DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Elimination of 21 CFR 610.30 Test for Mycoplasma

Docket No. FDA-2018-N-4757

Preliminary Regulatory Impact Analysis
Initial Regulatory Flexibility Analysis
Unfunded Mandates Reform Act Analysis

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Table of Contents

I. Introduction and Summary

A. Introduction

We have examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, Executive Order 13771, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104-4). Executive Orders 12866 and 13563 direct us to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Executive Order 13771 requires that the costs associated with significant new regulations "shall, to the extent permitted by law, be offset by the elimination of existing costs associated with at least two prior regulations." We believe that this proposed rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because this rule focuses on a small number of large firms, we propose to certify that the proposed rule will not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is $150 million, using the most current (2017) Implicit Price Deflator for the Gross Domestic Product. This proposed rule would not result in an expenditure in any year that meets or exceeds this amount.

Industry and the Food and Drug Administration (FDA) will largely maintain their current practices following the removal of the Test for Mycoplasma under Title 21 of the Code of Federal Regulations (CFR) 610.30, Subpart D (21 CFR 610.30 or the 610.30 Test for Mycoplasma). Although manufacturers of live virus vaccines and inactivated virus vaccines produced from *in vitro* living cell cultures may experience some unquantifiable cost savings from streamlining their testing procedures, we predict no quantifiable cost savings. FDA will also maintain its current practices, similarly generating no quantifiable cost savings. Therefore, we expect this proposed rule to be cost neutral.

We have developed a comprehensive Economic Analysis of Impacts that assesses the impacts of the proposed rule. The full analysis of economic impacts is available in the docket for this proposed rule (Ref. 1 of this proposed rule) and at https://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm

B. Summary of Costs and Benefits

This proposed rule would amend the biologics regulations under 21 CFR 610.30 (Ref. 1) by removing the specified test for mycoplasma in the production of live virus vaccines and inactivated virus vaccines produced from in vitro living cell cultures.

This proposed rule would be considered a deregulatory action under Executive Order 13771. Removing the 610.30 Test for Mycoplasma would provide manufacturers with the flexibility to determine the most appropriate and effective mycoplasma testing methods. As referenced below, FDA guidance dated after 21 CFR 610.30 was codified in 1973 (November 20, 1973; 38 FR 32056) outlines up-to-date scientific practices to identify mycoplasma in vaccine production. In practice, vaccine manufacturers can change their procedures at any time with submission and approval of a supplement to each vaccine licensing agreement. As a result, we do not expect the repeal of the 610.30 Test for Mycoplasma to significantly influence the behavior or procedures of vaccine manufacturers.

Because manufacturers already have the ability to pursue alternative testing procedures, we anticipate no measurable change in industry or FDA behavior from this proposed rulemaking. We therefore expect the elimination of the 610.30 Test for Mycoplasma to be cost neutral. This proposed rule will therefore produce no quantifiable savings, costs, or transfers. We also expect forgone benefits to be unlikely. Finally, we note that this proposed rulemaking may drive some manufacturers to streamline their procedures and search for more efficient mycoplasma testing methods. This optimization may produce some unquantifiable efficiencies.

II. Preliminary Regulatory Impact Analysis

A. Background

The goal of mycoplasma testing in the production of live virus vaccines and inactivated virus vaccines produced from *in vitro* living cultures is to assure these vaccines are not contaminated. Contaminated vaccines pose a health hazard, particularly in at-risk populations such as children and the elderly. The United States Public Health Service first addressed the issue of mycoplasma contaminants in viral vaccines by imposing a test in 1962. In 1973, the FDA codified mycoplasma testing in 21 CFR 610.30.

The 610.30 Test for Mycoplasma requires manufacturers to test for mycoplasma during manufacture of live and inactivated vaccines produced from *in vitro* living cell cultures. The regulation outlines a specific testing method that manufacturers must follow. These procedures require a minimum of 28 days to complete. If the results of testing reveal no evidence of contamination, vaccine manufacturers can distribute the vaccine. This testing helps to ensure that these viral vaccines are safe, pure, and potent.

FDA issued revised guidance in July 1993 (Points to Consider in the Characterization of Cell Lines Used to Produce Biologicals) (PTC) (Ref. 2) and in February 2010 (Guidance for Industry: Characterization and Qualification of Cell Substrates and Other Biological Materials Used in the Production of Viral Vaccines for Infectious Disease Indications) (2010 Cell Substrates

Guidance) (Ref. 3). The PTC introduced new procedures to address types of mycoplasmas capable of remaining undetected by existing tests. The 2010 Cell Substrates Guidance built on the 1993 PTC and permitted vaccine manufacturers to rely on "acceptable alternatives" to the 21 CFR 610.30 testing method. However, a vaccine producer must obtain FDA approval for modifications to mycoplasma testing in accordance with 21 CFR 601.12(b) or (c) and meeting the requirements of 21 CFR 610.9 (Ref. 4). Obtaining approval involves submitting a supplement to the vaccine licensing agreement.

B. Market Failure Requiring Federal Regulatory Action

This proposed rule revokes the 610.30 Test for Mycoplasma. In light of guidance issued in 1993 and 2010 after the establishment of 21 CFR 610.30 in 1973, this mandate no longer reflects the most up-to-date scientific practices to identify mycoplasma in live virus vaccines and inactivated virus vaccines produced from *in vitro* living cell cultures. Without this rulemaking, manufacturers of viral vaccines will conduct testing which may be duplicative.

C. Purpose of the Proposed Rule

Eliminating this regulation would provide vaccine manufacturers with the flexibility to determine the most appropriate and effective mycoplasma testing methods. This proposed rulemaking is part of FDA's retrospective review of regulations to promote improvement and innovation, in response to Executive Order 13563 of January 18, 2011. It is also part of FDA's efforts to evaluate existing regulations and make recommendations to the agency head regarding their repeal, replacement, or modification following Executive Order 13777 of February 24, 2017.

D. Baseline Conditions

Baseline conditions refer to the state of regulated mycoplasma testing prior to deregulation. Historically, manufacturers of live virus vaccines and inactivated virus vaccines produced from *in vitro* living cell cultures followed testing procedures outlined in the 610.30 Test for Mycoplasma; however, since 1993, supplemental testing not described in 21 CFR 610.30 has been required given that the test as described in 21 CFR 610.30 is incapable of detecting non-cultivatable mycoplasma strains. Vaccine manufacturers include alternative procedures in their Biologics License Applications.

At baseline, this means that manufacturers submitting applications for a new viral vaccine produced from *in vitro* living cell cultures test for mycoplasma as described in 21 CFR 610.30. However, because of the limitations of the required test, a manufacturer also selects additional testing which may be duplicative. Any manufacturers with licensing agreements approved prior to guidance in 1993 or 2010 would submit a supplement to change the mycoplasma testing procedure included in the original license. Supplement submission does not incur a fee.

Finally, it is important to note that manufacturers may choose to conduct testing in-house or contract the testing to an external laboratory. Moreover, because different national regulatory

authorities have different testing requirements, a manufacturer may choose tests that satisfy all national regulatory requirements. Further details on these practices are not publicly available.

E. Benefits of the Proposed Rule

1. Industry

Eliminating this regulation allows manufacturers of live virus vaccines and inactivated virus vaccines produced from *in vitro* living cell cultures the flexibility to determine the most appropriate and effective mycoplasma testing methods. Following repeal, manufacturers of these vaccines can decide whether to continue their current testing regimes. As described in sections II.B and IV.B of the preamble to the proposed rule, unless a manufacturer has received approval to substitute for the current required test, this testing regime must include the current mycoplasma test as described in 21 CFR 610.30. In practice, manufacturers of live virus vaccines and inactivated virus vaccines made from *in vitro* cell cultures also include one or more acceptable additional tests.

After removal of the regulation, if manufacturers make no testing changes, repeal leads to no cost savings. If manufacturers decide to change their mycoplasma testing procedures, they will likely select the testing regime that decreases costs without sacrificing vaccine quality. However, the choice of mycoplasma testing method, and therefore cost, depends on the testing method and vaccine. Freedom to choose the *most appropriate* mycoplasma test does not necessarily mean a manufacturer will adopt the *least costly* test. For example, an alternative testing method may cost more per lot of vaccine but result in other unquantifiable gains such as faster turnaround and improved accuracy. Moreover, the act of changing procedures itself may produce a one-time business cost. All manufacturers would also continue to submit supplements for FDA approval in order to change mycoplasma testing procedures, even in cases where vaccines received approval after the most recent guidance in 2010. We do not have the data that would allow us to estimate which choices a manufacturer would make after repeal of the mycoplasma test. However, we assume that each manufacturer will optimize the net benefits and costs of this decision to achieve its preferred outcome.

Repeal of the mycoplasma test may produce additional minor but unquantifiable benefits. Removing the requirement to test for mycoplasma by a specific method may encourage some manufacturers to streamline their methods by focusing on the most efficient mycoplasma tests and removing the test outlined in 21 CFR 610.30 from their procedures. Repeal may also act as a signaling effect that encourages industry to take a closer look at its operating practices, influencing not just manufacture of vaccines produced from *in vitro* living cell cultures but the production of other biological products. With greater flexibility, manufacturers may be able to better harmonize mycoplasma testing across international regulatory requirements. These streamlining actions may increase manufacturer efficiency as well as vaccine supply and potentially promote greater competition by reducing recurring costs and freeing resources for greater optimization.

2. FDA

The elimination of 21 CFR 610.30 concerns live virus vaccines produced from *in vitro* living cell cultures and inactivated virus vaccines produced from such living cell cultures. It pertains to the Office of Vaccines Research and Review (OVRR) in the Center for Biologics Evaluation and Research (CBER). Because FDA must approve all supplemental changes to a vaccine licensing agreement regardless of whether 21 CFR 610.30 is in place, we do not expect this deregulatory action to generate any cost savings for FDA.

3. Total Cost Savings

In sum, industry and FDA will largely maintain their current practices following the removal of the 610.30 Test for Mycoplasma. Though manufacturers of viral vaccines produced from in vitro living cell cultures may experience some unquantifiable cost savings from streamlining their testing procedures, we predict no quantifiable cost savings. FDA will also maintain its current practices, similarly generating no quantifiable cost savings. Therefore, we expect this proposed rule to be cost neutral.

F. Costs of the Proposed Rule

1. Foregone Benefits

We believe forgone benefits from eliminating the 610.30 Test for Mycoplasma do not pose a concern for two reasons: First, FDA considers the alternative testing methods described in up-to-date guidance to be equivalent to or better than the mycoplasma test described in 21 CFR 610.30. Second, all manufacturers of live virus vaccines and inactivated virus vaccines produced from *in vitro* living cell cultures must obtain FDA approval of their selected mycoplasma tests. In other words, repeal of the 610.30 Test for Mycoplasma will have no negative impacts on vaccine production, quality, or supply.

G. Distributional Effects

As described above, manufacturers currently test for mycoplasma and will continue to test for mycoplasma after repeal of the 610.30 Test for Mycoplasma. Because we expect manufacturer practices to remain largely the same before and after this deregulatory action, we do not expect this ruling to alter vaccine production, distribution, or cost in a measurable way. If vaccine supply and cost remain constant, we have no reason to believe that there would be a wealth transfer that would generate any distributional or equity concerns.

H. International Effects

Revoking the 610.30 Test for Mycoplasma affects the production of live virus vaccines and inactivated virus vaccines produced from in vitro living cell cultures licensed in the United States. As a result, the proposed rule should not create any adverse international effects.

I. Uncertainty and Sensitivity Analysis

Sections II(E) and II(F) of this preliminary regulatory impact analysis highlight the uncertainty considerations in this proposed rule. We are not certain how this rule will affect vaccine manufacturers because we cannot predict how vaccine manufacturers will choose to use the additional flexibility provided by the proposed rulemaking. The costs and/or benefits to consumers of the proposed provisions are also uncertain and remain unquantified.

III. Initial Small Entity Analysis

We have examined the economic implications of this proposed rule as required by the Regulatory Flexibility Act (5 U.S.C. 601-612). The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because this rule affects a limited number of large vaccine producers, we propose to certify that the proposed rule will not have a significant economic impact on a substantial number of small entities. This analysis, as well as other sections in this document, serves as the Initial Regulatory Flexibility Analysis, as required under the Regulatory Flexibility Act.

IV. References

1. **US Government.** *Code of Federal Regulations. Title 21, Subpart D-Mycoplasma § 610.30* Available at https://www.ecfr.gov/cgi-bin/text-idx?SID=b5052068636b9e6cb23c663f2dd8892e&mc=true&node=se21.7.610_130&rgn=div8.
2. **US Food and Drug Administration. Center for Biologics Evaluation and Research.** (1993). *Points to consider in Characterization of cell lines used to produce biologicals.* Rockville, MD: US Department of Health and Human Services. Available at https://www.fda.gov/downloads/biologicsbloodvaccines/safetyavailability/ucm162863.pdf.
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4. **US Government.** *Code of Federal Regulations. Title 21, Subpart B-General Provisions, Equivalent methods and processes, § 610.9* Available at https://www.ecfr.gov/cgi-bin/text-idx?SID=7151751025a3ad0461582ba1f92a3d93&mc=true&node=se21.7.610_19&rgn=div8