別紙様式第 2-1

別紙 3-5

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		回	報告日 年　月　日	第一報入手日 2004年11月8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			研究報告の公表状況	The Potential Risk of Simian Foamy Virus Transmission by Blood Transfusion. Issue Summary. Blood Products Advisory Committee Gaithersburg, MD October 21-22, 2004	公表国 米国	
販売名（企業名）						

研究報告の概要

最近のデータから，サル泡沫状ウイルス(SFV)および非ヒト霊長類に感染するその他のウイルスが輸血を介して伝播するリスクに対して関心が高まっている。FDAは，血液製剤諮問委員会(BPAC)に対し，この問題に対処するために取るべき措置について助言を求めた。本議題は，カメルーンでこのレトロウイルスが自然環境下で非ヒト霊長類からヒトへ伝播したという知見がLancet誌に最近掲載されたため，BPACに提出されたものである。そこでは，非ヒト霊長類が保有するレトロウイルスがヒト集団へ伝播し，最終的に供血が汚染される機序について示されている。BPACに対するFDAの質問は以下のとおり。

1) 既知疾患との関連がなくても，FDAはSFV伝播の可能性に対して懸念すべきか。
2) ヒトへのSFV感染および動物試験における血液を介したSFV伝播に関する最近の知見は，非ヒト霊長類の既知および未知の病原性ウイルスがヒトの供給血を汚染するかもしれないという懸念を高めるものであるか。
3) 現在得られている科学的データは，供血者の除外基準として「非ヒト霊長類と接触したこと」を新たに設けることについて検討の必要性を示すものであるか。検討すべき要因について議論されたい。

2004年10月26日，上記BPACに追随し，カナダ公衆衛生当局は以下のとおり勧告した。
非ヒト霊長類と直接接触のあった個人について，輸血および細胞，臓器，組織の提供の除外を検討すべきである。

使用上の注意記載状況・その他参考事項等

Epstein MA (2004) Simian retroviral infections in human beings. Lancet 364: 138-139.

Preliminary Risk Assessment on SFV and Deferral Policy for Blood and CTO Donation. Public Health Agency of Canada www.phac-aspc.gc.ca/id-mi/sfv-vss-20041021ra_e.html. updated 2005.10.26

報告企業の意見	今後の対応
Lancet誌に掲載された感染例はアフリカにおける発生例であるが，今後，世界の他の地域への感染リスクが拡散する可能性は否定できない。SFV感染リスク，血液製剤諮問委員会の見解，FDAの対応等の関連情報を収集・検討していく必要があると考える。	現時点で新たな安全対策上の措置を講じる必要は無いと考える。今後もSFV伝播のリスクに関する情報に注意を払い，情報収集に努める。

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Issue Summary
Blood Products Advisory Committee
October 21-22, 2004
Gaithersburg, MD

Topic II: The Potential Risk of Simian Foamy Virus Transmission by Blood Transfusion

Issue:

Recent data have renewed concern over the potential risk for transfusion transmission of simian foamy virus (SFV) and perhaps other viruses of nonhuman primates. FDA seeks advice from the Blood Products Advisory Committee (BPAC) on the approach that should be taken to address this concern.

Background:

The potential risk of transmission of SFV by blood transfusion is being brought to BPAC for discussion at this time because of a recent report in *The Lancet* that this retrovirus is being transmitted under "natural conditions" from nonhuman primates to the human population in Cameroon. The reported transmission of SFV to humans by non-occupational contact with nonhuman primates not only places a renewed focus on SFV transmission; it also provides yet another example of the working model of retrovirus cross-species transmission. It represents a mechanism by which SFV and other nonhuman primate retroviruses might enter the human population and ultimately the blood supply. This issue is made more urgent by recent research developments related to the possible transmission of SFV to nonhuman primates by blood transfusion, which will be presented by speakers at this advisory committee meeting.

The topic of SFV was discussed at the December 13, 2001 BPAC meeting because of evidence at that time that SFV was being transmitted to some humans with occupational exposure to nonhuman primates. The consensus of the committee was that more data were needed to determine whether SFV presented any risk to the safety of blood transfusions.

Discussion:

<u>Transmission to Humans by Occupational Exposure to Nonhuman Primates</u>
Transmission of SFV to humans due to occupational exposure to infected nonhuman primates has been reported to occur in 2-5% of persons working with nonhuman primates in research institutions and zoos (Heneine et al., 1998; Sandstrom et al., 2000; Switzer et al., 2004); most of the infected persons had histories of scratch or bite injuries caused by the nonhuman primates (Switzer et al., 2004). In the study by Switzer et al., examination of archived serum samples from six of the persons with antibodies to SFV showed that they had had antibodies to SFV for periods ranging from eight to 26 years (mean = 22

years). SFV gene sequences could be amplified from nine of the 10 with antibodies to SFV; sequence analysis indicated that eight isolates were of chimpanzee origin and one was of baboon origin. All ten individuals with antibodies to SFV reported that they were generally in good health. Three wives of infected individuals were shown to have no evidence of SFV infection. None of the 187 workers tested had antibodies to other simian retroviruses.

Transmission to Humans from Nonhuman Primates under "Natural Conditions"

A report of transmission of SFV to humans by non-occupational contact with nonhuman primates (Wolfe, et al., 2004a) and an accompanying commentary (Peeters, 2004) appeared in the March 20, 2004 issue of *The Lancet*. In fact, the exposure was only somewhat "non-occupational" in the generally accepted use of the term "occupational," since the authors felt that the transmission probably occurred as a result of the hunting, preparation, and consumption of food made from tissues of nonhuman primates, sometimes referred to as "bushmeat." Wolfe et al. studied 1,099 residents of a tropical forest area of Cameroon who had regular contact with blood or other body fluids of nonhuman primates. Antibodies to SFV were found in 10 persons; among these 10, SFV was found by RT- PCR in the peripheral blood lymphocytes of three. These three apparently had acquired SFV in three distinctly separate transmissions from nonhuman primates; they were each from different villages, and the sequences of their SFV showed that the SFV in each of them was from a different primate species, each consistent with their individual hunting and food preparation histories (gorilla, mandrill, and *Cercopithecus* spp, respectively). (SFV strains are known to be highly specific for each host species.)

SFV Epidemiology

The prevalence of SFV in the nonhuman primate adult population ranges from 31-61% in the wild (Hussain et al., 2003; Calattini et al., 2004b) and 70-90% in captivity (Hussain et al., 2003). (In contrast, the prevalence of simian immunodeficiency virus [SIV] among nonhuman primates in the wild in the same areas is about 16% and the prevalence of simian T lymphotropic virus [STLV] is about 11% [Peeters, 2004].)

Human-to-human spread of SFV has not yet been shown to occur. Nevertheless, there is clearly primate-to-primate transmission among nonhuman primates in the wild. Transmission between primates is believed to occur by means of saliva, since SFV can be isolated easily from the saliva of infected nonhuman primates. Transmission by bites theoretically could be one mechanism of transmission from captive nonhuman primates to their handlers (Switzer et al, 2004). In support of this theory, a gorilla strain of SFV was detected in two Cameroonian hunters who had separate histories of multiple bite injuries during fights with gorillas (Calattini, et al., 2004 a).

No evidence of transmission of SFV by human-to-human blood transfusion was found in a study of recipients of blood from one donor who was later discovered to have SFV infection (Boneva et al., 2002). Studies of archived specimens from this donor showed that he had been infected with SFV over a nineteen-year period from 1981 to 2000; he had donated blood six times between 1992 and 1997. Lookback studies of two recipients

of his red blood cells, one recipient of his leukocyte-reduced red blood cells, and one recipient of his platelets revealed no cases of transmission of SFV (Boneva et al., 2002). Derivatives made from plasma pools containing this donor's plasma were negative when tested for SFV by RT-PCR (Boneva et al., 2002). Although this study may provide a basis for optimism, its small size and the absence of information about viral load in the blood donor preclude any firm conclusions.

SFV and the Possibility of Pathogenesis in Humans

Recent reports provide strong evidence of persistent SFV infections in humans (Heneine et al., 1998, 2003; Switzer et al., 2004). Studies of stored serum samples have revealed human SFV infections lasting as long as 19 and 26 years (Heneine et al., 1998; Switzer et al., 2004).

Although a putative "human" foamy virus reported in 1971 (Epstein, 2004), isolated from a nasopharyngeal carcinoma from a patient from Kenya, was later shown by sequencing to be the chimpanzee strain of SFV (Wolfe et al., 2004b), no etiologic association between SFV and any human disease has been established so far. Repeated efforts to show an association with nasopharyngeal carcinoma or other human diseases have all been negative (Heneine et al., 2003). All SFV-infected individuals generally report being in good health, although this observation may reflect the fact that studies of human SFV have been conducted mainly among healthy employees of research facilities and zoos. Nevertheless, existing data on health outcomes of SFV are limited and one cannot exclude the possible occurrence of disease after long latency periods (Switzer et al. 2004; Heneine et al. 1998, 2003).

Theoretical Concerns: SFV as a Model for Cross-species Transmission of a Simian Retrovirus

The reported transmission of SFV to humans by non-occupational contact with nonhuman primates not only places a renewed focus on SFV transmission; it also provides yet another example of the working model of retrovirus cross-species transmission, or "species jumping," of which human immunodeficiency virus (HIV) and human T lymphotropic virus (HTLV) are the most significant examples. Two simian immunodeficiency virus (SIV) strains emerged to form HIV types 1 and 2, and two strains of another simian retrovirus, simian T lymphotropic virus (STLV), emerged to form HTLV types I and II. Human diseases associated with infections with these emerging retroviruses were not recognized for many years; in the case of HTLV I, this delay was due in part to the fact that fewer than 5% of persons infected with the virus develop a disease.

The Issue of Possible Blood Donor Exclusion for Nonhuman Primate Exposure

Even though no human disease has been linked definitively to SFV infection, the theoretical concerns described above may lead many people to urge taking precautionary measures. However, such precautionary regulatory measures require careful consideration of risk level and the impact on the availability of needed blood products.

Handlers of nonhuman primates in a laboratory setting are not the only people with close contact with nonhuman primates. In addition, zoo workers, people who have nonhuman primates as pets (there are about 15,000 households with such pets in the U.S.), and bench laboratory scientists and technicians who conduct testing of primate serum and tissues may be at risk for SFV infection. The risk for scientists conducting behavioral studies on nonhuman primates theoretically could be lower than that for scientists conducting other types of studies. It would be a challenge to define precisely which individuals would pose a risk if they donated blood.

Questions for the Committee:

1. In the absence of any known disease association, should FDA be concerned about the potential for transfusion transmission of SFV?

2. Do the recent evidence of SFV infections in humans and of transmissibility of SFV by blood in animal studies heighten concern that known and unknown pathogenic viruses of nonhuman primates could enter the human blood supply?

3. Do the available scientific data warrant possible consideration of donor exclusion criteria for exposure to nonhuman primates? Please discuss the factors that should be considered.

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別紙 3-7

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		回	報告日 年　月　日	第一報入手日 2005 年 1 月 12 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			研究報告の公表状況	Heat sensitivity of a SARS-associated coronavirus introduced into plasma products Yunoki, M. et al. Vox Sanguinis. 2004;87:302-303	公表国 英国	
販売名（企業名）						

研究報告の概要	使用上の注意記載状況・その他参考事項等
本稿では，重症急性呼吸器症候群 (SARS) の病原体である SARS コロナウィルス (SARS-CoV) の熱不活化について検討された。SARS コロナウィルスのフランクフルト-1 株を数種の血漿分画製剤の製造工程で導入し，直後に 60℃の液状加熱処理を行った。試験した製剤は，アンチトロンビン III 製剤，ハプトグロブリン製剤，25%人血清アルブミン製剤，および 熱/PEG 処理静注用人免疫グロブリン製剤である。4 種の製剤全ておいて，SARS コロナウィルスは，60 分間の熱処理で容易に不活化することが出来た。しかし，各製剤の組成が異なるため，短時間におけるウイルスの熱感受性にはばらつきが認められた。アンチトロンビン III 製剤中のウイルス感染性は，60℃30 分間加熱後も持続していた。以上の結果は，SARS コロナウイルスに汚染された原料血漿による感染リスクは，仮にあったとしても，60℃10 時間の熱処理工程により極めて低くなることを示すものである。	

報告企業の意見	今後の対応
本研究報告は，血漿分画製剤の製造工程で実施されている 60℃，10 時間の加熱処理により，SARS コロナウイルスは生存できないことを示すものである。弊社のヒト血漿アルブミン，ヒト血漿タンパク製剤，およびフェリチン (コージネイト FS の製造工程で使用) にも同様の加熱処理が行われている。ヒト免疫グロブリン製剤については加熱処理が行われていないが，コロナウイルスはエンベロープを有するウイルスであり，本剤の製造工程における分画，限外濾過，S/D 処理では，高レベルのエンベロープウイルス除去能が確認されている。	現時点では，弊社の血漿分画製剤の添付文書，採漿方法および製造工程に対して新たな安全対策上の措置を講じる必要は無いと考える。引き続き関連情報の収集に努める。

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Vox Sanguinis (2004) 87, 302–303

SHORT COMMUNICATION

Heat sensitivity of a SARS-associated coronavirus introduced into plasma products

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Vox Sanguinis

Background and Objectives Various measures to inactivate/remove viruses have been implemented for manufacturing plasma-derived products. Here, we examined the heat inactivation ability of an agent of the severe acute respiratory syndrome (SARS), SARS coronavirus (CoV).

Materials and Methods The Frankfurt-1 strain of SARS-CoV was incorporated in manufacturing processes of several products by using samples collected immediately before liquid heat treatment at 60 °C.

Results SARS-CoV was easily inactivated by this treatment for 60 min in all in-process samples. However, the different composition of the tested samples affected the heat sensitivity of the virus strain: the infectivity of the virus in Antithrombin III preparation still remained after heating for 30 min at 60 °C.

Conclusion If by rare chance SARS-CoV contaminates source plasma, there should be no or only minor risk of this virus infection, due to sufficient inactivation by the 60 °C 10 h liquid heating step, although we must pay attention to the composition used for blood product preparation.

Received: 26 August 2004, revised 9 September 2004, accepted 10 September 2004

Key words: SARS-CoV, plasma-derived products, viral safety, virus inactivation.

Introduction

Various measures are available to inactivate or remove viruses during the manufacture of plasma-derived products. In the present study we evaluated the ability of liquid heat treatment to inactivate a coronavirus (CoV) associated with severe acute respiratory syndrome (SARS). The virus was introduced into several products during their manufacture and processing, immediately before liquid heat treatment at 60 °C.

Materials and methods

We used Vero E6 cells, cultured in minimal essential medium (MEM) containing 10% fetal bovine serum (FBS), 100 U/ml penicillin and 100 μg/ml streptomycin, for propagation of the Frankfurt-1 strain of SARS-CoV [1]. The Frankfurt-1 strain of SARS-CoV was kindly provided by Dr John Ziebuhr (University of Würzburg, Würzburg, Germany), through Dr Fumihiro Taguchi (National Institute of Infectious Diseases, Tokyo, Japan). For the infectivity assay, Vero E6 cells were seeded in a 96-well microplate (4×10^5 cells/ml, 0·1 ml/well) and, after overnight culture at 37 °C in 5% CO_2/air, the cells were inoculated with serial 10-fold dilutions of the virus stock solution (0·1 ml/well, five wells per dilution). On day 3 of culture, virus infectivity [the tissue culture infectivity dose 50% ($TCID_{50}$/ml), $\log_{10}$] was calculated by using Karber's method [2].

The four products tested (all supplied by the Benesis Corporation, Osaka, Japan) were:

(1) A heat-treated/polyethylene glycol (PEG)-treated intravenous immunoglobulin preparation (Kenketsu Venoglobulin®-IH).

(2) An anti-thrombin III preparation (Neuart®).

(3) A haptoglobin preparation (Haptoglobin Injection-Yoshitomi).

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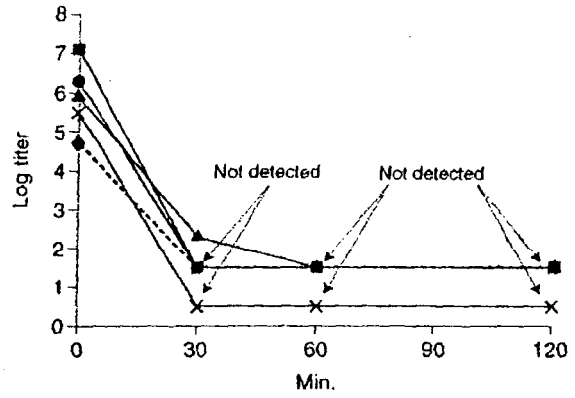

Fig. 1 Inactivation kinetics of a SARS-associated coronavirus (SARS-CoV). The Frankfurt-1 strain was inoculated, at either 10% (v/v, solid line) or 1% (v/v, broken line), into in-process solutions of a heat-treated/polyethylene glycol-treated intravenous immunoglobulin preparation (◆), an anti-thrombin III preparation (▲), a haptoglobin preparation (■), and a 25% human serum albumin preparation (●), each collected immediately before liquid heat treatment. The virus in these products was then treated at 60 °C for up to 2 h. The virus was also inoculated (10% v/v) into minimal essential medium (MEM) containing 2% fetal bovine serum (FBS) and then heat treated as a control (x). The data shown represent the virus infectivities remaining after heat treatment.

(4) A 25% human serum albumin preparation (Kenketsu Albumin-Wf).

In-process samples of the plasma-derived products used in the study were collected immediately before the 10-h liquid heat treatment at 60 °C that is used in the manufacture. The samples were inoculated with SARS-CoV, followed by heat treatment in liquid at 60 °C for 0·5–2 h, after which the remaining infectivity was titrated as described above.

Results and discussion

In all four in-process samples, Frankfurt-1 was rapidly inactivated to below the detection limit within 60 min. However, its infectivity in the anti-thrombin III preparation persisted, despite heating for 30 min at 60 °C, although the same amount of heating inactivated the virus in the other three preparations (Fig. 1). This result was confirmed by an independent experiment (data not shown). Furthermore, when Frankfurt-1 was inoculated into the solutions containing the stabilizer alone (without protein), 30 min of heating inactivated the virus to below the detection limit in all four products (data not shown), suggesting that the combination of the blood product preparation and its stabilizer affected the heat sensitivity of the virus. Rabenau and his colleagues also conducted experiments using the SARS-CoV FFM-1 strain. As in our study, they found that while the virus was stabilized by heating at 56 °C for 30 min in the presence of 20% FBS, it was inactivated at 60 °C in the presence and absence of 20% FBS [3]. In this context therefore we must take into consideration the combination of the plasma products and the stabilizer.

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