Table 5. Removal of prion by depth filters*.

Step	Sample	Spiking agent	Method	Before	Filtered	Retained	Clearance/reduction		Method	Ref.
							Filtered	*Retained*		
Seitz Supra P80‡ (Pall)	Supernatant of 8% ethanol precipitation	Hamster PrP^{Sc} Sc237	BH	3.5	3.4	ND	0.1	NA	CDI	[16]
			MF	3.5	3.6	ND	0.0	NA	CDI	
			CLDs	3.0	3.0	ND	0.0	NA	CDI	
			Purified	1.0	1.0	ND	0.0	NA	CDI	
	Supernatant of 38% ethanol precipitation		BH	0.9	0.0	ND	≥0.9	NA	CDI	
			MF	1.1(H) 0.8(L)	0.0(H) 0.0(L)	ND	≥1.1(H) ≥0.8(L)	NA	CDI	
			CLDs	0.9	0.0	ND	≥0.9	NA	CDI	
			Purified	2.4	0.0	ND	≥2.4	NA	CDI	
AP 20 (Millipore)	Supernatant I + III	Mouse PrP^{BSE} 301V	MF	7.0(H) 4.0(L)	4.6(H) 3.4(L)	ND	2.4(H) 0.6(L)	NA	BA	[39]
		Hamster PrP^{Sc} 263K	MF	ND	ND	ND	<1.0(L)	NA	WB	
	Supernatant I + III	Hamster PrP^{Sc} 263K	MF	ND	ND	ND	<1.0	NA	WB	[18]
Seitz KS 80 (Pall)	Supernatant I + III (AP20 filtered described as above)	Mouse PrP^{BSE} 301V	MF	6.3(H) 4.6(L)	≤3.2(H) ≤3.2(L)	ND	≥3.1(H) ≥1.4(L)	NA	BA	[39]
	Resuspended fraction V	Hamster PrP^{Sc} 263K	MF	ND	ND	ND	≥4.9	NA	WB	[18]

Note: data are referred from indicated reports and partially altered.

**Values given are expressed in log_{10} form. ‡Sonicated BH including 0.1% lysolecitin and followed by 0.45-0.22-0.1 µm serially filtered. The spiking agent was added before precipitation and CDI was performed after precipitation and after depth filtration. §Salt strip 1 M NaCl followed by 2 M. ¶0.22 µm-filtered prior depth filter. ‖0.22 µm filtered. ‖‖Yunoki* et al. *Unpublished Data.*

*BA: Bioassay (*in vivo *study); BH: Brain homogenate; BSE: Bovine spongiform encephalopathy; CDI: Conformation-dependent immunoassay; CDLs: Caveolae-like domains; dsBH: Detergent treated and sonicated BH; E: Early filtrate; H: High titer of prion on assay of spiked feed stock; IVIG: Intravenous immunoglobulin; L: Low titer of prion on assay of spiked feed stock; La: Late filtrate; M: Middle filtrate; MF: Microsomal fraction; NA: Not applicable; ND: Not determined; PrP: Prion protein; Sc: Scrapie; sMF: Sonicated MF; WB: Western blotting (*in vitro *study).*

Table 5. Removal of prion by depth filters* (cont.).

Step	Sample	Spiking agent	Method	Before	Filtered	Retained	Clearance/reduction		Method	Ref.
							Filtered	*Retained*		
Seitz K200P (Pall)	Resuspended fraction II	Hamster PrP^{Sc} 263K	MF	ND	ND	ND	≥2.8	NA	WB	[18]
Delipid 1 (Cuno)	Clarified fraction V suspension	Hamster PrP^{Sc} 263K	MF	ND	ND	ND	2.3	NA	WB	[18]
Zetaplus Delipid Plus (Cuno)	IVIG	Hamster PrP^{Sc} 263K	sMF	2.8	2.5	ND	0.3	NA	WB	##
			sMF#	4.1	2.7	ND	1.4	NA	WB	
			MF	2.8	1.1	ND	1.7	NA	WB	
Zetaplus 30LA (Cuno)	IVIG	Hamster PrP^{Sc} 263K	sMF	2.8	<0.4	ND	≥2.4	NA	WB	##
			MF	3.5	<0.4	ND	≥3.1	NA	WB	
Zetaplus 90SP (Cuno)	Supernatant III	Hamster PrP^{Sc} 263K	dsBH‡	7.9	<2.7(E) 4.2(M) 4.3(La)	7.4§	>3.3	0.5	WB	[45]
				7.1 <4.1¶	<2.7(E) <2.1(M) <2.0(La)	<3.6§	NA	NA	WB	
	Tris-buffered saline			7.0	6.2(E) 6.7(M) 6.0(La)	4.8§	0.1	2.2	WB	
Zetaplus 90LA (Cuno)	Clarified fraction V suspension	Hamster PrP^{Sc} 263K	sMF	3.5	<0.4	ND	≥3.1	NA	WB	##
			sMF#	4.5	<0.9	ND	≥3.6	NA	WB	
			MF	3.5	<0.4	ND	≥3.1	NA	WB	

Note: data are referred from indicated reports and partially altered.

**Values given are expressed in log_{10} form. ‡Sonicated BH including 0.1% lysolecitin and followed by 0.45-0.22-0.1 µm serially filtered. The spiking agent was added before precipitation and CDI was performed after precipitation and after depth filtration. §Salt strip 1 M NaCl followed by 2 M. ¶0.22 µm-filtered prior depth filter. #0.22 µm filtered. ##Yunoki* et al. *Unpublished Data.*

*BA: Bioassay (*in vivo *study); BH: Brain homogenate; BSE: Bovine spongiform encephalopathy; CDI: Conformation-dependent immunoassay; CDLs: Caveolae-like domains; dsBH: Detergent treated and sonicated BH; E: Early filtrate; H: High titer of prion on assay of spiked feed stock; IVIG: Intravenous immunoglobulin; L: Low titer of prion on assay of spiked feed stock; La: Late filtrate; M: Middle filtrate; MF: Microsomal fraction; NA: Not applicable; ND: Not determined; PrP: Prion protein; Sc: Scrapie; sMF: Sonicated MF; WB: Western blotting (*in vitro *study).*

summarized study results on the depth filtration of prions in 2004 [31]. However, since the mechanism and consistency of the filtration system is not clear, an evaluation study should be performed using individual manufacturing processes. Thus, it is clear that further knowledge is required regarding the depth filtration systems.

Conclusion

The current status of process evaluation methods for prion removal during manufacturing processes of plasma derivatives was introduced and discussed in this review. Problems to be stressed are:

- The form of pathogenic prions in blood is not clear, which in turn raises questions about the appropriateness of prion materials (spiking materials) used for evaluation studies;
- Preparation methods of prion materials for studies are very important to consider;
- Although some data are already available, the equivalency between model systems and vCJD/CJD must be strengthened.

The current status of the problems and the limitations of measures taken to overcome the problems are described. In addition, the difficulties in establishing conditions for down-scaled experiments are also discussed. More research on spiking materials of model systems for vCJD/CJD is necessary to know whether the currently used materials are appropriate for conducting process evaluation studies. Based on the outcome of such research, it should be carefully judged whether the spiking materials used by model systems are appropriate. At present, ethanol and PEG fractionations, filtration with virus-removal filters, depth filters, protein purification columns and so forth are thought to be effective for prion removal (to some extent).

For virus-removal filters, the partition mechanism is based on size exclusion. The performance of filters in different studies is consistent, and the pore size correlates well with prion removal. However, as aforementioned, variability in the performance is observed depending on the filtration conditions. In contrast to virus-removal filters, depth filters may remove prions more efficiently if process conditions can be optimized. Consequently, virus-removal and depth filters may have great potential for prion removal, although we do not know whether these filter steps (such as depth filters that are adventitiously effective, rather than effective by design) are perfect or not. Therefore, more work is required to establish the filtration conditions that are optimal for prion removal.

Future perspective

In the future, detection methods for pathogenic prions applicable for blood screening are likely to be introduced, and it is expected that the risks of vCJD/CJD transmission through blood will be further clarified. With the introduction of screening tests, it is expected that safety measures for plasma derivatives for prion contamination will be composed of two procedures, screening of source materials and removal during manufacturing processes (the same as for viruses). With progress in the status of pathogenic prions in blood, preparation methods for spiking materials will also likely be optimized. Equivalency between model systems and vCJD/CJD will probably be determined more precisely, although from a safety perspective such studies are challenging. Furthermore, if the usefulness of a quantitative infectivity assay method using cultured cells is confirmed for prion-clearance study, process evaluation could be performed using such an assay. Several techniques to effectively remove prions during the manufacturing process are now under development [46,47]. Once the processes are validated or effective removal has been demonstrated under a variety of process conditions, they may be introduced in actual manufacturing scenarios. The removal ability of processes and the accuracy of process evaluation will be highly improved by combining these new observations and techniques. These improvements will significantly contribute to the safety of plasma derivatives with respect to prion contamination; however, for safety assurance, there is no limit to improvement.

Acknowledgements

The authors thank Andy Bailey, ViruSure GmbH, and Akikazu Sakudo, Osaka University, Japan, for their critical review of this manuscript.

Executive summary

- Incidence of bovine spongiform encephalopathy (BSE) is falling, at least in the UK. Risk of variant Creutzfeldt–Jakob disease transmission derived from BSE-infected bovines is tending to decrease. On the other hand, the risk of human-to-human transmission by blood transfusion persists.

Executive summary

- Sensitive screening methods for the detection of prions in blood are not currently available. Therefore, for plasma derivatives, safety measures against prions are mainly geographical donor deferral and the removal of prions during manufacturing processes.
- Individual manufacturing processes for prion removal are usually evaluated by scaling down the actual manufacturing conditions to laboratory conditions, and using established scrapie strains as model systems. Since the status of the prion protein in blood is not known, the preparation method of prions as spiking materials for these experiments must be considered carefully.
- There are two different procedures to assay prions: *in vitro* study to detect prions by western blotting (WB) and so forth; and *in vivo* study to detect infectious prions by inoculating samples into animals. In some cases for only a slight amount of prion, even when WB demonstrates a negative result, due to the limitation of this technique, for example inappropriate use of antibody, infectivity may be detected in samples. Therefore, for process evaluation, differences between test methods must be considered carefully.
- Depending on process conditions, the prion-removal ability of the process may vary, even if the removal pattern is similar. Thus, the design of the evaluation study is very important. Each manufacturing process must be evaluated independently.
- At present, among the manufacturing processes of plasma derivatives, ethanol fractionation, polyethylene glycol fractionation, column chromatography and filtration with virus-removal filters and depth filters are considered to be effective for prion removal.
- The combination of processes that contribute to prion removal is necessary in order to improve the consistency of the manufacturing processes for prion removal.
- Consequently, the development of new techniques for screening and prion removal, and improvement of process evaluation methods is highly desirable.

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一般的名称	①乾燥抗 HBs 人免疫グロブリン ②ポリエチレングリコール処理抗 HBs 人免疫グロブリン		研究報告の公表状況	FDA/CBER/20060808	公表国 アメリカ	
販売名 （企業名）	①ヘブスブリン（ベネシス） ②静注用ヘブスブリン－IH（ベネシス）					

研究報告の概要

FDA/CBER 発行の 2002 年 1 月付" Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products"の修正ガイダンス案である。勧告内容は以下の通り。
1980 年以降にフランス国内で血液又は血液成分の投与を受けたことのあるドナーは全て永久供血停止とする。但し、この勧告に基づけば供血停止とされるドナーであっても、もし当該ドナーが、非注射剤製造用にのみ血液成分の採取を認める CBER 認可プログラムに関与する場合は、供血を続けるよう推奨する。当該ドナー由来の製品には特別なラベルを付するよう推奨する。
このガイダンス案は、輸血用全血並びに血液成分、及び注射剤の製造に供される血液成分（回収血漿、原料白血球並びに原料血漿を含む）に適用される。

報告企業の意見

FDA/CBER発行の2002年1月付" Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products"の修正ガイダンス案である。
これまで血漿分画製剤によってvCJDを含むプリオン病が伝播したとの報告はない。しかしながら、万一vCJD感染者の血漿が本剤の原料に混入した場合には、製造工程においてプリオンを低減し得るとの報告があるものの、製剤から伝播する可能性を完全には否定し得ない。そのため、弊社の血漿分画製剤の製造工程におけるTSE感染性低減に関する検証実験を加速し、自社データを早期に取得し、工程評価を行い、必要に応じて工程改善を実施する予定である。

今後の対応

vCJD の疫学情報については、今後も注視することとする。

使用上の注意記載状況・その他参考事項等

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

Guidance for Industry

Amendment (Donor Deferral for Transfusion in France Since 1980) to "Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products"

DRAFT GUIDANCE

This guidance 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.fda.gov/dockets/ecomments. 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, Training and Manufacturers Assistance (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 Dr. Sharyn Orton, Division of Blood Applications at 301-827-3524.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
August 2006

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Contains Nonbinding Recommendations

Draft – Not for Implementation

Guidance for Industry

Amendment (Donor Deferral for Transfusion in France Since 1980) to "Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products"

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

This draft guidance, which we are issuing as a level I guidance, is intended to amend the "Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products" (CJD/vCJD guidance), dated January 2002 (Ref. 1), by adding a donor deferral recommendation for donors who have received a transfusion of blood or blood components in France since 1980. After we review comments received on this draft guidance, we will amend the CJD/vCJD guidance by incorporating this donor deferral recommendation, update any outdated information, and reissue the revised CJD/vCJD guidance as a level II guidance document for immediate implementation.

This draft guidance applies to Whole Blood and blood components intended for transfusion, and blood components intended for use in further manufacturing into injectable products, including recovered plasma, Source Leukocytes and Source Plasma. Special provisions apply to donors of blood components intended solely for manufacturing of non-injectable products (see section III). Within this document, "donors" refers to donors of Whole Blood and blood components and "you" refers to blood collecting establishments.

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

Since the publication of the CJD/vCJD guidance, we have learned of additional information warranting revision to the guidance to address a possible increased risk of vCJD transmission from individuals who have been transfused in France since 1980. This revision is based on (1) the likelihood of exposure to the Bovine Spongiform Encephalopathy (BSE) agent in that country and (2) the recent documentation of three presumptive cases of transfusion-transmitted vCJD infection in the United Kingdom (U.K). As of August 1, 2005, 14 definite or probable cases of vCJD have been reported in France (Ref. 2).

Available data suggest that large amounts of U.K. beef exported to France during the peak years of the U.K. BSE epidemic constituted a substantial source of exposure in France to the BSE agent. An estimated 60% of U.K. bovine carcasses were exported to France (Ref. 3) accounting for approximately 6% of French consumption of beef products (Ref. 4). It is believed that the first recognized vCJD cases in France were infected by consuming imported U.K. beef because: 1) none of the individuals had lived in the U.K.; 2) the indigenous French BSE epidemic is relatively small and more recent than that in the U.K.; and 3) travels to the U.K. accounted for only 2% of the French total exposure to the BSE agent (Ref 3).

There have been a total of three presumptive cases of transfusion-transmitted vCJD, and all have been in the U.K. The first presumptive transfusion-transmitted case of vCJD by red blood cells was reported to the U.K. Parliament on December 17, 2003 (Ref. 5). A second presumptive case was reported in the U.K. in 2004 (Ref. 6). A third presumptive case was publicly announced by authorities in the U.K. in 2006 (Ref. 7).

On February 8, 2005, the Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC) discussed the available data and recommendations for deferral of U.S. donors transfused since 1980 in France and in other European countries. The TSEAC voted for deferral of blood donors who have received a transfusion of blood or blood components in France since 1980 but against deferral of Source Plasma donors with that same history. The TSEAC did not support deferral of blood donors or Source Plasma donors with history of transfusion in other European countries since 1980 (Ref. 8).

The incubation period for classical CJD may be as long as 38.5 years. Accumulating evidence suggests that the asymptomatic incubation periods of vCJD may be very long as well (sometimes exceeding 12 years from the time of exposure to the BSE agent), and blood collected as long as three years before otherwise healthy blood donors showed any sign of illness is presumed to have transmitted vCJD infection to recipients (Refs. 5 and 6). While the risk of dietary exposure to the BSE agent in France, as in the U.K. and other European countries, has almost certainly decreased in recent years thanks to successful efforts to control the BSE epidemic in cattle and to protect food from contamination with the BSE agent, an unknown but possibly significant number of blood donors might have already been infected in France during the peak years of the BSE outbreak in Europe. These considerations led FDA, consistent with the recommendations of the TSEAC, to conclude that it would be a prudent

preventive measure to indefinitely defer blood donors who have received transfusions of blood or blood components in France since 1980. Laboratory studies using model TSE agents have demonstrated that TSE infectivity may be reduced by certain plasma fractionation manufacturing steps (Ref. 9). While experimental studies are reassuring, not all products have been thoroughly studied. In addition, it remains uncertain whether the models accurately reflect the form of infectivity in blood, which has not been characterized. Therefore, as an added safeguard and prudent preventive measure, we also recommend that Source Plasma donors who have received a transfusion of blood or blood components in France since 1980 be indefinitely deferred. However, we believe that blood components collected solely for manufacturing into non-injectable products (e.g., materials used in in vitro diagnostic test kits) need not be deferred. We will continue to monitor the BSE epidemic and re-evaluate the necessity of deferring donors transfused in other European countries.

III. RECOMMENDATIONS

You should indefinitely defer all donors who have received a transfusion of blood or blood components in France since 1980.

NOTE: Donors who are otherwise deferred based upon this recommendation should continue to donate if they are participating in a CBER-approved program that allows collection of blood components solely for use in manufacturing of non-injectable products. We recommend special labeling for products obtained from such donors (see section VII.A of the CJD/vCJD guidance).

All other recommendations from the CJD/vCJD guidance remain unchanged.

IV. IMPLEMENTATION

We recommend that you implement this donor deferral recommendation within six months of the date that we finalize this draft guidance amendment. This draft guidance amendment will be finalized by reissuing the CJD/vCJD guidance inclusive of the amended language.

V. REFERENCES

1. FDA "Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products," January 2002; http://www.fda.gov/cber/gdlns/cjdvcjd.htm.
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