DATE: March 13, 2023

TO: Secretary Xavier Becerra

THROUGH: Kim Miller-Tolbert, Policy Advisor
Angela Ramirez, Deputy Chief of Staff
Stephen Cha, Counselor to the Secretary
Sarah Despres, Counselor to the Secretary

FROM: Julie Tierney, Chief of Staff, FDA
Lindsay Tobias, Special Assistant to the Chief of Staff, FDA

SUBJECT: Weekly Check-In with FDA

Details
What: Weekly Check-In with FDA
Date: Wednesday, March 15, 2023
Time: 11:00 AM – 11:30AM
Location: Via teleconference
Call: Yes
Internal or External Event: Internal to HHS/FDA

Topic:

FDA Weekly Check-In

Objective:

FDA will provide an update on high-priority legislative proposals accompanying its animal drug user fee re-authorization.

Secretary's Role:

To listen and ask questions.

List of Participants:
OS:

- Deputy Secretary Andrea Palm
- Sean McCluskie, Chief of Staff

- Angela Ramirez, Deputy Chief of Staff
- Sarah Despres, Counselor to the Secretary
- Steve Cha, Counselor to the Secretary
- Kamara Jones, Acting Assistant Secretary for Public Affairs
- Melanie Egorin, Assistant Secretary for Legislation
- Sam Bagenstos, General Counsel
- Katlin Backfield, Deputy General Counsel
- John Kraus, Deputy Assistant Secretary for Public Affairs

FDA:

- Robert Califf, Commissioner
- Janet Woodcock, Principal Deputy Commissioner
- Julie Tierney, Chief of Staff
- Tristan Colonius, Deputy Chief of Staff
- Andi Fristedt, Deputy Commissioner for Policy, Legislation, and International Affairs
- Kim Trzeciak, Associate Commissioner for Legislative Affairs
- Erica Jefferson, Associate Commissioner, Office of External Affairs
- Mark Raza, Chief Counsel
- Tracey Forfa, Director, Center for Veterinary Medicine
- William Flynn, Deputy Director for Science and Policy, Center for Veterinary Medicine
- Roxanne Schweitzer, Associate Director of Management, Center for Veterinary Medicine
- Timothy Schell, Director Office of Surveillance and Compliance, Center for Veterinary Medicine
- Ellen Hart, Senior Veterinary Medical Officer, Center for Veterinary Medicine

Agenda/Run of Show:

- Introductions (5 minutes, FDA)
- Presentation (15-20 minutes, FDA)
- Discussion (5 minutes, All)

Background:

Congress is in the process of re-authorizing the Animal Drug User Fee and Animal Generic Drug User Fee Acts (ADUFA/AGDUFA). These supplement appropriated funding for the pre-market activities of the FDA Center for Veterinary Medicine (CVM) animal drug review program and must be re-authorized on a 5-year cycle.

FDA negotiated recommendations with the respective industry groups and submitted them to Congress for consideration in January. You were briefed on those recommendations on January 10, 2023. In accordance with a Congressional directive, no recommendations for statutory language outside the user fee issues were discussed during negotiations. Since that time, FDA has begun to engage with Senate Committee on

Health, Education, Labor, and Pensions (HELP) and House Committee on Energy and Commerce (E&C) staff to discuss potential authorizing legislation that could resolve high-profile issues within CVM's purview. It is unclear whether the Committees will consider including any policy riders in the ADUFA/AGDUFA bills, but there has been ongoing interest from Committee staff in learning more about the issues of importance to the Agency and producing draft legislative text.

Novel claims for animal food

Under the law, products intended to affect the structure or function of the animal are regulated as drugs. As a result, products with certain claims, such as animal food ingredients intended to reduce methane emissions from animals by affecting the structure or function of the animal, must be regulated as drugs. The concern from stakeholders is that applying this regulatory approach to these types of animal food products is overly burdensome and not consistent with other global regulatory agencies.

After significant stakeholder input including a public listening session in October of 2022, CVM is proposing a legislative fix. The proposal would amend the definitions in Section 201 of the FD&C Act to add "zootechnical animal food substance," which would allow products with certain structure/function claims to be regulated as food additives. The products would include those with claims that affect emissions (e.g., of methane) from an animal or its waste, reduce the presence of foodborne pathogens of human health significance and those that alter the animal's gastrointestinal microbiome.

Regulating these products as animal food additives will allow the Agency to review safety and utility prior to marketing which is consistent with certain other animal food additives. This proposal addresses stakeholder concerns and provides a risk appropriate pathway to market for products with innovative technologies.

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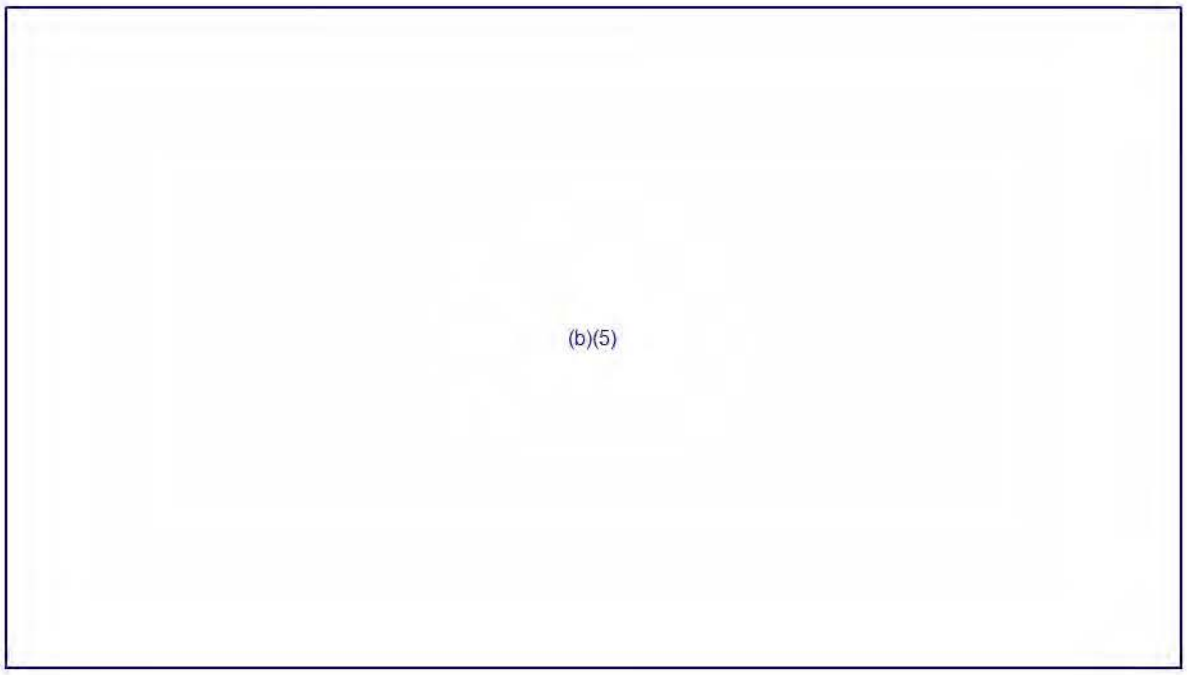

Attachments:

1. Slide Deck
2. Whitepaper

DATE: March 13, 2023

TO: Secretary Xavier Becerra

THROUGH: Kim Miller-Tolbert, Policy Advisor
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Sarah Despres, Counselor to the Secretary

FROM: Julie Tierney, Chief of Staff, FDA
Lindsay Tobias, Special Assistant to the Chief of Staff, FDA

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- Roxanne Schweitzer, Associate Director of Management, Center for Veterinary Medicine
- Timothy Schell, Director Office of Surveillance and Compliance, Center for Veterinary Medicine
- Ellen Hart, Senior Veterinary Medical Officer, Center for Veterinary Medicine

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Attachments:

1. Slide Deck
2. Whitepaper

DATE: March 28, 2023

TO: Secretary Xavier Becerra

THROUGH: Angela Ramirez, Deputy Chief of Staff
Stephen Cha, Counselor to the Secretary
Sarah Despres, Counselor to the Secretary

FROM: Julie Tierney, Chief of Staff, FDA
Lindsay Tobias, Special Assistant to the Chief of Staff, FDA

SUBJECT: Weekly Check-In with FDA

Details:
What: Briefing via teleconference
Date: March 30, 2023
Time: 10:00 AM – 10:45 AM
Location: Teleconference
Call: Yes
Internal Event: Yes

Topic: FDA Weekly Check-In

Objective:

1) Provide an overview on the Medication Guides: Patient Medication Information (PMI) proposed rule, and
2) Provide an overview on FDA's development of a rule, "Medical Devices; Laboratory Developed Tests (LDT)"

Secretary's Role: Listen and ask questions.

List of Participants:
OS:

- Deputy Secretary Andrea Palm
- Sean McCluskie, Chief of Staff
- Angela Ramirez, Deputy Chief of Staff
- Sarah Despres, Counselor to the Secretary
- Steve Cha, Counselor to the Secretary
- Kamara Jones, Acting Assistant Secretary for Public Affairs

- John Kraus, Deputy Assistant Secretary for Public Affairs
- Melanie Egorin, Assistant Secretary for Legislation
- Sam Bagenstos, General Counsel
- Katlin Backfield, Deputy General Counsel
- Kim Miller-Tolbert, Policy Advisor
- Elizbeth Gambling, Executive Secretary to the Department
- Christina Zielke, Policy Coordinator,

FDA:

Primary Team:

- Robert M. Califf, Commissioner, FDA
- Julie Tierney, Chief of Staff, FDA
- Tristan Colonius, Deputy Chief of Staff, FDA
- Andi Fristedt, Deputy Commissioner for Policy, Legislation, and International Affairs (OPLIA), Office of the Commissioner (OC)
- Lauren Roth, Associate Commissioner for Policy, Office of Policy (OP), OPLIA, OC
- Andrew Zacher, Senior Policy Analyst (OP), OPLIA, OC
- Kim Trzeciak, Associate Commissioner for Legislation, OPLIA, OC

PMI Team:

- Jacqueline Corrigan-Curay, Center for Drug Evaluation and Research (CDER)
- M. Khair ElZarrad, CDER
- Karen Hicks, CDER
- Bryon Pearsall, CDER
- Chris Diamant, CDER
- Kathy Schreier, CDER
- Jennifer Scharpf, Center for Biologics Evaluation and Research (CBER)
- Diane Maloney, CBER
- Julie Finegan, OPLIA
- Nnaemeka Chukwudebe, OPLIA
- Megan Andersen, OPLIA
- Beethika Khan, Associate Commissioner for Economics and Analysis, OPLIA
- Carolyn Wolff, OPLIA/Econ
- Sherene Sepehri, Office of the Chief Counsel (OCC)
- Deborah Chasan-Sloan, OCC

LDT Team:

- Jeff Shuren, Director, Center for Devices and Radiological Health (CDRH)
- Ellen Flannery, Deputy Center Director for Policy, CDRH
- Elizabeth Hillebrenner, Associate Director, CDRH
- Eitan Bernstein, Regulatory Counsel, CDRH
- Brittany Schuck, Deputy Office Director, Office of Health Technology 7, CDRH
- Beethika Khan, Associate Commissioner for Economics and Analysis, Office of

Economics and Analysis (OEA), OPLIA, OC
- Ephraim Leibtag, Chief Economist, OEA, OPLIA, OC
- Sheri Walker, Assistant Director, Economics Staff, OEA, OPLIA, OC
- Sara Beardsley, Attorney, OCC
- Marcy Busch, Attorney, OCC
- Siyeon Lee, Attorney, OCC

Agenda/ Run of Show:

- 10:00 – 10:05 Introductions/Welcome
- 10:05 – 10:20 Patient Medication Information (PMI) Proposed Rule Discussion & Questions
- 10:20 – 10:45 Laboratory Developed Tests (LDTs) Rule Development Discussion & Questions

Background – PMI

This briefing will describe the proposed rule to amend the existing prescription drug product labeling regulations for Medication Guides (21 CFR § 208) to require a new type of Medication Guide, referred to as Patient Medication Information, for prescription drug products used, dispensed, or administered on an outpatient basis, including blood and blood components transfused in an outpatient setting.

This proposed rule is intended to improve public health by replacing several different forms of patient labeling with a single, one-page document that provides clear, concise, accessible, and useful written prescription drug product information to help patients use their prescription drug products safely and effectively. The proposed rule would require applicants of all new and previously approved new drug applications (NDAs) and biologics license applications (BLAs) to create Patient Medication Information for prescription drug products that are to be used, dispensed, or administered on an outpatient basis. The proposed rule would also require applicants of new and approved abbreviated new drug applications (ANDAs) that refer to a listed drug for which FDA has approved Patient Medication Information to have Patient Medication Information that is the same as that of the reference listed drug (RLD) except for certain differences in labeling permitted under the law. FDA will create a Patient Medication Information template for approved ANDAs if (1) the ANDA references a listed drug whose approval has been withdrawn and (2) no Patient Medication Information was approved for the RLD before the approval of the RLD was withdrawn.

Patient Medication Information would be stored in an online central repository managed by FDA and would be freely accessible to the public, including patients, healthcare providers, and authorized dispensers.

Background - LDT:

FDA's regulations define in vitro diagnostic products (IVDs) as reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions (including a determination of the state of health) in order to cure, mitigate, treat, or prevent disease or its sequelae; and intended for use in the collection, preparation, and examination of specimens taken

from the human body. IVDs include tests that are performed on samples taken from the human body, such as blood or tissue, for purposes of detecting diseases or other conditions, monitoring a person's overall health, identifying patients who are likely to benefit from specific therapies, or otherwise helping to diagnose, cure, mitigate, treat, or prevent disease.

IVDs are devices under the FD&C Act. However, since 1976, when the FD&C Act was amended to create a comprehensive system for the regulation of devices intended for human use, FDA has generally exercised enforcement discretion with respect to a subset of IVDs known as laboratory developed tests (LDTs). FDA has generally considered LDTs to be IVDs that are intended for clinical use and that are designed, manufactured, and used within a single laboratory certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) (42 U.S.C. 263a) to perform high complexity testing.

LDTs and the LDT industry have evolved significantly since 1976, and the risks associated with LDTs are much greater today than they were at that time. In 1976, LDTs were mostly manufactured in small volumes by local laboratories. They were typically intended for use in diagnosing rare diseases or for other uses to meet the needs of a local patient population, or were generally similar to well-characterized, standard tests. They also tended to rely on manual techniques performed by laboratory personnel (without automation); to be used and interpreted by physicians or pathologists in a single institution responsible for the patient; and to be manufactured using components legally marketed for clinical use. Today, LDTs rely more frequently on high-tech instrumentation and software, and are often used in laboratories independent of the healthcare delivery entity. They are more commonly manufactured with instruments or other components not legally marketed for clinical use, and are often used to direct critical treatment decisions, to widely screen for common diseases, to predict personal risk of developing certain diseases, or to diagnose serious medical conditions such as cancer and heart disease. They are also often manufactured in high volume for large and diverse populations. These factors create a potential increased risk to patients in the absence of appropriate FDA oversight.

Given these and other changes, FDA is proposing to phase out the general enforcement discretion approach for LDTs to help assure the safety and effectiveness of LDTs and protect the public health. In addition, the proposed changes to FDA's general enforcement discretion approach would provide greater consistency in the oversight of IVDs, which in turn may help to incentivize the manufacture of innovative and appropriately safe and effective IVDs. Currently, IVD manufacturers who are not laboratories may be discouraged from investing time and resources into developing novel tests due to the concern that once the manufacturer receives marketing authorization for its test, clinical laboratories will develop similar tests and market their tests without complying with FDA requirements. By applying the same enforcement policies to laboratories and non-laboratories that manufacture IVDs, the proposed changes would incentivize those non-laboratory manufacturers to develop novel tests and enter the IVD marketplace, thereby spurring innovation and access to appropriately safe and effective tests.

Some have asserted that FDA lacks authority over LDTs for various reasons, including that Congress intended LDTs to be regulated under CLIA. Although the Centers for Medicare & Medicaid Services (CMS) regulates certain laboratories and laboratory personnel under CLIA,

CLIA requirements serve different purposes than the requirements in the FD&C Act. CLIA and its implementing regulations regulate the operations, inspection, and certification process for laboratories, but do not regulate laboratory test development; do not evaluate the performance of an LDT before the test is offered to patients and healthcare providers; do not assess clinical validity (*i.e.*, the accuracy with which a test identifies, measures, or predicts the presence or absence of a clinical condition or predisposition in a patient); do not regulate certain activities related to manufacturing, such as design controls and acceptance activities; do not provide human subject protections for patients who participate in LDT clinical research trials; and do not require adverse event reporting. Compliance with CLIA and its implementing regulations alone does not assure that LDTs are appropriately safe and effective.

FDA has signaled its intention to change its general enforcement discretion approach for LDTs for well over a decade. In 2010, in a notice announcing a public meeting regarding the oversight of LDTs, FDA stated its belief that the time had come to reconsider FDA's LDT enforcement discretion approach and noted that a risk-based oversight approach might be appropriate. Four years later, in 2014, FDA issued draft guidance documents that proposed a risk-based framework for the regulatory oversight of LDTs. FDA subsequently announced that it would not finalize those guidance documents to allow for further public discussion, and to provide an opportunity for Congress to develop legislation. We note that legislative proposals since that time have considered the establishment of modern regulatory frameworks that would transform FDA's regulation of in vitro clinical tests generally, including for test kits, LDTs, and all other IVDs, but no such bills have been enacted to date. We also note that in August 2020, at a time when FDA was issuing emergency use authorizations (EUAs) for certain COVID-19 LDTs, HHS posted a web statement that provided, among other things, that HHS had determined that FDA "will not require premarket review of laboratory developed tests ('LDT') absent notice-and-comment rulemaking." HHS subsequently withdrew that policy in November 2021. Over the last several years, FDA's concerns about inaccurate, unsafe, ineffective, or poor quality LDTs have increased, and FDA believes that it is time to change the general enforcement discretion approach for LDTs.

The proposed rule is currently in development, so details of the proposed rule and enforcement policy are subject to change. However, in its current form, the proposed rule would (if finalized) amend FDA's regulations to make explicit that IVDs are devices as defined in section 201(h) of the FD&C Act even if the manufacturer of the IVD is a laboratory. This amendment would expressly align the IVD definition in part 809 with the device definition in the FD&C Act, which does not differentiate between entities manufacturing the device, and would provide further clarity, including for stakeholders affected by the accompanying changes to FDA's general enforcement approach for LDTs. FDA also would phase out the general enforcement discretion approach for LDTs so that tests manufactured by a laboratory would generally fall under the same enforcement policies as other IVDs.

Under FDA's proposed phase-out policy, as would be described in the preamble to the proposed rule, FDA is proposing to gradually end its general enforcement discretion approach for LDTs over a period of six years. Specifically, FDA would end the general enforcement discretion approach with respect to the following requirements on the following schedule:

- Adverse event reporting and reporting of corrections and removals, starting **one year** after publication of a final phase-out policy;
- Registration and listing requirements, certain quality system (QS) requirements, labeling requirements, requirements regarding investigational use, and other requirements not covered during other stages of the phase-out policy, starting **four years** after publication of a final phase-out policy;
- Premarket approval (PMA) application requirements for high-risk tests, starting **five years** after publication of a final phase-out policy; and
- 510(k) requirements (certain LDTs may submit a *de novo* request instead) for moderate-risk tests (and low-risk tests that require a 510(k), *i.e.,* class I reserved tests), starting **six years** after publication of a final phase-out policy.

Regarding QS requirements in particular, although FDA and CMS regulation is different and complementary, compliance with CLIA requirements might be leveraged to provide some quality assurances that can be relevant to laboratories' manufacturing practices. Therefore, FDA intends to phase out its general enforcement discretion approach for some, but not all, of the device QS requirements.

While FDA's general enforcement discretion approach has been focused on LDTs, FDA is proposing a broader scope for the phase-out policy, to apply to clinical laboratory tests that are *offered* as LDTs (even if those tests do not fall within FDA's traditional understanding of an LDT). FDA recognizes that not all laboratories have understood the limited nature of FDA's general enforcement discretion approach and have been offering tests based on the approach even when they do not fit FDA's description of an LDT. FDA believes it is important to structure this new policy in a way that avoids undue disruption to the market.

The phase-out policy would not apply to tests that were clearly never included in the general enforcement discretion approach, including tests intended for declared emergencies/potential emergencies/material threats; direct-to-consumer (DTC) tests; or potentially tests that are intended as blood donor screening or human cells or tissue donor screening tests required for infectious disease testing under 21 CFR 610.40, 21 CFR 1271.80(c), or for ABO and D blood typing required under 21 CFR 640.5. For these tests, FDA's normal enforcement approach applies today, and would continue to apply.

In addition, FDA would continue to apply the general enforcement discretion approach to the following categories of tests, for which FDA believes there are other appropriate safeguards or oversight mechanisms in place that justify continuation of the general enforcement discretion approach:

- Tests intended solely for forensic (law enforcement) purposes;
- Tests intended solely for public health surveillance, meaning tests that are intended solely for use on systematically collected samples for analysis and interpretation of health data in connection with disease prevention and control, and test results are not reported to patients or their healthcare providers;
- Tests that involve only manual interpretation without the use of automated instrumentation or software; and

- Tests used in CLIA-certified high-complexity histocompatibility laboratories used in connection with organ, stem cell, and tissue transplantation to perform allele typing, for antibody screening and monitoring, or for conducting real and "virtual" crossmatch tests (still under discussion within FDA).

Notwithstanding the phase-out strategy described above, FDA would retain discretion to pursue enforcement action at any time against violative IVDs, and may enforce when necessary to protect the public health. This might be the case, for example, when FDA has concerns that (1) an IVD is not scientifically valid or there is an absence of sufficient data to support scientific validity; (2) the manufacturer of the IVD has engaged in deceptive promotion; and/or (3) the IVD presents a direct or indirect health hazard.

Timeline

FDA is pursuing a highly ambitious timeline for the proposed rule such that the rule may publish in August of this year. With this timeline, FDA's goal is to be in the best potential position to finalize the rulemaking early in 2024. FDA's target timeline is as follows, assuming expedited reviews and clearances:

Action	Begin HHS Clearance	Begin OMB Clearance	OFR Publication
LDT Proposed Rule	June 2023	July 2023	August 2023

This timeline is still under discussion, and the dates provided here are currently FDA's best estimate.

Anticipated Stakeholder Reaction

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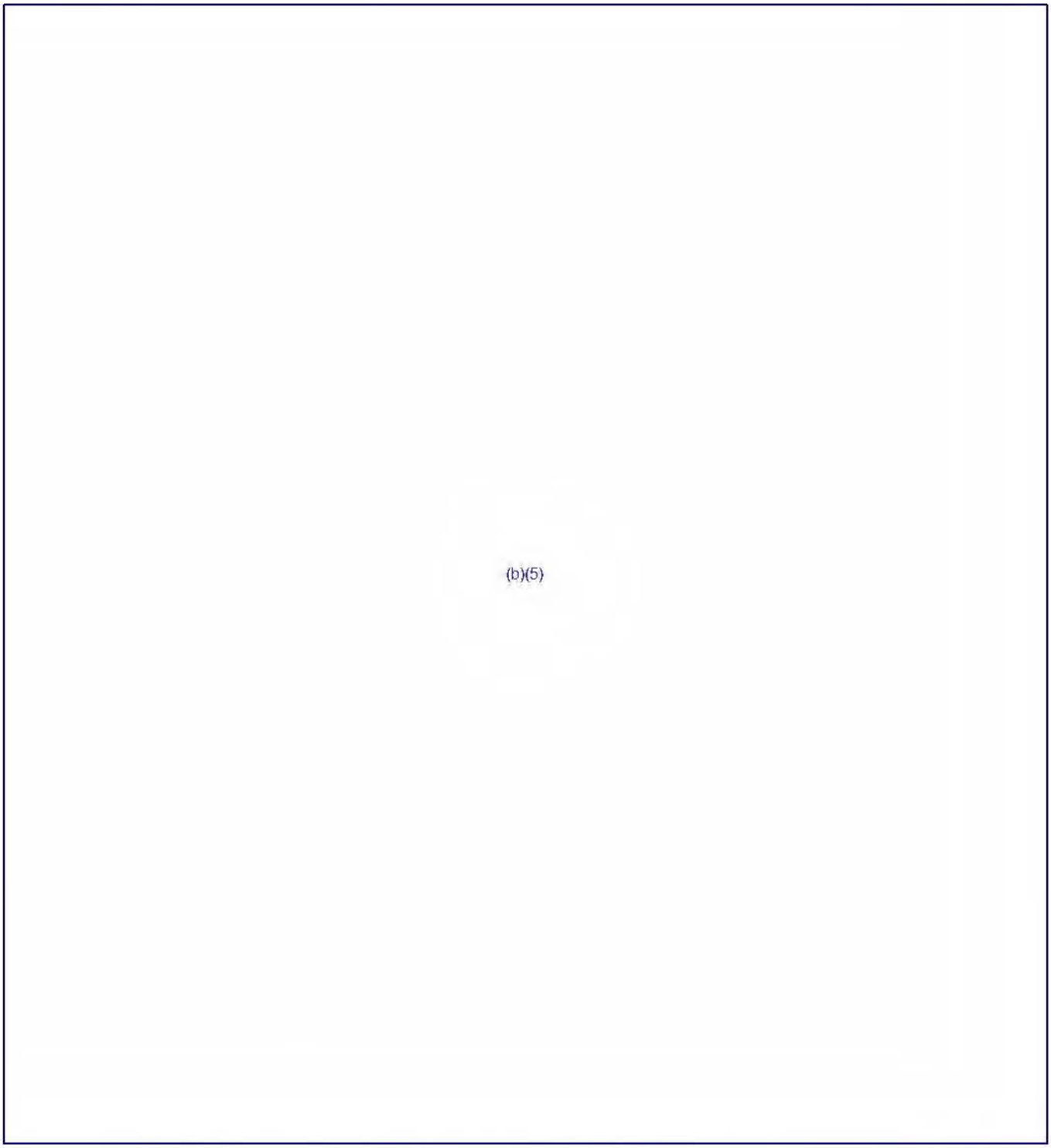

We also anticipate that stakeholders will provide comments regarding FDA's proposed phase-out strategy for enforcement and the applicability of QS requirements, among other topics.

Attachments:

PMI:

1. PMI Slide deck
2. PMI Proposed Rule
3. Response to Questions from HHS Counselor to the Secretary (June 2022): Proposed Rule entitled Medication Guides: Patient Medication Information

LDT:

4. LDT Slide deck