Guidance for Industry

Recommendations for the Assessment of Blood Donor Suitability, Blood Product Safety, and Preservation of the Blood Supply in Response to Pandemic (H1N1) 2009 Virus

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
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Guidance for Industry

Recommendations for the Assessment of Blood Donor Suitability, Blood Product Safety, and Preservation of the Blood Supply in Response to Pandemic (H1N1) 2009 Virus

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I. INTRODUCTION

This guidance document provides recommendations for assessing blood donor suitability and blood product safety and maintaining blood and blood product availability in response to pandemic (H1N1) 2009 virus. It is intended for establishments that manufacture Whole Blood and blood components intended for use in transfusion and blood components intended for further manufacture, including recovered plasma, Source Plasma and Source Leukocytes. Within this guidance, "you" refers to blood establishments; "we" refers to FDA.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

A. Epidemiology and Pathogenesis

The 2009 H1N1 pandemic is caused by a novel influenza A virus of swine origin. On April 26, 2009, then Department of Health and Human Services (DHHS) Acting Secretary Charles E. Johnson, pursuant to section 319 of the Public Health Service Act, 42 U.S.C. § 247d, declared a public health emergency when a novel swine-origin 2009 influenza A (H1N1) virus was identified in California, Texas, Kansas, and New York. The pandemic influenza H1N1 virus has since spread quickly to all fifty states and globally. In June 2009, the World Health Organization (WHO) declared a Phase 6 Level of Pandemic Influenza Alert. This declaration was based upon a standard definition reflecting worldwide spread of the pandemic (H1N1) 2009 virus and the observed

efficiency of human to human transmission. Importantly, a declaration of a pandemic is independent of the severity of illness caused by the virus or the degree of infrastructure disruption. On July 24 2009, DHHS Secretary Kathleen Sebelius renewed DHHS' April 2009 determination that a public health emergency exists nationwide involving pandemic influenza H1N1 that has significant potential to affect national security.

From April 15, 2009 to July 24, 2009, states reported to the Centers for Disease Control and Prevention (CDC) a total of 43,771 confirmed and probable cases of novel influenza A (H1N1) infection. Of these cases reported, 5,011 people were hospitalized and 302 people died.[1,2] From August 30, 2009 to October 24, 2009, 25,985 hospitalizations and 2,916 deaths attributed to influenza and influenza-like illnesses have been reported in the United States (U.S.). CDC has developed a model to estimate the true number of cases in the U.S. The model took the number of cases reported by states and adjusted the figure to account for known sources of underestimation (e.g., not all people with pandemic influenza H1N1 seek medical care, and not all people who seek medical care have specimens collected by their health care providers). Using this approach, it is estimated that more than one million people became infected with novel influenza A (H1N1) between April and June 2009 in the U.S.[3]

The symptoms of human influenza disease caused by pandemic (H1N1) 2009 virus are similar to the symptoms of seasonal flu and include fever, cough, sore throat, runny or stuffy nose, body aches, headache, chills and fatigue. A significant number of people who have been infected with pandemic (H1N1) 2009 virus also have reported diarrhea and vomiting.[4]

The most severe outcomes have been reported among individuals with underlying health problems that are associated with high risk of influenza complications. Pandemic (H1N1) 2009 virus currently remains sensitive to oseltamivir (Tamiflu) and zanamivir (Relenza), though sporadic cases of resistance to oseltamivir have been reported. At this time, there is insufficient information to predict how severe the pandemic (H1N1) 2009 virus outbreak will be in terms of illness and death or infrastructure disruption, or how it will compare with seasonal influenza.

B. Potential Impact of the H1N1 Pandemic on Blood Product Safety and Availability

There is limited information available on pandemic (H1N1) 2009 virus viremia, especially during the asymptomatic period. No case of transfusion transmitted seasonal

[1] http://www.cdc.gov/h1n1flu/update.htm, (Accessed Nov. 2, 2009).
[2] CDC discontinued reporting of confirmed and probable cases of novel H1N1 infection on July 24, 2009. The most recent total numbers of hospitalizations and deaths due to H1N1 are available on the CDC website. http://www.cdc.gov/h1n1flu/update.htm, (Accessed Nov. 2, 2009).
[3] http://www.cdc.gov/h1n1flu/surveillanceqa.htm, (Accessed Nov. 2, 2009).
[4] http://www.cdc.gov/h1n1flu/sick.htm, (Accessed Nov. 2, 2009).

influenza has ever been reported in the U.S. or elsewhere, and, to date, no cases of transfusion transmitted pandemic influenza H1N1 have been reported. At this time, the pandemic (H1N1) 2009 virus has not been isolated from blood or serum of asymptomatic, infected individuals; however, studies are ongoing. Furthermore, the potential for transmission of pandemic influenza H1N1 through blood transfusion remains unknown.

In some previous studies, other Influenza A viruses were isolated from blood, and throat secretions or nasopharyngeal mucosa of children with clinical manifestations of influenza (Refs. 1-2). The virus was isolated from blood and throat washings of 1/29 healthy asymptomatic contacts who became ill 12 hours after the specimens were obtained (Ref. 3). From another study, virus isolation was reported from lungs, adrenals and meninges (from autopsy) which indicated that viremia must have been present (Ref. 4). In humans experimentally infected by nasal inoculation, viremia was observed in 4/15 subjects using sensitive culture methods. Symptoms occurred 2 days after initial viremia and one patient remained asymptomatic throughout the study period (22 days) (Ref. 5). However, other investigators were unable to detect viremia in 27 subjects using a similar virus strain and assay methods (Ref. 6).

The pandemic influenza H1N1 virus is a large lipid-enveloped virus. Validation studies performed by product manufacturers have shown that viruses with similar characteristics to the pandemic influenza H1N1 virus are effectively inactivated and/or removed during manufacturing of plasma derivatives.

Due to its known potential for rapid spread, pandemic (H1N1) 2009 virus has the potential to cause disruptions in the blood supply. A significant number of blood donors, blood establishment staff, and vendors of blood-related supplies (e.g., manufacturers of reagents and blood bags) could be affected as individuals become ill or need to care for ill family members. At the same time, during a widespread outbreak of disease caused by the pandemic (H1N1) 2009 virus, it is anticipated that the demand for blood and blood components may be reduced due to postponement of elective surgery, were that to become necessary in some affected healthcare settings.

In addition, the usual paradigm for ensuring blood availability in response to local disasters (i.e., hurricanes) may not be available under severe pandemic scenarios. In local disasters, interregional transfer of blood from unaffected to affected areas has been an effective strategy. However, in a more severe pandemic scenario, international, national, and regional outbreaks may occur simultaneously and a pandemic wave may last for months. Therefore, advanced planning is reasonable to prepare for the possible need to mitigate the effects of a more severe pandemic and to help ensure that blood is available in affected areas

Standard precautions for avoidance of contact with respiratory secretions may help to reduce the transmission of pandemic (H1N1) 2009 virus in blood and plasma collection establishments. The CDC has issued recommendations for infection control in the

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community[5], places of business[6], and in health care settings[7]. CDC also has issued "Interim Infection Control Guidance on 2009 H1N1 Influenza for Personnel at Blood and Plasma Collection Facilities."[8] We recognize the importance of the CDC recommendations for infection control in blood and plasma collection establishments.

III. RECOMMENDATIONS

FDA, in communication with DHHS Office of Public Health and Science, CDC, and the AABB Interorganizational Task Force on Pandemic Influenza and the Blood Supply, monitors blood availability closely. Similarly, we anticipate that you will maintain close communications with your hospital customers to anticipate demand for blood and blood components.

While shortages are not forecast at present, we are reminding you of regulatory pathways and providing regulatory clarification that may be helpful to you both in dealing with the current outbreak and in continuing to stay prepared.

We will continue to review any new scientific information about the potential risk of transfusion transmission of pandemic (H1N1) 2009 virus. We also will monitor closely the impact of the pandemic on blood availability. As our knowledge base grows, we may revise the recommendations in this guidance document as appropriate.

A. Training of Back-Up Personnel

Under 21 CFR 211.25 and 21 CFR 606.20, personnel performing critical functions in blood establishments must be adequate in number, educational background, training and experience, including professional training as necessary, or combination thereof, to assure competent performance of their assigned functions. Given the unknown extent of the disease caused by pandemic (H1N1) 2009 virus, we recommend that you have adequate back-up personnel, in the event of anticipatable personnel shortages. We further recommend that where possible, more than one back-up person should be trained for each critical function. Any such back-up personnel should be trained pursuant to your existing training program. We also recommend that as provided in your training program, you document this training and/or re-training.

[5] http://www.cdc.gov/h1n1flu/guidance/exclusion.htm, (Accessed Nov. 2, 2009).
[6] http://www.cdc.gov/h1n1flu/business/guidance, (Accessed Nov. 2, 2009).
[7] http://www.cdc.gov/h1n1flu/guidelines_infection_control.htm, (Accessed Nov. 2, 2009).
[8] http://www.cdc.gov/h1n1flu/guidance/blood_facilities.htm.

B. Blood Donor Suitability, Donor Deferral and Product Management

Blood Donor Suitability

In general, a donor medical history is obtained at the time of blood collection. However, under 21 CFR 640.3(a) and 21 CFR 640.63(a), the suitability of a donor as a source of Whole Blood or Source Plasma, must be made on the *day of collection* from the donor. These regulations do not explicitly define the term *day of collection.* Occasionally, donor's responses to the donor questions presented before collection are found to be incomplete upon review by the blood establishment. You may clarify a donor's response to the donor history questionnaire or obtain omitted responses to questions within 24 hours of the collection.

Blood Donor Deferral

- Under current FDA regulations, blood donors must be in good health, as indicated in part by normal temperature and free of acute respiratory diseases on the day of collection (21 CFR 640.3(a), (b)(1) and (4) and 21 CFR 640.63(a), (c)(1) and (7)).

- Available data do not currently support donor deferral for exposure to or contact with a person who has confirmed or probable pandemic (H1N1) 2009 influenza or influenza-like symptoms.

- To ensure donors are in good health on the day of donation as required under 21 CFR 640.3(b) and 21 CFR 640.63(c), donors with a confirmed or probable case of pandemic (H1N1) 2009 virus infection should be deferred until at least 24 hours after they are free of fever without the use of fever reducing medications[9] and they are otherwise asymptomatic.

- Available data do not support the deferral of donors following vaccination with live attenuated influenza vaccines (LAIV) or inactivated influenza vaccines against pandemic (H1N1) 2009 virus or for prophylactic use of the antiviral medications oseltamivir (Tamiflu) and zanamivir (Relenza). However, consistent with the recommendation above, donors taking antiviral medications for confirmed or probable pandemic (HIN1) 2009 virus infection should be deferred until at least 24 hours after they are free of fever without the use of fever reducing medications[10] and they are otherwise asymptomatic.

[9] A daily dose of pediatric aspirin (81 mg) is not considered fever-reducing medication.
[10] A daily dose of pediatric aspirin (81 mg) is not considered fever-reducing medication.

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Blood Product Management

The recommendations in this section apply to donations of Whole Blood and blood components intended for transfusion. This section does not apply to blood components intended for further manufacture (recovered plasma, Source Plasma, Source Leukocytes) since validation studies have shown that viruses with similar characteristics to pandemic (H1N1) 2009 virus are effectively inactivated and/or removed during manufacturing of plasma derivatives.

- Upon receipt of post donation information about a donor with confirmed or probable pandemic (H1N1) 2009 disease or influenza like illness within 48 hours after the donation, the Medical Director should evaluate the safety of the previously donated products consistent with existing Standard Operating Procedures (SOPs).

C. Changes to an Approved Application

As provided under 21 CFR 601.12(c)(5), we have determined that the following changes to an approved application for licensed blood establishments may be submitted as a "Supplement-Changes Being Effected".

- Use of a different outside test lab, provided the test lab is registered with FDA and has been performing donor testing.
- Implementation of self-administered donor history questionnaires, provided you follow the critical control points described in FDA's "Guidance for Industry: Streamlining the Donor Interview Process: Recommendations for Self-Administered Questionnaires" (July 2003), and the submission contains the content recommended for all self-administered procedures and computer assisted interactive procedures outlined in the same guidance.

The recommendations set forth above supersede the recommendations in FDA's "Guidance for Industry: Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture" (July 2001) at section IV.C and FDA's "Guidance for Industry: Streamlining the Donor Interview Process: Recommendations for Self-Administered Questionnaires" (July 2003) at section IV.A, respectively (in both of these guidances, we previously had determined that these changes would require a "Supplement – Changes Being Effected in 30 Days").

IV. BIOLOGIC PRODUCT DEVIATION AND FATALITY REPORTING

Licensed manufacturers, unlicensed registered blood establishments, and transfusion services are subject to reporting requirements with respect to the reporting of product deviations under

21 CFR 606.171. Blood establishments are not expected to submit biological product deviation reports for post-donation information related to pandemic (H1N1) 2009 virus. If a complication of blood transfusion results in the fatality of a recipient, blood establishments must report the fatality to FDA as soon as possible (21 CFR 606.170(b)).

V. COLLECTION AND USE OF CONVALESCENT PLASMA

Plasma obtained after recovery from an acute infection (convalescent plasma) generally contains highly-specific antibodies directed at the infectious agent, and has theoretical potential to serve as a therapeutic product. In consideration that circumstances could arise where vaccines and antiviral drugs might not be sufficiently available, or where a patient is not responding to approved therapies, transfusion of convalescent plasma has been discussed as a possible empirical treatment during an influenza pandemic. (Ref. 7-8)

In July 2009, the WHO Blood Regulators Network issued a position paper[11] on the collection and use of convalescent plasma as an element in pandemic influenza planning. This paper recommends that scientific studies on the feasibility and medical effectiveness of the collection and use of convalescent plasma, and possibly fractionated immunoglobulins, should be explored through clinical trials. FDA encourages the development of new, safe and effective therapies for influenza. Because of its experimental nature, collection and administration of convalescent plasma should be conducted only under an Investigational New Drug Application. Blood establishments that intend to manufacture convalescent plasma should contact FDA to discuss their plans.

VI. IMPLEMENTATION

This guidance has been issued for comment purposes only.

[11] http://www.who.int/bloodproducts/brn/BRNPosition-ConvPlasma10July09.pdf, (Accessed Nov. 2, 2009).

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研究報告の概要

多くの生物種に影響を及ぼしている致死的な神経組織障害である伝染性海綿状脳症（TSEs）において、病原性の重要因子は宿主にコードされている正常型プリオン蛋白（PrP^{C}）の異常型アイソフォーム（PrP^{Sc}）の蓄積である。PrP^{C} から PrP^{Sc} への変換についての正確な機序は理解されていないが、宿主 PrP^{C} 発現はプリオン伝播に効果的な感染性プリオンの産生の必要条件であることは明らかである。哺乳類の TSEs については多くの研究が実施されているが、魚における TSE の病原性についてほとんどわかっていない。
ここで私達は、BSE 感染ウシ又はスクレイピー感染ヒツジより調製された脳ホモジネートを経口投与されたヨーロッパヘダイは臨床症状を現わさなかったが、投与 2 年後に採取されたヨーロッパヘダイの脳は神経変性の徴候と抗タイ PrP 抗体が上昇し陽性に反応する沈着物の蓄積を示したことを提示する。
非感染動物由来の脳を投与されたコントロール群はそのような徴候を示さなかった。
注目すべきことに、TSE 感染脳ホモジネートよりも BSE 感染物質を投与された魚に多数のプロテアーゼ K 抵抗性の沈着物が急速かつ広範囲に現れた。これらのプラーク様凝集はコンゴ好染性と偏光下における複屈折を示し、アミロイド様成分と一致した。プリオン、特に BSE を投与された魚の脳における神経変性と異常な沈着物は公衆衛生上の潜在的リスクに関する懸念を増大させる。
魚の養殖はヒトや他の動物種に対する高タンパク栄養源を供給する経済的で重要な産業であり、感染性哺乳動物 PrP^{Sc} に汚染されている養殖魚におけるプリオン病発生の予測は気がかりであり、更なる評価が必要である。

使用上の注意記載状況・その他参考事項等

代表としてテタノブリン IH 静注 250 単位の記載を示す。
2. 重要な基本的注意
(1)略
1)略
2)現在までに本剤の投与により変異型クロイツフェルト・ヤコブ病（vCJD）等が伝播したとの報告はない。しかしながら、製造工程において異常プリオンを低減し得るとの報告があるものの、理論的な vCJD 等の伝播のリスクを完全には排除できないので、投与の際には患者への説明を十分行い、治療上の必要性を十分検討の上投与すること。

報告企業の意見	今後の対応
BSE 感染ウシ及びスクレイピー感染ヒツジの脳ホモジネートを経口投与されたヨーロッパヘダイの脳は神経変性と抗タイ PrP 抗体に反応する沈着物の蓄積を示し、公衆衛生上の潜在的リスクに関する懸念を増大させる可能性があるとする報告である。 血漿分画製剤は理論的なvCJD伝播リスクを完全には排除できないため、投与の際には患者への説明が必要である旨を2003年5月から添付文書に記載している。2009年2月17日、英国健康保護庁(HPA)はvCJDに感染した供血者の血漿が含まれる原料から製造された第Ⅷ因子製剤の投与経験のある血友病患者一名から、vCJD異常プリオン蛋白が検出されたと発表したが、弊社の原料血漿採取国である日本及び米国では、欧州滞在歴のある献（供）血希望者を一定の基準で除外し、また国内でのBSEの発生数も少数であるため、原料血漿中に異常型プリオン蛋白が混入するリスクは1999年以前の英国に比べて極めて低いと考える。また、製造工程においてプリオンが低減される可能性を検討するための実験を継続して進めているところである。	本報告は本剤の安全性に影響を与えないと考えるので、特段の措置はとらない。

抗破傷風人免疫グロブリン

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Evaluation of the Possible Transmission of BSE and Scrapie to Gilthead Sea Bream (*Sparus aurata*)

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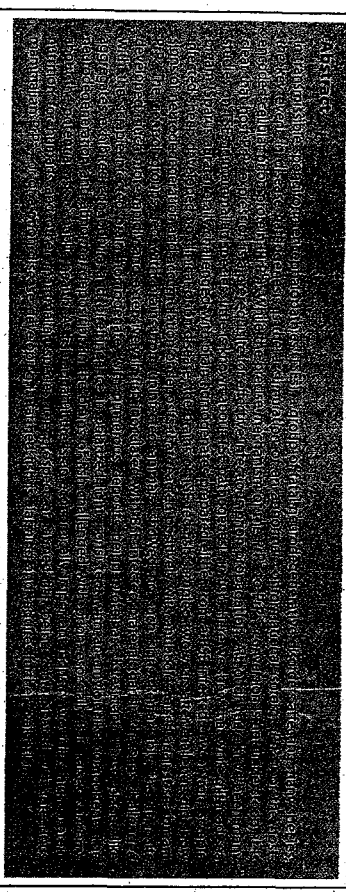

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Introduction

Transmissible spongiform encephalopathies or prion diseases are a group of fatal neurodegenerative disorders, including Creutzfeldt-Jakob disease (CJD), Fatal Familial Insomnia (FFI) and Gerstmann-Sträussler-Scheinker disease (GSS) in humans, scrapie in sheep and goats and bovine spongiform encephalopathy (BSE) in cattle [1].

The transmission of clinical prion diseases is limited by the so-called "species barrier" to conversion of endogenous host prion protein (PrP^{C}) to its abnormal, partially proteinase K-resistant conformational isoform, PrP^{Sc}. When high enough, this "barrier" can greatly impair or prevent potential interspecies transmissions, even under optimal conditions of dose and infection route. However, evidence of TSE replication without accompanying symptoms of clinical disease has prompted debate on the existence of asymptomatic infected individuals in an exposed population [2,3].

The identification of apparent PrP orthologues in lower vertebrates, including fish [4–16], raises the question of their susceptibility to prion diseases. While fish PrP-like sequences do not share high homology with their mammalian relatives (Table S1), they do contain several strongly conserved prion protein structural motifs [17]. Although mammalian to fish TSE transmission is considered unlikely [18], it is not certain that the species barrier would be high enough to prevent TSE transmission to fish.

The BSE epidemic has been linked to TSE-infected cattle feed [19] and the recognition of BSE in domestic cattle inevitably raised concerns about the potential risk to other ruminant and