DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Medicare & Medicaid Services

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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: Final rule.

SUMMARY: This final rule updates 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 final rule also makes technical changes to PT referral regulations to better align them with the CLIA statute.

DATES: Effective August 10, 2022, except for the amendments to §§ 493.2 and 493.801 through 493.959 (amendatory instructions 2 and 5 through 21), which are effective July 11, 2024.

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SUPPLEMENTARY INFORMATION:

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 the 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 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 2020, approximately 35,967 CLIA-certified 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.

Participation in PT is required under the CLIA statute for laboratories that perform moderate or high complexity testing. PT evaluates a laboratory's performance by testing unknown samples just as it would test patient samples. An HHS-approved PT program sends unknown samples to a laboratory for analysis. After testing, the laboratory reports its results to the PT program. The program grades the results using the CLIA grading criteria and provides the laboratory with its scores. PT is crucial to maintaining the quality of laboratory testing because it independently verifies the accuracy and reliability of laboratory testing, including the competency of testing personnel.

Testing has evolved significantly since 1992, and today's technology is more accurate and precise than the methods used when the PT regulations became effective 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 troponins, which are used to diagnose myocardial infarction, 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 proposed revisions to update the existing PT regulations in a proposed rule entitled, ''Clinical Laboratory Improvement Amendments of 1988 (CLIA) Proficiency Testing Regulations Related to Analytes and Acceptable Performance'', published in the February 4, 2019 **Federal Register** (84 FR 1536) (hereinafter the proposed rule).

Generally, a final rule must be issued within 3 years of publishing a proposed rule, except under exceptional circumstances. As discussed in a notice entitled, ''Clinical Laboratory Improvement Amendments of 1988 (CLIA) Proficiency Testing Regulations Related to Analytes and Acceptable Performance; Extension of Timeline for Publication of Final Rule'', published in the January 19, 2022, **Federal Register** (87 FR 2736) (hereinafter the notice of extension), we could not meet the February 4, 2022 deadline due to the necessary reallocation of resources to respond to the COVID–19 public health emergency. Therefore, in the notice of extension, we announced an extension of the timeline to publish the final rule by 1 year until February 4, 2023.

As part of the process for developing the proposed rule, HHS solicited input from the Clinical Laboratory Improvement Advisory Committee (CLIAC), the official Federal advisory committee charged with advising HHS regarding appropriate regulatory standards for ensuring accuracy, reliability, and timeliness of laboratory testing. Taking CLIAC's recommendations into account, CMS and CDC collaborated to develop a process to revise the list of required PT analytes listed in subpart I to determine which analytes should be retained, which should be deleted, and which analytes not currently listed in subpart I should be added to the regulations. Following the data-driven process and step-wise criteria used to select the candidate analytes to be included in the proposed rule, 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; the mechanism for grading current 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 proposed categories of required PT for each microbiology subspecialty at the above citations and the replacement of the list of specific organisms for each subspecialty with a proposed list of types of microorganisms.

Based on empirical data and clinical relevance, CMS and CDC next worked to determine or revise the acceptance limits (ALs) (as defined in § 493.2) for new and existing required analytes, respectively. Whenever possible, we proposed ALs as percentages. For each analyte, PT programs voluntarily provided data simulations using real PT data as a means of pilot testing our potential ALs. As stated in the proposed rule, ALs 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

The proposed rule, if finalized, would amend the 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 in the CLIA regulations.

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. CLIAC suggested revision of the regulations to include broad categories for the types of PT required for each microbiology subspecialty to allow flexibility for the 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 for microbiology subspecialties in future rulemaking. Based on these recommendations and our review, we proposed 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 (that is, replace the list with broader categories of organisms) 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 proposed 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 either: 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 493.911(a)(3): We proposed 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): For mycobacteriology, we proposed 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 493.913(a)(3): For mycobacteriology, we proposed 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 proposed the categories for which PT is required include, as applicable: direct fungal antigen detection; detection and identification of fungi and aerobic actinomycetes which included 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 493.915(a)(3): We proposed 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 proposed requiring PT for direct parasite antigen detection and detection and identification of parasites.

++ Section 493.917(a)(3): We proposed 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 proposed requiring PT, as applicable, for viral antigen detection; detection and identification of viruses; and antiviral susceptibility or resistance testing.

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

We proposed revising the requirements for evaluating a laboratory's performance at §§ 493.911(b) through 493.919(b) to be consistent with these categories. We did not propose to include antigen and toxin detection in the mycobacteriology subspecialty because no PT program currently offers applicable PT modules. We did not propose to include stains and antiparasitic susceptibility or resistance testing in the subspecialty of parasitology because no PT program offers applicable PT modules. We invited the public to comment on these proposals and specifically on the proposed categories of testing for the subspecialties listed above. We stated that if public comments indicate that applicable PT modules are available for antigen and toxin detection or stains and antiparasitic susceptibility or resistance testing, we may finalize their inclusion in the final rule, as applicable. If PT becomes available at some point in the future 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. We summarize and respond to the public comments on these proposals and summarize our final policies in section III.E. of this final rule.

++ Sections 493.911(b)(1), 493.913(b)(1), 493.915(b)(1), 493.917(b)(1), and 493.919(b)(1): We proposed amending these provisions to clarify that to achieve consensus, PT programs must attempt to grade using both participant and referee laboratories [1] 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. We summarize and respond to the public comments we received on these proposals and summarize our final policies in section III.D. of this final rule.

2. Major Groups of Microorganisms

In the proposed rule (84 FR 1536, 1538), we proposed to remove the lists of specific example organisms from each microbiology subspecialty and add a more general list of organisms. This change clarifies 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.

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 ensure 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 the current regulatory list. By restructuring to a more general list of organisms, it will be more apparent 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 proposed 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.

++ Section 493.911(a)(3): For bacteriology, we proposed 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.

++ Section 493.913(a)(3): For mycobacteriology, we proposed 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)(3): For mycology, we proposed that the 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)(3): For parasitology, we proposed that the annual program content must include intestinal parasites and blood and tissue parasites, if appropriate for the sample sources.

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

We summarize and respond to the public comments we received on these proposals and summarize our final policies in section III.E. of this final rule.

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 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 the inspecting agency is responsible for reviewing and taking 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 proposed 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. We believe that this change will enhance consistency among the PT programs when grading samples.

We summarize and respond to the public comments we received on these proposals and summarize our final policies in sections III.C. and III.E. of this final rule.

4. Gram Stain PT

CLIAC considered whether the 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 proposed 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.

We summarize and respond to the public comments on these proposals

[1] *https://www.ecfr.gov/current/title-42/chapter-IV/subchapter-G/part-493#493.2.*

and summarize our final policies in section III.E. of this final rule.

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. This requirement aims 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 immunocompromised 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. Still, they 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 proposed the following changes:

++ Section 493.911(a)(2): In bacteriology, we proposed 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 proposed 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 did not propose to make any changes to these subspecialties. We summarize and respond to the public comments we received on these proposals and summarize our final policies in section III.E. of this final rule.

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 detecting 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 proposed the following:

++ Section 493.911(a)(4): For bacteriology, we proposed requiring 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 proposed requiring 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 proposed requiring 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 proposed requiring 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 also proposed to revise the requirements for the 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.

We summarize and respond to the public comments we received on these proposals and summarize our final policies in section III.E. of this final rule.

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 that several modules 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 proposed to:

++ Retain the requirement for direct antigen detection for:

—Section 493.911(a)(1)(ii): Bacteriology.
—Section 493.919(a)(1)(i): Virology.

++ Add the requirement for direct antigen testing detection for:

—Section 493.915(a)(1)(i): Mycology.
—Section 493.917(a)(1)(i): Parasitology.

++ Require PT for bacterial toxin detection under § 493.911(a)(1)(iii). No changes were proposed for mycobacteriology.

++ 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).

We summarize and respond to the public comments we received on these proposals and summarize our final policies in section III.E. of this final rule.

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

In addition to determining which analytes should be added or deleted, CMS and CDC proposed to establish or change, if necessary, the criteria for acceptable performance, which include the target value and ALs, for the analytes. 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 all laboratories 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. As discussed in section II.B. of the proposed rule, for all new and currently required non-microbiology analytes, we proposed to amend certain analytes in §§ 493.927, 493.931, 493.933, 493.937, and 493.941 to include percentages with or without fixed ALs. Additionally, we proposed to tighten ALs for certain current analytes in §§ 493.927, 493.931, 493.933, 493.937, 493.941, and 493.959.

We summarize and respond to the public comments we received on these proposals and summarize our final policies in section III.F. of this final rule.

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. 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 requiring PT for every analyte to derive benefits generalizable to all test methods is unnecessary. 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 conducted by CDC and the Association of Public Health Laboratories (APHL) in 2013, many laboratories voluntarily purchased PT materials for many nonrequired analytes. Keeping this in mind, as discussed in section II.B.2. of the proposed rule, we proposed adding 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.

(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 11 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). The expected impact on laboratories and PT programs was also considered (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 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 below the 500,000 threshold that we determined to be clinically important based on literature already footnoted in section II.B.2.b. of the 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 the 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 payment, as well as the most current MarketScan Commercial Claims and Encounters (CCAE) and MarketScan Medicaid Multi-state data sets [2] 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 test we considered for addition to, or deletion from, subpart I 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, to evaluate the testing trends for the proposed analytes. We analyzed national testing trends based upon Medicare Part B payment data [3] 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 payment for the proposed analytes.

We estimated the 2009 national test volumes based upon two data sets: (1) Medicare Part B payment 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 no estimation of total counts was necessary for this sector. MarketScan data, 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 categories for the entire United States. The Agency for Healthcare Research and Quality (AHRQ) 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 United States. 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 provide a relative sense of the number of tests being performed annually per analyte. No other accurate data were available to us.

As noted previously in this section, 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 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 related to each analyte under consideration to assess patient and public health impact of

[2] 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.*

[3] *https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4698806/.*

testing. Because there was no standardized, generally accepted way to assess this impact on clinical care and public health, we used the following 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).[4] We accessed several data sources, including tests listed in the CDC Guide to Community Preventive Services; [5] National Healthcare Priorities/Disparities reports; [6] clinical practice guidelines including the National Guideline Clearinghouse (NGC) database available from AHRQ (*https://www.guideline.gov/*); critical values available in publications; and (CAP) Q-Probes.

In reviewing published LPGs, we hypothesized that if there were 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).

To review critical values, which are pre-determined limits for specific analytes that, when exceeded, may suggest that immediate clinical intervention is required, we assessed analytes included in published on ''critical values'' lists. This approach allowed us to gauge the importance of an accurate result because an incorrect result could lead to a life-threatening intervention or a failure to intervene. We reviewed published literature and critical values posted online from 16 institutions, including small hospitals, university hospitals, and reference laboratories.

As mentioned earlier in this proposed rule, we also assessed the clinical impact of an analyte by reviewing its medical device classification (Class I, II, or III) as categorized by the Food and Drug Administration's risk classification list. Similarly, 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,[7] the National Healthcare Quality and Disparities Report,[8] and the CDC Hormone Standardization Program.[9] For some analytes that are important to measure towards addressing health disparities and have public health impact, such as blood lead, we consulted with subject matter experts in CDC's 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 the proposed rule.

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 on 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 the 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 previously in this final rule, 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).

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[4] *http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfClia/Search.cfm.*

[5] *https://www.thecommunityguide.org.*

[6] *https://www.ahrq.gov/research/findings/nhqrdr/index.html.*

[7] *https://www.uspreventiveservicestaskforce.org/Page/Name/recommendations.*

[8] *https://www.ahrq.gov/research/findings/nhqrdr/index.html.*

[9] *https://www.cdc.gov/labstandards/hs.html.*

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, direct measurement Ferritin Gamma glutamyl transferase Hemoglobin A1c Phosphorus Prostate specific antigen, total Total iron binding capacity (TIBC), direct measurement 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

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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 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 the use of 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 result from 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. For some anticonvulsant drugs, there may have been changes in medical practice, including alternative drugs and other treatments, possibly decreasing the need to measure them. We identified 13 currently required analytes with national test volumes less than our 500,000 annual test volume threshold.

b. Estimated Impact on Patient and Public Health

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 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 of deleting these analytes on clinical medicine and public health. 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 B e 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 previously in this final rule, we proposed 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

''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 is 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 indicate that such an evaluation is inappropriate.

Based on input from PT programs, we recognize, that peer grouping is generally the way that target values are set for most analytes. Therefore, in the proposed rule, we proposed to continue allowing PT programs to use peer grouping to set the target values. In addition, we proposed 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 AL that were originally specified in each specialty and subspecialty of the CLIA '88 regulations in subpart I effectively allow for 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 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 believed it was 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 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 proposed to use fixed ALs, preferably as percentage limits rather than concentration units.

There are 53 analytes (existing or proposed) for which we proposed a percentage-based AL, for which biological variability data were published. There were no biological variability data for several analytes (for example, therapeutic drugs). 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. 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 on biological variability would be untenable because the current analytical accuracy for such testing would not be expected 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. We believe 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 successfully made 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 the proposed rule, we proposed 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. 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 fairer and more realistic ALs, we proposed 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 proposed 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 proposed to change the ALs to percentages. Over the years, there have been many proposed criteria for establishing goals for analytical performance. The various possible approaches were reviewed and a hierarchy was established based on a 1999 consensus conference. These strategies were reconsidered at 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. 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, we believe the most important factor for monitoring progress 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 proposals for acceptance limits in percentages. 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 publicly available estimates of allowed total error based upon estimates of biological variability to approximate the proposed AL. CDC has shown in a recent poster [10] 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 proposed 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 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 that were previously required to perform PT under CLIA '67. Howerton, et al., 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. This is consistent with CLIA's intent to ensure accurate clinical testing regardless of the setting where testing is performed. There are several factors

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

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 proposed to make criteria for acceptable performance for existing analytes listed in subpart I (§§ 493.927, 493.931, 493.933, 493.937, 493.941 and 493.959) tighter, so they are in closer agreement with analytical accuracy goals which are based upon biological variability and simulation data.

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 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 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 in this final rule. We then requested narrowly tailored data from PT programs as described previously in this final rule 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 proposed ALs.

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 likely meet 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 modeled statistically. Finally, the distribution of unsatisfactory and unsuccessful PT scores is not randomly distributed across all participants.

++ Sections 493.923(a), 493.927(a), 493.931(a), 493.933(a), 493.937(a), 493.941(a), and 493.959(b): We proposed 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 proposed to amend 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 added ALs based on percentages or target values in addition to retaining the qualitative target values. We proposed to make this allowance in CLIA for reporting PT which reflects current practice.

++ Section 493.931(b): We proposed 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.

++ Section 493.933: We proposed adding the following analytes: estradiol, folate (serum), follicle stimulating hormone, luteinizing hormone, progesterone, prolactin, parathyroid hormone, testosterone, and vitamin B12.

++ Section 493.937(a): We proposed revising 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 proposed 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 differentiated the criteria for units of reporting of the analyte prothrombin time. We proposed to amend the criteria for acceptable performance to reflect both in seconds and/or INR (international normalized ratio) and to add the requirement that laboratories must report prothrombin time for PT the same way they report it for patient results. We also proposed to add criteria for acceptable performance for directly measured INR for prothrombin time. Additionally, we proposed to require laboratories performing both cell counts and differentials to conduct PT for both (that is, the ''or'' would be changed to an ''and''). Finally, we proposed changing the criteria for acceptable performance for ''cell identification'' from 90 percent to 80 percent. We proposed 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 zero 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 proposed changing the criteria for acceptable performance for unexpected antibody detection from 80 percent accuracy to 100 percent accuracy. We proposed this change because it is critical for laboratories to identify any unexpected antibody when crossmatching blood in order to protect public health and not impact patient care.

++ Sections 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 proposed amending these provisions to clarify that to achieve 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 previously

allow for scoring either with participants or with referees before calling a sample ungradable.

C. Additional Proposed Changes

We proposed to amend § 493.2 by modifying the definition of an existing term and defining new terms as follows:

- *Target value:* We proposed removing the reference to NRSCL and NCCLS and retaining the other options for setting target values in this final rule.
- *Acceptance Limit:* We proposed defining this term to mean the symmetrical tolerance (plus and minus) around the target value.
- *Unacceptable score:* We proposed defining this term to mean PT results that are outside the criteria for acceptable performance for a single challenge or sample.
- *Peer group:* We proposed defining 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 proposed the following revisions to the regulation text at subpart A:

- Sections 493.20 and 493.25: We proposed 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 proposed 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 proposed to revise the regulation text at subpart H:

- Section 493.861: We proposed 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 proposed 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 proposed to revise the regulation text at subpart I:

- Section 493.901(a): We proposed to require that each HHS-approved PT program must have a minimum of 10 laboratory participants before offering any PT analyte. We recognize that PT programs do not grade results when there are fewer than 10 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 during the reapproval process 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 proposed 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 only allow laboratories to report PT results electronically with no other option such as facsimile or mailed PT submission forms. However, at this time, the PT programs that 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 proposed 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 proposed 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 proposed an additional requirement to the regulation that specifies 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. 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 proposed adding 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 proposed adding 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 also proposed adding a requirement that the PT program may request reconsideration should we determine that false or misleading information was provided if the PT program has failed to correct issues identified by HHS related to PT program requirements.

III. Analysis of and Responses to Public Comments

We received 107 public comments in response to the February 4, 2019,

proposed rule. The commenters represented individuals, PT programs, accreditation organizations, laboratory professional organizations, and businesses, including in vitro diagnostics manufacturers. Commenters were generally supportive of the proposed changes, and some noted that these changes would increase flexibility and be a positive change for both laboratories and PT programs, especially in the specialty of microbiology. A few commenters recommended clarification of proposed changes or suggested specific changes, including alternative language, to the proposed requirements. After analyzing the comments received, we have modified or deleted several provisions in this final rule. A few commenters raised issues that are beyond the scope of our proposals. We are not summarizing or responding to those comments in this final rule. However, we reviewed the comments to consider whether to take other actions, such as revising or clarifying the CLIA program operating instructions or procedures, based on the information or recommendations in those comments. Our responses to specific comments are as follows:

A. Delayed Effective Date and Ongoing Process for Updating PT Regulations (§§ 493.2 and 493.801 Through 493.959)

Comment: Several commenters requested that there be a delayed effective date or phase in approach for implementation of the updated PT requirements to give all affected constituents time to accommodate the changes. Two commenters suggested that CMS develop an ongoing process to make changes to the PT regulations to ensure timely implementation of the updates.

Response: We recognize that time will be needed for laboratories, PT programs, accreditation organizations, exempt States, and surveyors to adopt the updated PT requirements related to subparts H and I. As such we are delaying the effective date of the revisions to §§ 493.2 and 493.801 through 493.959 until 2 years after the publication of this final rule in the **Federal Register**. The delayed effective date reflects the timeframe that we believe PT programs will need to produce the PT samples to meet the revised regulations and incorporate any updates to PT reporting requirements. In addition, laboratories will need to implement the new PT requirements after the samples are available from the PT programs. We encourage laboratories to enroll in the new and revised analytes prior to the delayed effective date. We also appreciate the commenters' suggestions for a process to address needed PT changes more quickly on an ongoing basis. We will consider possible ways to streamline the process going forward in light of the required timeframe for rulemaking. We note that the regulations related to laboratories performing tests of moderate complexity and high complexity testing that also perform waived testing and proficiency testing enrollment, §§ 493.20 and 493.25, respectively, will be effective 30 days after the publication date of this final rule.

B. Definitions (§ 493.2)

Comment: A commenter stated that the term ''unacceptable score,'' as defined at § 493.2, was confusing and should be replaced with ''unacceptable result.'' Other commenters pointed out that the organization of sub-bullets under the definition of ''target value'' was incorrect as the content in (iv) does not belong under (1), but should be included as (2) under the definition.

Response: We agree with commenters that the term ''unacceptable score'' could be confusing because it could be interpreted to mean a total analyte event score rather than the intended meaning of referring to a single challenge or sample result. Since this term is not included in the CLIA regulations except for the proposed amendments to § 493.2, we are not finalizing this term in § 493.2 in this final rule. With respect to the proposed definition of ''target value'', we agree with the commenter about the paragraphs included under that definition and are making the recommended change in this final rule.

Comment: While several commenters supported the inclusion of a definition for ''peer group'' in the proposed rule, other commenters expressed concerns about our proposal. Three commenters approved of our proposal to disallow peer-grouping to the reagent lot level, while two commenters did not agree with the proposal. One commenter noted that matrix effects, known to cause PT materials to behave differently from unmodified patient samples, are the reason underlying the need to use peer grouping to set target values and grade PT results. This commenter was concerned that the final rule would not account for the existence of matrix effects by not allowing peer grouping. One commenter suggested we consider conducting a scientific study to assess the contribution of calibration errors versus matrix effects in causing differences in PT results.

Response: In response to the comments about peer-grouping to the reagent lot level, PT is one of the important ways to detect problems in FDA-cleared/approved test methods. Differences between reagent lots used during testing may occur due to the manufacturing process. Allowing peer grouping to the lot level may inhibit the detection of these problems. We are not prohibiting PT programs from interacting with manufacturers to discover problems with reagent lots. However, the PT program has the responsibility for interpreting correct PT results. If a PT program determines that a specific reagent lot failure occurred, it should inform the affected laboratories and manufacturer. Concerning the comment about matrix effects, currently CLIA requires PT programs to demonstrate through a scientific protocol that bias, such as matrix effects, existed in PT materials before allowing peer-grouping to grade results. We are aware that PT programs have typically not used a scientific approach to determine if a peer group should be used as the process of demonstrating matrix effects is expensive and time-consuming. This rule finalizes the proposed definitions for both ''peer group'' and ''target value'' and will continue to allow peer-grouping for evaluation of PT results, without requiring prior demonstration of matrix effects. We do not expect there will be a change in how peer groups are identified by PT programs. Therefore, there will be no change in how target values are determined based upon the mean of peer group results. In response to the proposed study of commutability to demonstrate differences in PT results based on calibration errors, the comment is outside the scope of this final rule.

Comment: Two commenters suggested that CLIA should not require removal of outliers using a three standard deviation (3 SD) criterion when grading PT, as required under the proposed definition of target value in § 493.2. One commenter noted that the requirement to remove outliers was done to get a better estimate of the SD, which would only apply to one analyte after the final rule is effective. The other commenter stated that outlier removal using a 3 SD limit is not recommended according to ISO 13528:2015. Both commenters noted the need for robust methods to remove outliers, which can be especially problematic when the PT peer group is very small, such as a group that includes only 5 to 20 results.

Response: It is important that outliers be removed to set target values. Because a spurious PT result, including one due to a transcription error, could affect the peer group mean, especially when the peer group has relatively few laboratory

participants, PT programs should continue to discard aberrant results when calculating the peer group target. At this time, we do not have sufficient information to provide additional or alternative options for outlier removal. However, we recognize the need for PT programs to have valid modern approaches for outlier removal. Therefore, we are retaining the requirement to remove outliers as described in the definition for target value, using a 3 SD criterion. Regarding the comment referencing ISO requirements, we note that ISO standards do not apply to CLIA.

Summary of Final Actions

- We did not receive any comments on the proposed definition of ''acceptance limit'' and are finalizing the definition with a clarifying technical edit.
- Based on the public comments received, we are finalizing the proposed definition of ''peer group'' with a clarifying technical edit.
- We are revising and finalizing the proposed definition for ''target value.'' We have corrected the organization of the paragraphs and have moved the content of subparagraph (iv) to paragraph (2).
- We are not finalizing the proposed definition of ''unacceptable score.''

C. Enrollment and Testing of Samples (§§ 493.20(c) and 493.25(d))

Comment: A number of commenters expressed concerns or requested clarification about the proposal to amend §§ 493.20(c) and 493.25(d) to reflect that if laboratories certified to perform moderate and high complexity testing, respectively, also perform waived tests, compliance with § 493.801(a), which requires enrollment in PT, and (b)(7), requiring PT for the primary method of patient testing, are not applicable for the waived tests. However, as proposed, if laboratories voluntarily enrolled in PT for their waived testing, § 493.801(b)(1) through (6) would apply in cases of improper PT referral for those tests. Commenters expressed that laboratories may be discouraged from voluntarily enrolling in PT for waived tests if the possibility of sanctions for referred PT existed. Two commenters recommended that PT should be required for all testing, including waived testing. One commenter requested clarification of whether laboratories would need to verify the accuracy of waived tests twice per year.

Response: Subsection (d)(2)(C) of the CLIA statute states that subsections (f) and (g) shall not apply to a laboratory issued a Certificate of Waiver. Subsection (f) is related to issuing standards that, at a minimum, allow a laboratory to consistently perform testing to ensure accurate and reliable test results, including the requirement for all laboratories that perform nonwaived testing to enroll in an approved PT program and to verify the accuracy of tests twice per year. Subsection (g) speaks to inspecting laboratories for compliance with subsection (f) and are generally done on a biennial basis. However, sanctions related to PT referral are in subsection (i), which is not limited to nonwaived laboratories but rather allows sanctions to be taken against ''any laboratory'', including a Certificate of Waiver laboratory, that intentionally refers PT samples to another laboratory. Some Certificate of Waiver laboratories and other laboratories that perform waived testing have voluntarily chosen to enroll in PT for waived testing over the history of the CLIA program to ensure the quality of their testing. We have no reason to believe these laboratories will be discouraged from continuing their enrollment in PT. As a result, we are finalizing the new requirements at §§ 493.20(c) and 493.25(d) to ensure that the CLIA regulations align with the statute.

Summary of Final Actions

- We are finalizing the proposed revisions at §§ 493.20(c) and 493.25(d).
- We are finalizing the proposed revisions at §§ 493.801 and 493.861. Section 493.801 will require laboratories to report PT results for microbiology organism identification to the highest level that they report results on patient specimens. Section 493.861 will amend 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 received no comments on the proposed revisions at §§ 493.801 and 493.861.

D. PT Program Approval and Administration (§§ 493.901, 493.903, 493.905)

Comment: Two commenters urged CMS not to change the current codes used for specific analytes when PT programs report PT results to CMS and to create new codes for the analytes being added.

Response: We understand the commenters to be referring to certain analyte-specific codes that are used as an internal data system designation for PT programs to report PT analyte results to us. Although these codes are not explicitly referenced in the regulations, we agree with the commenters and note that the current analyte-specific codes for PT will remain the same. New analyte-specific codes will be generated for the newly required PT analytes.

Comment: Many commenters remarked on the requirement proposed at § 493.901(a) having at least 10 laboratory participants for an analyte before a program is approved to offer that analyte. Commenters stated that this requirement could inhibit development of new PT, and be detrimental to both laboratories and PT programs, especially smaller programs, which could find it harder to compete. Some commenters pointed out that PT programs offering newly required analytes would naturally have relatively fewer participating laboratories. One commenter requested clarification on whether this requirement would apply only to newly required analytes or to all PT analytes. Some commenters pointed out that PT programs may not initially know how many laboratories would enroll, and the programs would need time to develop their market. One commenter stated that this requirement would be a burden and result in more ungraded events.

Response: The requirement for at least 10 laboratory participants would only apply for PT analytes required in subpart I, and therefore, should not impact the development of PT for new or emerging analytes to the extent that they are not listed in subpart I. We realize that PT programs seeking HHS approval for the first time may not know how many laboratories would enroll in their program, and we did not intend to require at least 10 laboratory participants when PT programs apply for initial approval. We intend to review the number of laboratory participants for each program and each HHS-approved analyte during the annual reapproval process. If a PT program has fewer than 10 participants, we may not reapprove the PT program for a specific analyte. As a result of the comments, in this final rule, we are clarifying the requirement at § 493.901(a) to state ''for each specialty, subspecialty, and analyte or test for which the proficiency testing program is seeking reapproval'' to better reflect the PT approval process.

Comment: A number of commenters representing several PT programs and accreditation organizations commented on the requirement proposed at § 493.901(c)(6) that 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. There was general opposition due to perceived burden and expense, both to PT

programs and laboratories, and possibilities for errors. Some commenters stated that they are currently unable to know when every PT result is entered or changed if done electronically based on the technology used for laboratories to submit results. There were also questions about the circumstances under which PT programs would be required to provide audit trails. One commenter agreed with this proposed change but recommended that we provide more guidance to laboratories on how to meet this requirement.

Response: We appreciate the information provided by the commenters expressing the challenges with meeting this requirement. We do require laboratories to maintain documentation of their submissions to PT programs (see § 493.801(b)(5)). However, based on the comments received, we are not finalizing the requirement proposed at § 493.901(c)(6).

Comment: Several commenters expressed concerns about the requirement proposed at § 493.901(c)(9) that a contractor performing administrative responsibilities as described in §§ 493.901 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. A commenter noted that many essential PT program functions are currently performed by for-profit entities or subcontractors. There was a general consensus among commenters that many important administrative functions could not be performed without contractual arrangements with for-profit entities, such as transportation services.

Response: We recognize that some functions required as part of the PT process, such as transportation services, are provided by for-profit entities. Other business functions may also be provided by for-profit contractors, such as obtaining and manufacturing the PT specimens/products, initial testing to establish approximate target values as prescribed by the PT program, aliquoting and labeling samples, testing to assure homogeneity and stability of samples, long-term storage of samples for use in future PT events, and storage of aliquoted PT samples for additional testing as may be requested by the clients, or required by us. Also, ''for-profit'' entities can be used or contracted for distributing/mailing out the PT kits to the laboratories. This proposed requirement was not intended to address those aspects of PT program operations, but rather the technical and scientific responsibilities as described in §§ 493.901 and 493.903. These technical and scientific responsibilities include, but are not limited to, processes for selecting appropriate target values to be included in challenges as part of the annual PT program or grading PT results, determining target values, reporting scores to CMS, and determining organisms included in microbiology PT samples. In an effort to clarify the intent of the proposed requirement, we are changing ''administrative responsibilities'' to ''technical and scientific responsibilities'' in the provision being finalized at § 493.901(c)(8), previously proposed at § 493.901(c)(9).

Comment: While commenters agreed with the requirement proposed at §§ 493.901(e) to allow HHS to require on-site visits as part of the initial approval of PT programs, they indicated the need for sufficient advance notice of an on-site visit. Also, there were two suggestions to use an independent third party if on-site visits were to be conducted.

Response: We would coordinate the timing of the visit with the PT program and generally provide advance notice of the on-site visit. On-site visits will be conducted by CMS, and not by a third party. As a result, we are finalizing the new requirement at § 493.901(e) as proposed.

Comment: We received comments concerning the requirement proposed at § 493.901(f) that HHS may require a PT program to reapply for approval using the process for initial applications if significant problems are encountered during the reapproval process. While no commenters disagreed with the proposed requirement, one commenter requested that we use this option sparingly, and another commenter requested clarification on when this option would be used.

Response: We intend to use this option cautiously and only when issues arise that we consider be significant, for example, complaints of quality issues related to the PT program. As a result, we are finalizing the new requirement at § 493.901(f).

Comment: Commenters suggested clarification was needed regarding the requirement proposed at § 493.903(a)(3) that PT programs must not change or add any information on the PT result submission. They requested clarification on what data could not be changed, noting that some changes, such as adding or changing a method code, would not necessarily affect test results submitted but would be important for appropriate peer grouping. Commenters expressed concern that PT programs would not be able to add a methodology if inadvertently left off by the laboratory, thus affecting appropriate peer grouping. Commenters questioned if exceptions might be made if errors were made by the PT program and not the laboratory.

Response: As explained in the proposed rule (84 FR 1536, 1547), it is not appropriate for a PT program to change or add information on the PT result submission from a laboratory, including, but not limited to, the testing methodology, results, data, or units. If a laboratory inadvertently enters the wrong methodology or omits a methodology, the PT program should not assume to know the correct methodology and make that change or addition. We would consider it acceptable for the PT program to enter the methodology in cases where the PT program form does not include the methodology used by the laboratory for testing and the laboratory has manually written the methodology on the result submission form. This would also apply to units of measure. Under no circumstances should a PT program change a laboratory's submitted result. It is the laboratory's responsibility to provide correct and complete information and to investigate and correct errors that lead to PT failures. As a result, we are finalizing the requirement at § 493.903(a)(3) as proposed.

Comment: Commenters expressed concerns regarding the potential impact on laboratories and PT programs of the requirement proposed at § 493.905(a) allowing HHS to withdraw the approval of a PT program at any point in the calendar year if the PT program provides false or misleading information required for program approval or if the PT program fails to correct issues identified by HHS related to PT program requirements.

Response: We may withdraw approval of the PT program if HHS determines the PT program fails to meet any of the required criteria for approval. After we withdraw approval of a PT program, approval of the PT program would remain in effect for 60 days from the date of written notice to the PT program of this action. A PT program will be required to notify all of its participating laboratories of our withdrawal of approval within 30 days from the date of written notice to the PT program. We believe the 30-day notification by the PT program in this situation, and the additional 30 days before approval is withdrawn, gives laboratories sufficient time to enroll in an alternative PT program. PT programs may request reconsideration from us in accordance with subpart D of part 488 regarding the

withdrawal of approval if the false or misleading information or issues identified by us have been addressed within 60 days. We believe that the 60-day timeframe gives the PT programs sufficient time to mitigate any issues related to withdrawal of approval.

Summary of Final Actions

- We are finalizing the proposed changes to §§ 493.901(a), (c)(8), (e), (f), 493.903(a)(3), and 493.905.
- Based on comments received, we are not finalizing the proposed addition at § 493.901(c)(6).

E. Proposed Changes to Microbiology PT (§§ 493.911 Through 493.919)

Comment: Commenters suggested clarification is needed regarding methods or platforms for which PT is proposed to be required, specifically for laboratories that use molecular, nucleic acid amplification, mass spectrometry testing or next generation sequencing for microorganism identification and susceptibility testing in all microbiology subspecialties. A commenter also questioned whether PT is required only for FDA-cleared test systems. The commenters stated this clarification would help prevent confusion among laboratories.

Response: PT is not required by method or specific technology for microbiology subspecialties (§§ 493.911 through 493.919), including whether a test system is FDA-cleared, or analytes in non-microbiology specialties or subspecialties (§§ 493.921 through 493.959). Regardless of the method, a laboratory uses for microorganism identification and susceptibility testing, PT is required for these categories of microbiology testing. When CLIAC deliberated on appropriate PT for microbiology, they suggested the inclusion of broad categories of testing performed in microbiology, rather than the types of services offered by laboratories, described in §§ 493.911 through 493.919, to allow flexibility for the inclusion of new technologies. Each laboratory needs to identify the method or test system used when submitting PT results for programs to properly grade the PT. If a laboratory performs microbiology testing for which PT is not available or required, they need to verify the accuracy of those procedures at least twice per year, as described at § 493.1236(c)(1). If available, voluntary PT may be a way the laboratory chooses to meet this requirement.

Comment: Commenters supported the removal of the types of services offered by laboratories in each microbiology subspecialty and replacement of the types of services with general categories of testing for which PT is required. However, they had questions about the proposed option in bacteriology for detection of growth or no growth in culture media. They questioned whether this option was included or relevant for all microbiology subspecialties and all specimen types and whether it should be removed as an option under the category for identification of bacteria since bacteria are not identified when only growth is detected. A commenter also noted that this category may not be appropriate for cultures from normally sterile sites or those that are expected to contain normal flora. Another commenter requested for clarification of how this category would apply to urine colony counts. A commenter suggested changing the language in bacteriology to ''presence or absence of bacteria without identification,'' with similar changes in other subspecialties. Another commenter suggested changing the language in bacteriology to ''growth or no growth in culture media or identification of bacteria to the highest level that the laboratory reports results on patient specimens.'' Other language changes suggested by commenters included revising this category to ''growth or no growth of acid-fast bacilli'' in mycobacteriology and ''growth of yeast, growth of mold, or specimen negative for fungi'' in mycology.

Response: We recognize the need for clarification of this option based on the comments received. The option was proposed in bacteriology at § 493.911(a)(1)(iv)(A); mycobacteriology at § 493.913(a)(1)(ii)(A); and mycology at § 493.915(a)(1)(ii)(A) under the proposed categories for microorganism detection and identification. Similar language proposed for parasitology at § 493.917(a)(1)(ii)(A) specified detection of the presence or absence of parasites. This option was not proposed for virology. Specimen types are not included in any of the PT categories in microbiology and a challenge for growth or no growth, or presence or absence, was not proposed and may not be appropriate for all specimen types or sites, or appropriate as a response for all laboratories. It is one of two options included under the category of detection and identification of bacteria, mycobacteria, fungi and aerobic actinomycetes, and parasites, in the respective microbiology subspecialties. It was proposed as an option for laboratories that perform limited microbiology testing to detect the presence of microorganisms and then refer growth from culture or specimens containing the microorganisms detected to another laboratory for identification. In response to the question about applicability of this option for laboratories that perform urine colony counts, PT is not required for colony counts. If the laboratory performs identification of the bacterial growth, PT is required for the identification. If the laboratory performs the colony count only and refers the isolate for identification, an appropriate result for the PT challenge would be to report detection or growth of bacteria. In response to the suggestions for revisions to the language for this option in each of the subspecialties, after considering the suggestions from commenters, for clarification in this final rule we have changed the language at § 493.911(a)(1)(iv)(A) to ''detection of the presence or absence of bacteria without identification.'' We changed the language at § 493.913(a)(1)(ii)(A) to ''detection of the presence or absence of mycobacteria without identification, ''and at § 493.915(a)(1)(ii)(A) to ''detection of the presence or absence of fungi and aerobic actinomycetes without identification.'' In parasitology, we added ''without identification'' to the end of the phrase currently at §§ 493.917(a)(1)(ii)(A) and 493.917(b)(1) to be consistent with the other microbiology subspecialties. In these subspecialties, we also revised the performance criteria at §§ 493.911(b)(1), 493.911(b)(7)(i), 913(b)(1), 493.913(b)(5)(i), 493.915(b)(5)(i), and 493.917(b)(5)(i) to correspond to these changes. For example, in bacteriology this change now specifies that the performance criterion is the correct detection of the presence or absence of bacteria without identification. This may be achieved when performing a culture and looking for bacterial growth or when using another test method that detects the presence of bacteria without any type of identification being performed.

Comment: Two commenters recommended clarification of the proposed categories of direct antigen and toxin detection, with specific questions about the applicability of this category and which antigens or toxins are required in the subspecialties of bacteriology (§ 493.911), mycobacteriology (§ 493.913), and mycology (§ 493.915). One commenter questioned whether the intent of the proposal was to require PT for only *Clostridium difficile* toxin or also for other toxins in bacteriology. The same commenter requested clarification on which direct antigen tests are proposed to be required in mycology. Another commenter questioned whether antigen

detection was intended to be required for mycobacteriology, as it was not proposed and no programs currently offer this PT.

Response: The requirement for PT for laboratories that perform direct antigen testing has been part of the CLIA regulations in the subspecialties of bacteriology and virology since PT was first required in 1994 and it was included as one of the required categories of microbiology PT in the proposed rule. As with other microbiology PT, the microorganisms for which it is required are not specified in the regulations. Rather, the regulations require that PT programs determine the reportable bacteria or viruses to be detected using direct antigen techniques. In this rule, required PT for direct antigen detection is included in bacteriology at § 493.911(a)(1)(ii); mycology at § 493.915(a)(1)(i); parasitology at § 493.917(a)(1)(i); and virology at § 493.919(a)(1)(i). Required PT for toxin detection is included in bacteriology at § 493.911(a)(1)(iii). As in the previous rule, the microorganisms for which direct antigen or toxin detection are required are not specified in the regulations. Rather, in all subspecialties for which this category is required, the regulations state the PT program determines the organisms to be reported by direct antigen or toxin detection. PT for direct antigen or toxin detection may be part of a combination module or offered as an individual five-challenge module in each subspecialty. If a laboratory performs direct antigen or toxin testing for which PT is not available, they are required to verify the accuracy of those procedures at least twice per year, as described at § 493.1236(c)(1).

Comment: A few commenters addressed the proposed requirements for microbiology stains, with agreement that Gram stain PT should require bacterial morphology as well as gram-reaction. Commenters requested for clarification regarding the level of detail required for bacterial morphology as part of PT and whether Gram stain PT would be required when a Gram stain is performed as part of organism identification. Commenters also questioned the proposed inclusion of Gram stains and acid-fast stains in bacteriology and mycobacteriology, but lack of requirements for stain challenges in other microbiology subspecialties.

Response: In this rule, we are finalizing the proposed requirement at § 493.911(b)(1) that includes bacterial morphology when performing Gram stain PT. This may apply to either a Gram stain required as an individual challenge or as part of bacterial identification. PT program instructions specify which tests are to be performed on each sample, thus identifying which samples require Gram stains. Morphology should include the basic shape and arrangement of bacteria. However, as stated at § 493.911(b)(1), the PT program determines the reportable staining and morphological characteristics to be interpreted by Gram stains. In response to the commenters who questioned whether PT was proposed for stains in mycology and virology, at this time, PT programs do not offer challenges for stains in these subspecialties. Thus, they were not proposed. In parasitology, although specific stains were not proposed as a required PT category, the sample types required at § 493.917(a)(2) include PVA (polyvinyl alcohol) fixed specimens and blood smears, both of which are used in parasite identification. Because a variety of stains are used by laboratories to facilitate identification of intestinal, blood, and tissue parasites, and in some cases, parasites can be identified directly in wet mounts without using a stain, no stains were included for this microbiology subspecialty. Each laboratory participating in PT for parasite identification should follow the staining procedures they use for patient specimens.

Comment: Commenters supported the removal of specific lists of microorganisms from the microbiology subspecialty requirements and replacement with general groups of organisms to be included over time. In addition, commenters requested clarification of the required groups in bacteriology, mycology, and virology. In bacteriology, one commenter suggested expansion of the groups to include Gram-negative cocci or coccobacilli, and another requested clarification of whether the groups of cocci include coccobacilli or diplococci. A third commenter suggested bacterial strains included in PT should be those routinely encountered in specimens. In mycology, two commenters expressed concern about inclusion of dimorphic fungi as a required category, noting that the majority require handling in a biosafety level 3 laboratory and are unable to be shipped. Comments pertaining to groups of organisms for virology recommended viral groups that must be included, and one organization questioned whether a PT program needed to offer all viruses and all specimen sources to be approved for virology PT. Specifically, the commenter questioned whether a program could offer PT challenges for susceptibility or resistance testing based on a single specimen source, such as urine. Another commenter requested for clarification regarding appropriate specimen sources to be included in virology modules and questioned whether combinations of viruses needed to be incorporated in a single PT sample.

Response: The PT requirements for the microbiology subspecialties specify that the organisms included are those that are commonly occurring in patient specimens or are important emerging pathogens. The groups identified for each of the five subspecialties are general groups to be included over time and annually, if appropriate for the sample sources. They are not intended to be the only groups that could potentially be included. In bacteriology, Gram-positive or Gram-negative coccobacilli or diplococci could be included as challenges in addition to, or as more specific subgroups of the individual morphologies listed for bacteriology at § 493.911(a)(3). No changes are being made in this final rule to the bacteriology groups that were proposed. As stated by the commenters for mycology, dimorphic fungi were proposed at § 493.915(a)(3)(ii)(C) as a group of organisms to be included in mycology over time and more specifically, required on an annual basis. We recognize the commenters concerns with the proposed inclusion of this group of fungi, some of which must be manipulated at a biosafety level 3. In response to these concerns, we have removed the dimorphic fungi from the groups of annually required organisms in mycology. However, over time, we encourage PT programs to include a variety of organisms in each subspecialty, as appropriate, to test a laboratory's ability to detect and identify the spectrum of organisms that might be found in patient specimens. In mycology, this may occasionally include dimorphic fungi, such as *Sporothrix schenckii,* that can be handled under biosafety level 2 conditions. In response to the questions about the PT requirements for virology at § 493.919(a)(3), the proposed rule did not specify that all viruses or specimen sources needed to be included for a PT program to be approved. However, it was proposed that if appropriate for sample sources offered, the types of viruses included annually must be representative of the groups of medically important viruses listed. Generally, with this rule, PT programs must continue to offer the same types of virology challenges and modules that have been offered in the past. Lastly, PT

samples containing combinations of viruses were not proposed and are not required in this final rule.

Comment: Several commenters indicated that the proposed requirement in all microbiology subspecialties for laboratories to detect and identify organisms to highest level performed on patient specimens was unclear. One commenter recommended changing the description of the category for identification of bacteria to ''the highest level that the laboratory reports results on patient specimens.'' Two commenters suggested identification needed to be clarified as to whether the intent was presumptive or definitive identification and others questioned how this requirement should be applied with respect to identification at the genus or species level. The commenters stated more specific and better-defined criteria are needed, as well as the incorporation of language to allow for abbreviated reporting frequently used in reporting mixed cultures. They also questioned whether this information would need to be transmitted from PT programs to CMS and State agencies and one noted it would take time to implement this requirement. Another commenter stated it is the responsibility of inspectors to review patient reporting practices and not that of PT programs.

Response: We agree that the language proposed in all subspecialties for identification of microorganisms to the highest level that it performs procedures on patient specimens may be unclear, and we agree that the revised description provided by the commenter earlier more clearly specifies that this requirement refers to how a laboratory reports results on patient specimens. As a result, we have incorporated the change suggested by the commenter and made conforming changes in this rule for all subspecialties at §§ 493.911(b)(2), 493.913(b)(2), 493.915(b)(2), 493.917(b)(2), and 493.919(b)(2). We expect that this will clarify that if a laboratory reports patient results to the genus level, that is the expectation for PT. Similarly, if a laboratory reports patient results to the species level, that would be the expectation for reporting patient results. In response to the question about incorporation of language to allow for reporting abbreviated results, if this is the practice for reporting results to the highest level on patient specimens, it may be an acceptable PT practice as well. In all subspecialties, PT programs determine the organisms that must be reported as part of their identification. We believe the delayed implementation of specific portions of this final rule will allow PT programs to incorporate updates needed for reporting results to CMS. We agree with the commenters who stated that it is the responsibility of laboratory inspectors to review patient reporting practices and not the responsibility of PT programs and this was part of a CLIAC recommendation made prior to the development of the proposed PT rule. It was not our intent that PT programs take on this responsibility and it was not included in the proposed rule.

Comment: Multiple commenters supported the proposed changes to decrease the required percentage of mixed culture challenges from at least 50 percent to at least 25 percent in bacteriology, mycobacteriology, and mycology. The change, if finalized, would specify that at least 25 percent of the PT samples must contain mixtures of the principal organisms and appropriate normal flora.

Response: We agree with the commenters and appreciate their support of these proposed changes. This is in alignment with a CLIAC recommendation stating such and was proposed at §§ 493.911(b)(1), 493.913(b)(1), 493.915(b)(1). We are finalizing these changes in this rule.

Comment: Some commenters recommended changes to the microbiology subspecialties for which susceptibility or resistance testing PT was proposed to be required. A commenter noted that it would be difficult to comply with the requirement for susceptibility or resistance testing in mycology since samples are limited, there are few FDA-cleared methods or breakpoints for fungi, and there is extensive variability in the testing. Another commenter recommended that susceptibility or resistance testing may not be added to required PT in mycology and may be removed in mycobacteriology since few laboratories perform this testing. A third commenter stated the value of requiring PT for *M. tuberculosis* susceptibility testing is limited since programs often send out the same strain that is susceptible to all drugs tested. With respect to virology, a commenter disagreed with requiring susceptibility or resistance testing in this subspecialty and proposed requiring PT for viral loads. Another commenter indicated that since only one PT program currently offers antiviral susceptibility testing, that does not meet the specified criterion of requiring that three programs offer PT for an analyte or test, and it may not be required in virology. Finally, a commenter questioned whether a PT program should be required to offer susceptibility or resistance testing PT in virology if they offered other virology PT.

Response: We agree with the commenters' reasons for suggesting that PT not be required for susceptibility or resistance testing in mycology and virology at this time. Therefore, we are removing the proposed requirements for inclusion of this category of required PT § 493.915(a)(1)(iii) for mycology and at § 493.919(a)(1)(iii) for virology in this final rule. If this testing becomes less variable and PT availability increases in these subspecialties in the future, we may propose to include it in rulemaking at that time. In the meantime, if a laboratory performs susceptibility or resistance testing on patient specimens in mycology or virology, they are required to verify the accuracy of those procedures at least twice per year, as described at § 493.1236(c)(1). Voluntary PT may be a way the laboratory chooses to meet this requirement. With respect to the requirement for susceptibility or resistance testing in mycobacteriology, we are aware that small numbers of laboratories perform this testing and subscribe to PT and that only one program currently offers susceptibility testing PT in mycobacteriology. We also recognize that PT programs are less likely to send out resistant strains of mycobacteria, especially *M. tuberculosis,* due to biosafety concerns when shipping or working with these organisms. For these reasons, in addition to the fact that mycobacteriology is unique in that only two PT events per year are required, we are removing the requirement at § 493.913(a)(1)(iii) for susceptibility or resistance testing in mycobacteriology in this final rule. As stated previously, if a laboratory performs susceptibility or resistance testing on patient specimens in mycobacteriology, they are required to verify the accuracy of those procedures at least twice per year, the same frequency as required PT in this subspecialty. Laboratories may choose to subscribe to voluntary PT as a way to meet the requirement or they may use another mechanism to meet the requirement that does not include shipping strains of organisms that require special precautions.

Comment: Commenters questioned or requested clarification of the proposed requirements specified for antimicrobial susceptibility or resistance testing, including clarification of the definition or intent of resistance testing, questioning whether it meant testing for resistance mechanisms or markers for specific organisms. One commenter stated clarification was needed as to whether susceptibility testing is optional if a laboratory performs

identification. Another commenter suggested the language for this category of PT in bacteriology be clarified to state ''antimicrobial susceptibility or resistance testing of select bacteria.''

Response: The category of antimicrobial susceptibility or resistance testing was included in the proposed rule in for the subspecialties of bacteriology at § 493.911(a)(1)(v); mycobacteriology at § 493.913(a)(1)(iii); mycology at § 493.915(a)(1)(iii); and virology at § 493.919(a)(1)(iii). Resistance testing was included in this proposed category as it was previously recommended by CLIAC to be required along with susceptibility testing. As discussed in the previous comment, the proposed requirement for susceptibility or resistance testing in mycobacteriology, mycology, and virology has been removed from this final rule. With respect to the proposed requirement for this category in bacteriology, we agree with the commenters that the interpretation of ''resistance testing'' may not be clear, and that in some cases, bacterial resistance may be determined as part of an organism identification. For these reasons, we have removed resistance testing from the required category proposed in bacteriology and in this final rule we are requiring antimicrobial susceptibility testing of select bacteria, as suggested by the commenter, at § 493.911(a)(1)(v), since antimicrobial susceptibility testing is not performed on every bacterium that is isolated in a culture and PT programs specify which challenges require that susceptibility testing be performed. This also addresses the comment suggesting a change in the description of this bacteriology category for clarification. If laboratories perform resistance testing separate from bacterial identification, they are required to verify the accuracy of those procedures at least twice per year, as previously stated, and may enroll in voluntary PT to do so. In response to the recommended clarification of whether susceptibility testing is optional when a laboratory performs identification, laboratories must follow PT program instructions when determining which tests to perform on a microbiology sample. The programs must clearly identify which samples require that susceptibility testing be performed on bacteria that are identified and those results reported for PT purposes.

Comment: Several commenters agreed with the proposed increase in the number of required susceptibility or resistance testing challenges from one to two per event in all microbiology subspecialties except parasitology, where PT for susceptibility testing is not required. They indicated that increasing the number of challenges and requiring one Gram-positive and one Gram-negative challenge per event in bacteriology would help identify issues with patient testing. Other commenters disagreed with this proposed change, expressing concerns that this requirement would provide too much information to laboratories about PT sample content and make the PT results more predictable. One commenter stated that including two susceptibility challenges per event lacked value and relevance. Others suggested that requiring a mixture of challenges throughout the year was preferred over the requirement to include one Gram-positive and one Gram-negative challenge per event.

Response: We agree with the commenters who supported the proposed change to increase the number of required susceptibility or resistance challenges to two per event and are finalizing that change in this rule at § 493.911(a)(4). This change was recommended by CLIAC, and we believe it will provide a better assessment of laboratory testing performance over time. We also agree with the commenters who suggested that we should not specify a predictable pattern of susceptibility testing challenges in bacteriology, requiring that each event must include one Gram-positive and one Gram-negative challenge. As a result, in this rule, we are revising the requirement to indicate that each year, a minimum of two samples per testing event of susceptibility testing challenges must include a mixture of Gram-positive and Gram-negative challenges.

Comment: A PT program commented on the proposed requirements to change scoring for the microbiology subspecialties by including separate category scores in addition to the overall subspecialty scores. The program inquired about the intent of this proposed change and suggested that it would increase the complexity of determining scores and it may be especially challenging to score laboratories that perform a mixture of detection and identification procedures. The commenter also noted the proposed scoring method would give PT programs discretion in the interpretation of the requirement which could result in laboratories choosing the program that uses the most advantageous method. The commenter advocated for simplifying the subspecialty scoring process rather than increasing complexity for efficiency and increasing the value to laboratories.

Response: The four categories of testing proposed for microbiology PT were recommended by CLIAC to replace the types of laboratory services that are part of the current regulations. The types of services guided the scoring of microbiology subspecialties since there are no specific analytes in this laboratory specialty. However, since only a single score is given for each subspecialty, many times representing a combination of results for different types of testing, it is not possible for laboratory surveyors to readily determine if a laboratory is having problems with one area of their microbiology testing. No changes were made to the scoring process for microbiology in the proposed rule other than aligning the requirements for evaluation of a laboratory's performance at §§ 493.911(b) through 493.919(b) to be consistent with the categories of testing and facilitate the identification of problems in any one of the categories.

Summary of Final Actions

- We are finalizing the proposed revisions at §§ 493.911 through 493.919 by removing the types of services listed for each microbiology subspecialty and inserting a more general list of organisms.
- We are finalizing the proposed revisions at §§ 493. 911(a), 493.913(a), and 493.915(a) that are related to growth or no growth and mixed culture requirements (50 percent to 25 percent).
- We are finalizing the proposed performance criteria revisions at §§ 493.911(b), 493.913(b), 493.915(b), 493.917(b), and 493.919(b).
- We are finalizing the proposed addition of ''without identification'' to the end of the phrase currently in the subspecialty of parasitology at § 493.917(a)(1)(ii)(A) to be consistent with the other subspecialties.
- We are finalizing the proposed revised requirement at §§ 493.911(b)(2), 493.913(b)(2), 493.915(b)(2), 493.917(b)(2), and 493.919(b)(2) to clarify and emphasize that laboratories should detect and identify organisms to the highest level that they report results on patient specimens.
- We will amend §§ 493.911(b)(1), 493.913(b)(1), 493.915(b)(1), 493.917(b)(1), 493.919(b)(1) 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 are finalizing the proposed revisions to § 493.911(a) through (b) related to Gram stains, direct antigen detection, bacterial toxin detection, and performance and scoring related to

direct antigen and bacterial toxin detection for the subspecialty of bacteriology.

- We are finalizing the proposed addition to § 493.915(a) related to requiring direct antigen testing for the subspecialty of mycology.
- We are finalizing the proposed addition to § 493.917(a) related to requiring direct antigen testing for the subspecialty of parasitology.
- We are finalizing the proposed revision to § 493.919(a) related to requiring direct antigen testing for the subspecialty of virology.
- We are removing the reference to resistance testing in the subspecialty of bacteriology and have removed references to ''resistance testing'' in the requirement for antimicrobial susceptibility testing of select bacteria at § 493.911.
- We are not finalizing the proposed requirements for PT of antimicrobial susceptibility and resistance testing in the subspecialties of mycobacteriology, mycology, and virology and have removed the requirement at §§ 493.913, 493.915, and 493.919.

F. Proposed Changes to PT for Non-Microbiology Specialties and Subspecialties (§§ 493.921 Through 493.959)

1. Required Analytes

Comment: Several commenters agreed that the list of required analytes should be updated. Some commenters stated that the process for analyte inclusion and removal was thorough, understandable, and transparent. One commenter stated the inclusion threshold for new analytes that only included three PT programs, rather than four, could result in an unfair market advantage, raise PT costs for laboratories, or result in logistical difficulties in obtaining PT.

Response: In response to the comments, we reviewed our analyses and determined that there were no proposed analytes that would not have made the requirement for being offered by at least four PT programs, as was suggested by the commenter. We believe that the fact that there are already at least three programs available to choose from for each new analyte or test gives laboratories several options and should not result in increased costs or logistical difficulties in obtaining PT. All PT programs received notification of the proposed analytes or tests at the same time when the proposed rule was published. Whether a PT program elects to offer a particular analyte is a business decision of the PT program, and outside of our purview.

Comment: A small number of commenters mentioned concerns about the possibility that either inclusion of the PT analytes or the ALs we proposed would have a negative impact on access to testing. A few commenters suggested that for the ALs proposed for some analytes, some existing test systems would not meet the new requirements. For example, one manufacturer stated that the proposed ALs for creatine kinase isoenzymes may be challenging for some testing platforms to meet. A similar comment was made for proposed ALs for troponin I and hematocrit.

Response: During the phase in period, manufacturers will have time to improve test accuracy, and laboratories will have time to switch to higher accuracy test methods if those they use do not provide results that are able to meet the criteria for acceptable performance specified in the regulations. Clinicians and patients should be able to expect accurate testing, and assuring overall accuracy is the goal of performing PT. Therefore, these changes should drive the health care system toward more accurate methods. We have no reason to believe that access to testing will be impacted.

Comment: Several commenters supported the list of analytes that were proposed for addition and deletion, and commenters supported the process we used for determining the list of analytes for which PT is to be required. No commenters questioned any of the proposed new analytes. However, one commenter stated that a current analyte, T3 uptake, should be deleted because it lacked clinical utility. An accreditation organization and an individual commented that determination of creatine kinase (CK) MB fraction by electrophoresis should be discouraged, and therefore, it should be excluded from the required PT for creatine kinase isoenzymes. Rather, the commenters noted that PT should only be required for laboratories that use immunochemical methods when testing for this analyte. Some commenters recommended inclusion of analytes that we had considered but decided not to include. One commenter suggested that we require PT for several immunosuppressant drugs for which PT is not currently required.

Response: We had initially considered all the analytes that commenters recommended for either inclusion or deletion, but the suggested analytes did not meet one or more of our inclusion or deletion criteria. Both the inclusion and deletion processes, which were described in the proposed rule, were based upon per-analyte estimates of the availability and the number of programs already offering PT, the nationwide volume of patient testing, the impact on patient or public health of offering PT, and the cost and feasibility of PT implementation. We did not propose deletion of T3 uptake because test volumes were above the threshold for consideration. With respect to the suggestion to discourage laboratories from using electrophoretic methods to test for CK–MB isoenzymes, the method used is not a basis for requiring or not requiring PT for any test or analyte. Each laboratory needs to identify the method or test system used when submitting PT results for programs to properly grade the PT. To the extent that test results are used for clinical decision making, the test results should be accurate. The immunosuppressant drugs that were suggested were not done in sufficient volumes to meet the threshold for consideration in the proposed rule, so they were not proposed to be required.

Comment: For a few analytes that can be detected or quantified in more than one way, some commenters requested clarification concerning which analyte would require PT. For example, a commenter questioned if PT was proposed to be required whether LDL cholesterol was calculated or measured directly. Several commenters requested clarification concerning whether drugs were to be measured in total or free forms. One commenter mentioned a need to specify the sample type that should be tested if the analyte can be tested in more than one type of body fluid.

Response: For LDL cholesterol, which can be measured both directly and as an estimation based on other measured lipids, PT is only required for directly measured (not calculated) LDL cholesterol. For all drugs, we intend that the measured form must be total drug. For the specialty of chemistry, in subpart I the sample types for which PT is required are specified for each under each subspecialty, at § 493.931(b) for general chemistry, § 493.933(b) for endocrinology, and § 493.937(b) for toxicology. If a laboratory performs patient testing on other sample types than those listed, they are required to verify the accuracy of testing with those alternative sample types at least twice per year, as described at § 493.1236(c)(1). If available, voluntary PT may be a way the laboratory chooses to meet this requirement.

Comment: A few commenters requested clarification of what should be considered high sensitivity C-reactive protein, as opposed to traditional C-reactive protein, as included in the

proposed rule. A related comment suggested that we should require PT for all assays for C-reactive protein.

Response: Although traditional C-reactive protein has been used as a general marker of inflammation for many years, it did not meet the threshold for inclusion as a required PT analyte. In this rule we are finalizing the proposed PT requirement for high sensitivity C-reactive protein and we appreciate the need to define which test methods would be considered ''high sensitivity'' testing. High sensitivity C-reactive protein concerns testing related to cardiac ischemia, either for frank cardiac events or for risk stratification, which requires more sensitive test methods to detect lower concentrations. We are deferring to laboratories to know whether their assay is a high sensitivity method used to detect cardiac pathology, or the traditional, less sensitive C-reactive protein. PT programs must label their PT offerings accordingly.

Comment: One commenter suggested that we should specify the N-terminal region of pro-B-natriuretic peptide (BNP), which was included as a required analyte in the proposed rule because this is the epitope usually detected by antibodies used in most test methods.

Response: We agree with the commenter that the N-terminal region of pro-B-natriuretic peptide (BNP) is the part of the peptide that is usually measured, but we did not want to restrict the requirement for PT. Therefore, in this rule we are finalizing the name as proposed: proBNP.

2. Scoring and Acceptance Limits

Comment: With respect to scoring and ungradable samples, one commenter requested clarification about how performance on an analyte was determined for a PT event when one of the PT samples was not able to be graded. The commenter questioned what the denominator of graded samples would be. An accreditation organization agreed with our proposal to require PT programs to attempt to reach consensus using both laboratory and referee laboratories before deciding a sample is ungradable due to lack of consensus.

Response: If a sample for a particular PT event is ungradable, for example, because consensus could not be reached, it is still considered to be part of the denominator of five PT samples for that event, and in this case, the laboratory is given credit for passing the challenge. Therefore, if one of the remaining PT samples in the event is missed, the event score is 80 percent, and the event score is ''satisfactory'' for the majority of required PT.

Comment: Several commenters stated that the process used for simulating the impact of scoring PT using several alternative ALs to determine the optimal limit to require was unclear.

Response: As discussed in the proposed rule, we requested PT programs to examine the impact of various ALs on their aggregated sample failure rates, using the peer grouping approaches they had previously used. A number of the PT programs provided simulated results, applying various possible percentage-based ALs to actual results from previous PT events, and were able to help us select appropriate ALs. We selected ALs using a target miss rate (per sample) in the 1 to 2 percent range. Our intent was to assure that the ALs would work across the clinically important range and not inappropriately fail results that were accurate for clinical decision making. Therefore, we examined error rates at all concentrations that PT programs used throughout the 2 years of PT data they shared with us.

Comment: We received a number of comments related to the proposal to use percentage-based ALs whenever possible. While some commenters supported the proposed changes, others suggested changes to specific proposed ALs for both current and newly proposed analytes. Generally, these comments concerned whether the proposed limits would be workable across the clinically important measurement interval for all test methods and platforms. In almost all cases, the comments recommended less stringent ALs, either across the entire analytical measurement range or specifically at low concentrations, where test methods are generally less accurate. Commenters pointed out that unless there is allowance for low concentrations, PT programs would be discouraged from using PT samples with low concentrations, to the detriment of assuring accurate testing across the analytical range. Supporting this, some commenters stated that it is not clinically important to be as accurate as the percentage-based limits would require. Commenters suggested that we use a combination of a percentage and a concentration limit for certain analytes, such that PT samples with relatively low concentrations would be more fairly assessed. In some cases, commenters recommended a concentration limit that differed from a concentration limit we had proposed. A small number of commenters were generally concerned about moving from familiar 3 SD-limits to percentage based ALs for some currently required analytes.

Response: In response to commenters' concerns about the use of percentage limits when scoring PT analytes at low concentrations, in this final rule, we are including ''concentration limits'' such as are already used for glucose and some other analytes for many newly required analytes and some previously required analytes. When adding concentration limits and using combined ALs, programs are directed to score with whichever of the specifications is more tolerant, allowing for fairer and more realistic ALs that will allow PT programs to cover the clinically important range of results. We re-examined previously acquired simulation data from PT programs and have added concentration limits for 13 analytes. Specifically, we created concentration thresholds for alanine aminotransferase, aspartate aminotransferase, cholesterol (high density lipoprotein), CK–MB isoenzymes, glucose, carcinoembryonic antigen, human chorionic gonadotropin, vitamin B12, acetaminophen, carbamazepine, lithium, phenobarbital, and salicylate. Concerning the switch from current 3 SD limits to percentage-based limits, we believe that the new ALs will be workable, fair, and clinically relevant. As stated in the proposed rule, ALs based on analytical variability within a peer group, such as the use of 3 SD limits, are ill-suited to know whether testing results are sufficiently accurate for clinical purposes.

Comment: Two commenters noted that CLIA ALs have been used in ways other than their intended purpose of identifying laboratories with unacceptable performance. One commenter noted that ALs have been used as goals for ideal performance, for example, setting quality control acceptable limits. Another commenter pointed out that ALs have been used for verifying analytical performance, for example, accuracy.

Response: We agree with the comments and reemphasize that ALs must not be used as the criteria to establish performance goals in clinical laboratories. Goals for accuracy and precision must be based upon clinical needs and manufacturer's FDA-approved or -cleared labeling; PT performance is not the best assessment of these. Proficiency testing is intended to identify laboratories that are not performing with acceptable analytic accuracy; it is not intended, nor suited, to provide goals for analytical accuracy or clinical performance.

Comment: Many commenters stated the proposed AL for hemoglobin A1c (HbA1c) was too loose and not reflective of the testing accuracy of current test methods. Many individuals and organizations commented that the AL should be 6 percent, and several recommended lowering the limit to 5 percent. Several comments requested that CLIA ALs should not ''change'' from the current 6 percent, despite the fact that HbA1c is currently not a CLIA-required PT analyte, and therefore, no ALs are specified in the regulations. Many commenters expressed concerns that using a threshold higher than 6 percent would in some way subvert the substantial progress made by the National Glycohemoglobin Standardization Program (NGSP), working collaboratively with test method manufacturers, to improve accuracy of HbA1c testing. Commenters suggested that manufacturers would allow the accuracy of their test methods to deteriorate if CLIA added HbA1c with an AL as loose as 10 percent. A PT program proposed that we use an AL of 10 percent for non-commutable PT materials and a limit of 6 percent for commutable (accuracy-based) PT materials. Another PT program commented in favor of a 10 percent limit, noting that non-commutable PT materials may be less accurate with certain test methods and, moreover, PT is not intended to directly reflect accuracy needed for clinical testing.

Response: We appreciate the importance of HbA1c for diagnosis and monitoring patient management, and the need for testing accuracy that is sufficient to meet clinical needs, and we support the progress that continues to be made to improve the accuracy of HbA1c testing. As mentioned in the previous comment, CLIA PT ALs are intended to identify, and hopefully remediate, laboratories that are not providing results as accurate as their peers. CLIA PT ALs should not be used as accuracy goals by manufacturers or by standardization initiatives such as the NGSP. CLIA should not impose a requirement that limits access to critically important patient testing, especially if it is based on PT results that may not reflect the accuracy of patient testing.

One PT program has demonstrated progressive improvements in accuracy of testing by laboratories enrolled in their accuracy-based PT program, which uses commutable patient samples. We are aware that, over time, the program has incrementally tightened their ALs for the accuracy-based PT. This progress has been possible without CLIA requiring PT for HbA1c, and therefore, adding a PT requirement for HbA1c should not impede further progress in the future. Accreditation organizations have the flexibility to require their laboratories to meet a more stringent requirement than CLIA. They also have the option of using the CLIA limit and using a second, more stringent, AL for educational purposes. Either approach would allow these organizations to continue to tighten the limits for HbA1c for their accredited laboratories. We acknowledge the importance of standardization programs, like the NGSP, having the latitude to continuously adjust their accuracy goals to monitor and encourage improvements in the accuracy of HbA1c testing. We do not believe that a CLIA AL that is looser than the limit in use by the accuracy-based PT program would cause manufacturers to allow testing accuracy to deteriorate, as many commenters have suggested.

The AL adopted in CLIA regulations must not be too tight for laboratories that do not participate in an accuracy-based PT program that uses commutable PT materials. In simulation studies performed before issuing the proposed rule, laboratories using non-commutable PT samples had poorer performance, especially when scoring using any AL less than 10 percent. This might have occurred because laboratories not enrolled in accuracy-based PT use different test methods or because the PT they use is non-commutable. CLIA does not specify whether laboratories are required to participate in PT based on whether it is commutable or non-commutable. The same AL apply regardless of the PT samples' commutability.

After analyzing the comments received in response to the proposed rule, we requested the PT programs that offer HbA1c to simulate results that would be obtained if they used 5 percent, 6 percent, 8 percent, and 10 percent as the AL. We requested programs to indicate miss rates and unsatisfactory rates based upon different HbA1c concentrations in their materials, and to disclose performance based upon their testing platform or peer groups used. Based upon these more recent simulated results, we found that it will be possible to use a tighter AL than 10 percent. After this analysis, we are setting the AL for HbA1c at 8 percent in this final rule. The performance improvements we saw between the first and later simulations may reflect improvements in the accuracy of testing for HbA1c.

Comment: Commenters stated that rather than using the proposed AL of 20 percent for LDL cholesterol, we should require an AL of 12 percent, which is the accuracy target used by the National Cholesterol Education Program.

Response: Because the commenters suggested an AL tighter than was proposed, we requested PT programs to simulate the impact of using that limit. Based upon reanalysis of new data shared by PT programs, we confirmed that the proposed AL of 20 percent is appropriate for scoring PT for LDL cholesterol, and we are finalizing that limit in this rule.

Comment: With respect to PT for blood lead, we proposed a change from the current AL of ±4 mcg/dL or 10 percent (greater) to ±2 mcg/dL or 10 percent (greater). One commenter supported the proposed AL, consistent with efforts to improve the ability of laboratories to detect very low concentrations of blood lead in patient specimens. Conversely, another commenter stated that the reduction of the concentration AL from 4 mcg/dL to 2 mcg/dL would result in more instances of nonconsensus, which would result in more ungraded samples and events. Another commenter expressed concerns about the impact of the proposed limits on failures for certain testing platforms.

Response: We agree with the commenter who emphasized the public health importance of the need for accuracy at low concentrations of blood lead, to detect and prevent cases of childhood lead poisoning, and are finalizing the proposed AL for blood lead at 2 mcg/dL ±10 percent (greater) in this rule. We appreciate the commenters' concerns, however, one outcome of more stringent ALs may be that laboratories switch to test methods that are more accurate across the range of testing and better able to meet clinical needs. We believe that manufacturers of analytical platforms that may fail to achieve consensus, or otherwise perform poorly, will improve their accuracy during the phase-in period. To address concerns regarding unintended consequences that may increase health disparities, we will monitor changes in PT participation for all analytes after this rule becomes effective as this is required as part of PT oversight under CLIA. This includes the methods used for testing each PT analyte required by CLIA.

Comment: A few commenters provided suggestions related to the addition of troponin I and troponin T as required analytes in routine chemistry. One commenter was concerned that adding troponins to the required list for PT may potentially limit access to point-of-care cardiac triage testing of potential cardiac events in rural settings. The

same commenter also suggested that the ALs for troponin I and troponin T should be expanded to ±40 percent, with no suggested changes to the associated concentration limits. A couple of commenters suggested that the same, percentage-based AL would work for both generic and high sensitivity troponins. A small number of commenters suggested that we should require PT for high sensitivity troponin assays in addition to traditional troponin assays.

Response: Troponin I and troponin T are used to make decisions about the use of lifesaving, yet not risk-free, interventions, such as cardiac catheterization and therapeutic thrombolysis. Therefore, it is important that such testing be both accessible and accurate. We believe that requiring PT for the troponins is important and must not inhibit access to testing. We reviewed our simulation data to see if the same concentration limit would work for both troponin I and T. We determined that we must use the proposed, different ALs, and, therefore, are finalizing the AL for troponin I as ±0.9 ng/mL or 30 percent (greater) and for troponin T as ±0.2 ng/mL or 30 percent (greater). At the time we proposed these changes, troponin I and T were not frequently tested as ''high sensitivity'' analytes, that is, at very low limits of detection. Also, there were not enough PT program offerings to meet our threshold for inclusion for high sensitivity troponins. Therefore, we are not requiring PT for ''high sensitivity'' troponin I or T.

Comment: A few commenters stated that some proposed percentage-based ALs were too tight, regardless of whether a concentration threshold was included. Commenters stated that the proposed percentage ALs for immunoglobulin A (±15 percent), immunoglobulin E (±15 percent), amylase (±15 percent), and leukocyte count (±5 percent) were too tight. The commenters recommended ALs be set at ±20 percent for immunoglobulin A, ±25 percent for immunoglobulin E, and ±10 percent for leukocyte count. No recommendation was provided for amylase.

Response: We re-examined simulation data that had been submitted by PT programs and revised percentage limits as appropriate. Specifically, in this rule we are finalizing the AL for immunoglobulin A to ±20 percent, amylase to ±20 percent, and leukocyte count to ±10 percent. We determined that adding a concentration limit for these analytes was not necessary or adequate to make the AL workable at a lower concentration. For immunoglobulin E, we did not determine that it was necessary to increase the AL to ±25 percent; therefore, we are finalizing the AL for immunoglobulin E in this rule at ±20 percent.

Comment: Some commenters expressed concerns related to proposing ALs based on allowable total error derived from estimates of biological variability (BV). There was a comment that the use of BV data was in flux at this time. One commenter noted that estimates of BV that we used may be incorrectly wide due to errors in the way estimates were made, specifically that they may overestimate BV because the results are based upon analytical test methods that have inherent variability. One commenter stated that BV cannot be directly related to clinical outcomes. The same commenter stated that when setting ALs both BV and state-of-the art performance should be considered.

Response: We appreciate the concerns expressed and note that the ALs we proposed were not based strictly on estimates of BV. Moreover, we are aware that the field of estimating BV data has changed in the last few years. However, any impact of suboptimal estimations of BV on the ALs we proposed was likely negligible because we always tested potential ALs using simulations. ALs that were too tight to be workable were eliminated even if they were not as stringent as our estimates of BV might have suggested were necessary. In other words, consistent with one of the comments, we used state-of-the-art performance, demonstrated through simulations, to finalize the proposed ALs. In some cases, we showed through simulations that it was possible to use ALs that are tighter than the ''minimal'' threshold based upon estimates of BV and in these cases we used a somewhat tighter AL, but only if the data from PT programs supported the tighter limit. As a result, changes in the estimates of BV we used would not have affected our proposed ALs.

After re-examining the literature, we reconfirmed that BV is the only tenable approach to establishing new limits. We agree that clinical outcomes may not be reflected in BV data, but the preferred outcomes studies were not available to us.

Comment: Commenters generally favored the proposal to require separate PT for cell identification and differentials rather than including an option to participate in PT for one or the other. It was pointed out that the results can be used for different purposes in patient treatment. There were questions, however, questioning whether there should be separate scores for cell identification and differentials or if they should be averaged. One commenter recommended that the three standard deviation criteria for acceptable performance for differentials should be changed to a percentage-based criterion and another suggestion was made to include ±1.0 (whichever is greater) for low target values or absolute values (that is, basophils). An additional commenter requested clarification as to whether PT would be required for both manual and automated flow through differentials for laboratories that use platforms that can report flow through differentials.

Response: We appreciate the support from commenters who recognized the need to recognize cell identification and differentials as two separate analytes and are finalizing that change in this rule. As separate analytes they may be scored individually. We are finalizing the criteria for acceptable performance for both analytes in this rule. We are not changing the criterion for differentials to percentage-based because we have no BV data on which to base that change. As such, we are also not including the ±1.0 option for low target values. In response to the question regarding PT requirements for laboratories that perform both manual and automated flow through differentials, a laboratory should perform PT in the same manner as they perform testing on patient specimens. PT is required for the primary method of testing used for patient testing.

Comment: A few commenters supported the proposal to change the consensus requirement for cell identification from 90 percent to 80 percent. One commenter requested for clearer justification for the change.

Response: This change was proposed because it is not possible to score 90 percent on a 5-challenge PT panel. We are finalizing the change in this rule.

Comment: An accreditation organization made several suggestions about how standard deviations should be calculated when they are required as ALs for white blood cell differentials. For peer group sizes of 20 or more, they recommended that we continue to require elimination of outliers before calculation of the standard deviation. The commenter stated that when the peer group size is between 5 and 19 laboratories, robust methods as described in ISO 13528, ISO Guide 35, or ASTM E–691, should be used. They recommended that, alternatively, the standard deviation could be an average standard deviation determined from previous rounds of PT, calculated according to ISO 13528. They also noted that mention of 3 SD to set ALs should

be removed from parts of the regulation that no longer include 3 SD limits.

Response: As mentioned by the commenter, this final rule includes only one analyte with a three standard deviation limit. We agree that this recommendation would allow more accurate estimates of 3 SD ALs for relatively small peer group sizes. We also agree that robust statistical methods must be used to calculate the standard deviations when the peer group size is between 5 and 19 laboratories. However, we are not specifying the statistical approach that needs to be used. We appreciate the commenter's suggestion to remove reference to 3 SD ALs in relevant sections of this final rule and have done so in §§ 493.931(c)(2) and 493.933(c)(2).

Comment: A few commenters recommended that the international normalized ratio (INR) should be listed as a separate analyte in the specialty of hematology, the same way blood cell counts and white blood cell differentials are separate analytes, rather than including INR as a mechanism for reporting prothrombin time results, as was proposed. The commenters agreed that laboratories should report prothrombin time results in seconds, as an INR, or both as appropriate, in the same way that they report patient results. Commenters also stated that separating the prothrombin time and INR would allow for separate ALs for each of them.

Response: It is important for laboratories to report PT results the same way that they report patient results. If patient results are reported in seconds or as INR results, laboratories should report the same way to PT programs. If the laboratory reports patient results in both seconds and as an INR, they should report both to PT programs. The AL for prothrombin time at ±15 percent is applicable for both seconds and INR. When we referenced ''directly measured INR'' in the preamble to the proposed rule, we were referring to those devices that internally calculate and display the INR value rather than giving a value in seconds. The 15 percent AL for INR applies regardless of how it is derived.

Comment: Two commenters remarked on the proposed change to the criteria for acceptable performance of unexpected antibody detection in immunohematology from 80 percent to 100 percent accuracy. While one commenter agreed with this proposed change, the other disagreed. The opposition was concerned with the possibility that laboratories that use less sensitive, but safe, methods could be penalized, and it could limit patient access to care.

Response: We believe that the criteria for acceptable performance for unexpected antibodies should be 100 percent rather than 80 percent. We are finalizing this change because it is critical for laboratories to detect any unexpected antibody when crossmatching blood to protect the public health and not impact patient care. It is important that antibodies are detected to lessen the possibly of a transfusion reaction due to incompatible blood products.

Comment: Concerning appropriate units for reporting PT results or some other aspect of the AL, some commenters noted that we inadvertently deleted titers for some ALs. It was pointed out that for some analytes we incorrectly suggested that the AL should be qualitative. Some commenters noted inaccuracies in the units we used for quantitative analytes.

Response: We appreciate the commenters careful examination of the proposed limits and we made appropriate adjustments that are now reflected in the final rule. In response to comments about proposed units for reporting PT results, unintentional uses of incorrect units have been corrected in this final rule.

Summary of Final Actions

- We are finalizing the proposed revision at §§ 493.923(a), 493.927(a), 493.931(a), 493.933(a), 493.937(a) and 493.941(a) to remove the option that PT samples ''at HHS option, may be provided to HHS or its designee for on-site testing.''
- We are finalizing the proposed addition of 29 analytes and the deletion of five analytes. See section II of this final rule. Additional analytes can be found in section II.B.1. of this final rule, Table 1, and deleted analytes are listed in section II.B.6 of this final rule.
- We are amending §§ 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) 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.

- Section 493.927 (General Immunology)

++ We are correcting typographical or editorial errors in the proposed criteria for acceptable performance for alpha-1-antitrypsin, alpha-fetoprotein (tumor marker), complement C3, complement C4, antinuclear antibody, antistreptolysin O.

++ We are modifying the proposed AL for immunoglobulin A (IgA) of ±15 percent and finalizing the AL for IgA as ±20 percent based on public comments.

++ We are finalizing the proposed criteria for acceptable performance for antinuclear antibody, antistreptolysin O, rheumatoid factor, and rubella.

- Section 493.931 (Routine Chemistry)

++ We are finalizing the proposed ALs in the criteria for acceptable performance.

++ We are correcting the units for prostate specific antigen (total).

++ We are making a technical change to CK–MB isoenzymes to address measurement by electrophoresis or direct mass determination.

++ We are also modifying the proposed criteria for acceptable performance for hemoglobin A1c of ±10 percent and finalizing the AL for hemoglobin A1c to ±8 percent based on public comments.

- Section 493.933 (Endocrinology)

++ We are finalizing the proposed percentage based ALs in the criteria for acceptable performance.

- Section 493.937 (Toxicology)

++ We are finalizing the proposed concentration limits and percentage based ALs in the criteria for acceptable performance.

++ We are finalizing the proposed requirement that PT programs must provide samples that cover the full range of samples that could occur in patient specimens.

++ We are correcting the units for phenytoin and vancomycin.

- Section 493.941 (Hematology)

- We are finalizing the proposed AL for leukocyte count.

++ We are finalizing the proposed revision to units of reporting for prothrombin time to include seconds and INR (international normalized ratio) and that laboratories must report prothrombin time in the same was as they report patient results.

++ We are finalizing the proposed requirement that laboratories performing both cell counts and differentials must enroll and participate in PT for both.

++ We are finalizing the proposed change to the criteria for acceptable performance for ''cell identification'' from 90 percent to 80 percent.

- Section 493.959 (Immunohematology)

++ We are finalizing the proposed change to the criteria for acceptable performance for unexpected antibody detection from 80 percent to 100 percent.

IV. Collection of Information Requirements

Under the Paperwork Reduction Act of 1995, we are required to provide 30-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. In order to fairly evaluate whether an information collection should be approved by OMB, section 3506(c)(2)(A) of the Paperwork Reduction Act of 1995 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 estimate of the information collection burden.
- The quality, utility, and clarity of the information to be collected.
- Recommendations to minimize the information collection burden on the affected public, including automated collection techniques.

We are soliciting public comment on each of these issues for the following sections of this document that contain 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 proposed 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 34,113 laboratories which is 341 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 per year and would take approximately 1 hour. The total annual burden is 341 hours (341 laboratories × 1 hour). A Clinical Laboratory Technologists/Technicians (29–2010) would perform this task at an hourly wage of $27.36 as published in 2021 by the Bureau of Labor Statistics.[11] The wage rate would be $54.72 to include overhead and fringe benefits. The total cost would be $18,660 (341 hours × $54.72).

B. Optional On-Site Visits to PT Programs

At § 493.901(e), we proposed 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 of the PRA at 5 CFR 1320.3(b)(2).

C. PT Program Reapproval

At § 493.901(f), we proposed 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 × 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 (43–9199) would perform this task at an hourly wage of $20.47 as published in 2021 by the Bureau of Labor Statistics.[12] The wage rate would be $40.94 to include overhead and fringe benefits. The total cost would be $3,685 (90 hours × $40.94).

D. Withdrawal of Approval of a PT Program

At § 493.905, we proposed 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 also proposed 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).

E. Submission of PT Data by Laboratories

At § 493.901(c)(6), we proposed 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. As discussed in section II.C. of this final rule, based on public comments from PT programs and laboratories that this requirement would be burdensome and expensive, we are not finalizing this proposal.

Table 2 reflects the total burden and associated costs for the provisions included in this final rule.

[11] *https://www.bls.gov/oes/tables.htm.*

[12] *https://www.bls.gov/oes/tables.htm.*

TABLE 2: Summary of All Burden in This Final Rule

Information Collection Requests	Burden Hours Increase/Decrease (+/-)*	Cost (+/-)*
A. Clarification for Reporting of Microbiology Organism Identification	+341	+18,660
B. Optional On-Site Visits to PT Programs	+0	+0
C. PT Program Reapproval	+90	+3,685
D. Withdrawal of Approval of a PT Program	+0	+0
TOTAL	**+431**	**+22,345**

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 to ensure the accuracy and reliability of testing currently being used for clinical decision-making and improved patient outcomes. 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 and better assess clinical laboratory performance. We based our decision to update the regulations and incorporate the changes being finalized in this rule in part, as discussed above, upon advice from the Clinical Laboratory Improvement Advisory Committee (CLIAC), a Federal advisory committee charged with providing recommendations to HHS on revisions needed to CLIA. The members of CLIAC are knowledgeable about laboratory medicine and quality.

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)).

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. We prepared the RIA and found that this PT final rule does not meet the threshold of section 3(f)(1) of the Executive Order for a significant regulatory action. In addition, our upper limit of estimated impact is under the threshold of $165 million for the year of 2022 under the Unfunded Mandates Reform Act (UMRA). Nevertheless, we have voluntarily performed an RIA, as would be required for an economically significant regulation.

This rule revises the CLIA PT requirements and affects approximately 35,967 clinical laboratories subject to participation in PT, resulting in some cost implications (Table 5). In addition, as a result of this final rule, the eight existing CLIA-approved PT programs will incur some costs as they modify their programs to meet the specified requirements. It will also have an effect on CLIA-exempt States regarding State PT requirements.

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 being nonprofit organizations or by meeting the Small Business Administration definition of a small business (having revenues of less than $8.0 million to $41.5 million in any 1 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 2021 [13] and 100 percent of PT programs are nonprofit organizations. Individuals and States are not included in the definition of a small entity. As its measure of significant economic impact on a substantial number of small entities, HHS uses a change in revenue of more than 3 to 5 percent. We do not believe that this threshold will be reached by the requirements in this final rule. Therefore, the Secretary has certified that this final rule will not have a significant economic impact on a substantial number of small entities. We have included several provisions in this rule to address the requirements of the RFA and provide regulatory relief or minimize burden for small entities such

[13] *https://www.aha.org/statistics/fast-facts-us-hospitals.*

as laboratories and PT programs. The first is incorporating a phase-in period for implementation of this rule. This phase-in will provide time for laboratories to identify PT programs offering the newly required PT and subscribe to PT for any of the analytes or tests that they offer. It will also provide the time needed by PT programs to add new analytes and tests to their programs, which requires the identification of new sources of PT materials and revision of administrative processes to accommodate the revised requirements. Other changes that will decrease burden, which are incorporated in this rule as a result of public comments from laboratories and PT programs, were several proposed revisions to microbiology PT. These proposed changes included adding PT requirements for susceptibility or resistance testing in the subspecialties of mycology and virology and adding a PT requirement for resistance testing in bacteriology. Because public comments indicated these requirements would be difficult to comply with due to limited materials and variability in the testing, we are not finalizing those changes in this rule, which mitigates burden that would have been placed on both laboratories and PT programs. In addition, because of similar public comments that questioned the value of currently required PT for susceptibility testing in mycobacteriology, we are removing this requirement in this final rule. These changes will provide regulatory flexibility and reduce burden to small entities.

In addition, section 1102(b) of the Social Security 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 604 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 final rule will have a significant impact on small rural hospitals and we are unable to estimate the number of laboratories that support small rural hospitals. Such hospitals often provide limited laboratory services and may refer testing for the newly required analytes to larger hospitals. For the small rural hospitals with laboratories that perform testing for the new analytes, we expect they are already performing PT for other analytes and minimal effort will be required since they should already have PT policies and procedures in place. Therefore, the Secretary has certified that this final rule will not have a significant impact on the operations of a substantial number of small rural hospitals.

Section 202 of the 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 2022, that threshold is approximately $158 million. This rule will not impose an unfunded mandate on States, tribal governments, or the private sector of more than $165 million annually and thus does not meet the UMRA threshold.

Executive Order 13132 establishes certain requirements that an agency must meet when it promulgates a final rule that imposes substantial direct requirement costs on State and local governments, preempts State law, or otherwise has Federalism implications. The changes in this rule will 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. This rule will not impose substantial direct compliance costs on State and local governments that are not required by statute. A significant number of laboratories affected by this rule are not operated by State or local governments. Therefore, promulgation of this rule will not cause substantial additional costs to State and local governments.

C. Anticipated Effects

This final rule will impact approximately 35,967 clinical laboratories (total of Certificate of Compliance and Certificate of Accreditation laboratories, as of January 2020) required to participate in PT under the CLIA regulations implemented by the February 28, 1992 final rule, eight current CLIA-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 will result from the changes made in this rule, we are providing an analysis of the potential impact based on available information and certain assumptions. Implementation of these requirements will result in changes that will have both quantifiable 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) PT changes to the microbiology specialty; and (2) PT changes to non-microbiology specialties. This was done because the PT requirements differ for microbiology 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, whereas in the other specialties and subspecialties, PT participation is required and scores are given based on specific required analytes listed in the regulations.

1. Quantifiable Costs for Laboratories

CDC receives catalogs from all CLIA-approved PT programs annually. We estimated material costs for purchasing PT materials based on the range of 2020 catalog prices from the eight CLIA-approved PT programs. In estimating the labor costs for performing PT for all laboratory specialties that will be affected by this regulatory change, we assumed the average national clinical laboratory fee schedule [14] as an estimate of the cost the laboratory incurs when testing each sample (or challenge). 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 calculated that, on average, the cost impact would be between $695 and $2,511 per laboratory, with laboratories testing fewer analytes bearing a smaller burden.

a. Costs of PT Changes to the Microbiology Specialty

Changes to the microbiology specialty include changes in each of the subspecialties (bacteriology, mycobacteriology, mycology, parasitology, and virology) that will replace the types of services offered and the examples of organisms to be included over time with a list of categories of tests and groups of microorganisms for which PT is required. In addition, this rule finalizes other changes in the CLIA regulations, Subpart I for each individual subspecialty. These changes will have a cost impact on laboratories. As stated in

[14] CMS Clinical Laboratory Fee Schedule Files: *https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/Clinical-Laboratory-Fee-Schedule-Files.*

CLIA at § 493.801(a)(2)(ii) and § 493.1236(c)(1), for tests or procedures performed by the laboratory that are not listed in 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 do not have a way to estimate how many microbiology laboratories voluntarily enroll in PT to meet this requirement, we assume the added burden of performing the newly required PT would be minimal for those already performing voluntary PT. For the 5,341 affected microbiology laboratories, the estimated cost of the quantifiable changes to required PT for each microbiology subspecialty follows.

To estimate the costs that will be incurred by laboratories to purchase PT materials to meet the revised requirements for the microbiology specialty, we compiled a range of PT material cost estimates per each challenge using 2020 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. Individual 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 2020 catalog prices from the eight CLIA-approved PT programs for microbiology. 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. However, we do not have a way of estimating the number of laboratories or the cost of this voluntary participation.

In estimating the number of microbiology laboratories that will be impacted by each of the regulatory changes, we determined the numbers of Certificate of Compliance (CoC) and Certificate of Accreditation (CoA) laboratories for each microbiology subspecialty using the CMS Quality Improvement and Evaluation System (QIES) database. To categorize the laboratories as described below, the QIES database was used to determine the accreditation organization for each CoA laboratory.

We designated two laboratory categories when estimating the impact of the final PT rule in microbiology:

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

Category M1: Laboratories Already Participating in Required Microbiology PT

For 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 Newly Required Microbiology PT

We used Certificate of Accreditation data to estimate the number of laboratories that are subject to the microbiology PT requirements in this rule 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 6,999 COLA-accredited laboratories offer testing for the microbiology tests that are being added 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 Certificate of Compliance laboratories and laboratories accredited by deemed status organizations other than the College of American Pathologists (CAP) (who did not provide data) with regard to test volumes and the microbiology testing they provide. 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. For the newly required microbiology PT, 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 on all affected laboratories.

(1) Costs of the PT Changes in the Bacteriology Subspecialty

In the bacteriology subspecialty, the changes being finalized in this rule 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 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 will be impacted by this change, we calculated the number currently enrolled in Gram stain PT. Since this change will require that these laboratories report bacterial morphology in addition to Gram stain reaction on each challenge, we estimate the cost impact would be minimal. We estimated the range of costs 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 clinical laboratory fee schedule; 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 (Table 3) and 15 challenges for the high estimate (Table 4).

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 new 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 new 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 clinical laboratory fee schedule; 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 (Table 1) and 15 challenges for the high estimate (Table 3).

Currently, one sample or challenge per testing event is required for antimicrobial susceptibility testing in bacteriology. To evaluate the impact of increasing the required antimicrobial susceptibility testing from one challenge per year to 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 clinical laboratory fee schedule; 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 (Table 3). Considering all of the potential cost impacts, the range of estimated impact for the proposed bacteriology subspecialty changes for the first year is $169,128 to $1,058,207.

(2) Costs of the PT Changes in the Mycobacteriology Subspecialty

Changes to add a second antimycobacterial susceptibility or resistance testing challenge per event were proposed for the mycobacteriology subspecialty. However, as discussed in section III.E. of this final rule, due to public comments, those changes are not being finalized. In addition, due to the public comments received, the requirement for susceptibility testing in mycobacteriology is being removed altogether in this rule. Although there may be a cost savings for the small number of laboratories that perform antimycobacterial susceptibility testing, we are assuming that the majority of these laboratories will continue to subscribe to PT for this test to meet the requirement at §§ 493.801(a)(2)(ii) and 493.1236(c)(1) to verify the accuracy of testing twice per year. As such, we are not anticipating a significant cost savings by removing this requirement and are not able to estimate the impact.

(3) Costs of the PT Changes in the Mycology Subspecialty

In the mycology subspecialty, the changes being finalized in this rule that may have a cost impact include the addition of required PT for direct fungal antigen detection and detection of the presence or absence of fungi and aerobic actinomycetes without identification. To evaluate the impact of the required 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 new 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 new 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 clinical laboratory fee schedule; 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 (Table 3) and 15 challenges for the high estimate (Table 4).

The newly required detection of the presence or absence of fungi and aerobic actinomycetes without identification impacts 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 using the same methodology as was performed to determine the impact of the proposal to include direct fungal antigen detection (Tables 1 and 2). Considering the cost impact of this rule in the mycology subspecialty, the range estimated for the first year is $3,288 to $61,940.

(4) Costs of the PT Changes in the Parasitology Subspecialty

In the parasitology subspecialty, the change being finalized in this rule 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 new PT requirement. Since CAP-accredited laboratories are already required to perform PT if they perform direct parasite antigen detection, we assumed they are already meeting the new PT requirement 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 clinical laboratory fee schedule; 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 (Table 3) and 15 challenges for the high estimate (Table 4). Considering the potential cost impact of this rule in the parasitology subspecialty, the range estimated for the first year is $8,098 to $458,136.

(5) Costs of the PT Changes in the Virology Subspecialty

In the virology subspecialty, the proposed change that would have had a cost impact was the addition of two antiviral susceptibility or resistance testing challenges per year. However, as a result of the public comments received, that change is not being finalized in this rule. Therefore, we do not estimate a cost impact resulting from this rule in the subspecialty of virology.

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TABLE 3: Low Estimate for Microbiology PT Regulatory Changes

Regulatory Change	Total Number of Affected M1 Laboratories	Total Number of Affected M2 Laboratories	Labor[1]	Supply/Material Cost[2]	TOTAL Low Estimate for One Challenge	Total Low Estimate for Microbiology Regulatory Changes
Gram Stain including Morphology	31	0	$4.27	$4.53	$272.80	$180,513.47
Bacterial Toxin Detection	0	546	$16.00	$12.80	$15,724.80	
Antimicrobial susceptibility testing	4,299	0	$23.62	$12.00	$153,130.38	
Direct fungal antigen detection	0	37	$12.61	$16.80	$1,088.17	
Detection of the presence of absence of fungi and aerobic actinomycetes without identification	0	92	$7.71	$16.20	$2,199.72	
Direct parasite antigen detection	0	336	$12.90	$11.20	$8,097.60	

[1]Average national CMS clinical laboratory fee schedule (https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/Clinical-Laboratory-Fee-Schedule-Files).
[2]Low 2020 PT catalog price per challenge.

TABLE 4: High Estimate for Microbiology PT Regulatory Changes

Regulatory Change	Total Number of Affected M1 Laboratories	Total Number of Affected M2 Laboratories	Labor[1]	Supply/Material Cost[2]	TOTAL High Estimate /for one challenge	TOTAL High Estimate/for 15 challenges	Total High Estimate for Microbiology Regulatory Changes
Gram Stain including Morphology	31	0	$4.27	$15.40	$609.77	$9,146.55	$1,340,032.50
Bacterial Toxin Detection	0	546	$16.00	$83.00	$54,054.00	$810,810.00	
Antimicrobial susceptibility testing	4,299	0	$23.62	$31.80	$238,250.58	N/A	
Direct fungal antigen detection	0	37	$12.61	$33.40	$1,702.37	$25,535.55	
Detection of the presence or absence of fungi and aerobic actinomycetes without identification	0	92	$7.71	$18.67	$2,426.96	$36,404.40	
Direct parasite antigen detection	0	336	$12.90	$78.00	$30,542.40	$458,136.00	

[1] Average national CMS clinical laboratory fee schedule (https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/Clinical-Laboratory-Fee-Schedule-Files).
[2]High 2020 PT catalog price per challenge.

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b. Costs of PT Changes to the Non-Microbiology Specialties/Subspecialties

The changes being finalized in this rule in specialties and subspecialties other than microbiology include adding 30 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 35,967 clinical laboratories that will be affected (18,938 Certificate of Compliance and 17,029 Certificate of Accreditation laboratories). The changes to required PT will be a new burden for some laboratories, but many laboratories are already paying for PT of these analytes. As previously mentioned, in CLIA §§ 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 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 newly required analytes by grouping all affected laboratories into four categories: (1) CAP enrolled in CAP PT program, (2) CAP enrolled in 7 non-CAP PT Program, (3) Non-CAP not enrolled in 7 non-CAP PT program, and (4) Non-CAP enrolled in 7 non-CAP PT program), calculating the number of laboratories in each category and calculating the costs using the analyte price, test reimbursement rate and labor cost to update PT policies and procedures. We also tightened ALs and added concentration limits for several currently required analytes, which may have an impact on laboratories, but the cost impact is not included in our estimate. In addition, with this rule, we are finalizing the removal of five 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 new analytes: PT programs may offer analytes as an individual analyte or as part of a module that combines multiple analytes; some of the new analytes may already be offered but at a frequency other than the CLIA-required frequency ($3 \times 5 = 15$ 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, as an individual analyte or as part of a module, we used a range of estimates based upon the PT 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 determine 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 providers. For the higher cost estimate, we used the highest individual analyte price. In some cases, PT programs offer PT for the new analytes at different frequencies, that is, different numbers of events per year and different numbers of challenges per event. Therefore, to accurately estimate future costs, we had to calculate the increased frequency for each analyte in order to achieve three events/year with five challenges per event.

Implementation of this final rule will have different impacts on different laboratories mainly because laboratories either have a Certificate of Compliance or a Certificate of Accreditation and may be accredited by different accreditation organizations and purchase PT from different PT programs. 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 as a result of this final rule, 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. Laboratories not accredited by the CAP may purchase PT materials from any CLIA-approved PT program, including the CAP PT program. Therefore, we have designated four categories to estimate the cost impact of this rule.

Category 1: Laboratories Accredited by the CAP That Purchase Material From the CAP PT Program

The CAP provided us with the number of CAP-accredited laboratories that are enrolled in their PT program for each new 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. We estimate the costs for laboratories accredited by CAP that purchase material from the CAP PT program to be $4,498,535.

Category 2: CAP-Accredited Laboratories That Purchase PT Materials From Other PT Programs

For the analytes we are adding in this rule, CAP-accredited laboratories are required to enroll in a CLIA-approved PT program. Ordinarily CAP-accredited laboratories enroll in the CAP PT program but 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 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 non-CAP PT program. We estimate the costs for CAP-accredited laboratories that purchase PT materials from other PT programs will range from $0 to $1,304,343.

Category 3: Laboratories Not Accredited by CAP That Are Not Already Enrolled in Other PT Programs

To derive the minimum and maximum number of laboratories not already enrolled in a PT program that may provide testing for the newly required analytes, we began by

estimating that there are 22,119 laboratories that perform nonwaived testing and are not accredited by the CAP in the US. To facilitate the calculations, we presumed that laboratories not accredited by CAP will not purchase CAP PT. From the QIES database, we derived the number of laboratories not accredited by 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 6,999 COLA-accredited laboratories that perform testing for each new 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 new analyte could be used to estimate the minimum 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 new 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 CoC and non-CAP-accredited CoA laboratories that may provide testing for each new analyte.

For each new 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 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 CAP and not enrolled in one of the non-CAP PT programs, we took the high estimate of CoC laboratories and CoA laboratories not accredited by the CAP 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 QIES to cap 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 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 seven non-CAP PT programs and the maximum cost per sample that was the highest across all seven 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. We estimate the costs for laboratories not accredited by CAP and not already enrolled in other PT programs will range from $7,047,880 to $58,710,510.

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 from the PT event summaries from each PT program. 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. We estimate the costs for laboratories not accredited by CAP and already enrolled in non-CAP PT programs will be $1,051,614.

c. Costs for Laboratories, Deemed Accreditation Organizations, Exempt States, and PT Programs To Update Policies and Procedures

We expect that the 35,967 CoC and CoA laboratories will incur costs for the time needed to review the revised PT regulations and update their policies, procedures, and information technology (IT) systems, as needed, to be in compliance with the updated regulations. We assume a one-time burden of 4 to 8 hours per laboratory will be needed for this. A general management level employee (13–1111) would perform this task at an hourly wage of $46.91 per hour as published in 2020 by the Bureau of Labor Statistics (*https://www.bls.gov/oes/current/oes_nat.htm*). The wage rate would be $93.82 to include overhead and fringe benefits. Therefore, we estimate the one-time costs for CoC and CoA laboratories will range from $13,497,696 to $26,995,392 ($93.82 × 35,967 × 4 or 8 hours). Similarly, seven approved accreditation organizations and two exempt States will need to review the regulations and may need to revise their survey policies and procedures to be consistent with the updated requirements. We estimate a one-time burden of 10 to 15 hours to review the revised regulations and to develop policies and procedures needed to reflect the new PT requirements. We assume the person performing this review will be a business management level employee (11–1021) paid $60.45 per hour as published in 2020 by the Bureau of Labor Statistics (*https://www.bls.gov/oes/current/oes_nat.htm*). The wage rate would be $120.90 to include overhead and fringe benefits. Therefore, we estimate the one-time costs for accreditation organizations and exempt States to update their policies and procedures will range from $10,881 to $16,322. For PT programs, we estimate a one-time burden of 30 to 35 hours for them to review the updated regulations, revise their policies and procedures, and add new analytes or microbiology tests that they choose to offer. We assume the person performing this job will be a business management level employee paid $60.45 per hour as published in 2020 by the Bureau of Labor Statistics (*https://www.bls.gov/oes/current/oes_nat.htm*). The wage rate would be $120.90 to include overhead and fringe benefits. Therefore, we estimate the one-time costs for PT programs will range from $36,270 to $42,315.

d. Results

We estimate that the overall impact of adding requirements for the new analytes in the specialties and subspecialties other than microbiology will range from approximately $13 to $66 million for the first year (Table 5). Because of the larger number of non-CAP accredited laboratories, and the fact that they 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 $7 and $59 million for the first year. We also estimate that laboratories not accredited by CAP that are enrolled in PT programs other than CAP will have a relatively minor impact, $1 million for the first year (Table 5).

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TABLE 5: Low and High Estimates for Non-microbiology PT Regulations Changes

Category	Low Estimate	High Estimate
1. Laboratories accredited by CAP that purchase material from the CAP PT program	$4,498,535.16	$4,498,535.16
2. Laboratories accredited by CAP that purchase PT materials from other PT programs	$0.00	$1,304,342.82
3. Laboratories not accredited by CAP that are not already enrolled in other PT programs	$7,047,879.53	$58,710,509.52
4. Laboratories not accredited by CAP that are enrolled in other PT programs	$1,051,614.08	$1,051,614.08
Total increased cost	$12,598,028.77	$65,565,001.58

Table 6 shows the total estimated range of annual cost for the changes (including both microbiology and non-microbiology) in undiscounted 2020 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 2020 for the calculations displayed in Table 6 and we assume costs in future years to be the same as costs in the base year.

TABLE 6: Total Estimated Annual Costs of PT Regulations Changes (All specialties in both microbiology and non-microbiology)

	Undiscounted (2020 $)			Discounted at 3 percent			Discounted at 7 percent		
	Primary	Low[#]	High[&]	Primary	Low	High	Primary	Low	High
2020	$60,141,226	$26,323,389	$93,959,062	$56,688,874	$24,812,319	$88,565,429	$52,529,677	$22,991,868	$82,067,485
2021	$60,141,226	$26,323,389	$93,959,062	$55,037,742	$24,089,630	$85,985,853	$49,093,156	$21,487,727	$76,698,584
2022	$60,141,226	$26,323,389	$93,959,062	$53,434,701	$23,387,991	$83,481,411	$45,881,454	$20,081,988	$71,680,920
2023	$60,141,226	$26,323,389	$93,959,062	$51,878,350	$22,706,787	$81,049,914	$42,879,863	$18,768,213	$66,991,514
2024	$60,141,226	$26,323,389	$93,959,062	$50,367,330	$22,045,424	$78,689,237	$40,074,639	$17,540,386	$62,608,892

[#] Total low cost is the sum of Table 3 (microbiology), Table 4 (non-microbiology).

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

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d. Non-Quantifiable Costs

A number of non-quantifiable cost impacts will also result for PT programs and laboratories when this rule becomes effective.

As with any required PT, implementation of this final regulation does not require approved PT programs to offer additional analytes. Several programs already offer the analytes or tests that will be required, and, in these cases, we expect there to be a minimal cost impact on the PT programs. 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. We have included an estimate of those costs in this RIA. 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 will mean offering an analyte or test for the first time, while for others it will mean increasing the yearly number of events and/or challenges per event. The costs will 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. 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.

When this rule becomes effective, some PT programs may cease offering the analytes that are no longer required, 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.

Although we cannot precisely predict how the 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. For those laboratories that currently purchase PT for the five analytes for which PT is no longer required, we cannot estimate the lowered expenditure for laboratories that stop buying PT materials and must begin doing something else to verify accuracy. Based on 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 what they currently spend on PT for the analytes deleted, 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.

e. Benefits

While we cannot quantify the benefits that implementation of this final rule revising the PT requirements will bring, we believe that the changes will improve the accuracy and reliability of testing and allow for quicker identification of unacceptable practice in laboratories, especially those laboratories that have not previously participated in PT. 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 will benefit physicians and healthcare providers while not impacting access to testing.

PT performance partially reflects daily clinical laboratory performance. Updating ALs 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. 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.

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. 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 in this final rule will result in any costs on the IVD industry, we expect the IVD industry to potentially benefit by the changes made in this rule, from having the ability to track PT results for the added analytes to 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 [5] that is expected to occur when this final rule becomes effective with this new rule.

D. Alternatives Considered

A number of alternatives were considered in finalizing the changes in this rule. We considered 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. Similarly, public comments received in response to the proposed rule did not suggest changes to 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, 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. In this final rule, we will continue to require five challenges per event, with a successful event score defined under

CLIA '88 as a minimum of four out of five challenges (80 percent) falling within the criteria for acceptable performance.

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 cost impact of more than five million dollars to laboratories who would be required to perform susceptibility 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 now adding in this rule 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 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 ALs as they were established in CLIA '88, but we rejected this approach as outdated given advancements in technology. We considered the option of enforcing 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.

E. Accounting Statement and Table

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

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TABLE 7: Accounting Statement

Category	Primary Estimate	Minimum Estimate	Maximum Estimate	Source Citation (RIA, preamble, etc.)
BENEFITS				
Monetized benefits	NA	NA	NA	NA
Annualized qualified, but Unmonetized, benefits	More effective detection of laboratories that provide inaccurate laboratory test results. Increased confidence in laboratory test results.	NA	NA	Preamble and Impact Analysis
(Unqualified benefits)	NA	NA	NA	NA
COSTS				
Annualized monetized costs	$60,141,226	$26,323,389	$93,959,062	Impact analysis
Annualized qualified, but Unmonetized, benefits	NA	NA	NA	NA
Qualitative (unquantified) costs	NA	NA	NA	NA
TRANSFERS				
Annualized monetized transfers: "on budget"	NA	NA	NA	NA
From whom to whom?	NA	NA	NA	NA
Annualized monetized transfers: "off-budget"	NA	NA	NA	NA
From whom to whom?	NA	NA	NA	NA
Category	Effects			Source Citation (RIA, preamble, etc.)
Effects on State, local, and/or tribal governments	NA	NA	NA	NA
Effects on small businesses	NA	NA	NA	NA
Effects on wages	NA	NA	NA	NA
Effects on growth	NA	NA	NA	NA

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F. Conclusion

We estimate that the total cost for laboratories to participate in PT for the analytes and tests in this rule will be between $26 and $94 million in 2020 dollars. Although the effect of the changes will increase costs, implementation of these changes in this 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 will 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. However, we described actions being taken in finalizing this rule to reduce burden and minimize the impact on small entities such as laboratories and PT programs.

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

VI. Analysis of and Responses to Public Comments on the Paperwork Reduction and Regulatory Impact Analysis

We have provided an analysis of the potential impact of this final rule, based upon available information and certain assumptions. We have prepared the Paperwork Reduction Act and the Regulatory Impact Analysis representing the costs and benefits of the final rule based on analysis of identified variables and data sources needed for this change. We requested that commenters provide any additional data that would assist us in the analysis of the potential impact of this regulation on CLIA-certified laboratories, but we did not receive any additional data.

Therefore, based on our analysis and assessment of the overall annual costs to the laboratories affected by this final rule, we are finalizing the provisions in this rule. The comments and our responses are set forth below:

Comment: As part of regulatory impact analysis for the proposed rule, we described the benefits of PT and the need to update the regulations. Commenters representing accreditation organizations and laboratory professional organizations were supportive of the proposed changes, especially the expansion of the list of required PT analytes. The commenters noted that PT is a valuable quality indicator and measure of laboratory performance and they emphasized that the accuracy and reliability of laboratory testing is critical to patient safety and the delivery of quality healthcare services. A few commenters stated that PT is burdensome and expensive, one of them adding that the benefits of PT in reducing testing errors has not been documented through studies or other evidence.

Response: We appreciate the comments that expressed support for the changes in the proposed rule and recognized the value of PT as a measure of laboratory quality and a mechanism to detect and prevent errors that can affect patient safety. However, we agree with the commenters who stated that it is difficult to quantify the value of PT and we recognize the financial and other resource costs associated with performing PT. Based on the positive comments received and previously published studies (7–10), we believe that PT is a useful adjunct to identify poor-performing laboratories and to help laboratories ensure the quality of their testing which directly affects patients, and ultimately the public's health.

Comment: We received comments from accreditation organizations, professional organizations, businesses, and individuals concerning our estimate of the impact of the proposed rule. Several commenters stated that we had underestimated the overall impact, including the impact on individual laboratories and accreditation organizations, especially the administrative burden of new PT. While one commenter stated our methodology was correct, others disagreed, and one commenter stated that we failed to consider bigger changes to the way PT is conducted which could reduce costs. A few commenters suggested that we conduct a more comprehensive impact analysis.

Response: We acknowledge that our analysis was limited by the availability of data and our ability to estimate all aspects of the proposed changes. In the proposed rule, we solicited comments and data to facilitate the determination of quantifiable estimates of the impact in the final rule. We did not receive any suggestions of alternative methods or data on which to base our estimates. Therefore, in this final rule we have used similar methodology to that used in the proposed rule with exceptions as follows. We added a range of estimates to cover the one-time costs that would be expected for CoC and CoA laboratories subject to PT to review the updated regulations; modify policies, procedures, and IT systems as needed; and enroll in appropriate PT to be in compliance with the revised requirements. We also modified the impact analysis to include estimation of the one-time costs for the seven deemed accreditation organizations and two exempt States to review the updated regulations and revise their survey policies and procedures to be consistent with the new PT requirements. Lastly, we added similar one-time estimates for PT programs to review the updated regulations, modify policies and procedures, and determine if they will choose to offer the new analytes or microbiology PT. We recognize that there will be ongoing costs for laboratories, deemed accreditation organizations, exempt States, and PT programs based on the revised list of required analytes and changes to microbiology PT. However, we are unable to project these costs since, although we do not know the number, some laboratories are already participating in PT for the new analytes and microbiology tests as a way of meeting the requirement to verify the accuracy of testing twice per year. For these laboratories, the ongoing additional costs may be minimal. Similarly, the accreditation organizations and exempt States may already be reviewing voluntary PT data for some of the newly required analytes and tests. With respect to ongoing costs for PT programs, we are also unable to estimate the costs. As previously described in this rule regarding the criteria used to select new analytes and microbiology PT, we are aware that at least three programs already offer PT for these analytes and tests, and we are unsure how many additional programs will choose to offer them since they are not required by CLIA to do so. For those that already offer the additional PT, we expect the ongoing costs to be minimal.

Comment: Several commenters recommended that the effects of the recent Protecting Access to Medicare Act of 2014 (PAMA) regulations should be considered as part of the regulatory impact analysis in light of PAMA's impact on laboratory testing reimbursement under Medicare.

Response: We recognize the impact of PAMA on Medicare payment for laboratory testing. However, PAMA was implemented in 2018 and those changes were independent of the CLIA PT changes that are now being finalized. We do not have data that would allow us to determine the cumulative effects of the two rules that were implemented at two separate points in time. We did use the CMS CLFS for 2020, which included post-PAMA payment rates, as

one part of our estimate of the costs of performing PT, as no other data sources were suggested by commenters.

Comment: A commenter noted that the RIA had not accounted for the costs of disallowing the use of for-profit entities by PT programs for conducting any part of their business and suggested that the final rule should include this economic assessment.

Response: The proposed rule did not specify that for-profit entities were disallowed for use by PT programs for conducting any part of their business. In this final rule, we are clarifying that the provision being finalized at § 493.901(c)(8), previously proposed at § 493.901(c)(9), requires that technical and scientific responsibilities, such as grading PT, must be carried out by nonprofit organizations, Federal or State agencies, or entities acting as a designated Federal or State agency. This is an inherent function of an approved PT program and should not result in additional costs for the programs. Contractors used to perform tasks such as manufacturing or transportation of samples are not required to be non-profit entities.

Chiquita Brooks-LaSure, Administrator of the Centers for Medicare & Medicaid Services, approved this document on June 21, 2022.

Rochelle P. Walensky, MD, MPH, Director of the Centers for Disease Control and Prevention, approved this document on June 17, 2022.

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 amends 42 CFR part 493 as set forth below:

PART 493—LABORATORY REQUIREMENTS

■ 1. The authority citation for part 493 continues to read as follows:

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

■ 2. Amend § 493.2 by—

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

■ b. Revising the definition of ''Target value''.

The additions and revision read as follows:

§ 493.2 Definitions.

* * * * *

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

* * * * *

Peer group means 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 means:

(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);

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

(iii) If a definitive method or reference methods are not available, the mean of a peer group; or

(2) If the peer group consists of fewer than 10 participants, the mean of all participant responses after removal of outliers (as defined in paragraph (1) of this definition) unless acceptable scientific reasons are available to indicate that such an evaluation is not appropriate.

* * * * *

■ 3. Amend § 493.20 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. Amend § 493.25 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. Amend § 493.801 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. Amend § 493.861 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. Amend § 493.901 by—

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

■ b. Adding new paragraph (a);

■ c. In newly redesignated paragraph (c)(7) by removing ''; '' and adding in its place ''; and'';

■ d. Adding new paragraph (c)(8);

■ e. Revising newly redesignated paragraph (e); and

■ f. Adding new paragraph (f).

The additions and revisions read as follows:

§ 493.901 Approval of proficiency testing programs.

* * * * *

(a) Require a minimum of 10 laboratory participants for each specialty, subspecialty, and analyte or test for which the proficiency testing program is seeking reapproval;

* * * * *

(c) * * *

(8) A contractor performing technical and scientific responsibilities as described in this section and § 493.903 (including, but not limited to, processes for selecting appropriate target values to be included in challenges as part of the annual PT program or grading PT results, determining target values, reporting scores to CMS, and determining organisms included in microbiology PT samples) 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. Amend § 493.903 by—

■ 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 new 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) *Effect on approval status.* 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 of its withdrawal of approval. Approval of the PT program remains in effect for 60 days from the date of notification. The proficiency testing program must notify all of its participating laboratories of the withdrawal of approval within 30 days from the date of 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 proficiency testing program that is dissatisfied with a determination to disapprove the program may request that CMS reconsider the determination, in accordance with subpart D of part 488.

■ 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 the presence or absence of bacteria without identification; or

(B) Identification of bacteria; and

(v) Antimicrobial susceptibility testing of select bacteria.

(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 testing 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 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 testing, the program must provide at least two samples per testing event. The program must annually provide samples that include Gram-positive organisms and samples that include Gram-negative organisms 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 the presence or absence of bacteria without identification, identification of bacteria, and antimicrobial susceptibility 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 10 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 the laboratory reports results 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 the presence or absence of bacteria without identification is the correct detection of the presence or absence of bacteria without identification. 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 $1/(1+1) \times 100 = 50$ percent.

(8) For antimicrobial susceptibility 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 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 responses reported by the laboratory divided by the actual number of correct susceptibility responses determined by the program, multiplied by 100. For example, if a laboratory offers susceptibility testing using three antimicrobial agents, and the laboratory reports correct responses for two of the three antimicrobial agents, the laboratory's grade would be $\frac{2}{3} \times 100 = 67$ 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; and

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

(A) Detection of the presence or absence of mycobacteria without identification; or

(B) Identification of mycobacteria.

(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.

(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 contain acid-fast organisms and challenges that do not contain acid-fast organisms.

(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 (6) 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 the presence or absence of mycobacteria without identification, and identification of mycobacteria. 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 10 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 the highest level that the laboratory reports results 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 (5) of this section as determined in paragraph (b)(6) 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 the presence or absence of mycobacteria without identification is the correct detection of the presence or absence of mycobacteria without identification. 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 $1/(1+1) \times 100 = 50$ percent.

(6) The score for a testing event in mycobacteriology is the average of the scores determined under paragraphs (b)(4) through (5) 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; and

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

(A) Detection of the presence or absence of fungi and aerobic actinomycetes without identification; or

(B) Identification of fungi and aerobic actinomycetes.

(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.

(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) Hyaline hyphomycetes;

(D) Mucormycetes; and

(iii) Aerobic actinomycetes.

(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 (6) of this section.

(1) The program determines the reportable fungi to be reported by direct fungal antigen detection, detection of the presence or absence of fungi and aerobic actinomycetes without identification, and identification of fungi and aerobic actinomycetes. 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 10 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 the laboratory reports results 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 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 the presence or absence of fungi and aerobic actinomycetes without identification is the correct detection of the presence or absence of fungi and aerobic actinomycetes without identification. 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 $1/(1+1) \times 100 = 50$ 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.

■ 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 for 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 the presence or absence of parasites without identification; 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 that 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 the presence or absence of parasites without identification, 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 10 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 the laboratory reports results 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 the presence or absence of parasites without identification is the correct detection of the presence or absence of parasites without identification. 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 $1/(1+1) \times 100 = 50$ 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 for 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; and

(ii) Detection and identification of viruses.

(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.

(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.

(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 (6) of this section.

(1) The program determines the viruses to be reported by direct viral antigen detection, and detection and identification of viruses. 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 10 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 the laboratory reports results 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 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 $1/(1+1) \times 100 = 50$ percent.

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

■ 15. Amend § 493.923 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 for 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 10 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. Amend § 493.927 by revising paragraphs (a), (b), (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:

TABLE 1 TO PARAGRAPH (b)—ANALYTE OR TEST PROCEDURE

Alpha-l antitrypsin.
Alpha-fetoprotein (tumor marker).
Antinuclear antibody.
Antistreptolysin O (ASO).
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 10 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) 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.

TABLE 2 TO PARAGRAPH (c)(2)—CRITERIA FOR ACCEPTABLE PERFORMANCE

The criteria for acceptable performance are—Analyte or test	Criteria for acceptable performance
Alpha-1 antitrypsin	Target value ± 20%.
Alpha-fetoprotein (tumor marker)	Target value ± 20%.
Antinuclear antibody (ANA)	Target value ±2 dilutions or positive or negative.
Antistreptolysin O	Target value ±2 dilutions or positive or negative.
Anti-Human Immunodeficiency virus (HIV)	Reactive (positive) or nonreactive (negative).
Complement C3	Target value ±15%.
Complement C4	Target value ±20% or ±5 mg/dL (greater).
C-reactive protein (HS)	Target value ±30% or ±1 mg/L (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 ±20%.
IgE	Target value ±20%.
IgG	Target value ±20%.
IgM	Target value ±20%.
Infectious mononucleosis	Target value ±2 dilutions or positive or negative.
Rheumatoid factor	Target value ±2 dilutions or positive or negative.
Rubella	Target value ±2 dilutions or positive or negative or immune or nonimmune.

* * * * *

■ 17. Amend § 493.931 by revising paragraphs (a), (b), (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 shipments.

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

TABLE 1 TO PARAGRAPH (b)—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, (direct measurement).
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 (PSA), total.
Sodium.
Total iron binding capacity (TIBC) (direct measurement).
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 10 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.

TABLE 2 TO PARAGRAPH (c)(2)—CRITERIA FOR ACCEPTABLE PERFORMANCE

The criteria for acceptable performance are— Analyte or test	Criteria for acceptable performance
Alanine aminotransferase (ALT/SGPT)	Target value ±15% or ±6 U/L (greater).
Albumin	Target value ±8%.
Alkaline phosphatase	Target value ±20%.
Amylase	Target value ±20%.
Aspartate aminotransferase (AST/SGOT)	Target value ±15% or ±6 U/L (greater).
Bilirubin, total	Target value ±20% or ±0.4 mg/dL (greater).
Blood gas pCO2	Target value ±8% or ±5 mm Hg (greater).
Blood gas pO2	Target value ±15% or ±15 mmHg (greater).

TABLE 2 TO PARAGRAPH (C)(2)—CRITERIA FOR ACCEPTABLE PERFORMANCE—Continued

The criteria for acceptable performance are— Analyte or test	Criteria for acceptable performance
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 (HDL)	Target value ±20% or ±6 mg/dL (greater).
Cholesterol, low density lipoprotein (LDL), direct measurement.	Target value ±20%.
Creatine kinase (CK)	Target value ±20%.
CK–MB isoenzymes	Target value ± 25% or ±3 ng/mL (greater) or MB elevated (presence or absence).
Creatinine	Target value ±10% or ±0.2 mg/dL (greater).
Ferritin	Target value ±20%.
Gamma glutamyl transferase	Target value ±15% or ±5 U/L (greater).
Glucose (excluding measurements devices cleared by FDA for home use.).	Target value ±8% or ±6 mg/dL (greater).
Hemoglobin A1c	Target value ±8%.
Iron, total	Target value ±15%.
Lactate dehydrogenase (LDH)	Target value ±15%.
Magnesium	Target value ±15%.
Phosphorus	Target value ± 10% or ±0.3 mg/dL (greater).
Potassium	Target value ±0.3 mmol/L.
Prostate Specific Antigen, total	Target value ±20% or ±0.2 ng/mL (greater).
Sodium	Target value ±4 mmol/L.
Total Iron Binding Capacity (TIBC). (direct measurement)	Target value ±20%.
Total Protein	Target value ±8%.
Triglycerides	Target value ±15%.
Troponin I	Target value ± 30% or ±0.9 ng/mL (greater).
Troponin T	Target value ±30% or ±0.2 ng/mL (greater).
Urea nitrogen	Target value ±9% or ±2 mg/dL (greater).
Uric acid	Target value ±10%.

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■ 18. Amend § 493.933 by revising paragraphs (a), (b), (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.

TABLE 1 TO PARAGRAPH (b)—ANALYTE OR TEST

Cancer antigen (CA) 125.
Carcinoembryonic antigen (CEA).
Cortisol.
Estradiol.
Folate, serum.
Follicle stimulating hormone.
Free thyroxine.
Human chorionic gonadotropin (HCG) (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 10 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.

TABLE 2 TO PARAGRAPH (C)(2)–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% or ±1 ng/dL (greater).
Cortisol	Target value ±20%.
Estradiol	Target value ±30%.
Folate, serum	Target value ±30% or ±1 ng/mL (greater).
Follicle stimulating hormone	Target value ±18% or ±2 IU/L (greater).
Free thyroxine	Target value or ±15% or ±0.3 ng/dL (greater).
Human chorionic	Target value ±18% or ±3
gonadotropin (excluding urine pregnancy tests done by visual color comparison categorized as waived tests).	mIU/mL (greater) or positive or negative.
Luteinizing hormone	Target value ±20%.
Parathyroid hormone	Target value ±30%.
Progesterone	Target value ±25%.
Prolactin	Target value ±20%.
Testosterone	Target value ±30% or ±20 ng/dL (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% or ±30 pg/mL (greater).

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■ 19. Amend § 493.937 by revising paragraphs (a), (b), (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.

TABLE 1 TO PARAGRAPH (b)—ANALYTE OR TEST PROCEDURE

Acetaminophen, serum.
Alcohol (blood).
Blood lead.
Carbamazepine, total.
Digoxin, total.
Gentamicin.
Lithium.
Phenobarbital.
Phenytoin, total.
Salicylate.
Theophylline.
Tobramycin.
Valproic Acid, total.
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 10 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.

TABLE 2 TO PARAGRAPH (c)(2)—CRITERIA FOR ACCEPTABLE PERFORMANCE

The criteria for acceptable performance are— Analyte or test	Criteria for acceptable performance
Acetaminophen	Target value ±15% or ±3 mcg/mL (greater).
Alcohol, blood	Target Value ±20%.
Blood lead	Target Value ±10% or ±2 mcg/dL (greater).
Carbamazepine, total	Target Value ±20% or ±1.0 mcg/mL (greater).
Digoxin, total	Target Value ±15% or ± 0.2 ng/mL (greater).
Gentamicin	Target Value ±25%.
Lithium	Target Value ±15% or ±0.3 mmol/L (greater).
Phenobarbital	Target Value ±15% or ±2 mcg/mL (greater).
Phenytoin total	Target Value ±15% or ± 2 mcg/mL (greater).
Salicylate	Target Value ±15% or ±2 mcg/mL (greater).
Theophylline	Target Value ±20%.
Tobramycin	Target Value ±20%.
Valproic Acid, total	Target Value ±20%.
Vancomycin	Target Value ±15% or ±2 mcg/mL (greater).

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■ 20. Amend § 493.941 by revising paragraphs (a), (b), (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.

TABLE 1 TO PARAGRAPH (b)—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 10 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.

TABLE 2 TO PARAGRAPH (c)(2)—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 hematocrit)	Target ±4%.
Hemoglobin	Target ±4%.
Leukocyte count	Target ±10%.
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.

TABLE 2 TO PARAGRAPH (c)(2)—CRITERIA FOR ACCEPTABLE PERFORMANCE—Continued

The criteria for acceptable performance are: Analyte or test	Criteria for acceptable performance
Prothrombin time (seconds or INR)	Target ±15%.

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■ 21. Amend § 493.959 by revising paragraphs (b), (d)(1) and (2) to read as follows:

§ 493.959 Immunohematology.

* * * * *

(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 10 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 10 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—

TABLE 2 TO PARAGRAPH (d)(2)—CRITERIA FOR ACCEPTABLE PERFORMANCE

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 24, 2022.

Xavier Becerra,

Secretary, Department of Health and Human Services.

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