Guidance for Industry

Application of Current Statutory Authority to Nucleic Acid Testing of Pooled Plasma

DRAFT GUIDANCE

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Comments and suggestions regarding this draft document should be submitted within 60 days of publication of the *Federal Register* notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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Draft - Not for Implementation

GUIDANCE FOR INDUSTRY[1]

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I. SUMMARY

The purpose of this draft guidance document is to seek public comment on the development and implementation of nucleic acid testing for infectious agents, such as Human Immunodeficiency Virus (HIV), when such testing is intended for use in blood donor screening and/or manufacturing of blood products. The Food and Drug Administration (FDA) is issuing this draft guidance document in response to requests from manufacturers for guidance in the development of nucleic acid testing of pooled plasma for infectious agents. During the comment period, the agency will process submissions related to nucleic acid testing of blood and blood products under the investigational new drug provisions, [21 U.S.C. 355(i)] and 21 CFR part 312.

II. INTRODUCTION

Current data suggests that nucleic acid testing may be of value in the detection of infectious agents in blood and plasma. To date, there are no approved nucleic acid tests for blood donor screening, but manufacturers are developing investigational nucleic acid tests for the detection of infectious agents in pooled plasma. Manufacturers and other interested parties have inquired how the agency intends to regulate nucleic acid testing of plasma pools. While the agency considers such testing to be an interim step, and seeks to encourage the development of nucleic acid tests to screen individual donations, FDA also encourages the development of nucleic acid tests of pooled plasma as donor screening tests that would allow for donor deferral, donor notification and counseling, and "lookback" activities, including retrieval of implicated products and notification of transfusion recipients.

Assays used to detect a virus in plasma from blood donors (e.g., HIV antigen test, hepatitis B surface antigen test) are regulated by FDA and required to be licensed under section 351 of the Public Health Service Act (PHS Act), [42 U.S.C. 262]. Consistent with the regulation of other donor screening tests for infectious agents, FDA believes nucleic acid tests for testing plasma pools should be licensed. In order to

[1]This draft guidance document represents the agency's current thinking regarding nucleic acid testing of pooled plasma for viral detection in blood and blood products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

gather information to support the effectiveness (including the sensitivity and specificity) of such tests, FDA believes clinical studies should be performed under an investigational new drug (IND) application and results should be submitted to support approval of the test under a Biologics License Application (BLA).

III. BACKGROUND

Nucleic acid tests are biological products within the "biological products" definition contained in the Public Health Service Act[2]. Nucleic acid tests are also medical devices within the "device" definition contained in the Federal Food Drug and Cosmetic Act[3]. FDA has determined that submission of a BLA is necessary to ensure adequate review of the safety and effectiveness of *in vitro* tests, such as nucleic acid tests, used for donor screening and related blood banking practices.[4]

The Public Health Service Act provides that no person may introduce or deliver for introduction into interstate commerce any biological product unless a biologics license is in effect for the biological product [42 U.S.C. 262(a)(1)(A)]. However, 21 CFR 601.21 provides "[a] biological product undergoing development, but not yet ready for a product license, may be shipped or otherwise delivered from one State or possession into another State or possession provided such shipment or delivery" is made pursuant to the investigational new drug (IND) provisions of the Federal Food, Drug, and Cosmetic Act and related regulations, 21 CFR part 312.

These provisions are applicable to nucleic acid tests, since they are "biological products." Accordingly, until the tests are licensed as biological products, all distributions of the tests must be made in accordance with the IND regulations and provisions. In this draft guidance, FDA offers suggestions that

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[2]"[T]he term 'biological product' means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings" [42 U.S.C. 262(i)].

[3]"The term 'device' . . . means an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article, including any component, part, or accessory, which is (1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them, (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or (3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes" [21 U.S.C. 321(h)].

[4]See Intercenter Agreement dated October 31, 1991, between FDA's Center for Biologics Evaluation and Research and FDA's Center for Devices and Radiological Health.

sponsors of INDs and biologics license applicants may use in order to assure that the quality of the scientific evaluation of the nucleic acid test is adequate to permit an evaluation of the test's effectiveness and safety, see e.g., 21 CFR 312.22, and to assist in the development of data supporting a biologics license application. [See 42 U.S.C. 262(a)(2)(B)].

In September 1994, in response to increasing interest in applying nucleic acid tests to detect infectious agents in blood and blood products, FDA sponsored a "Conference on Feasibility of Genetic Technology to Close the HIV Window in Donor Screening" (59 FR 38983, August 1, 1994). At the time, the majority of participating experts expressed the opinion that nucleic acid techniques were not ready for use in large-scale. The meeting did renew interest in considering other direct viral detection methods for donor screening, such as tests for HIV-1 antigen, as an interim measure to further reduce the risk of HIV-1 transmission through blood and blood products. On August 8, 1995, FDA issued a guidance to all registered blood and plasma establishments entitled "Memorandum on the Recommendations for Donor Screening with a Licensed Test for HIV-1 Antigen" (61 FR 3042, January 30, 1996), that recommended screening of blood and plasma for HIV-1 antigen (in addition to tests for anti-HIV-1) as an interim measure pending the availability of better technology to detect the virus.

In December 1994, FDA advised manufacturers that it believed that one nucleic acid test, polymerase chain reaction testing for Hepatitis C Virus, should be instituted as an additional lot-release test for final containers of certain fractionated immune globulin products. Because final container testing may not be as sensitive as testing of unfractionated plasma, ongoing efforts to improve the safety of plasma products have led to the suggestion that nucleic acid testing methods be applied instead to small pools of plasma prior to fractionation. Manufacturers have approached FDA about using nucleic acid technology to test plasma pools to detect infectious agents.

In 1996, FDA approved a nucleic acid test for quantitation of viral ribonucleic acid (RNA) in the plasma of persons infected with HIV as an aid in determining patient prognosis. Neither this test, nor any other nucleic acid test, has been approved by FDA for blood donor screening to date. At present these methods may not be practical to permit large-scale testing of individual units of blood or plasma.

FDA notes that nucleic acid testing has been recommended for a range of numbers of pooled samples. The upper limit on this size range may be affected by the sensitivity of the test, the ability of the manufacturer to track and quarantine units, and the need to destroy positive pools without depleting the supply of blood products. The greatest public health benefit will come from testing of plasma pools of a size that allows identification of an individual positive unit(s). FDA believes that the donor(s) of a positive unit should be considered positive for the infectious agent, e.g., HIV, and implementation of donor deferral, donor notification and counseling, and retrieval of implicated products should occur.

IV. REGULATORY CONCERNS

This document represents the agency's current thinking regarding the development and implementation of nucleic acid testing of pooled plasma in further improving the safety of the nation's blood products. FDA views it as essential that nucleic acid tests be sensitive, specific, reproducible, consistently manufactured,

and in compliance with current good manufacturing practices (cGMPs). It is also important to ensure that the implementation of the testing be done in a way that permits optimal product safety and donor tracking and notification. These criteria should be demonstrated in studies conducted under an IND application by the test manufacturer (whether a blood establishment, a manufacturer of plasma derivatives, kit manufacturer, or independent testing laboratory). Information obtained in these studies would support safety and efficacy of the test for the purpose of filing license applications. Other important issues to be addressed in the IND clinical studies and license application include the impact of sample pool size on the sensitivity of the test, the validation of primer pairs including their ability to detect virus variants, specimen and reagent stability, intra-assay and inter-assay reproducibility, validation of instruments and software, lot-release requirements, interfering substances, and more. Further information specific to testing for HIV-1 is available from FDA in a draft guidance document entitled "Guidance for Industry in the Manufacture and Clinical Evaluation of *In Vitro* Tests to Detect Nucleic Acid Sequences of Human Immunodeficiency Virus Type 1" announced in the *Federal Register* of July 10, 1998 (63 FR 37402), and the document entitled "Points to Consider in the Manufacture and Clinical Evaluation of *In Vitro* Tests to Detect Antibodies to the Human Immunodeficiency Virus Type 1" announced in the *Federal Register* of November 28, 1989 (54 FR 48943).

A. Recommendations for the Manufacturer of a Plasma-Derived Product Being Tested by a Nucleic Acid Test

FDA considers the addition of nucleic acid testing to donor screening in the manufacture of a product to be a major change in manufacturing that should be reported and approved as a prior approval supplement before distribution of the product (21 CFR 601.12(b)). Accordingly, plasma collection centers, fractionators, or manufacturers of plasma-derived products who wish to test plasma or pools of plasma using nucleic acid testing, should file a supplement to each approved application. Individually licensed products may be cross-referenced in a single supplement. The supplement should include information on validation of instrumentation and software, pooling methods for sample testing, tracking, and cGMPs. Also, the applicant should discuss how identification of positive units and procedures for donor notification will be performed. FDA is prepared to approve the supplement for the final manufactured plasma derivative while clinical studies of nucleic acid tests on plasma pools are ongoing under an IND.

FDA does not consider final product testing of products made from pooled plasma to be donor screening, because it may be extremely difficult to ascertain the identity of individual donors. Therefore, reagents and procedures used in final product testing need not be licensed separately as screening tests. However, manufacturers instituting final product testing should submit supplements to their license applications documenting and validating implementation of this testing as an additional analytical test on the final product.

B. Recommendations for the Manufacturer of a Nucleic Acid Test for Plasma-Derived Product(s)

FDA recognizes that the complexities of conducting accurate nucleic acid testing may require specialized laboratories and that manufacturers may wish to pursue different testing formats. In all cases, FDA would expect the blood product manufacturer to file a supplement for each licensed product. The supplement would describe the nucleic acid test to be performed, and would include a validated mechanism for identifying positive units and notifying donors (as discussed in the preceding section). In all cases, studies validating the performance of the nucleic acid testing system would be performed under an approved IND. This IND may be submitted by the blood product manufacturer, jointly with an independent laboratory or test manufacturer, or separately by an independent laboratory or test manufacturer.

To address regulatory requirements that are in addition to those described in the previous paragraph, FDA suggests four different regulatory approaches that may be used to obtain approval of a license for nucleic acid testing of pooled plasma.

One approach would allow the blood product manufacturer to take full responsibility for testing. In this case, the blood product manufacturer would submit an IND application describing manufacturing, preclinical data, and proposed clinical validation of the test procedure. Once the blood product manufacturer had gathered sufficient data, the blood product manufacturer would file a BLA containing manufacturing details and clinical trial data in support of the application for licensure of the testing procedure. The blood product manufacturer would assume responsibility for the quality of the test employed and the testing process. In addition, other manufacturers who wished to use this test pursuant to an agreement with the blood product manufacturer, would file individual application supplements for each product, reporting the testing to FDA as a manufacturing change. In order to verify the reliable performance of the test after licensing, FDA would provide reference panels to the manufacturers. The manufacturers would conduct the nucleic acid testing on the reference panels. If the test accurately identified infectious agents in the reference panel, then the related product lots could be released.

Alternatively, if the manufacturer of a blood product wished to send plasma or small pools of plasma to an independent testing laboratory, the testing laboratory would conduct testing under an IND, and would file a BLA containing manufacturing details and clinical trial data in support of the application for licensure of the testing procedure. The testing laboratory would assume responsibility for the quality of the test employed and the testing process. After licensing, the testing laboratory could provide testing services to many blood product manufacturers. The blood product manufacturer would submit individual application supplements for each product for which the licensed nucleic acid test method would be used. Once again, FDA would monitor performance of the test after licensing by requiring, as a condition of lot release, testing of reference panels provided by FDA.

In a third scenario, the blood product manufacturer might develop an in-house nucleic acid

test, with an arrangement to have reactive samples retested by an independent testing laboratory. FDA would regard this arrangement as shared manufacturing. The blood product manufacturer would submit preclinical data and evidence that the "in-house" nucleic acid test was no less sensitive, analytically, than that of the "outside" test laboratory and would be responsible for control of the "in-house" reagents. Both the blood product manufacturer and the independent laboratory would conduct studies under either a joint or separate INDs. The independent laboratory would submit a BLA for licensure of the "outside" test and the blood product manufacturer would submit a BLA supplement for the "in-house" test. The combined tests would be licensed under shared manufacturing for use as a donor screening test. The post-market performance of the combined test method would be monitored by lot-release testing using reference panels provided by CBER.

A fourth approach involves the use of a nucleic acid test kit developed independently and shipped for use by a blood product manufacturer. In this case, the test kit manufacturer would file an IND, followed by a BLA, either jointly with the blood product manufacturer or separately. Performance of the test kit would be subject to lot-release testing by CBER.