別紙様式第2-1

No. 31

医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
				2009. 3. 18	該当なし	
一般的名称	解凍人赤血球濃厚液		研究報告の公表状況	山田典栄, 四柳宏, 小板橋俊, 長瀬良彦, 高橋秀明, 奥瀬千晃, 安田清美, 鈴木通博, 伊東文生, 飯田清美, 飯野四郎, 小池和彦. 第37回日本肝臓学会東部会; 2008 Dec 3-4; 東京.	公表国 日本	
販売名(企業名)	解凍赤血球濃厚液「日赤」(日本赤十字社) 照射解凍赤血球濃厚液「日赤」(日本赤十字社) 解凍赤血球-LR「日赤」(日本赤十字社) 照射解凍赤血球-LR「日赤」(日本赤十字社)					

研究報告の概要

○首都圏におけるB型急性肝炎の最近の動向

目的:わが国のB型急性肝炎(AH-B)はいまだ減少傾向にない。近年は慢性化率の高いgenotype AによるAH-Bが増加している。今回、2006年以降のB型急性肝炎の実態を2005年以前と比較し、現行のHBワクチンの有効性について検討した。

方法:首都圏3施設において診療したAH-B146例(1994-2005年109例、2006-2008年37例)に対しgenotype、感染経路、臨床経過を検討した。また、ワクチンの予防効果を検討するため63例に対し、a determinant regionのアミノ酸配列を決定した。

結果:(1)genotypeは1994-2005年ではA38%、B10%、C51%、D1%であった。2006-2008年ではA70.3%、B13.5%、C13.5%、F2.7%であり、Aの割合が急増していた。2006-2008年のgenotypeAの感染経路は同性間性交渉54%、異性間性交渉25%、不明21%であり、性交渉の相手は不特定の場合が多かったが、日本人特定パートナーからの感染を2例認めた。genotypeA26例中、慢性化1例、慢性化阻止のため核酸アナログを使用した2例を認めた。HIV抗体検査を37例中14例で施行し、陽性の2例はHBVgenotypeAだった。(2)ワクチン株3株間でAA126、131、143のアミノ酸配列の不一致を認めた。a determinant regionのアミノ酸配列は、genotype間で最高11個異なり、genotypeAの1例でVaccine-Induced Escape Mutantである145番のアミノ酸変異、genotypeCの4例で131番の変異を認めた。

考察:首都圏においてHBVgenotypeAは急増しており、新規日本人キャリアからの二次感染が疑われる。genotype間でアミノ酸配列は大きく異なり、ワクチンによる感染予防のためには十分な抗体価を誘導する必要がある。Vaccine-Induced Escape Mutantの蔓延状況を調査する必要がある。

結論:genotypeAのB型肝炎は急速に広がりつつあり、現行のワクチンの感染防御に関する検討、ユニバーサルワクチンを含めた感染対策の検討が必要である。

使用上の注意記載状況・その他参考事項等

解凍赤血球濃厚液「日赤」
照射解凍赤血球濃厚液「日赤」
解凍赤血球-LR「日赤」
照射解凍赤血球-LR「日赤」

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

報告企業の意見	今後の対応
首都圏においてHBVgenotypeAは急速に増加しており、新規日本人キャリアからの二次感染が疑われることが急性B型肝炎症例の検討から明らかになったとの報告である。	日本赤十字社では、HBs抗原検査及びHBc抗体検査を実施することに加えて、HBVについて20プールでスクリーニングNATを行い、陽性血液を排除している。また、これまでの凝集法と比べて、より感度の高い化学発光酵素免疫測定法(CLEIA)及び精度を向上させた新NATシステムを導入した。HBV感染に関する新たな知見等について今後も情報の収集に努める。

O-85 首都圏における B 型急性肝炎の最近の動向

○山田典栄1, 四柳 宏1, 小板橋俊1, 長瀬良彦2, 高橋秀明1, 奥瀬千晃1, 安田清美1, 鈴木通博1, 伊東文生1, 飯野四郎1, 小池和彦3
聖マリアンナ医大消化器・肝臓内科1, 東京大感染症内科2, 川崎市立多摩病院消化器肝臓内科3, 清川病態肝臓病研究センター4

【目的】わが国における B 型急性肝炎 (AH-B) はいまだ減少傾向にない. さらに近年は慢性化率の高い genotype A による AH-B が増加している. 今回, 2006 年以降の B 型急性肝炎の実態について調査し 2005 年以前と比較を行った. また, 現行の HB ワクチンの有効性について検討した.

【方法】首都圏 3 施設において診療した AH-B 146 例 (1994-2005 年 109 例, 2006-2008 年 37 例) に対し genotype, 感染経路, 臨床経過に関する検討を行った. また, ワクチンの予防効果を検討するため 63 例に対し, a determinant region のアミノ酸配列を決定した.

【結果】(1) genotype は 1994 年から 2005 年では type A 38%, type B 10%, type C 51%, type D 1% であった. 2006 年から 2008 年では type A 70.3%, type B 13.5%, type C 13.5%, type F 2.7% であり, type A の割合が急増していた. 2006 年から 2008 年の type A の感染経路は同性間性交渉 54%, 異性間性交渉 25%, 不明 21% であった. 性交渉の相手は不特定の場合が多かったが日本人特定パートナーからの感染を 2 例認めた. Type A 26 例中, 慢性化 1 例, 慢性化阻止のため核酸アナログを使用した症例 2 例を認めた. HIV 抗体検査を 37 例中 14 例で施行し 2 例で HIV 陽性でありいずれも HBVtype A であった. (2) ワクチン株 3 株間で AA126, 131, 143 のアミノ酸配列の不一致を認めた. A determinant region のアミノ酸配列は, genotype 間で最高 11 個異なり, アミノ酸の最大性・最小性および 2 次構造も異なっていた. また Type A の 1 例で Vaccine-Induced Escape Mutant として知られる 145 番のアミノ酸変異, type C の 4 例で 131 番のアミノ酸変異を認めた.

【考察】首都圏において HBV type A は急速に増加しており, 新規日本人キャリアからの二次感染が生じていることが疑われる. Genotype 間でのアミノ酸配列は大きく異なっており, ワクチン接種による B 型肝炎の予防のためには十分な抗体価を誘導する必要がある. また, Vaccine-Induced Escape Mutant の蔓延状況を調査する必要がある.

【結論】Genotype A の B 型肝炎は急速に広がりつつあり, 現行の HB ワクチンの感染防御に関するさらなる検討, およびユニバーサルワクチンを含めた感染対策を検討する必要がある.

O-86 抗 HIV 療法後の免疫再構築により B 型慢性肝炎の急性増悪をきたしたと考えられた 1 例

○吉野有紀子, 本間史子, 勅江恭子, 坂本夏美, 齋藤広信, 阿部和道, 高橋敏史, 横川眞子, 入澤篤志, 大平弘正
福島県立医科大学内科学第 2 講座

【症例】72 歳男性

【主訴】発熱

【既往歴】60 歳時: B 型慢性肝炎で 2 か月間入院. 輸血歴なし.

【家族歴】肝疾患なし.

【生活歴】喫煙: なし. 飲酒: 機会飲酒.

【海外渡航歴】60 歳頃から頻回にタイ, ミャンマーへ旅行.

【現病歴】

平成 19 年 2 月より 39℃ の発熱が出現し 4 月 11 日近医に入院. 抗生剤で改善に乏しく抗 HIV 抗体陽性であったため, 4 月 25 日当院内科を紹介された. 血液検査でトランスアミナーゼ正常, WBC 4100/μl, Ly 6% (CD4 39/μl), HBs 抗原陽性, HBs 抗体陰性, HBc 抗体陽性, HBe 抗原陰性, HBe 抗体陰性, HBV-DNA (TMA) 8.7 LGE 以上, HBV genotype, Ba, precore 野生型, core promotor 変異型, HAV IgM 陰性, HCV 抗体陰性, CMV IgM 陰性, CMV IgG 陽性, HIV-1 RNA 120,000 copies/ml であった. 5 月 16 日よりエムトリシタビン・フマル酸テノホビルジソプロキシル (TDF/FTC), リトナビル, 経口アタザナビルによる抗 HIV 療法が開始. 6 月 20 日, AST 92 IU/l, ALT 95 IU/l, ALP 309 IU/l, TB 22 mg/dl と肝障害が出現. HBV-DNA (TMA) は 5.8 LGE と低下していた. 7 月 4 日 AST 503 IU/l, ALT 657 IU/l, ALP 473 IU/l, TB 38 mg/dl と肝障害の増悪を認め当科紹介され入院.

【入院後経過】

肝機能障害の進行は CD4 の増加, HBV-DNA 量の低下の時期と一致しており, 抗 HIV 療法後の免疫再構築による B 型慢性肝炎の急性増悪と考えられた. TDF/FTC を内服していたため SNMC 投与にて経過観察していたところ肝機能は徐々に改善し 7 月 12 日に退院となった.

【考察】

HIV/HBV 重複感染患者における抗 HIV 療法は, HBV にも抗ウイルス効果を示す TDF を含む多剤併用療法 (HAART) が考慮される. HAART の効果がみられた際に, 免疫再構築に関連した免疫応答の改善が起こり, 細胞傷害性キラー T 細胞などを介する HBV 排除のため肝機能の悪化をみる場合がある. 本症例も臨床経過から免疫再構築による肝機能障害と考えられた. HIV/HBV 重複感染患者の治療は, 薬剤耐性の問題や HAART の longterm 使用に伴う HBV 増殖の問題などがあり, 個々の症例の病態に応じた治療計画が必要である. 当科で経験した HIV/HBV 重複感染患者の経過と問題点について若干の文献的考察を加えて報告する.

別紙様式第2-1

No. 11

医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
				2009. 4. 10	該当なし	
一般的名称	人赤血球濃厚液		研究報告の公表状況	FDA, CBER. Available from: http://www.fda.gov/cber/gdlns/chagas.htm	公表国 米国	
販売名(企業名)	赤血球濃厚液-LR「日赤」(日本赤十字社) 照射赤血球濃厚液-LR「日赤」(日本赤十字社)					

研究報告の概要

○業界向けガイダンス案－輸血用全血・血液製剤およびヒト細胞・組織およびヒト細胞・組織由来製剤(HCT/Ps)の*Trypanosoma cruzi*が伝播する危険性を低減するための血清学的検査の使用

FDAは、輸血用全血・血液成分製剤、ヒト細胞・組織及びヒト細胞・組織由来製剤(HCT/Ps)の*Trypanosoma cruzi* (*T. cruzi*)が伝播する危険性を低減するための血清学的検査実施を勧告する。

・全ての供血に対し、供血者血液を用いて認可された*T.cruzi*抗体のスクリーニングを行う。

・再検査にて*T.cruzi*抗体陽性となった供血者及びシャーガス病の既往がある供血者は供血無期延期とし、その旨を本人に通知する。

・認可された確認検査の手段が無いことから、再検査で陽性となった供血者についてのリエントリーは推奨しない。

・再検査で陽性となった供血者には、感染の可能性について通知し、専門医や地域の保健機関等を紹介し、医学的診断検査に基づいたカウンセリングを実施する。

・認可された試験法では、*T.cruzi*以外の病原体との交差反応が認められることがあるため、リーシュマニア症等の*T.cruzi*以外の病原体への曝露や、スクリーニング検査の偽陽性などについても検討することが望ましい。

・再検査にて陽性となった供血者の一連の供血については製剤を確保し、廃棄又は研究用に転用とする。

・過去の供血についてはルックバック(製剤の回収と受血者への通知)を実施する。

・認可された*T.cruzi*検査法を用いて血液検査を行うこと。認可された検査法以外であっても、*T.cruzi*抗体陰性となった場合は、ドナーの適格性決定に使用してよい。陽性となった場合はドナー不適格とする。

報告企業の意見	今後の対応
米国FDAより、輸血用全血・血液成分製剤、ヒト細胞・組織及びヒト細胞・組織由来製剤(HCT/Ps)の*Trypanosoma cruzi*が伝播する危険性を低減するための血清学的検査実施についてのガイダンス草案が策定されたとの報告である。	日本赤十字社は、輸血感染症対策として献血時に海外渡航歴の有無を確認し、帰国(入国)後4週間は献血不適としている。また、シャーガス病の既往がある場合には献血不適としている。日本在住の中南米出身献血者については、厚生労働科学研究「献血血の安全性確保と安定供給のための新興感染症等に対する検査スクリーニング法等の開発と献血制限に関する研究」班と共同して検討する予定である。今後も引き続き情報の収集に努める。

使用上の注意記載状況・その他参考事項等

赤血球濃厚液-LR「日赤」
照射赤血球濃厚液-LR「日赤」

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

(2)

Guidance for Industry

Use of Serological Tests to Reduce the Risk of Transmission of *Trypanosoma cruzi* Infection in Whole Blood and Blood Components for Transfusion and Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

DRAFT GUIDANCE

This guidance document is for comment purposes only.

Submit comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this draft guidance are available from the Office of Communication, Outreach and Development (OCOD) (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

For questions on the content of this guidance, contact OCOD at the phone numbers listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
March 2009

TABLE OF CONTENTS

Guidance for Industry

Use of Serological Tests to Reduce the Risk of Transmission of *Trypanosoma cruzi* Infection in Whole Blood and Blood Components for Transfusion and Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

We, FDA, are notifying you, establishments that manufacture Whole Blood and blood components intended for use in transfusion, and establishments that make eligibility determinations for donors of HCT/Ps, about FDA approval of a Biologics License Application (BLA) for an enzyme-linked immunosorbent assay (ELISA) test system for the detection of antibodies to *Trypanosoma cruzi* (*T. cruzi*). This test is intended for use as a donor screening test to reduce the risk of transmission of *T. cruzi* infection by detecting antibodies to *T. cruzi* in plasma and serum samples from individual human donors, including donors of Whole Blood and blood components intended for use in transfusion, and HCT/P donors (living and cadaveric (non-heart beating)). This guidance document does not apply to the collection of Source Plasma.

In addition, we are providing you with recommendations for unit and donor management, labeling of Whole Blood and blood components, and procedures for reporting implementation of a licensed *T. cruzi* test at your facility or at your contract testing laboratory, as required for blood establishments under Title 21 Code of Federal Regulations 601.12 (21 CFR 601.12). For establishments that make donor eligibility determinations for HCT/P donors, we are notifying you that we have determined *T. cruzi* to be a relevant communicable disease agent under 21 CFR 1271.3(r)(2), and are providing you with recommendations for testing and screening donors for antibodies to *T. cruzi*.

The recommendations made in this guidance with respect to HCT/Ps are in addition to recommendations made in the document entitled "Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)," dated August 2007 (Ref. 1).

We recommend that you implement the recommendations provided in this guidance within one year after a final guidance is issued.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe FDA'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 FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Chagas disease is caused by the protozoan parasite, *T. cruzi*. The disease is found primarily in Mexico and Central and South America; the pathogenic agent has rarely been reported to cause human infection in the United States (U.S.) by natural vector transmission (Ref. 2). Natural infections are transmitted mainly when the feces of certain blood sucking insects (triatomine bugs, commonly referred to as kissing or chinch bugs) that harbor the infection are rubbed into a bug bite, other wound, or directly into the eyes or mucous membranes. Other primary forms of transmission include congenital (mother to unborn infant), organ transplantation, and blood transfusion. Current estimates are that at least 11 million persons in Mexico and Central and South America carry the parasite chronically and could present a potential source of infection should they become donors. The presence of the pathogenic agent in U.S. and Canadian donors is increasing due to immigration of infected individuals from endemic areas. Some experts estimate that there may be as many as 100,000 persons unknowingly infected with *T. cruzi*, who reside in the U.S. and Canada.

Vector-borne infections are mostly mild in the acute phase and then persist throughout life, usually without symptoms. Acute infection in patients with compromised immune systems, for example, from cancer therapy or organ transplantation, can be very serious and sometimes fatal. Treatment options are limited, but are most effective early in the infection. The lifetime risk of severe cardiac complications (cardiomegaly, heart failure and arrhythmias) or intestinal disorders (megacolon, megaesophagus) in infected individuals averages about 30% (range of 10 to 40% depending on a variety of factors) and may occur many years after the initial infection. During the acute phase of vector-borne Chagas disease, parasites are found in skin lesions at the site of transmission. The parasites are then spread through the bloodstream to various tissues, particularly skeletal muscle (Ref. 3). During the chronic stage of Chagas disease, most persons who harbor the parasite are asymptomatic and unaware of their infection. During this phase, parasites have been demonstrated in muscle (especially cardiac muscle), nerves, and digestive tract, but there has been very little investigation of tissue distribution during that phase (Refs. 3 through 10).

A. Donor Screening Tests for Chagas Disease in the United States

At the September 1989 Blood Products Advisory Committee (BPAC) meeting, the committee recommended testing donors of Whole Blood and blood components for Chagas disease when a suitable test became available. In a 1995 BPAC meeting, the committee considered whether the performance characteristics of the two FDA-approved tests then available for diagnosis of Chagas disease would be suitable for blood donor screening. The committee concluded that the tests discussed were not suitable for blood donor screening. Furthermore, the committee sought clarification of the criteria that FDA would use to license a Chagas test for donor screening. At the September 2002 meeting of BPAC, FDA presented its current considerations on the regulatory pathway and standards for licensing a donor screening test for Chagas disease and encouraged manufacturers to develop tests based on those considerations (Ref. 11).

In December 2006, FDA granted a license to one manufacturer of an ELISA test system for the detection of antibodies to *T. cruzi* in individual living blood and HCT/P donors. Since the end of January 2007, a number of blood centers representing a large proportion of U.S. blood collections have been testing donors using this licensed assay. In February 2009, FDA licensed this ELISA test system for the detection of antibodies to *T. cruzi* in cadaveric (non-heart beating) HCT/P donors.

Blood donor testing by an ELISA test system identifies donors that are repeatedly reactive for antibodies to *T. cruzi*. The presence of antibodies to *T. cruzi* is strong evidence that a donor is infected with this parasite. Most donors that are repeatedly reactive by an ELISA test system for antibodies to *T. cruzi* have chronic, asymptomatic infections acquired years earlier during residence in areas endemic for *T. cruzi*. Therefore, prior donations from a donor who is repeatedly reactive on an ELISA test system were likely to harbor *T. cruzi* parasites.

At the April 2007 BPAC meeting, FDA requested comments on scientific issues related to the implementation of blood donor testing for infection with *T. cruzi* (Ref. 12). Issues discussed by the committee included the need for additional data on the incidence and risk of transmission of *T. cruzi* by transfusion, the severity of Chagas disease, the performance of the antibody test, and, the lack of a licensed supplemental test for confirmatory testing.

The committee also commented on the design of research studies to validate a strategy for selective testing of repeat blood donors. The committee noted that a period of universal testing of all blood donors would generate critical data on the prevalence of *T. cruzi* infections in donors and that donor questions for selective donor screening needed validation.

B. Risk of *T. cruzi* Infection from Transfusion of Whole Blood and Blood Components

Blood donations from individuals from endemic areas are the primary source of risk for *T. cruzi* infection from transfusion. Studies in the mid-1990s (Ref. 1) estimated that the rate of seropositive blood donors in the U.S. ranged from 1 in 5400 to 1 in 25,000, depending on where the studies were conducted. However, more recent studies suggest that these rates have increased in the areas where donor testing has been performed over a period of time. For example, a rate of 1 in 2000 was found recently in the Los Angeles metropolitan area (Ref. 14). Transfusion transmission in endemic areas has been a major public health concern, and many countries considered endemic for *T. cruzi* infection screen blood donors for the presence of antibody. Therefore, in response to changes in donor demographics, we are now recommending blood donor testing in the U.S.

In the U.S. and Canada, only seven cases of transfusion-transmitted *T. cruzi* infections (Refs. 15 through 19) and five cases of infection from organ transplantation (Refs. 20 and 21) have been documented. However, transmission in immunocompetent patients is not likely to be apparent, and in many cases, even if symptoms appear, infection may not be recognized (Ref. 22).

Studies in blood centers which question donors about birth and/or residence in a *T. cruzi*-endemic country have shown such questions to be incompletely effective at identifying the seropositive donors. Studies also have looked at the rate of transfusion transmission from *T. cruzi* antibody-positive individuals. Published lookback studies in the U.S. and in Mexico of 22 transfusion recipients of seropositive donations, identified five of these recipients (22.7%) who later tested positive for antibodies suggesting transfusion transmission of *T. cruzi* (Refs. 18, 23 and 24). This transmission rate of 22.7% is consistent with the literature from Latin America on rates of blood-borne transmission from seropositive donors in Mexico and Central and South America (Ref. 25). However, we are aware that lookback studies conducted using the licensed ELISA test indicate that the risk of *T. cruzi* by transfusion of a seropositive unit in the U.S. may be much lower risk than previously thought. We note that these studies have confirmed the demographic characteristics of the typical seropositive donor as described in the first two paragraphs of section II. However, the data also suggest that there are seropositive individuals who acquired their infections within the U.S. (Ref. 26). Despite this new data, the rate of transfusion transmission of *T. cruzi* in the U.S. continues to be uncertain because of the limited number of studies conducted to date and the rate of transfusion transmission remains under investigation.

C. Risk of *T. cruzi* Infection to Recipients of Donated HCT/Ps

Based on the risk of transmission, severity of effect, and availability of appropriate screening measures and/or tests, we have determined *T. cruzi*, the agent for Chagas disease, to be a relevant communicable disease agent or disease under 21 CFR 1271.3(r)(2). This determination was based on the following information.

Contains Nonbinding Recommendations

Draft – Not for Implementation

1. Risk of Transmission

There is a risk of transmission of *T. cruzi* by HCT/Ps and there has been sufficient incidence and/or prevalence to affect the potential donor population.

Recognizing the risk of transmission from donated HCT/Ps, countries endemic for *T. cruzi* infection have instituted various practices to minimize transmission through transfusion or transplantation including screening donors for the presence of *T. cruzi* antibodies. Further, when human leukocyte antigen-matched bone marrow is obtained from an infected individual, the donor receives anti-parasitic treatment before the bone marrow is taken for transplantation. The World Health Organization recommends that:

- a heart from an infected donor not be transplanted;
- a liver from an infected donor only be transplanted to recipients already positive for Chagas disease, except in emergency cases; and
- when other organs are transplanted from a Chagas-positive donor, the recipient should receive prophylactic treatment for Chagas disease (Ref. 3).

Published data regarding the transmissibility of *T. cruzi* indicate that vertical transmission (congenitally from mother to infant), oral transmission (through breast milk or contaminated food) and conjunctival transmission (from contact with contaminated hands) have occurred (Ref. 3). In animal studies, *T. cruzi* has been shown to infect multiple tissues, including skeletal muscle, heart, bladder, peripheral nerve, liver, spleen, adrenal gland, brain, adipose tissue, ocular tissue, osteoblasts, chondroblasts, macrophages, and fibroblasts (Refs. 27 through 30). Human placental cells also have been experimentally infected with *T. cruzi* (Ref. 31). As noted previously in this section, *T. cruzi* has been transmitted via blood transfusions and organ transplantation (Refs. 20 through 22, and 32).

At the BPAC meeting of April 26, 2007, the committee noted that, though some HCT/Ps are processed in a manner that might inactivate *T. cruzi* in HCT/Ps from seropositive donors, current data are insufficient to identify specific effective processing methods that consistently render HCT/Ps free of *T. cruzi*. The committee concluded that, absent such data, it would be prudent to test HCT/P donors to decrease the risk of transmitting infection with *T. cruzi* (Ref. 12).

Information about prevalence of *T. cruzi* in the U.S. is provided in section II.B. of this document.

2. Severity of Effect

T. cruzi infections can be fatal or life-threatening, result in permanent impairment of a body function or permanent damage to a body structure, and/or necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

3. Availability of Appropriate Screening and/or Testing Measures

Appropriate screening measures have been developed for *T. cruzi*, such as the medical history interview. (Screening measures for *T. cruzi* are discussed in section IV.A. of this document.)

A donor screening test for *T. cruzi* has been licensed and labeled for use in testing blood specimens from living and cadaveric donors of HCT/Ps (see section IV.B. of this document). You must use a donor screening test for *T. cruzi* that is specifically labeled for cadaveric specimens instead of a more generally labeled donor screening test when applicable and when available (21 CFR 1271.80(c)). Current FDA-licensed, cleared or approved donor screening tests for use in testing HCT/P donors are listed at http://www.fda.gov/cber/tissue/prod.htm.

III. RECOMMENDATIONS FOR DONORS OF WHOLE BLOOD AND BLOOD COMPONENTS INTENDED FOR USE IN TRANSFUSION

A. Blood Donor Testing and Management

1. Donor Testing

We recommend testing of all donations of allogeneic units of blood using a licensed test for antibodies to *T. cruzi*. You must follow the regulations under 21 CFR 610.40(d) for determining when autologous donations must be tested.

2. Donor Deferral

We recommend that all donors who are repeatedly reactive on a licensed test for *T. cruzi* antibody or who have a history of Chagas disease be indefinitely deferred and notified of their deferral.

Contains Nonbinding Recommendations

Draft – Not for Implementation

3. Confirmatory Testing and Donor Reentry

At this time, there is no FDA licensed supplemental test for antibodies to *T. cruzi* that can be used for confirmation of true positive screening test results. FDA is not recommending reentry criteria for blood donors deferred indefinitely on the basis of a repeatedly reactive screening test for antibodies to *T. cruzi* due to the absence of a licensed supplemental test for antibodies to *T. cruzi*.

4. Donor Counseling and Physician Referral

We recommend that donors who are repeatedly reactive using a licensed test for antibodies to *T. cruzi* be informed about the likelihood and medical significance of infection with *T. cruzi*. Additional medical diagnostic testing may provide information useful in donor counseling.

All repeatedly reactive donors should be referred to a physician specialist. It also may be useful to refer them to their state and local health departments or to other appropriate community resources.

5. Further Testing of Repeatedly Reactive Donors for Cross–Reacting Diseases

Because the licensed test has demonstrated some reactivity in donors infected with pathogens other than *T. cruzi*, we recommend that medical follow up be considered for donors who are repeatedly reactive by the licensed test for antibodies to *T. cruzi* but who have no apparent basis for exposure to *T. cruzi* or who have negative results on more specific medical diagnostic tests. For example, testing for leishmaniasis may be appropriate in persons with geographic risk for exposure to *Leishmania* parasites and who appear to have a falsely reactive screening test for antibodies to *T. cruzi*.

B. Product Management

1. Index Donations

We recommend that blood components from repeatedly reactive index donations be quarantined and destroyed or used for research. Components determined to be unsuitable for transfusion must be prominently labeled: "NOT FOR TRANSFUSION," and the label must state the reason the unit is considered unsuitable (e.g., the component is positive for *T. cruzi* (21 CFR 606.121(f)).

2. Lookback (Product Retrieval and Recipient Notification)

Within 3 calendar days after a donor tests repeatedly reactive by a licensed test for *T. cruzi* antibody, you should:

- identify all in-date blood and blood components previously donated by such a donor, going back either 10 years (or indefinitely where electronic records are available), or else 12 months prior to the most recent time that this donor tested negative with a licensed test for *T. cruzi* antibody, whichever is the lesser period (the lookback period);
- quarantine all previously collected in-date blood and blood components held at your establishment; and
- notify consignees of all previously collected in-date blood and blood components to quarantine and return the blood components to you or to destroy them.

In addition, when you identify a donor who is repeatedly reactive by a licensed test for *T. cruzi* antibodies and for whom there is additional information indicating risk of *T. cruzi* infection, such as geographical risk for exposure in an endemic area, or medical diagnostic testing of the donor, we recommend that you:

- notify consignees of all previously distributed blood and blood components collected during the lookback period; and
- if blood or blood components were transfused, encourage consignees to notify the recipient's physician of record of a possible increased risk of *T. cruzi* infection.

We recommend that when there is additional information indicating risk of *T. cruzi* infection you make such notifications within 12 weeks of obtaining the repeatedly reactive test result.

There currently is no licensed *T. cruzi* supplemental test. When such a test is available, a positive test result will provide additional information indicating risk of *T. cruzi* infection.

Retrospective Review of Records

If you are a blood establishment that implemented screening with a licensed test for antibodies to *T. cruzi* prior to the effective date of this guidance, you may wish to perform a retrospective review of records to identify donors:

- with repeatedly reactive test results by a licensed test for *T. cruzi* antibodies; and
- for whom there is additional information indicating risk of *T. cruzi* infection, such as geographical risk for exposure in an endemic area, or medical diagnostic testing of the donor. There currently is no licensed *T.*

Contains Nonbinding Recommendations

Draft – Not for Implementation

If a donor is identified at risk of infection during the retrospective review, you may want to consider performing all the lookback actions described above.

3. Autologous Donations

Although autologous use of blood does not increase a patient's/donor's risk of illness from a pre-existing infection, FDA regulations under 21 CFR 610.40(d) and (e) require testing of autologous blood donors under certain circumstances to prevent inadvertent allogeneic exposures to unsuitable units.

a. We recommend that blood components from autologous donors that are repeatedly reactive by a licensed test for *T. cruzi* antibody be released for autologous use only with approval of the autologous donor's referring physician. Establishments should provide the results of additional testing for antibodies to *T. cruzi*, as available to the autologous donor's referring physician.

b. Each autologous donation must be labeled as required under 21 CFR 610.40(d)(4), as appropriate. Given the seriousness of *T. cruzi* infections, autologous donations that are repeatedly reactive by a licensed test for *T. cruzi* antibody must bear a biohazard label as required under 21 CFR 610.40(d)(4).

4. Circular of Information

Consistent with other donor screening tests, the instruction circular, also known as the "Circular of Information" must be updated to state that a licensed test for antibodies to *T. cruzi* was used to screen donors and that the results of testing were negative (21 CFR 606.122(h)).

5. Biological Product Deviation Report and Fatality Report

Under 21 CFR 606.171, licensed manufacturers, unlicensed registered blood establishments, and transfusion services must report any event and information associated with the manufacturing, if the event either represents a deviation from current good manufacturing practice, applicable regulations, applicable standards, or established specifications that may affect the safety, purity, or potency of the product; or represents an unexpected or unforeseeable event that may affect the safety, purity, or potency of the product, and it occurs in your facility or another facility under contract with you and involves distributed blood or blood components. For additional information regarding reporting, you may refer to

FDA guidance, "Guidance for Industry: Biological Product Deviation Reporting for Blood and Plasma Establishments," dated October 2006 (Ref. 33). Also, when a complication of blood collection or transfusion (e.g., involving *T. cruzi*) is confirmed to be fatal, you must notify FDA in accordance with 21 CFR 606.170(b).

C. Reporting the Test Implementation

1. If you are a licensed blood establishment and you begin using a licensed serological test for the detection of antibodies to *T. cruzi* according to the manufacturer's product insert at your facility, then you must notify us of the testing change in your Annual Report (AR), in accordance with 21 CFR 601.12(d). If you already have an approved supplement to your BLA to use a contract laboratory to perform infectious disease testing of blood products, and the contract laboratory will now perform a serological test for antibodies to *T. cruzi*, you must report this change in your AR (21 CFR 601.12(d)).

2. If you are a licensed blood establishment and you use a new contract laboratory to perform a serological test for antibodies to *T. cruzi* (and the laboratory already performs infectious disease testing for blood products), then you must report this change by submission of a "Changes Being Effected" supplement, in accordance with 21 CFR 601.12(c)(1) and (c)(5). If your contract laboratory has not previously performed infectious disease testing for blood products, then you must report this change as a major change in a prior approval supplement, in accordance with 21 CFR 601.12(b).

IV. RECOMMENDATIONS FOR DONORS OF HCT/Ps

A. Donor Screening—Risk Factors or Conditions

Under 21 CFR 1271.75(d), you must determine to be ineligible any potential donor who is identified as having a risk factor for or clinical evidence of relevant communicable disease agents or diseases. Ineligible potential donors include those who exhibit one or more of the following conditions or behaviors.

- Persons who have had a medical diagnosis of *T. cruzi* infection based on symptoms and/or laboratory results.
- Persons who have tested positive or reactive for *T. cruzi* antibodies using an FDA-licensed or investigational *T. cruzi* donor screening test (Ref. 1).

B. Donor Testing

1. You must test blood specimens from all HCT/P donors for antibodies to *T. cruzi* using an FDA-licensed donor screening test (21 CFR 1271.80(c)).

2. Any HCT/P donor whose specimen tests negative (or non-reactive) for antibodies to *T. cruzi* may be considered to be negative (or non-reactive) for purposes of making a donor eligibility determination.

3. Any HCT/P donor whose specimen tests positive (or reactive) for antibodies to *T. cruzi* is ineligible to be a donor (21 CFR 1271.80(d)(1)).

V. REFERENCES

1. Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), August 2007. http://www.fda.gov/cber/tissue/docs.htm

2. Dorn, P. L., L. Perniciaro, M. J. Yabsley, D. M. Roellig, G. Balsamo, J. Diaz and D. Wesson (2007). "Autochthonous transmission of *Trypanosoma cruzi*, Louisiana." Emerg Infect Dis 13(4): 605-7.

3. WHO Expert Committee on the Control of Chagas Disease (2000: Brasilia, Brazil), Control of Chagas Disease: second report of the WHO expert committee, 2002.

4. Bellotti, G., E. A. Bocchi, A. V. de Moraes, M. L. Higuchi, M. Barbero-Marcial, E. Sosa, A. Esteves-Filho, R. Kalil, R. Weiss, A. Jatene and F. Pileggi (1996). "In vivo detection of *Trypanosoma cruzi* antigens in hearts of patients with chronic Chagas' heart disease." Am Heart J 131(2): 301-7.

5. Vago, A. R., A. M. Macedo, S. J. Adad, D. D. Reis and R. Correa-Oliveira (1996). "PCR detection of *Trypanosoma cruzi* DNA in oesophageal tissues of patients with chronic digestive Chagas' disease." Lancet 348(9031): 891-2.

6. Añez, N., H. Carrasco, H. Parada, G. Crisante, A. Rojas, C. Fuenmayor, N. Gonzalez, G. Percoco, R. Borges, P. Guevara and J. L. Ramirez (1999). "Myocardial parasite persistence in chronic chagasic patients." Am J Trop Med Hyg 60(5): 726-32.

7. Jones, E.M., D. G. Colley, S. Tostes, E. R. Lopes, C. L. Vnencak-Jones, and T. L. McCurley (1993): "Amplification of a *Trypanosoma cruzi* DNA sequence from inflammatory lesions in human chagasic cardiomyopathy." Am J Trop Med Hyg 48(3): 348-357.

8. Vago, A. R., L. O. Andrade, A. A. Leite, D. d'Avila Reis, A. M. Macedo, S. J. Adad, S. Tostes Jr., M.C. V. Moreira, G. B. Filho, S. D. J. Pena (2000). "Genetic characterization of *Trypanosoma cruzi* directly from tissues of patients with chronic Chagas disease: Differential distribution of genetic types into diverse organs." American Journal of Pathology 156(5): 1805-1809.

9. Virreira, M., G. Serrano, L. Maldonado, and M. Svoboda (2006). "*Trypanosoma cruzi*: Typing of genotype (sub)lineages in megacolon samples from bolivian patients." Acta Tropica 100(3): 252-255.

10. da Silva Manoel-Caetano, F., C.M. Carareto, A. A. Borim, K. Miyazaki, and A.E. Silva (2008). "kDNA gene signatures of Trypanosoma cruzi in blood and oesophageal mucosa from chronic chagasic patients." Trans R Soc Trop Med Hyg 102(11): 1102-1107.

Contains Nonbinding Recommendations

Draft – Not for Implementation

11. Blood Products Advisory Committee, 74th Meeting, September 12, 2002 http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3892t1-03.pdf.

12. Blood Products Advisory Committee, 89th Meeting, April 26-27, 2007 http://www.fda.gov/ohrms/dockets/ac/07/minutes/2007-4300M.pdf.

13. Leiby, D. A., R. M. Herron, Jr., E. J. Read, B. A. Lenes and R. J. Stumpf (2002). "*Trypanosoma cruzi* in Los Angeles and Miami blood donors: impact of evolving donor demographics on seroprevalence and implications for transfusion transmission." Transfusion 42(5): 549-55.

14. Strong, D. M. and K. Shoos-Lipton (2006). "Information Concerning Implementation of a Licensed Test for Antibodies to *Trypanosoma cruzi*." AABB Bulletin #06-08.

15. Saulnier Sholler, G. L., S. Kalkunte, C. Greenlaw, K. McCarten and E. Forman (2006). "Antitumor activity of nifurtimox observed in a patient with neuroblastoma." J Pediatr Hematol Oncol 28(10): 693-5.

16. Young, C., P. Losikoff, A. Chawla, L. Glasser and E. Forman (2007). "Transfusion-acquired *Trypanosoma cruzi* infection." Transfusion 47(3): 540-4.

17. Cimo, P. L., W. E. Luper and M. A. Scouros (1993). "Transfusion-associated Chagas' disease in Texas: report of a case." Tex Med 89(12): 48-50.

18. Leiby, D. A., B. A. Lenes, M. A. Tibbals and M. T. Tames-Olmedo (1999). "Prospective evaluation of a patient with *Trypanosoma cruzi* infection transmitted by transfusion." N Engl J Med 341(16): 1237-9.

19. Lane, D. J., G. Sher, B. Ward, M. Ndao, D. Leiby, B. Hewlett and E. Bow (2000). "Investigation of the second case of transfusion transmitted Chagas disease in Canada." 42nd Annual Meeting of the American Society of Hematology, San Francisco, CA.

20. CDC. C.F. Zayas, C. Perlino, A. Caliendo, D. Jackson, E. J. Martinez, P. Tso, T. G. Heffron, J. L. Logan, B. L. Herwaldt, et.al. (2002). "Chagas disease after organ transplantation--United States, 2001." MMWR Morb Mortal Wkly Rep 51(10): 210-2.

21. CDC. L. Mascola, B. Kubak, S. Radhakrishna, T. Mone, R. Hunter, D. A. Leiby, M. Kuehnert, A. Moore, F. Steurer, G. Lawrence and H. Kun (2006). "Chagas disease after organ transplantation--Los Angeles, California, 2006." MMWR Morb Mortal Wkly Rep 55(29): 798-800.

22. Leiby, D. A., F. J. Rentas, K. E. Nelson, V. A. Stambolis, P. M. Ness, C. Parnis, H. A. McAllister, Jr., D. H. Yawn, R. J. Stumpf and L. V. Kirchhoff (2000). "Evidence of *Trypanosoma cruzi* infection (Chagas' disease) among patients undergoing cardiac surgery." Circulation 102(24): 2978-82.