医薬品
医薬部外品　　研究報告　調査報告書
化粧品

識別番号・報告回数			報告日	第一報入手日 2010 年 5 月 7 日	新医薬品等の区分 該当なし	厚生労働省処理欄
一般的名称	人ハプトグロビン		研究報告の公表状況	FDA/2010/05	公表国 アメリカ	
販売名 （企業名）	ハプトグロビン静注 2000 単位「ベネシス」　（ベネシス）					

研究報告の概要

抗 HBc 抗体が繰り返し反応したという以前の検査が偽陽性であり、また B 型肝炎ウイルス（HBV）感染の証拠がないとの決定に基づき、ドナー延期されていたドナーのドナー集団への再資格化の方法と再登録のための手順についての推奨事項を提示するため、輸血用の全血または血液成分の採取業者に対し FDA はこのガイダンスを発行する。
このガイダンスは、2008 年 5 月付けの同タイトルのドラフトガイダンスの最終版である。
推奨
A. 抗 HBc 抗体が 2 回以上繰り返し陽性反応の検査結果のためだけで無期限にドナー延期されてきたドナーは、以下の場合、ドナー集団に再登録することができる。
1. 繰り返し陽性反応の抗 HBc 抗体検査の最後の検査から最短 8 週間後の当該ドナーの追跡検体で FDA が承認した HBs 抗原、抗 HBc 抗体、及び NAT（<2IU/mL が 95%の検出率の感度）による HBV DNA 検査で陰性
および
2. その新しい献血前の血液検体が FDA が承認した HBs 抗原、抗 HBc 抗体、及び NAT による HBV DNA 検査で陰性後、そのドナーが全血および血液成分のドナーとしての適格基準にすべて適合している。
B. 抗 HBc 抗体が 2 回以上繰り返し陽性反応検査でドナー延期されたドナーで、そのドナーの検体または献血検査が以下の場合、無期限に延期を続けなければならない。
1）HBs 抗原検査で繰り返し陽性（中和検査陽性であるか否かにかかわらず）
2）抗 HBc 抗体検査で繰り返し陽性
または 3）HBV NAT 陽性
HBs 抗原、抗 HBc 抗体、または NAT による HBV DNA の陽性結果はドナーカウンセリングに役立つかもしれない。
C. 抗 HBc 抗体検査結果のため延期されたドナーの追跡検査の実施を希望する場合、ドナーへの通知目的または医学的理由のための 8 週間の待機期間が終わる前にそれを実施してよい。追跡検査の HBs 抗原、抗 HBc 抗体および NAT による HBV DNA の陰性結果は、ドナーカウンセリングに役立つかもしれない。3 項目（HBs 抗原、抗 HBc 抗体、NAT による HBV DNA）すべての結果が陰性の場合のみ、再登録の資格を得る。もし、8 週間の待機期間で HBV NAT で陽性、あるいは HBs 抗原または抗 HBc 抗体が陽性となれば再登録にふさわしくなく、無期限に延期することを推奨する。

使用上の注意記載状況・その他参考事項等

2. 重要な基本的注意
(1) 本剤の原材料となる献血者の血液については、HBs 抗原、抗 HCV 抗体、抗 HIV-1 抗体、抗 HIV-2 抗体、抗 HTLV-Ⅰ抗体陰性で、かつ ALT(GPT)値でスクリーニングを実施している。更に、プールした試験血漿については、HIV-1、HBV 及び HCV について核酸増幅検査(NAT)を実施し、適合した血漿を本剤の製造に使用しているが、当該 NAT の検出限界以下のウイルスが混入している可能性が常に存在する。本剤は、以上の検査に適合した血漿を原料として、Cohn の低温エタノール分画で得た画分から人ハプトグロビンを濃縮・精製した製剤であり、ウイルス不活化・除去を目的として、製造工程において 60℃、10 時間の液状加熱処理及びウイルス除去膜によるろ過処理を施しているが、投与に際しては、次の点に十分注意すること。

報告企業の意見	今後の対応
B 型肝炎コア抗原抗体（Anti-HBc）の検査で反応がみられたことから献血が延期された血液ドナーの再登録に関する検証方法の推奨で、2008 年 5 月の草案ガイダンスの最終版である。 万一、原料血漿に HBV が混入したとしても、BVD 及び BHV をモデルウイルスとしたウイルスバリデーション試験成績から、本剤の製造工程において十分に不活化・除去されると考えている。	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。

Guidance for Industry

Requalification Method for Reentry of Blood Donors Deferred Because of Reactive Test Results for Antibody to Hepatitis B Core Antigen (Anti-HBc)

Additional copies of this 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 email ocod@fda.hhs.gov, or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.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
[May 2010]

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Contains Nonbinding Recommendations

Guidance for Industry

Requalification Method for Reentry of Blood Donors Deferred Because of Reactive Test Results for Antibody to Hepatitis B Core Antigen (Anti-HBc)

This guidance represents 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 issuing this guidance to provide you, establishments that collect Whole Blood or blood components intended for transfusion, with recommendations for a requalification method or process for the reentry of deferred donors into the donor pool based on a determination that previous tests that were repeatedly reactive for antibodies to hepatitis B core antigen (anti-HBc) were falsely positive and that there is no evidence of infection with hepatitis B virus (HBV). Currently, donors who are repeatedly reactive on more than one occasion for anti-HBc (samples from more than one collection from the same donor are repeatedly reactive for anti-HBc) must be indefinitely deferred in accordance with Title 21 Code of Federal Regulations, section 610.41(a) (21 CFR 610.41(a)). Although it may seem unlikely that two anti-HBc tests would be falsely positive, such situations have occurred with some frequency because of the relative non-specificity of these tests. The result is that many otherwise suitable donors are indefinitely deferred because of their anti-HBc test results, even though medical follow-up of such donors indicates that they are not infected with HBV.

The availability of FDA-licensed hepatitis B virus nucleic acid tests (HBV NAT), which are particularly sensitive when single samples are tested, provides an additional, powerful method of determining whether a donor who has been deferred because of anti-HBc reactivity is truly infected with HBV. Due to the availability of FDA-licensed HBV NAT and the improved specificity of anti-HBc assays, we are recommending in this guidance a reentry algorithm for donors deferred due to falsely positive repeatedly reactive tests for anti-HBc. This guidance finalizes the draft guidance of the same title dated May 2008.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the 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

A. Clinical Significance of Donor Screening for Hepatitis B Virus Infection

HBV is an enveloped virus with a partially duplex circular deoxyribonucleic acid (DNA) genome of approximately 3,200 bases. It is a major human pathogen that causes acute and chronic hepatitis, cirrhosis and hepatocellular carcinoma (Ref. 1). The mortality of acute HBV infection is about 1%. Most primary infections in adults are self-limited. The virus is cleared from the blood and liver, and individuals develop a lasting immunity. However, 2% to 6% of persons above the age of 5 years, and 30% to 90% of infected children under the age of 5 years (Ref. 2) develop chronic infections that generally are asymptomatic (i.e., a carrier state), but may not be benign. About 20% of chronically infected individuals develop cirrhosis, and chronically infected subjects have 100 times higher risk of developing hepatocellular carcinoma than non-carriers. In the United States, deaths from chronic HBV infection are estimated to range from 3,000 to 5,000 individuals per year (Ref. 2).

Currently, HBV is transmitted by blood transfusions more frequently than hepatitis C virus or human immunodeficiency virus. The residual risk of post-transfusion HBV infection from donations screened for hepatitis B surface antigen (HBsAg) and anti-HBc has been estimated as 1 in 205,000 (Ref. 3) to 1 in 269,000 (Ref. 4) per donated unit. The major cause of HBV transmission by blood is attributable to donations from asymptomatic donors with acute HBV infections who have not yet developed HBsAg or anti-HBc (i.e., donors in the seronegative window period) and, in some cases, from donors with chronic infections in which serological markers are not detected (occult hepatitis B). Seronegative blood donations from infected individuals can transmit hepatitis B. In such cases, lookback studies using polymerase chain reaction have shown that HBV DNA can be detected at low levels in the donor's blood (Ref. 5).

HBsAg becomes detectable in blood 30 to 60 days after infection followed by the emergence of anti-HBc. Viremia develops several weeks before HBsAg is detected, and can reach 10^9-10^{10} virions/ml in acute infections (Ref. 1). Upon clearance of the HBV infection by the immune response, the HBsAg disappears from the blood of individuals, while detectable anti-HBc and antibody to hepatitis B surface antigen (anti-HBs) usually persist indefinitely. However, there is evidence that anti-HBc can decrease and even disappear over a period of decades in resolved infections (Ref. 6). Nonetheless, in chronically infected individuals, tests for HBsAg and anti-HBc usually remain positive for life and lower viral titers can be detected in blood for a long period although they tend to decline over time.

HBV NAT assays for detection of HBV DNA have been developed, and have been licensed for screening blood donations using a minipool sample format. These assays are also indicated for testing samples from individual donations, thus increasing test

sensitivity. In a meeting of the Blood Products Advisory Committee (Committee or BPAC) on October 21, 2004 (Ref. 7), we requested scientific comment on a reentry algorithm for donors deferred for repeatedly reactive anti-HBc test results on more than one occasion. The algorithm was based on follow-up testing of the donor for HBsAg, anti-HBc, and HBV DNA by sensitive HBV NAT. Under this plan, HBV DNA testing using an FDA-licensed NAT would replace a previously considered recommendation for donor reentry that included antibody to hepatitis B surface antigen (anti-HBs) testing. We no longer propose additional testing for anti-HBs as part of donor reentry because extensive hepatitis B vaccination programs have been in place for a number of years, resulting in many individuals having anti-HBs from vaccination. As a result, anti-HBs now has questionable value as a marker of hepatitis B infection. While the Committee did not take a formal vote on the algorithm, the Committee discussed this approach and did not express concerns about the adequacy of this plan as a reentry algorithm.

Since the 2004 BPAC meeting referred to above, we have licensed qualitative tests for the direct detection of HBV DNA in human plasma from donors, including donors of Whole Blood and blood components, Source Plasma and other living donors, that have sensitivities of <2 International Units (IU)/mL (about 10 copies HBV DNA/mL) at 95% detection for HBV DNA when specific procedures are used.[1] The availability of sensitive, FDA-licensed, HBV NAT assays provides an additional, powerful method of determining whether a donor, who has been deferred because of anti-HBc reactivity, is truly infected by HBV. Due to the availability of FDA-licensed HBV NAT assays and the improved specificity of anti-HBc assays, we are recommending a reentry algorithm for anti-HBc in this guidance. Empirical studies support utility of this algorithm (Ref. 8).

B. Rationale and Procedure for the Requalification Method for Reentry

Under 21 CFR 610.40(a), you must test each donation of human blood or blood component intended for use in preparing a product, including donations intended as a component of, or used to prepare, a medical device, for evidence of infection due to HBV, among other communicable disease agents. Testing for evidence of infection of HBV includes testing for the presence of HBsAg and anti-HBc. In addition, some blood establishments also test blood donations for HBV DNA by HBV NAT.

Under 21 CFR 610.41(a), as a general matter, you must defer donors who test reactive[2] with respect to the battery of screening tests required under 21 CFR 610.40. However, donors who test repeatedly reactive for anti-HBc on only one occasion do not need to be

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[1] COBAS AmpliScreen HBV Test (Roche Molecular Systems, Inc., Pleasanton, California): Triplicate testing using the multiprep specimen processing procedure.
Procleix® ULTRIO® Assay (Gen-Probe, Inc., San Diego, California): Testing 6 replicates.

[2] In 21 CFR 610.41(a), FDA requires that blood establishments defer donors who test reactive by a screening test for evidence of infection due to a communicable disease agent(s) listed in section 610.40(a). In section 610.41(a)(1), however, a donor who tests reactive for anti-HBc on only one occasion is not required to be deferred. In this guidance, we refer to reactive test results for HBsAg and anti-HBc as "repeatedly reactive" to accurately describe the testing algorithms for HBsAg and anti-HBc.

deferred (21 CFR 610.41(a)(1)). Donations collected from these donors are not suitable for allogeneic transfusions (21 CFR 610.40(h)(1) and (2)) (Ref. 9), but such donations, if otherwise nonreactive when tested for communicable disease agents as required under 21 CFR 610.40, may be used for further manufacturing into plasma derivatives without FDA prior approval. (21 CFR 610.40 (h)(2)(v). Donors who test reactive on more than one occasion do not fall within this exception and must be deferred (21 CFR 610.41(a)).

Under 21 CFR 610.41(b), "a deferred donor subsequently may be found to be suitable as a donor of blood or blood components by a requalification method or process found acceptable for such purposes by FDA."[3]

Until now, we have not recommended a requalification method for reentry of donors deferred due to repeatedly reactive test results for anti-HBc because there was no supplemental (additional, more specific) test available. Although donor screening for anti-HBc has contributed to blood safety, a large proportion of donors with anti-HBc reactivity who fulfill all other donor suitability criteria have been indefinitely deferred on the basis of potentially false positive anti-HBc test results (Refs. 10, 11). It is estimated that as many as 21,500 potentially eligible donors were deferred annually in the late 1980s and 1990s because of false positive anti-HBc results, and that over 200,000 donors could be eligible for reentry (Ref. 10).

For purposes of reentering into the donor pool, a donor who has been indefinitely deferred because of having tested repeatedly reactive for anti-HBc on more than one occasion, we recommend in Section III of this guidance that, after a minimum of 8 weeks following the last repeatedly reactive anti-HBc test, you obtain from the donor a new, pre-donation blood sample (i.e., a blood sample that is obtained before the next donation) for follow-up testing, using FDA-licensed tests for HBsAg, anti-HBc and HBV DNA by NAT. If the new, pre-donation blood sample test results are negative for HBsAg, anti-HBc and HBV DNA, the donor may return to donate blood. When the donor returns to donate, after the tests for HBsAg, anti-HBc, and HBV DNA on the pre-donation sample have been determined to be negative, we recommend that you reenter the donor as eligible to donate Whole Blood and blood components, provided that the donor meets all eligibility criteria. Note that the reentry of a donor permits prospective donations from a reentered donor who meets donor suitability criteria. It does not affect the status of previous collections from that donor.

For donor retesting, we recommend that a minimum 8-week (56 days) period elapse following the last repeatedly reactive anti-HBc test, because this time period provides sufficient confidence that at least one of the three HBV markers (HBsAg, anti-HBc, and HBV DNA) will be detectable if the donor had been truly infected with HBV at the time of the last anti-HBc reactive donation (Ref. 1). In addition, eight weeks is the minimum time period permitted between donations of Whole Blood, with limited exceptions (21

[3] A deferred donor may serve as an autologous donor in accordance with 21 CFR 610.40 and 21 CFR 610.41. Note that a deferred donor that donates for autologous use is not deemed to be reentered and remains deferred, until the criteria for reentry are met.

CFR 640.3(b)).

For purposes of reentry, we recommend that you use an FDA-licensed HBV NAT labeled as having a sensitivity of ≤ 2 IU/mL at 95% detection rate [1 IU = ~5 copies]. Donors with negative results for HBV DNA at this level of sensitivity are highly unlikely to be infected with HBV (Ref. 12). Depending upon the assay and the platform used, this sensitivity may only be achieved when testing individual donor samples.

III. RECOMMENDATIONS

A. You may reenter into the donor pool, a donor who has been indefinitely deferred solely because of repeatedly reactive tests for anti-HBc on more than one occasion if (see flow chart in the Appendix):

1. After a minimum of 8 weeks following the last repeatedly reactive anti-HBc test, you collect a follow-up sample from the donor, and this sample tests negative on FDA-licensed tests for HBsAg, anti-HBc, and HBV DNA by NAT (sensitivity at 95% detection rate of ≤2 IU /mL)

and

2. When the donor presents to donate, after the new, pre-donation blood sample tests negative on FDA-licensed tests for HBsAg, anti-HBc, and HBV DNA by NAT, you determine that the donor meets all eligibility criteria for donors of Whole Blood and blood components.

B. You should continue to indefinitely defer a donor who was deferred for anti-HBc reactivity on more than one occasion and whose sample or donation tests: 1) repeatedly reactive on the HBsAg test (whether or not the neutralization test is positive); 2) repeatedly reactive on the anti-HBc test; or 3) reactive on the HBV NAT. Positive results on tests for HBsAg, anti-HBc or HBV DNA by NAT may be useful in donor counseling.

C. If you wish to perform follow-up testing on a donor who is deferred because of anti-HBc test results, you may do so before the end of the 8-week waiting period for donor notification purposes or for medical reasons. Negative test results on follow-up for HBsAg, anti-HBc, and HBV DNA by NAT (sensitivity at 95% detection rate of ≤ 2 IU/mL), may be useful in donor counseling. However, only negative results for all three tests (HBsAg, anti-HBc, and HBV NAT), obtained at least 8 weeks after the last repeatedly reactive anti-HBc result, would qualify the donor for reentry. If you obtain a reactive HBV NAT, or repeatedly reactive HBsAg or anti-HBc, or positive HBsAg result on any of these tests during this 8-week waiting period, the donor would not be eligible for reentry, and we recommend that you defer the donor indefinitely.

A donor who has been requalified as described above in Section III. A. 1 and 2 may on subsequent occasions be indefinitely deferred solely because of repeatedly reactive tests for anti-HBc on more than one occasion. You may reenter such a donor into the donor pool by again following all procedures described in Section III. A.

IV. IMPLEMENTATION

We consider the recommendations in this guidance to be an acceptable requalification method for reentry of donors deferred due to falsely positive repeatedly reactive tests for anti-HBc. Licensed establishments implementing these recommendations must report this change to FDA as required under 21 CFR 601.12(a). We consider implementation of recommendations in this guidance in their entirety and without modification to be a minor change to an approved license application. Therefore, licensed establishments are not required to have FDA prior approval and may submit a statement of this change in an annual report under 21 CFR 601.12(d), indicating the date that the revised standard operating procedures were implemented. Unlicensed establishments implementing recommendations in this guidance in their entirety and without modification are not required to report this change.

We do not consider implementation of an alternative requalification method from that described in this guidance to be acceptable, unless approved by FDA for such purpose. In accordance with 21 CFR 610.41(b), you must not reenter a donor unless the requalification method or process is found acceptable for such purposes by FDA. Licensed establishments intending to use an alternative requalification method must submit a supplement for prior approval, as required under 21 CFR 601.12(b). Similarly, under 21 CFR 610.41(b), FDA must find an alternative requalification method proposed by an unlicensed establishment to be acceptable before it is implemented.

V. REFERENCES

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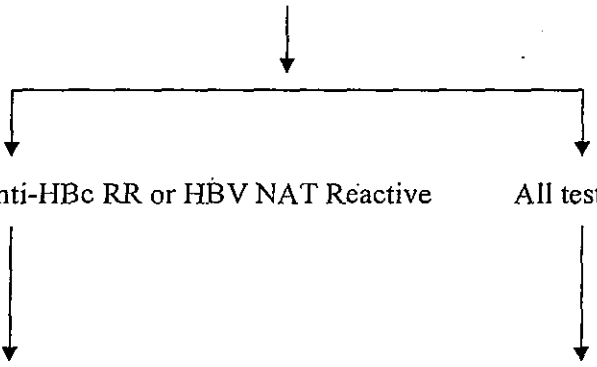
APPENDIX

REQUALIFICATION PROCESS FOR DONORS DEFERRED BECAUSE OF REPEATEDLY REACTIVE TEST RESULTS FOR ANTI-HBc

Donors previously deferred solely because of repeatedly reactive (RR) anti-HBc test on more than one occasion

After a minimum of 8 weeks[1] following the last repeatedly reactive anti-HBc test result, test a follow-up sample using FDA-licensed HBsAg and anti-HBc tests, and HBV NAT[2]



HBsAg RR[3] or Anti-HBc RR or HBV NAT Reactive

Defer donor indefinitely

All tests negative

Reenter donor
(Donor eligible for future donations, provided donor meets eligibility criteria)

[1] If, for donor notification purposes or for medical reasons, you wish to perform follow-up testing on a donor who is deferred because of repeatedly reactive anti-HBc test results before the end of the 8-week waiting period and the blood sample tests HBsAg RR or anti-HBc RR or HBV NAT reactive, the donor should be indefinitely deferred. If, however, the sample tests negative on all three of these tests, the donor should be retested after a minimum of 8 weeks following the last repeatedly reactive anti-HBc test result using licensed HBsAg and anti-HBc tests, and HBV NAT. If, at that time, the sample tests negative on all three of these tests (HBsAg, anti-HBc, and HBV NAT), the donor may be eligible to donate.

[2] The sensitivity of the HBV NAT used should be $\leq$ 2 IU/mL, at 95% detection rate.

[3] Regardless of the neutralization test result.

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
				2010. 4. 14	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		公表国
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)		Kermode-Scott B. BMJ. 2010 Apr 9;340:c1974. doi: 10.1136/bmj.c1974.	カナダ

研究報告の概要

○カナダは慢性疲労症候群(CFS)の既往歴を有する供血者からの供血を禁止した
カナダの国内血液事業は、予防措置として、レトロウイルスXMRVとの関連が示唆される、CFSの既往歴を有する供血者からの供血を2010年5月から禁止することを発表した。この措置を行ったのは世界でカナダが初めてである。これは2009年10月に発表された、CFSとXMRVとの関連を示唆する報告を受けての決定である。当局は、XMRVがより理解され、CFSへの影響や関連した病気について明らかになるまで、既往歴のある患者からの献血を延期することで安全な血液供給を保護するとしている。

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

報告企業の意見	今後の対応
カナダは世界で初めて慢性疲労症候群の既往歴を有する供血者からの供血を禁止したとの報告である。	日本赤十字社では、献血の問診時に献血者の健康状態を把握・確認している。平成22年5月18日に開催された平成22年度第1回血液事業部会運営委員会において、XMRVとCFSとの関連について、現時点で緊急的な対応をとる必要はないものの、引き続き情報収集を行い、新たな知見等が得られれば、本委員会において対応を検討することとされた。今後も引き続き、情報の収集に努める。

commitment to improve health in the poorest countries, he said, but "we need to be able to see clearly where the money is going and then identify best practices where these financial commitments to health are making the greatest difference in saving lives."

The *Lancet*'s editor, Richard Horton, said that the findings raised a red flag over the effectiveness of international aid. "It may be entirely rational for governments to move donor money around according to their priorities. But the risk is that redistributing health money to other sectors may diminish donor confidence in aid programmes [and] erode taxpayer commitment to government spending on international development," he said.

In an accompanying article Gorik Ooms, of the Institute of Tropical Medicine in Belgium, gave three possible reasons for the "crowding out" effect: governments compensating for exceptional generosity to the health sector by diverting funds to other areas; governments preventing increases in recurrent health expenditure in anticipation of future unpredictability of international aid; and governments smoothing aid by spending it over several years (doi:10.1016/S0140-6736(10)60207-3).

TONY KARUMBA/AFP/GETTY IMAGES

Between 15% and 30% of Sudan's own spending on health was replaced by foreign aid

In a commentary Devi Sridhar and Ngaire Woods, of the University of Oxford, cautioned against concluding that international aid should be channelled through non-governmental organisations, as they would bypass domestic institutions that improve governance and sustain aid in the long term. They added that collaborative target setting between donors and recipients could result in governments following the priorities of donors rather than meeting their own needs (doi:10.1016/S0140-6736(10)60486-2).

Cite this as: *BMJ* 2010;340:c2015

Debate still rages as medical abortion finally arrives in Italy

Michael Day MILAN

Medical abortion became available in Italy last week after a 15 year battle between women's groups and the Catholic church.

But while the major regions of Tuscany, Emilia Romagna, and Lombardy finally made the procedure available, others, such as Piedmont, seemed to be dragging their heels.

And within hours of the first mifepristone pill (also known as RU486) being given on Thursday there was fresh controversy when the 29 year old recipient discharged herself from the clinic in the southern city of Bari, in contravention of guidelines stating that the patient must stay in hospital for the duration of medical abortion.

The health ministry says that the proviso is essential to reduce the risk of complications that have been linked to medical abortion and has advised regions not following the guidelines they will be committing a crime.

Some advocates of mifepristone, such as Silvio Viale, a consultant gynaecologist at the Sant'Anna Hospital in Turin, criticised the regulations, which are at odds with those in other countries: "They make no sense, as demonstrated by the experience of other countries such as France," he said.

Cite this as: *BMJ* 2010;340:c2001

J-P MOCZULSKI/AFP/GETTY IMAGES

Studies in the UK and Netherlands failed to confirm a report suggesting a link between a virus and CFS

Canada bans blood from people with history of CFS

Barbara Kermode-Scott CALGARY, ALBERTA

Canada's national blood service has announced that from next month it will ban blood donations from people with a medical history of chronic fatigue syndrome (CFS), as a precautionary measure. It is the first country in the world to do so.

"Canadian Blood Services takes the safety of the blood supply very seriously," said Dana Devine, the agency's vice president of medical, scientific, and research affairs. "Until recently Canadian Blood Services has accepted blood donations from donors who report a history of [chronic fatigue syndrome] but are now well."

Dr Devine cited a report published in *Science* last October (2009;326:585-9, doi:10.1126/science.1179052) suggesting a link between the syndrome and the presence of a retrovirus, the xenotropic murine leukaemia virus related virus (XMRV).

The study, which looked at peripheral blood mononuclear cells from patients with chronic fatigue syndrome, identified DNA from XMRV in 68 of 101 patients (67%) but in only eight of 218 (3.7%) healthy control patients. Cell culture experiments showed that patient derived XMRV is infectious and that both cell associated and cell free transmission of the virus are possible.

"Given the lack of clarity around XMRV, we are changing the way we manage donors such that any donor who has a medical history of [the syndrome] will be indefinitely deferred from donating blood," Dr Devine said.

Studies conducted in early 2010 in the United Kingdom and in the Netherlands were unable to confirm the findings of the *Science* study, she noted (*BMJ* 2010;340:c1033).

Health officials in the United States are also investigating the association between XMRV and chronic fatigue syndrome and its potential significance for the blood supply.

Cite this as: *BMJ* 2010;340:c1974

医薬品　研究報告　調査報告書

識別番号・報告回数	F	第1報	報告日 2010年04月28日	第一報入手日 2010年04月12日	新医薬品等の区分 該当なし	機構処理欄
一般的名称	1. 乾燥濃縮人血液凝固第８因子（6343406） 2. ルリオクトコグアルファ（遺伝子組換え）（6343432） 3. 乾燥人血液凝固因子抗体迂回活性複合体（6343414）		研究報告の公表状況	http://www.promedmail.org/pls/apex/f?p=2400:1001:227625764564573 5::NO::F2400_P1001_BACK_PAGE,F2400_P1001_PUB_MAIL_ID:1010,82111	公表国 アメリカ	
販売名（企業名）	1. ヘモフィルM（634340612）(Baxter) 2. リコネイト（634343201） 3. ファイバ（634341401） 4. ガンマガード（634342002） 5. プラズマプロティンフラクション（634342204					

研究報告の概要

（概要）：Xenotropic murine leukemia virus-related virus（XMRV）と血液供給に関する調査

異種指向性マウス白血病ウイルス関連ウイルス［xenotropic murine leukemia virus-related virus ］（XMRV）として知られるそのウイルスは、マウス白血病ウイルスとの類似性からガンマレトロウイルス属に分類されるが、HIVはレンチウイルス属と分類される。危険の有無については明らかではなく、公衆衛生担当官によれば感染が広がっている証拠はないという。しかし、感染拡大の潜在的可能性と、XMRVはHIVと同様に感染することを示す初期データがあるため、これを懸念して担当官は備蓄血液を保護する対策をとる必要性について早く見極めようとしている。

XMRV は2006年に、家族性前立腺癌のまれな形態として患者の腫瘍サンプル内に発見された。その後の研究により、このウイルスが慢性疲労症候群（chronic fatigue syndrome［CFS］）に関連しており、測定可能なレベルで健康な人の血液にも存在していることが発見された。しかし、他のいくつかの試験においてはCFS患者の血液中にXMRVを検出できなかったこともあり、上記の証拠が決定的とはいえず、このウイルスがどの程度蔓延しているのか、また病気の原因になるのか明らかになっていない。

XMRVが注視されるのは、新種の感染病がここ数十年間に人類に増えており、潜在的脅威と考えられるものもあるため、監視方法を改善しようという努力倍増の一環である。Whittemore Peterson Institute for Neuro-Immune Disease（ホイットモアピーターソン神経免疫病研究所），国立癌研究所、Cleveland Clinic（クリーブランド病院）に勤務する論文の共著者らは、その試験において対照群とされた健康被験者218人中約4%にもXMRVを検出した。この数字を外挿し、米国において1千万人、世界中で数億人以下がXMRVに感染していると公衆衛生課は推定して

使用上の注意記載状況・その他参考事項等

［使用上の注意記載事項］：記載なし

報告企業の意見	今後の対応
2006年に、家族性前立腺癌のまれな形態として発見された異種指向性マウス白血病ウイルス関連ウイルス（XMRV）は、マウス白血病ウイルスとの類似性からガンマレトロウイルス属に分類される。 リコネイト、ファイバ、ガンマガード、プラズマプロテインフラクション及びブミネートは、HBs抗原、抗HCV抗体、抗HIV-1抗体及び抗HIV-2抗体等が陰性の血漿を原料として製造され、またHBV-DNA、HCV-RNA、HIV-1-RNA、HIV-2-RNA及びHAV-RNAについてプールした試験血漿で核酸増幅検査（NAT）を実施し、適合を確認している。また、プールした試験血漿で核酸増幅検査（NAT）を実施し、10^5IU/ml以下であることを確認した健康人血漿を用い、さらに、製剤ごとウイルス不活化を実施している。 ヘモフィルM はFDAで許可された方法にて供血者１人１人をHBs抗原陰性、HIV抗体陰性であることを確認した原料血漿を使用し、クリオプレシピテートをTNBP/Triton-X-100で処理することによってウイルスを不活	今後も同様の情報収集に努める。

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	機構処理欄
一般的名称	4. 乾燥イオン交換樹脂処理人免疫グロブリン（6343420） 5. 加熱人血漿たん白（6343422） 6. 人血清アルブミン（6343410）		研究報告の公表状況		公表国	
販売名（企業名）	） 6. ブミネート（634341005）					

研究報告の概要

いる。世界に推計1700万人患者がおり、特に治療法のないCFSとXMRVは関連があると考えられているが、この点について患者支援者らが注意深く調査を続けている。
XMRVウイルスが備蓄血液に混入するのを防ぐために行われている検査に関しては、FDA許可の臨床検査はなく、公衆衛生課によればまだ診断基準を定めているところだという。
国立衛生研究所の資金を受け、FDAや疾病予防管理センター(CDCP)等連邦政府機関も参加し対策班が立ち挙げられた。また、米国の備蓄血液をほぼすべて収集する国内施設の協会であるAABB［American Association of Blood Banks］（米国血液銀行協会）もXMRV特別チームを編成した。

使用上の注意記載状況・その他参考事項等

報告企業の意見	今後の対応
化し、抗FVIIIモノクローナル抗体を用いたイムノアフィニティークロマトグラフィーで夾雑たん白、ウイルス等を除去している。なお本邦にて1992年以降、輸入・販売の実績がない。 XMRVはレトロウィルスであり、HIVと同様に処理工程で除去・不活化されると考えられ、現時点では使用上の注意の改訂、医師等への文書による情報伝達等の安全対策は特に必要ないと判断しているが、引き続き、当該生物由来製品等によるものと疑われる感染症並びに同一生物種等から人に感染すると認められる疾病に関する情報の収集に努める所存である。	

Archive Number 20100406.1100
Published Date 06-APR-2010
Subject PRO/EDR> Xenotropic murine leukemia virus-related virus: blood supply probe

XENOTROPIC MURINE LEUKEMIA VIRUS-RELATED VIRUS: BLOOD SUPPLY PROBE
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A ProMED-mail post
<http://www.promedmail.org>
ProMED-mail is a program of the
International Society for Infectious Diseases
<http://www.isid.org>

Date: Sun 4 Apr 2010
Source: The Wall Street Journal, Health [edited]
<http://online.wsj.com/article/SB10001424052702303450704575160081295988608.html?mod=WSJ_business_whatsNews>

An infectious virus linked to 2 diseases is drawing the attention of public-health officials, who are investigating the potential threat to the nation's blood supply. It isn't clear if the virus, known as XMRV [xenotropic murine leukemia virus-related virus], poses a danger, and public-health officials say there isn't evidence of spreading infection. But because of concern over the potential for widespread infection and preliminary evidence that XMRV is transmitted similarly to HIV [human immunodeficiency virus], officials are quickly trying to determine if action is needed to protect the blood supply.

XMRV was discovered in 2006 when it was found in tumor samples from men with a rare form of familial prostate cancer. Research has also linked the virus to chronic fatigue syndrome [CFS] and found it in measurable levels in the blood of healthy people [see ProMED-mail Chronic fatigue syndrome: gammaretrovirus link 20091009.3499]. But the evidence isn't conclusive, as several other studies failed to find XMRV in the blood of people with chronic fatigue syndrome, and it isn't known how prevalent the virus is or whether it causes disease [see ProMED-mail Chronic fatigue syndrome: gamma retrovirus link disputed 20100107.0078]. "These are early days trying to understand the public health significance of XMRV," said Jay Epstein, director of the Office of Blood Research and Review at the Food and Drug Administration. Efforts are under way to find effective tests for the virus and determine its prevalence, led by a working group funded by the National Institutes of Health and including federal agencies such as the FDA and the Centers for Disease Control and Prevention. Blood banks, academic institutions, and at least one advocacy group are also involved.

The focus on XMRV is part of a growing effort to better monitor emerging infections -- disorders that have either increased in humans in recent decades or are deemed a potential threat. Currently there are 12 tests used to block infectious agents from entering the blood supply, such as HIV or hepatitis C [virus], and more screens are under study, including those for dengue, human variant Creutzfeldt-Jakob disease, and agents that cause malaria. There is no FDA-licensed lab test for XMRV, and officials say they are still setting standards for diagnosing it.

Public-health officials increasingly recognize that even infections not typically found in the US can quickly come here because of global travel. Many viruses also have long incubation periods, making it harder to recognize that the virus was transmitted by a blood transfusion. In an October 2009 report, a federal advisory committee on blood safety and availability concluded that biovigilance in the US is a "patchwork of activities, not a cohesive national program." The incidence of infectious diseases being transmitted through transfusions is small, typically only a handful each year, according to the American Red Cross and data reported to the FDA. About 16 million units of whole blood and red blood cells were donated in the US in 2006, the latest data available, according to the 2007 National Blood Collection and Utilization Report. The American Red Cross, which collects almost half of blood donations in the US, estimated that about 10 000 donors a year turn out to be infected with pathogens that officials screen for. Nearly half are hepatitis C virus [positive].

Michael P Busch, who runs the Blood Systems Research Institute in San Francisco and is a member of the XMRV working group, notes that everyone harbors benign viral infections. These viruses are transmitted in every blood transfusion, but aren't known to cause diseases in recipients, says Dr Busch. Even if XMRV is found to be present in large numbers of blood donors, Dr Busch notes, it is still necessary to determine if XMRV causes diseases.

The working group was established after a paper was published in October [2009] in the journal Science [abstract available at <http://www.sciencemag.org/cgi/content/abstract/1179052>], where researchers reported finding the virus in a majority of 101 patients with chronic fatigue syndrome. The study's co-authors at the Whittemore Peterson Institute for Neuro-Immune Disease, the National Cancer Institute and the Cleveland Clinic, also found the virus in nearly 4 percent of 218 healthy people used as controls in the study. Extrapolating from those numbers, public-health officials estimated that up to 10 million people in the US and hundreds of millions of people globally could be infected with XMRV.

The apparent link to CFS, which affects an estimated 17 million people worldwide, and has no specific treatments, has been closely followed by the patient advocacy community. The Whittemore Peterson institute, established by the family of a chronic fatigue patient, has started collecting blood from CFS patients who got their diagnosis following a blood transfusion and plan to launch their own study of the issue, says Annette Whittemore, founder and president of the institute.

The CFIDS [chronic fatigue and immune dysfunction syndrome] Association of America, an advocacy group for chronic fatigue syndrome, set up a bank to collect biospecimens to be used in potential studies about CFS, including XMRV-related ones. Researchers at Emory University and the University of Utah published a study last week [1 Apr 2010] showing that XMRV may be treatable with drugs that treat HIV. (see Singh IR, Gorzynski JE, Drobysheva D, Bassit L, Schinazi RF, 2010 Raltegravir Is a Potent Inhibitor of XMRV, a Virus Implicated in Prostate Cancer and Chronic Fatigue Syndrome. PLoS ONE 5(4): e9948. <http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0009948>).

The AABB [American Association of Blood Banks], an association of facilities that collect virtually all of the US blood supply, has also set up an XMRV task force, although the virus doesn't appear on a list of infectious agents evaluated by a special AABB transfusion-risk committee, as concerns came out after the latest list was put together.

Labs in Europe reported earlier this year that they haven't been able to replicate the XMRV findings in patients with chronic fatigue syndrome or prostate cancer. And public-health experts say a key issue in sorting out the disparate findings is to reach agreement on tests that are sensitive and reliable in identifying XMRV in the blood.

The federal working group's project has 3 phases. 1st, labs at 6 participants -- including the FDA, the National Cancer Institute, the CDC, and the Whittemore Peterson lab -- are using a panel of blood samples to try to establish which of the labs' tests are sensitive and reliable enough to find XMRV in the blood. Results are expected in a few weeks.

In the 2nd phase, also launched, a panel of around 350 different blood samples developed by Dr. Busch's team will be sent to four different labs. Some of the samples are from chronic fatigue patients known to have XMRV. Others from healthy donors have been spiked with the virus or have tested negative. All the samples are blinded, and the study will see whether the different labs can agree on XMRV positive status for chronic fatigue patients.

A 3rd phase may be launched later, using frozen specimens in federal repositories dating to the 1970s. These repositories link donors to recipients and will allow researchers to see if XMRV was transferred in transfusions and help determine prevalence in the past as well as today, as well as geographical clusters or associations with age and gender.

"There is a balance to what we are doing," says Simone A Glynn, branch chief of transfusion medicine and cellular therapies at the National Heart, Lung and Blood Institute and chairperson of the XMRV working group. "You do not want to transfuse an infectious agent that causes problems. But you do not want to take blood out of the system that is not causing any problems."

[Byline: Amy Dockser Marcus]

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Communicated by:
ProMED-mail Rapporteur Brent Barrett

[Xenotropic murine leukemia virus-related virus (XMRV) on account of its similarity to murine leukemia virus is classified as a member of the genus _Gammaretrovirus_, whereas human immunodeficiency virus is classified in the genus _Lentivirus_. While the link between MLRV and human disease, and chronic fatigue syndrome in particular, remains controversial, it is certainly prudent to further refine diagnostic procedures in order to determine the extent of the presence of XMRV in the human blood supply and any correlation with human disease. The outcome of the research in progress is a matter of general interest. - Mod.CP]

[see also:
Chronic fatigue syndrome: gamma retrovirus link disputed 20100107.0078
2009

Chronic fatigue syndrome: gammaretrovirus link 20091009.3499]
.....cp/mj/mpp

human being send mail to: owner-promed@promedmail.org.
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