT programs to offer additional analytes. Several programs already offer the analytes or tests that would be required by laboratories, and in these cases, we expect minimal impact on the PT programs. If the proposed changes outlined in this rule are finalized, we expect there will initially be some increased expenditures for PT programs to implement the changes, even if they are only scaling up currently offered PT. At the same time, PT programs will also increase revenue received if they increase the PT analytes or tests they offer. We have no way to estimate how many programs may choose to offer additional PT analytes or tests, but we assume that most will implement the changes included in the final rule. For some programs, this would mean offering an analyte or test for the first time, while for others it would mean increasing the yearly number of events and/or challenges per event. The costs would be relatively less for the programs that are already offering the PT analytes or tests, including those currently offering challenges at less than the PT frequency required under CLIA. There are also differences in what the PT programs charge laboratories for PT which would change the impact of the final rule. In part, these differences depend upon the total number of samples distributed per year and how the PT is packaged; some PT is sold as modules that group several related analytes together. Because CLIA-approved PT programs are required to maintain non-profit status, any increased revenue that results from an expanded PT menu will not be turned into profit. We have attempted to account for the

quantifiable impacts in our estimates for laboratories.

If the proposed analyte deletions are finalized, some PT programs may cease offering the deleted analytes, others may continue to offer them at a frequency less than that required under CLIA, and still others may continue to offer them at the PT frequency required under CLIA. For these reasons, we are unable to estimate the cost impact to PT programs for this change. We solicit comments and data that would help us estimate the impact of the PT changes on PT programs in the final rule.

Although we cannot precisely predict how the proposed changes may affect clinical laboratories, we do not expect there to be major changes in how they function. We have quantified the costs we expect laboratories to incur but there may be costs associated with other administrative functions related to PT ordering, result reporting, and record keeping that we are not able to estimate. For those laboratories that currently purchase PT for the five analytes we propose to delete, we cannot estimate the lowered expenditure for laboratories that stop buying PT materials and must begin doing something else to verify accuracy. Based upon our focus groups and surveys, we know there are a variety of things laboratories may do to externally verify accuracy, ranging from splitting samples with other laboratories to purchasing PT materials voluntarily. Also, we do not know the extent to which split samples are tested, or how many patient samples might be tested in this way; there is no stated minimum number of specimens that must be tested semi-annually to verify accuracy. Therefore, we have not attempted to estimate the costs for alternative approaches that may be adopted to verify accuracy for the deleted analytes. Regardless of how laboratories might be impacted, we expect that they will not spend more than they currently spend on PT for the analytes we propose to delete, but we cannot estimate this. By not attempting to estimate the number of

laboratories that may stop buying PT material for the deleted analytes, we may be slightly overestimating the net impact.

3. Benefits

While we cannot quantify the benefits that the proposed changes will bring, if finalized, we believe that the changes will facilitate more rapid identification of unacceptable practices in laboratories, especially for those laboratories that have not previously participated in PT. There are very few published reports that have investigated the impact of PT performance on testing accuracy or patient outcomes. In part this is because performing PT is now a standard practice for most analytes we are considering to add, so it is not possible to separate cohorts of PT users from non-users[26],[27],[28],[29]. In addition, remediation after identification of problems should also occur more quickly and clinical test results of marginal or inferior quality are less likely to be used as analytical systems will improve. All of these things will serve to minimize the potential adverse impact to patients and benefiting physicians and healthcare providers that could occur with inaccurate testing.

PT performance partially reflects daily clinical laboratory performance (Stull, Hearn, Hancock, Handsfield, and Collins, 1998). Updating acceptance limits will benefit laboratories by helping to ensure the accuracy and reliability of testing and providing a mechanism for laboratories to be held accountable for clinically appropriate patient test results, which directly affects the public's health (Astles, Tholen, and Mitchell, 2016).

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26 Reilly AA Salkin IF McGinnis MR et al. . Evaluation of mycology laboratory proficiency testing. J Clin Microbiol . 1999;37:2297–2305.

27 Parsons PJ Reilly AA Esernio-Jenssen D et al. . Evaluation of blood lead proficiency testing: comparison of open and blind paradigms. Clin Chem . 2001;47:322–330.

28 Shahangian S and Snyder SR. Laboratory Medicine Quality Indicators: A Review of the Literature. American Journal of Clinical Pathology, 2009; 131: 418–431.

29 Jenny RW and Jackson KY. PT performance as a predictor of accuracy of routine patient testing for theophylline. Clin Chem 1993; 39:76-81.

Both clinical laboratories and patients can benefit from continued monitoring of PT to help assess the success of intervention efforts to improve the overall quality of clinical laboratory testing.[30]

Another benefit that may result from adding new PT analytes and tests and updating the limits for acceptable PT performance under CLIA includes the generation of additional information on test performance and sources of errors that PT programs can share with laboratories (Howerton, Krolak, Manasterski, and Handsfield, 2010). Such information can also be used as a source of training and can help to maintain the competency of testing personnel (Garcia, et al, 2014).

Last, while we do not anticipate that the changes being proposed in this rule would incur any costs on the IVD industry, we expect the IVD industry to potentially benefit by the changes made in this proposed rule when finalized. Having the ability to track PT results for the added analytes will enable better and faster detection of problems with product manufacturing, including reagent problems. We are aware that some IVD manufacturers enroll in PT and are able to track the performance of the peer groups using their instruments in summary reports issued by the PT programs.

Ultimately, we believe that laboratories, healthcare providers, patients, and the IVD industry will benefit from improved analytical performance (Howerton, Krolak, Manasterski, and Handsfield, 2010) that is expected to occur when this rule becomes finalized.

D. Alternatives Considered

In proposing these changes, several alternatives were considered. We considered

[30] Bainbridge, J., C.L. Wilkening, W. Rountree, R. Louzao, J. Wong, N. Perza, A. Garcia, T.N. Denny The Immunology Quality Assessment Proficiency Testing Program for CD3+4+ and CD3+8+ Lymphocyte Subsets: A ten year review via longitudinal mixed effects modeling. NIH Public Access Author Manuscript (July 2014).

the possibility of changing either the required frequency of PT events per year or changing the number of required PT challenges per event. Responses from our national survey did not support changing either parameter, nor did CLIAC recommend any changes to the required PT frequency or number of challenges per event. We did not perceive a benefit from either reducing or increasing the number of events per year. Reducing the number of events to two per year and keeping all other factors the same would cost less compared to the proposed rule, but it would delay the potential time it takes to identify a poor performing laboratory as "unsuccessful" to at least 12 months, instead of the current 8 months. Increasing the number of events might help to identify a laboratory with testing issues slightly earlier, but increasing the number of events would increase costs. We are proposing to continue to require five challenges per event, with a passing score generally defined as a minimum of four challenges falling within the criteria for acceptable performance. A minimum of five challenges per event are necessary to follow the approach taken in the final regulation implementing CLIA'88 which states that a minimum event score should be 80 percent to be successful allowing for one missed result per event.

For the microbiology specialty, we considered the possibility of including required PT analytes in each subspecialty at a frequency of three events per year with five challenges per event. We determined that the increase in required PT would result in an additional impact of over $5.3 million to laboratories that would be required to perform susceptibility or resistance testing for 15 challenges per year. For the non-microbiology specialties and subspecialties, we could have opted not to add any new PT analytes, but testing of the analytes we are proposing to add is widespread and is important in clinical decision making and public health testing. We also considered adding all analytes for

which there was at least one existing PT program, but we believed this alternative would have been excessively burdensome as it would mean adding hundreds of new required analytes which may not be necessary to identify problematic laboratory performance. We could have left the acceptance limits as they were established in CLIA '88, but we believe those are outdated given advancements in technology. We considered retaining the definition of peer group established in CLIA '88, but we decided this would be too expensive and ultimately unworkable because it would require PT programs to perform commutability testing using analyzers from multiple peer groups every time a new batch of PT materials was created. We are requesting public comments related to alternative changes to be considered to assist us in finalizing this rule.

E. Accounting Statement and Table

We have prepared the following accounting statement showing the classification of expenditures associated with the provisions of this proposed rule.

TABLE 6: Accounting Table

Category	Primary Estimate	Minimum Estimate	Maximum Estimate	Units			Source Citation
				Year Dollars	Discount Rate	Period Covered	
Benefits							
Qualitative	• More effective detection of laboratories that provide inaccurate laboratory test results. • Increased confidence in laboratory test results.						Preamble and Impact Analysis
Costs							
Annualized Monetized $/year	$72,416,336	$26,503,031	$118,329,642	2017	0%	2019-2028	Impact Analysis
	$70,307,122	$25,731,098	$114,883,148	2017	3%	2019-2028	
	$67,678,819	$24,769,188	$110,588,450	2017	7%	2019-2028	

F. Regulatory Reform Analysis under EO 13771

Executive Order 13771, titled Reducing Regulation and Controlling Regulatory Costs, was issued on January 30, 2017 and requires that the costs associated with

significant new regulations "shall, to the extent permitted by law, be offset by the elimination of existing costs associated with at least two prior regulations." This proposed rule, if finalized, is considered an EO 13771 regulatory action. We estimate that this rule would generate $58.0 million in annualized costs in 2016 dollars, discounted at 7 percent relative to year 2016 over a perpetual time horizon. Details on the estimated costs of this rule can be found in the preceding analyses.

G. Conclusion

We estimate that the cost to laboratories to participate in PT for the analytes and tests proposed in this rule would cost between $26,503,031 and $118,329,642 in 2017 dollars. Although the effect of the changes proposed will increase laboratory costs, implementation of these changes in a final rule will increase the confidence of laboratory professionals and the end-users of test results, including physicians and other healthcare providers, patients, and the public, in the reliability and accuracy of test results.

We have determined that this rule would not have a significant economic impact on a substantial number of small entities or a significant impact in the operations of a substantial number of small rural hospitals and for these reasons, we are not preparing analyses for either the RFA or section 1102(b) of the Act.

In accordance with the provisions of Executive Order 12866, this proposed regulation was reviewed by the Office of Management and Budget.

List of Subjects in 42 CFR Part 493

Administrative practice and procedure, Grant programs-health, Health facilities, Laboratories, Medicaid, Medicare, Penalties, Reporting and recordkeeping requirements

For the reasons set forth in the preamble, the Centers for Medicare & Medicaid Services proposes to amend 42 CFR part 493 as set forth below:

PART 493—LABORATORY REQUIRMENTS

1. The authority citation for part 493 is revised to read as follows:

Authority: 42 U.S.C. 263a, 1302, 1395x(e), the sentence following 1395x(s)(11) through 1395x(s)(16).

2. Section 493.2 is amended by—

a. Adding the definitions of "Acceptance limit" and "Peer group" in alphabetical order;

b. Revising the definition of "Target value"; and

c. Adding the definition of "Unacceptable score" in alphabetical order.

The additions and revision read as follows:

§493.2 Definitions.

* * * * *

Acceptance limit is the symmetrical tolerance (plus and minus) around the target value.

* * * * *

Peer group is a group of laboratories whose testing process utilizes similar instruments, methodologies, and/or reagent systems and is not to be assigned using the reagent lot number level.

* * * * *

Target value for quantitative tests is:

(1) If the peer group consists of 10 participants or greater:

(i) The mean of all participant responses after removal of outliers (that is, those

responses greater than three standard deviations from the original mean, as applicable); or

(ii) The mean established by a definitive method or reference methods; or

(iii) The mean of a peer group, in instances when a definitive method or reference methods are not available; or

(iv) If the peer group consists of fewer than 10 participants, "target value" means the overall mean after outlier removal (as defined in paragraph (1) of this definition) unless acceptable scientific reasons are available to indicate that such an evaluation is not appropriate.

(2) [Reserved]

* * * * *

Unacceptable score is a PT result that is outside of the criteria for acceptable performance for a single challenge or sample.

* * * * *

3. Section 493.20 is amended by revising paragraph (c) to read as follows:

§493.20 Laboratories performing tests of moderate complexity.

* * * * *

(c) If the laboratory also performs waived tests, compliance with §493.801(a) and (b)(7) and subparts J, K, and M of this part is not applicable to the waived tests. However, the laboratory must comply with the requirements in §493.15(e), §§493.801(b)(1) through (6), 493.1771, 493.1773, and 493.1775.

4. Section 493.25 is amended by revising paragraph (d) to read as follows:

§493.25 Laboratories performing tests of high complexity.

* * * * *

(d) If the laboratory also performs waived tests, compliance with §§493.801(a) and 493.801(b)(7) and subparts J, K, and M of this part are not applicable to the waived tests. However, the laboratory must comply with the requirements in §§493.15(e), 493.801(b)(1) through (6), 493.1771, 493.1773, and 493.1775.

5. Section 493.801 is amended by –

a. Redesignating paragraphs (b)(3) through (6) as paragraphs (b)(4) through (7), respectively; and

b. Adding new paragraph (b)(3).

The addition reads as follows:

§493.801 Condition: Enrollment and testing of samples.

* * * * *

(b) * * *

(3) The laboratory must report PT results for microbiology organism identification to the highest level that it reports results on patient specimens.

* * * * *

6. Section 493.861 is amended by revising paragraph (a) to read as follows:

§493.861 Standard; Unexpected antibody detection.

(a) Failure to attain an overall testing event score of at least 100 percent is unsatisfactory performance.

* * * * *

7. Section 493.901 is amended by—

a. Redesignating paragraphs (a), (b), (c), and (d) as paragraphs (b), (c), (d), and (e), respectively;

b. Adding new paragraph (a);

c. Redesignating newly redesignated paragraphs (c)(6) and (7) as paragraphs (c)(7) and (8), respectively;

d. Adding new paragraph (c)(6);

e. Revising newly redesignated paragraph (c)(8);

f. Adding paragraph (c)(9);

g. Revising newly redesignated paragraph (e); and

h. Adding paragraph (f).

The additions and revisions read as follows:

§493.901 Approval of proficiency testing programs.

* * * * *

(a) Require a minimum of ten laboratory participants before offering a proficiency testing analyte;

* * * * *

(c) * * *

(6) For those results submitted electronically, a mechanism to track changes to any result reported to the proficiency testing program and the reason for the change;

* * * * *

(8) A process to resolve technical, administrative, and scientific problems about program operations; and

(9) A contractor performing administrative responsibilities as described in this section and §493.903 must be a private nonprofit organization or a Federal or State agency, or an entity acting as a designated agent for the Federal or State agency.

* * * * *

(e) HHS may require on-site visits for all initial proficiency testing program applications for CMS approval and periodically or when problems are encountered for previously HHS-approved proficiency testing programs either during the reapproval process or as necessary to review and verify the policies and procedures represented in its application and other information, including, but not limited to, review and examination of documents and interviews of staff.

(f) HHS may require a proficiency testing program to reapply for approval using the process for initial applications if significant problems are encountered during the reapproval process.

8. Section 493.903 is amended—

a. In paragraph (a)(1) by removing the period and adding ";";

b. In paragraph (a)(2) by removing ";" and adding in its place "; and"; and

c. By adding paragraph (a)(3).

The addition reads as follows:

§493.903 Administrative responsibilities.

* * * * *

(a) * * *

(3) Not change submitted laboratory data and results for any proficiency testing event;

* * * * *

9. Section 493.905 is revised to read as follows:

§493.905 Nonapproved proficiency testing programs.

(a) If a proficiency testing program is determined by HHS to fail to meet any criteria contained in §§493.901 through 493.959 for approval of the proficiency testing

program, CMS will notify the program and the program must notify all laboratories enrolled of the nonapproval and the reasons for nonapproval within 30 days of the notification. CMS may disapprove any proficiency testing program that provides false or misleading information with respect to any information that is necessary to meet any criteria contained in §§493.901 through 493.959 for approval of the proficiency testing program.

(b) *Request for reconsideration.* Any PT program that is dissatisfied with a determination to disapprove the program, as applicable, may request that CMS reconsider the determination, in accordance with subpart D of part 488 of this chapter.

10. Section 493.911 is revised to read as follows:

§493.911 Bacteriology.

(a) *Program content and frequency of challenge.* To be approved for proficiency testing for bacteriology, the annual program must provide a minimum of five samples per testing event. There must be at least three testing events provided to the laboratory at approximately equal intervals per year. The samples may be provided to the laboratory through mailed shipments. The specific organisms included in the samples may vary from year to year.

(1) The annual program must include, as applicable, samples for:

(i) Gram stain including bacterial morphology;

(ii) Direct bacterial antigen detection;

(iii) Bacterial toxin detection; and,

(iv) Detection and identification of bacteria which includes one of the following:

(A) Detection of growth or no growth in culture media;

(B) Identification of bacteria; and

(v) Antimicrobial susceptibility or resistance testing.

(2) An approved program must furnish HHS and its agents with a description of samples that it plans to include in its annual program no later than 6 months before each calendar year. The program must include bacteria commonly occurring in patient specimens and other important emerging pathogens. The program determines the reportable isolates and correct responses for antimicrobial susceptibility or resistance for any designated isolate. At least 25 percent of the samples must be mixtures of the principal organism and appropriate normal flora. Mixed cultures are samples that require reporting of one or more principal pathogens. Mixed cultures are not "negative" samples such as when two commensal organisms are provided in a PT sample with the intended response of "negative" or "no pathogen present." The program must include the following two types of samples to meet the 25 percent mixed culture criterion:

(i) Samples that require laboratories to report only organisms that the testing laboratory considers to be a principal pathogen that is clearly responsible for a described illness (excluding immuno-compromised patients). The program determines the reportable isolates, including antimicrobial susceptibility or resistance for any designated isolate; and

(ii) Samples that require laboratories to report all organisms present. Samples must contain multiple organisms frequently found in specimens where multiple isolates are clearly significant or where specimens are derived from immuno-compromised patients. The program determines the reportable isolates.

(3) The content of an approved program must vary over time, as appropriate. The types of bacteria included annually must be representative of the following major groups

of medically important aerobic and anaerobic bacteria, if appropriate for the sample sources:

(i) Gram-negative bacilli.

(ii) Gram-positive bacilli.

(iii) Gram-negative cocci.

(iv) Gram-positive cocci.

(4) For antimicrobial susceptibility or resistance testing, the program must provide at least two samples per testing event that include one Gram-positive and one Gram-negative organism that have a predetermined pattern of susceptibility or resistance to the common antimicrobial agents.

(b) *Evaluation of a laboratory's performance.* HHS approves only those programs that assess the accuracy of a laboratory's responses in accordance with paragraphs (b)(1) through (9) of this section.

(1) The program determines the reportable bacterial staining and morphological characteristics to be interpreted by Gram stain. The program determines the bacteria to be reported by direct bacterial antigen detection, bacterial toxin detection, detection of growth or no growth in culture media, identification of bacteria, and antimicrobial susceptibility or resistance testing. To determine the accuracy of each of the laboratory's responses, the program must compare each response with the response which reflects agreement of either 80 percent or more of ten or more referee laboratories or 80 percent or more of all participating laboratories. Both methods must be attempted before the program can choose to not grade a PT sample.

(2) A laboratory must identify the organisms to highest level that it performs these procedures on patient specimens.

(3) A laboratory's performance will be evaluated on the basis of the average of its scores for paragraph (b)(4) through (8) of this section as determined in paragraph (b)(9) of this section.

(4) The performance criteria for Gram stain including bacterial morphology is staining reaction, that is, Gram positive or Gram negative and morphological description for each sample. The score is the number of correct responses for Gram stain reaction plus the number of correct responses for morphological description divided by 2 then divided by the number of samples to be tested, multiplied by 100.

(5) The performance criterion for direct bacterial antigen detection is the presence or absence of the bacterial antigen. The score is the number of correct responses divided by the number of samples to be tested, multiplied by 100.

(6) The performance criterion for bacterial toxin detection is the presence or absence of the bacterial toxin. The score is the number of correct responses divided by the number of samples to be tested multiplied by 100.

(7) The performance criterion for the detection and identification of bacteria includes one of the following:

(i) The performance criterion for the detection of growth or no growth in culture media is the presence or absence of bacteria or growth. The score is the number of correct responses divided by the number of samples to be tested multiplied by 100.

(ii) The performance criterion for the identification of bacteria is the total number of correct responses for bacterial identification submitted by the laboratory divided by the number of organisms present plus the number of incorrect organisms reported by the laboratory multiplied by 100 to establish a score for each sample in each testing event. Since laboratories may incorrectly report the presence of organisms in addition to the

correctly identified principal organism(s), the scoring system must provide a means of deducting credit for additional erroneous organisms that are reported. For example, if a sample contained one principal organism and the laboratory reported it correctly but reported the presence of an additional organism, which was not considered reportable, the sample grade would be 1/ (1+1)×100=50 percent.

(8) For antimicrobial susceptibility or resistance testing, a laboratory must indicate which drugs are routinely included in its test panel when testing patient samples. A laboratory's performance will be evaluated for only those antimicrobials for which susceptibility or resistance testing is routinely performed on patient specimens. A correct response for each antimicrobial will be determined as described in paragraph (b)(1) of this section. Scoring for each sample is based on the number of correct susceptibility or resistance responses reported by the laboratory divided by the actual number of correct susceptibility or resistance responses determined by the program, multiplied by 100. For example, if a laboratory offers susceptibility or resistance testing using three antimicrobial agents, and the laboratory reports correct responses for two of the three antimicrobial agents, the laboratory's grade would be 2/3×100=67 percent.

(9) The score for a testing event in bacteriology is the average of the scores determined under paragraphs (b)(4) through (8) of this section based on the type of service offered by the laboratory.

11. Section 493.913 is revised to read as follows:

§493.913 Mycobacteriology.

(a) *Program content and frequency of challenge.* To be approved for proficiency testing for mycobacteriology, the annual program must provide a minimum of five samples per testing event. There must be at least two testing events provided to the

laboratory at approximately equal intervals per year. The samples may be provided through mailed shipments. The specific organisms included in the samples may vary from year to year.

(1) The annual program must include, as applicable, samples for:

(i) Acid-fast stain;

(ii) Detection and identification of mycobacteria which includes one of the following:

(A) Detection of growth or no growth in culture media; or

(B) Identification of mycobacteria; and

(iii) Antimycobacterial susceptibility or resistance testing.

(2) An approved program must furnish HHS and its agents with a description of the samples it plans to include in its annual program no later than 6 months before each calendar year. At least 25 percent of the samples must be mixtures of the principal mycobacteria and appropriate normal flora. The program must include mycobacteria commonly occurring in patient specimens and other important emerging mycobacteria. The program determines the reportable isolates and correct responses for antimycobacterial susceptibility or resistance for any designated isolate.

(3) The content of an approved program may vary over time, as appropriate. The mycobacteria included annually must contain species representative of the following major groups of medically important mycobacteria, if appropriate for the sample sources:

(i) *Mycobacterium tuberculosis* complex; and

(ii) *Mycobacterium* other than tuberculosis (MOTT).

(4) The program must provide at least five samples per testing event that include challenges that are acid-fast and challenges which do not contain acid-fast organisms.

(5) For antimycobacterial susceptibility or resistance testing, the program must provide at least two samples per testing event that have a predetermined pattern of susceptibility or resistance to the common antimycobacterial agents.

(b) *Evaluation of a laboratory's performance.* HHS approves only those programs that assess the accuracy of a laboratory's response in accordance with paragraphs (b)(1) through (7) of this section.

(1) The program determines the reportable mycobacteria to be detected by acid-fast stain. The program determines the mycobacteria to be reported by detection of growth or no growth in culture media, identification of mycobacteria, and for antimycobacterial susceptibility or resistance testing. To determine the accuracy of each of the laboratory's responses, the program must compare each response with the response that reflects agreement of either 80 percent or more of ten or more referee laboratories or 80 percent or more of all participating laboratories. Both methods must be attempted before the program can choose to not grade a PT sample.

(2) A laboratory must detect and identify the organism to the highest level that it performs these procedures on patient specimens.

(3) A laboratory's performance will be evaluated on the basis of the average of its scores for paragraph (b)(4) through (6) of this section as determined in paragraph (b)(7) of this section.

(4) The performance criterion for acid-fast stains is positive or negative or the presence or absence of acid-fast organisms. The score is the number of correct responses divided by the number of samples to be tested, multiplied by 100.

(5) The performance criterion for the detection and identification of mycobacteria includes one of the following:

(i) The performance criterion for the detection of growth or no growth in culture media is the presence or absence of bacteria or growth. The score is the number of correct responses divided by the number of samples to be tested multiplied by 100.

(ii) The performance criterion for the identification of mycobacteria is the total number of correct responses for mycobacterial identification submitted by the laboratory divided by the number of organisms present plus the number of incorrect organisms reported by the laboratory multiplied by 100 to establish a score for each sample in each testing event. Since laboratories may incorrectly report the presence of mycobacteria in addition to the correctly identified principal organism(s), the scoring system must provide a means of deducting credit for additional erroneous organisms reported. For example, if a sample contained one principal organism and the laboratory reported it correctly but reported the presence of an additional organism, which was not considered reportable, the sample grade would be $1/(1+1)\times100=50$ percent.

(6) For antimycobacterial susceptibility or resistance testing, a laboratory must indicate which drugs are routinely included in its test panel when testing patient samples. A laboratory's performance will be evaluated for only those antimycobacterial agents for which susceptibility or resistance testing is routinely performed patient specimens. A correct response for each antimycobacterial agent will be determined as described in paragraph (b)(1) of this section. Scoring for each sample is based on the number of correct susceptibility or resistance responses reported by the laboratory divided by the actual number of correct susceptibility or resistance responses as determined by the program, multiplied by 100. For example, if a laboratory offers susceptibility or resistance testing using three antimycobacterial agents and the laboratory reports correct

responses for two of the three antimycobacterial agents, the laboratory's grade would be 2/3×100=67 percent.

(7) The score for a testing event in mycobacteriology is the average of the scores determined under paragraphs (b)(4) through (6) of this section based on the type of service offered by the laboratory.

12. Section 493.915 is revised to read as follows:

§493.915 Mycology.

(a) *Program content and frequency of challenge.* To be approved for proficiency testing for mycology, the annual program must provide a minimum of five samples per testing event. There must be at least three testing events provided to the laboratory at approximately equal intervals per year. The samples may be provided through mailed shipments. The specific organisms included in the samples may vary from year to year.

(1) The annual program must include, as applicable, samples for:

(i) Direct fungal antigen detection;

(ii) Detection and identification of fungi and aerobic actinomycetes which includes one of the following:

(A) Detection of growth or no growth in culture media; or

(B) Identification of fungi and aerobic actinomycetes; and

(iii) Antifungal susceptibility or resistance testing.

(2) An approved program must furnish HHS and its agents with a description of the samples it plans to include in its annual program no later than 6 months before each calendar year. At least 25 percent of the samples must be mixtures of the principal organism and appropriate normal background flora. The program must include fungi and aerobic actinomycetes commonly occurring in patient specimens and other important

emerging fungi. The program determines the reportable isolates and correct responses for antifungal susceptibility or resistance for any designated isolate.

(3) The content of an approved program must vary over time, as appropriate. The fungi included annually must contain species representative of the following major groups of medically important fungi and aerobic actinomycetes, if appropriate for the sample sources:

(i) Yeast or yeast-like organisms;

(ii) Molds that include;

(A) Dematiaceous fungi;

(B) Dermatophytes;

(C) Dimorphic fungi;

(D) Hyaline hyphomycetes;

(E) Mucormycetes; and

(iii) Aerobic actinomycetes.

(4) For antifungal susceptibility or resistance testing, the program must provide at least two challenges per testing event that include fungi that have a predetermined pattern of susceptibility or resistance to the common antifungal agents.

(b) *Evaluation of a laboratory's performance.* HHS approves only those programs that assess the accuracy of a laboratory's response, in accordance with paragraphs (b)(1) through (8) of this section.

(1) The program determines the reportable fungi to be reported by direct fungal antigen detection, detection of growth or no growth in culture media, identification of fungi and aerobic actinomycetes, and antifungal susceptibility or resistance testing. To determine the accuracy of a laboratory's responses, the program must compare each

response with the response reflects agreement of either 80 percent or more of ten or more referee laboratories or 80 percent or more of all participating laboratories. Both methods must be attempted before the program can choose to not grade a PT sample.

(2) A laboratory must detect and identify the organisms to highest level that it performs these procedures on patient specimens.

(3) A laboratory's performance will be evaluated on the basis of the average of its scores for paragraphs (b)(4) through (6) of this section as determined in paragraph (b)(7) of this section.

(4) The performance criterion for direct fungal antigen detection is the presence or absence of the fungal antigen. The score is the number of correct responses divided by the number of samples to be tested, multiplied by 100.

(5) The performance criterion for the detection and identification of fungi and aerobic actinomycetes includes one of the following:

(i) The performance criterion for the detection of growth or no growth in culture media is the presence or absence of fungi or growth. The score is the number of correct responses divided by the number of samples to be tested multiplied by 100.

(ii) The performance criterion for the identification of fungi and aerobic actinomycetes is the total number of correct responses for fungal and aerobic actinomycetes identification submitted by the laboratory divided by the number of organisms present plus the number of incorrect organisms reported by the laboratory multiplied by 100 to establish a score for each sample in each testing event. Since laboratories may incorrectly report the presence of fungi and aerobic actinomycetes in addition to the correctly identified principal organism(s), the scoring system must provide a means of deducting credit for additional erroneous organisms that are reported. For

example, if a sample contained one principal organism and the laboratory reported it correctly but reported the presence of an additional organism, which was not considered reportable, the sample grade would be 1/ (1+1)x100=50 percent.

(6) For antifungal susceptibility or resistance testing, a laboratory must indicate which drugs are routinely included in its test panel when testing patient samples. A laboratory's performance will be evaluated for only those antifungal agents for which susceptibility or resistance testing is routinely performed on patient specimens. A correct response for each antifungal agent will be determined as described in paragraph (b)(1) of this section. Scoring for each sample is based on the number of correct susceptibility or resistance responses reported by the laboratory divided by the actual number of correct susceptibility or resistance responses as determined by the program, multiplied by 100. For example, if a laboratory offers susceptibility or resistance testing using three antifungal agents and the laboratory reports correct responses for two of the three antifungal agents, the laboratory's grade would be 2⁄3×100=67 percent.

(7) The score for a testing event is the average of the sample scores as determined under paragraphs (b)(4) through (6) of this section.

13. Section 493.917 is revised to read as follows:

§493.917 Parasitology.

(a) *Program content and frequency of challenge.* To be approved for proficiency testing in parasitology, the annual program must provide a minimum of five samples per testing event. There must be at least three testing events provided to the laboratory at approximately equal intervals per year. The samples may be provided through mailed shipments. The specific organisms included in the samples may vary from year to year.

(1) The annual program must include, as applicable, samples for:

(i) Direct parasite antigen detection; and

(ii) Detection and identification of parasites which includes one of the following:

(A) Detection of presence or absence of parasites; or

(B) Identification of parasites.

(2) An approved program must furnish HHS and its agents with a description of the samples it plans to include in its annual program no later than 6 months before each calendar year. Samples must include both formalinized specimens and PVA (polyvinyl alcohol) fixed specimens as well as blood smears, as appropriate for a particular parasite and stage of the parasite. The majority of samples must contain protozoa or helminths or a combination of parasites. Some samples must be devoid of parasites.

(3) The content of an approved program must vary over time, as appropriate. The types of parasites included annually must be representative of the following major groups of medically important parasites, if appropriate for the sample sources:

(i) Intestinal parasites; and

(ii) Blood and tissue parasites.

(4) The program must provide at least five samples per testing event that include challenges which contain parasites and challenges that are devoid of parasites.

(b) *Evaluation of a laboratory's performance.* HHS approves only those programs that assess the accuracy of a laboratory's responses in accordance with paragraphs (b)(1) through (6) of this section.

(1) The program determines the reportable parasites to be detected by direct parasite antigen detection, detection of presence or absence of parasites, and identification of parasites. It may elect to establish a minimum number of parasites to be identified in samples before they are reported. Parasites found in rare numbers by referee

laboratories are not considered in a laboratory's performance; such findings are neutral. To determine the accuracy of a laboratory's response, the program must compare each response with the response which reflects agreement of either 80 percent or more of ten or more referee laboratories or 80 percent or more of all participating laboratories. Both methods must be attempted before the program can choose to not grade a PT sample.

(2) A laboratory must detect and identify or concentrate and identify the parasites to the highest level that it performs these procedures on patient specimens.

(3) A laboratory's performance will be evaluated on the basis of the average of its scores for paragraphs (b)(4) through (5) of this section as determined in paragraph (b)(6) of this section.

(4) The performance criterion for direct parasite antigen detection is the presence or absence of the parasite antigen. The score is the number of correct responses divided by the number of samples to be tested, multiplied by 100.

(5) The performance criterion for the detection and identification of parasites includes one of the following:

(i) The performance criterion for the detection of presence or absence of parasites is the presence or absence of parasites. The score is the number of correct responses divided by the number of samples to be tested, multiplied by 100.

(ii) The performance criterion for the identification of parasites is the total number of correct responses for parasite identification submitted by the laboratory divided by the number of parasites present plus the number of incorrect parasites reported by the laboratory multiplied by 100 to establish a score for each sample in each testing event. Since laboratories may incorrectly report the presence of parasites in addition to the correctly identified principal organism(s), the scoring system must provide a means of

deducting credit for additional erroneous organisms that are reported and not found in rare numbers by the program's referencing process. For example, if a sample contained one principal organism and the laboratory reported it correctly but reported the presence of an additional organism, which was not considered reportable, the sample grade would be 1/(1+1)×100=50 percent.

(6) The score for a testing event is the average of the sample scores as determined under paragraphs (b)(4) through (5) of this section.

14. Section 493.919 is revised to read as follows:

§493.919 Virology.

(a) *Program content and frequency of challenge.* To be approved for proficiency testing in virology, a program must provide a minimum of five samples per testing event. There must be at least three testing events at approximately equal intervals per year. The samples may be provided to the laboratory through mailed shipments. The specific organisms included in the samples may vary from year to year.

(1) The annual program must include, as applicable, samples for:

(i) Viral antigen detection;

(ii) Detection and identification of viruses; and

(iii) Antiviral susceptibility or resistance testing.

(2) An approved program must furnish HHS and its agents with a description of the samples it plans to include in its annual program no later than 6 months before each calendar year. The program must include other important emerging viruses and viruses commonly occurring in patient specimens. The program determines the reportable isolates and correct responses for antiviral susceptibility or resistance for any designated isolate.

(3) The content of an approved program must vary over time, as appropriate. If appropriate for the sample sources, the types of viruses included annually must be representative of the following major groups of medically important viruses:

(i) Respiratory viruses;

(ii) Herpes viruses;

(iii) Enterovirus; and

(iv) Intestinal viruses.

(4) For antiviral susceptibility or resistance testing, the program must provide at least two challenges per testing event that include viruses that have a predetermined pattern of susceptibility or resistance to the common antiviral agents.

(b) *Evaluation of laboratory's performance.* HHS approves only those programs that assess the accuracy of a laboratory's response in accordance with paragraphs (b)(1) through (7) of this section.

(1) The program determines the viruses to be reported by direct viral antigen detection, detection and identification of viruses, and antiviral susceptibility or resistance testing. To determine the accuracy of a laboratory's response, the program must compare each response with the response which reflects agreement of either 80 percent or more of ten or more referee laboratories or 80 percent or more of all participating laboratories. Both methods must be attempted before the program can choose to not grade a PT sample.

(2) A laboratory must detect and identify the viruses to the highest level that it performs these procedures on patient specimens.

(3) A laboratory's performance will be evaluated on the basis of the average of its scores for paragraphs (b)(4) through (6) of this section as determined in paragraph (b)(7) of this section.

(4) The performance criterion viral antigen detection is the presence or absence of the viral antigen. The score is the number of correct responses divided by the number of samples to be tested, multiplied by 100.

(5) The performance criterion for the detection and identification of viruses is the total number of correct responses for viral detection and identification submitted by the laboratory divided by the number of viruses present plus the number of incorrect virus reported by the laboratory multiplied by 100 to establish a score for each sample in each testing event. Since laboratories may incorrectly report the presence of viruses in addition to the correctly identified principal organism(s), the scoring system must provide a means of deducting credit for additional erroneous organisms that are reported. For example, if a sample contained one principal organism and the laboratory reported it correctly but reported the presence of an additional organism, which was not considered reportable, the sample grade would be $1/(1+1)\times100=50$ percent.

(6) For antiviral susceptibility or resistance testing, a laboratory must indicate which drugs are routinely included in its test panel when testing patient samples. A laboratory's performance will be evaluated for only those antiviral agents for which susceptibility or resistance testing is routinely performed patient specimens. A correct response for each antiviral agent will be determined as described in paragraph (b)(1) of this section. Scoring for each sample is based on the number of correct susceptibility or resistance responses reported by the laboratory divided by the actual number of correct susceptibility or resistance responses as determined by the program, multiplied by 100.

For example, if a laboratory offers susceptibility or resistance testing using three antiviral agents and the laboratory reports correct responses for two of the three antiviral agents, the laboratory's grade would be 2/3×100=67 percent.

(7) The score for a testing event is the average of the sample scores as determined under paragraphs (b)(4) and (6) of this section.

15. Section 493.923 is amended by revising paragraphs (a) and (b)(1) to read as follows:

§493.923 Syphilis serology.

(a) *Program content and frequency of challenge.* To be approved for proficiency testing in syphilis serology, a program must provide a minimum of five samples per testing event. There must be at least three testing events at approximately equal intervals per year. The samples may be provided through mailed shipments. An annual program must include samples that cover the full range of reactivity from highly reactive to non-reactive.

(b) * * *

(1) To determine the accuracy of a laboratory's response for qualitative and quantitative syphilis tests, the program must compare the laboratory's response with the response that reflects agreement of either 80 percent or more of ten or more referee laboratories or 80 percent or more of all participating laboratories. Both methods must be attempted before the program can choose to not grade a PT sample.

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16. Section 493.927 is amended by revising paragraphs (a), (b), and (c)(1) and (2) to read as follows:

§493.927 General immunology.

(a) *Program content and frequency of challenge*. To be approved for proficiency testing for immunology, the annual program must provide a minimum of five samples per testing event. There must be at least three testing events at approximately equal intervals per year. The annual program must provide samples that cover the full range of reactivity from highly reactive to nonreactive. The samples may be provided through mailed shipments.

(b) *Challenges per testing event*. The minimum number of challenges per testing event the program must provide for each analyte or test procedure is five. Analytes or tests for which laboratory performance is to be evaluated include:

Alpha-l antitrypsin.

Alpha-fetoprotein (tumor marker).

Antinuclear antibody.

Antistreptolysin O.

Anti- human immunodeficiency virus (HIV).

Complement C3.

Complement C4.

C-reactive protein (high sensitivity).

HBsAg.

Anti-HBc.

HBeAg.

Anti-HBs.

Anti-HCV.

IgA.

IgG.

IgE.

IgM.

Infectious mononucleosis.

Rheumatoid factor.

Rubella.

(c) * * *

(1) To determine the accuracy of a laboratory's response for quantitative and qualitative immunology tests or analytes, the program must compare the laboratory's response for each analyte with the response that reflects agreement of either 80 percent or more of ten or more referee laboratories or 80 percent or more of all participating laboratories. The proficiency testing program must indicate the minimum concentration that will be considered as indicating a positive response. Both methods must be attempted before the program can choose to not grade a PT sample.

(2)(i) For quantitative immunology analytes or tests, the program must determine the correct response for each analyte by the distance of the response from the target value. After the target value has been established for each response, the appropriateness of the response must be determined by using either fixed criteria or the number of standard deviations (SDs) the response differs from the target value.

Criteria for Acceptable Performance

The criteria for acceptable performance are—

Analyte or test	Criteria for acceptable performance
Alpha-1 antitrypsin	Target value ± 20% or positive or negative.
Alpha-fetoprotein (tumor marker).	Target value ± 20% or positive or negative.
Antinuclear antibody	Target value ±3 SD or positive or negative.

Antistreptolysin O	Target value ±3 SD or positive or negative.
Anti-Human Immunodeficiency virus (HIV)	Reactive (positive) or nonreactive (negative).
Complement C3	Target value ±15% or positive or negative.
Complement C4	Target value ±5 mg/dL or 20% (greater) or positive or negative.
C-reactive protein (HS)	Target value ±1 mg/dL or 30% (greater).
HBsAg.....	Reactive (positive) or nonreactive (negative).
anti-HBc.....	Reactive (positive) or nonreactive (negative).
HBeAg.....	Reactive (positive) or nonreactive (negative).
Anti-HBs.....	Reactive (positive) or nonreactive (negative).
Anti-HCV.....	Reactive (positive) or nonreactive (negative).
IgA	Target value ±15%.
IgE	Target value ±20%.
IgG	Target value ±20%.
IgM	Target value ±20%.
Infectious mononucleosis	positive or negative.
Rheumatoid factor	Target value ±3 SD or positive or negative
Rubella	Target value ±3 SD or positive or negative or immune or nonimmune

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17. Section 493.931 is amended by revising paragraphs (a), (b), and (c)(1) and (2) to read as follows:

§493.931 Routine chemistry.

(a) *Program content and frequency of challenge*. To be approved for proficiency testing for routine chemistry, a program must provide a minimum of five samples per testing event. There must be at least three testing events at approximately equal intervals per year. The annual program must provide samples that cover the clinically relevant range of values that would be expected in patient specimens. The specimens may be provided through mailed.

(b) *Challenges per testing event*. The minimum number of challenges per testing event a program must provide for each of the following analyte or test procedure is five serum, plasma or blood samples.

Analyte or Test Procedure

Alanine aminotransferase (ALT/SGPT)

Albumin

Alkaline phosphatase

Amylase

Aspartate aminotransferase (AST/SGOT)

Bilirubin, total

Blood gas (pH, pO2, and pCO2)

B-natriuretic peptide (BNP)

proBNP

Calcium, total

Carbon dioxide

Chloride

Cholesterol, total

Cholesterol, high density lipoprotein

Cholesterol, low density lipoprotein

Creatine kinase (CK)

CK-MB isoenzymes

Creatinine

Ferritin

Gamma glutamyl transferase

Glucose (Excluding measurements on devices cleared by FDA for home use)

Hemoglobin A1c

Iron, total

Lactate dehydrogenase (LDH)

Magnesium

Phosphorus

Potassium

Prostate specific antigen, total

Sodium

Total iron binding capacity

Total Protein

Triglycerides

Troponin I

Troponin T

Urea Nitrogen

Uric Acid

(c) * * *

(1) To determine the accuracy of a laboratory's response for qualitative and quantitative chemistry tests or analytes, the program must compare the laboratory's response for each analyte with the response that reflects agreement of either 80 percent or more of ten or more referee laboratories or 80 percent or more of all participating laboratories. Both methods must be attempted before the program can choose to not grade a PT sample.

(2) For quantitative chemistry tests or analytes, the program must determine the correct response for each analyte by the distance of the response from the target value. After the target value has been established for each response, the appropriateness of the response must be determined by using either fixed criteria based on the percentage difference from the target value or the number of standard deviations (SD) the response differs from the target value.

Criteria for Acceptable Performance

The criteria for acceptable performance are—

Analyte or test	Criteria for acceptable performance
Alanine aminotransferase (ALT/SGPT).	Target value ±15%.
Albumin	Target value ±8%.
Alkaline phosphatase	Target value ±20%.
Amylase	Target value ±10%.
Aspartate aminotransferase (AST/SGOT)…	Target value ±15%.
Bilirubin, total	Target value ±20%.
Blood gas pCO2	Target value ±5 mm Hg or ±8% (greater).
Blood gas pO2	Target value ±15 mmHg or 15% (greater).

Blood gas pH	Target value ±0.04.
B-natriuretic peptide (BNP).....	Target value ±30%.
Pro B-natriuretic peptide (proBNP)…	Target value ±30%.
Calcium, total	Target value ±1.0 mg/dL.
Carbon dioxide	Target value ±20%.
Chloride	Target value ±5%.
Cholesterol, total	Target value ±10%.
Cholesterol, high density lipoprotein. ..	Target value ±20%.
Cholesterol, low density lipoprotein.. (direct measurement)	Target value ±20%.
Creatine kinase (CK)	Target value ±20%.
CK-MB isoenzymes	MB elevated (presence or absence) or Target value ±25% (greater).
Creatinine	Target value ±0.2 mg/dL or ±10% (greater).
Ferritin	Target value ±20%.
Gamma glutamyl transferase	Target value ±5 U/L or ±15% (greater).
Glucose (excluding measurements devices cleared by FDA for home use.)	Target value ±8% (greater).
Hemoglobin A1c	Target value ±10%.
Iron, total	Target value ±15%.
Lactate dehydrogenase (LDH).	Target value ±15%.
Magnesium	Target value ±15%.
Phosphorus	Target value ±0.3 mg/dL or ±10% (greater).

Potassium	Target value ±0.3 mmol/L.
Prostate Specific Antigen, total	Target value ±0.2 ng/dL or 20% (greater).
Sodium	Target value ±4 mmol/L.
Total Iron Binding Capacity.	Target value ±20%.
(direct measurement)	
Total Protein	Target value ±8%.
Triglycerides	Target value ±15%.
Troponin I	Target value ±0.9 ng/mL or 30% (greater).
Troponin T	Target value ±0.2 ng/mL or 30% (greater).
Urea nitrogen	Target value ±2 mg/dL or ±9% (greater).
Uric acid	Target value ±10%.

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18. Section 493.933 is amended by revising paragraphs (a), (b), and (c)(1) and (2) to read as follows:

§493.933 Endocrinology.

(a) *Program content and frequency of challenge*. To be approved for proficiency testing for endocrinology, a program must provide a minimum of five samples per testing event. There must be at least three testing events at approximately equal intervals per year. The annual program must provide samples that cover the clinically relevant range of values that would be expected in patient specimens. The samples may be provided through mailed shipments.

(b) *Challenges per testing event*. The minimum number of challenges per testing event a program must provide for each analyte or test procedure is five serum, plasma, blood, or urine samples.

Analyte or Test

Cancer antigen (CA) 125

Carcinoembryonic antigen (CEA)

Cortisol

Estradiol

Folate, serum

Follicle stimulating hormone

Free thyroxine

Human chorionic gonadotropin (excluding urine pregnancy tests done by visual color comparison categorized as waived tests)

Luteinizing hormone

Parathyroid hormone

Progesterone

Prolactin

Testosterone

T3 Uptake

Triiodothyronine

Thyroid-stimulating hormone

Thyroxine

Vitamin B12

(c) * * *

(1) To determine the accuracy of a laboratory's response for qualitative and quantitative endocrinology tests or analytes, a program must compare the laboratory's response for each analyte with the response that reflects agreement of either 80 percent or more of ten or more referee laboratories or 80 percent or more of all participating laboratories. Both methods must be attempted before the program can choose to not grade a PT sample.

(2) For quantitative endocrinology tests or analytes, the program must determine the correct response for each analyte by the distance of the response from the target value. After the target value has been established for each response, the appropriateness of the response must be determined by using either fixed criteria based on the percentage difference from the target value or the number of standard deviations (SDs) the response differs from the target value.

Criteria for Acceptable Performance

The criteria for acceptable performance are—

Analyte or test	Criteria for acceptable performance
Cancer antigen (CA) 125	Target value ±20%.
Carcinoembryonic antigen (CEA)…..	Target value ±15%.
Cortisol	Target value ±20%.
Estradiol	Target value ±30%.
Folate, serum	Target value ±1 ng/mL or ±30% (greater).
Follicle stimulating hormone.	Target value ±2 IU/L or ±18% (greater).
Free thyroxine.....	Target value ±0.3 ng/dL or ±15% (greater).
Human chorionic	Target value ±18% or positive or negative.

Gonadotropin (excluding urine pregnancy tests done by visual color comparison categorized as waived tests).	
Luteinizing hormone	Target value ±20%.
Parathyroid hormone	Target value ±30%.
Progesterone	Target value ±25%.
Prolactin	Target value ±20%.
Testosterone	Target value ±20 ng/dL or ±30% (greater).
T3 uptake	Target value ±18%.
Triiodothyronine	Target value ±30%.
Thyroid-stimulating hormone ..	Target value ±20% or 0.2 mIU/L (greater).
Thyroxine	Target value ±20% or 1.0 mcg/dL (greater).
Vitamin B12.....	Target value ±25%.

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19. Section 493.937 is amended by revising paragraphs (a), (b), and (c)(1) and (2) to read as follows:

§493.937 Toxicology.

(a) *Program content and frequency of challenge.* To be approved for proficiency testing for toxicology, the annual program must provide a minimum of five samples per testing event. There must be at least three testing events at approximately equal intervals per year. The annual program must provide samples that cover the full range of values

that could occur in patient specimens and that cover the level of clinical significance for the particular drug. The samples may be provided through mailed shipments.

(b) *Challenges per testing event.* The minimum number of challenges per testing event a program must provide for each analyte or test procedure is five serum, plasma, or blood samples.

Analyte or Test Procedure

Acetaminophen, serum

Alcohol (blood)

Blood lead

Carbamazepine

Digoxin

Gentamicin

Lithium

Phenobarbital

Phenytoin

Salicylate

Theophylline

Tobramycin

Valproic Acid

Vancomycin

(c) * * *

(1) To determine the accuracy of a laboratory's responses for quantitative toxicology tests or analytes, the program must compare the laboratory's response for each analyte with the response that reflects agreement of either 80 percent or more of ten or

more referee laboratories or 80 percent or more of all participating laboratories. Both methods must be attempted before the program can choose to not grade a PT sample.

(2) For quantitative toxicology tests or analytes, the program must determine the correct response for each analyte by the distance of the response from the target value. After the target value has been established for each response, the appropriateness of the response must be determined by using fixed criteria based on the percentage difference from the target value.

Criteria for Acceptable Performance

The criteria for acceptable performance are:

Analyte or test	Criteria for acceptable performance
Acetaminophen	Target value ±15%.
Alcohol, blood	Target Value ±20%.
Blood lead	Target Value ±10% or 2 mcg/dL (greater).
Carbamazepine	Target Value ±20%.
Digoxin	Target Value ±15% or ± 0.2 ng/mL (greater).
Gentamicin	Target Value ±25%.
Lithium	Target Value ±15%.
Phenobarbital	Target Value ±15%.
Phenytoin	Target Value ±15% or ± 2 mcg/dL (greater).
Salicylate	Target Value ±15%.
Theophylline	Target Value ±20%.
Tobramycin	Target Value ±20%.

Valproic Acid ..... Target Value ±20%.

Vancomycin ..... Target Value ±15% or ± 2 mcg/dL (greater).

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20. Section 493.941 is amended by revising paragraphs (a), (b), and (c)(1) and (2) to read as follows:

§493.941 Hematology (including routine hematology and coagulation).

(a) *Program content and frequency of challenge*. To be approved for proficiency testing for hematology, a program must provide a minimum of five samples per testing event. There must be at least three testing events at approximately equal intervals per year. The annual program must provide samples that cover the full range of values that would be expected in patient specimens. The samples may be provided through mailed shipments.

(b) *Challenges per testing event*. The minimum number of challenges per testing event a program must provide for each analyte or test procedure is five.

Analyte or Test Procedure

Cell identification

White blood cell differential

Erythrocyte count

Hematocrit (excluding spun microhematocrit)

Hemoglobin

Leukocyte count

Platelet count

Fibrinogen

Partial thromboplastin time

Prothrombin time (seconds or INR)

(c) * * *

(1) To determine the accuracy of a laboratory's responses for qualitative and quantitative hematology tests or analytes, the program must compare the laboratory's response for each analyte with the response that reflects agreement of either 80 percent or more of ten or more referee laboratories or 80 percent or more of all participating laboratories. Both methods must be attempted before the program can choose to not grade a PT sample.

(2) For quantitative hematology tests or analytes, the program must determine the correct response for each analyte by the distance of the response from the target value. After the target value has been established for each response, the appropriateness of the response is determined using either fixed criteria based on the percentage difference from the target value or the number of standard deviations (SD) the response differs from the target value.

Criteria for Acceptable Performance

The criteria for acceptable performance are:

Analyte or test	Criteria for acceptable performance
Cell identification	80% or greater consensus on identification.
White blood cell differential ...	Target ±3SD based on the percentage of different types of white blood cells in the samples.
Erythrocyte count	Target ±4%.
Hematocrit (Excluding spun	Target ±4%.

hematocrit).

Hemoglobin	Target ±4%.
Leukocyte count	Target ±5%.
Platelet count	Target ±25%.
Fibrinogen	Target ±20%.
Partial thromboplastin time	Target ±15%.

If a laboratory reports a prothrombin time in both INR and seconds, the INR should be reported to the PT provider program.

Prothrombin time (seconds or INR) ...	Target ±15%.

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21. Section 493.959 is amended by revising paragraphs (b) and (d)(1) and (2) to read as follows:

§493.959 Immunohematology.

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(b) *Program content and frequency of challenge*. To be approved for proficiency testing for immunohematology, a program must provide a minimum of five samples per testing event. There must be at least three testing events at approximately equal intervals per year. The annual program must provide samples that cover the full range of interpretation that would be expected in patient specimens. The samples may be provided through mailed shipments.

(d) * * *

(1) To determine the accuracy of a laboratory's response, a program must compare the laboratory's response for each analyte with the response that reflects agreement of either 100 percent of ten or more referee laboratories or 95 percent or more

of all participating laboratories except for antibody identification. To determine the accuracy of a laboratory's response for antibody identification, a program must compare the laboratory's response for each analyte with the response that reflects agreement of either 95 percent or more of ten or more referee laboratories or 95 percent or more of all participating laboratories. Both methods must be attempted before the program can choose to not grade a PT sample.

(2) *Criteria for acceptable performance.*

The criteria for acceptable performance are—

Analyte or test	Criteria for acceptable performance
ABO group	100% accuracy.
D (Rho) typing	100% accuracy.
Unexpected antibody detection	100% accuracy.
Compatibility testing	100% accuracy.
Antibody identification	80% + accuracy.

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Dated: June 25, 2018.

Seema Verma,

Administrator,

Centers for Medicare & Medicaid Services.

Dated: December 17, 2018.

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Robert Redfield, MD

Director,

Centers for Disease Control and Prevention and

Administrator,

Agency for Toxic Substances and Disease Registry

Dated: December 18, 2018.

Alex M. Azar II,

Secretary,

Department of Health and Human Services.

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