

# **Amendment to “Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease and Variant Creutzfeldt-Jakob Disease by Blood and Blood Products; Guidance for Industry”**

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## **Draft Guidance for Industry**

**This guidance document is for comment purposes only.**

Submit one set of either electronic or written comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance.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

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

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Biologics Evaluation and Research  
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**Contains Nonbinding Recommendations**

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*This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.*

**I. INTRODUCTION**

This guidance, when finalized, will amend the document entitled “Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease and Variant Creutzfeldt-Jakob Disease by Blood and Blood Products; Guidance for Industry” updated January 2016 (the “2016 vCJD Guidance”) (Ref. 1). The guidance provides revised recommendations intended to reduce the possible risk of transmission of variant Creutzfeldt-Jakob Disease (vCJD) by blood and blood products by: (1) revising and removing certain recommended deferrals for geographic risk of bovine spongiform encephalopathy (BSE) exposure; and (2) recommending deferral for individuals with a history of blood transfusion in Ireland from 1980 to the present.

The recommendations in this guidance apply to the collection of Whole Blood and blood components intended for transfusion or for use in further manufacturing into injectable and non-injectable products, including recovered plasma, Source Leukocytes and Source Plasma. Within this document, “donors” refers to donors of Whole Blood and blood components and “you” refers to blood collection establishments.

When this draft guidance is finalized, we, FDA, will amend the 2016 vCJD Guidance by incorporating into an updated final guidance any new recommendation adopted. All other recommendations in the 2016 vCJD Guidance will remain unchanged.

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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. CJD and vCJD

Creutzfeldt-Jakob Disease (CJD) is a rare but invariably fatal degenerative disease of the central nervous system, one of a group of transmissible diseases called transmissible spongiform encephalopathies (TSEs) or prion diseases. TSEs are associated with poorly understood transmissible agents (Refs. 2-7), now designated TSE agents or prions (Ref. 8). Cases of sporadic CJD—the most common human TSE—occur at low frequency by an unknown mechanism. CJD may be acquired by an identified exogenous exposure (usually iatrogenic) to infectious material, or it may be familial, associated with one of a number of mutations in the prion-protein-encoding (*PRNP*) gene. Clinical latency for iatrogenic CJD, following point exposures to contaminated materials, has sometimes exceeded 30 years (Ref. 9); incubation periods for kuru—another human TSE—have sometimes exceeded 50 years (Ref. 10).

In 1996, a previously unrecognized variant of CJD, now designated variant CJD (vCJD), was reported in the United Kingdom (U.K.) (Ref. 11). vCJD is distinguished from CJD by differences in clinical presentation, cerebral imaging, neuropathologic changes, and other features (Refs. 11-15). Laboratory and epidemiologic studies have linked vCJD to human infection with the agent of BSE, probably acquired from contaminated beef products (Refs. 16, 17). BSE was first recognized in the U.K. in 1985 and spread to most European countries and beyond (Ref. 18). The BSE and vCJD epidemics are currently in decline, although BSE has not been eradicated (Refs. 18, 19).

### B. vCJD Risk in Blood

Early studies with blood of experimentally TSE-infected animals suggested that blood contained very low levels of infectivity (orders of magnitude less than in brain) but often sufficient to transmit the disease to susceptible animals. These results and the unique accumulation of abnormal prion protein seen in lymphoid tissues of persons with vCJD (but not in other forms of CJD) led to concerns that transmission of vCJD by blood might pose a greater risk than for sporadic CJD (Ref. 20). U.K. authorities have reported four transmissions of vCJD infection (three overt, one latent) by transfusions of non-leukocyte reduced red blood cells (RBC) and one possible transmission of vCJD by plasma-derived Factor VIII (Refs. 21-24). vCJD infectivity is present in the blood of affected individuals during the asymptomatic phase of disease for at least 3.5 years prior to onset of overt illness. In the U.K., donors unknowingly infected with vCJD and healthy at the time of

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donation donated blood that transmitted vCJD to some recipients. These cases in the U.K. provided convincing epidemiological evidence that human blood carries the infectious vCJD agent and that the disease is transmissible by blood transfusion and plasma products (as it is with blood of TSE-infected animals). No cases of transfusion-transmitted vCJD (TTvCJD) have been reported in recipients of leukocyte reduced RBC. No cases of TTvCJD have been reported in the United States (U.S).

### **C. FDA Rationale for Revised Donor Deferral Recommendations for Geographic Risk of BSE Exposure**

Starting in 1999, FDA issued several guidance documents intended to reduce the risk of TTvCJD by recommending that blood establishments defer donors who had spent time in certain countries where the risk of dietary exposure to the BSE agent was higher than that in the U.S. (Ref. 1). The deferral policy is likely to have reduced the risk of TTvCJD (Ref. 25). However, the deferrals have also eliminated a substantial number of otherwise eligible blood donors, most of whom are unlikely to be infected with vCJD. Based on these considerations and on the likely beneficial effect of leukocyte reduction in preventing about 54% of TTvCJD (Refs. 26-28) and acknowledging a marked decline of the BSE and vCJD epidemics worldwide (Refs. 18, 19), FDA decided to review the currently recommended geographic deferral policies.

On June 1, 2015, the FDA Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC) discussed FDA's quantitative risk assessment estimating the effects of geographic donor deferrals in reducing the risk of TTvCJD. Based on results of the risk assessment, FDA is recommending a revised vCJD-related geographic deferral policy with consequent changes in the donor history questionnaire. A comparison of residual TTvCJD risk associated with current and modified deferral policies has been published (Ref. 25) and forms the basis of this draft amendment to the 2016 vCJD Guidance.

#### **1. Risk Assessment**

FDA developed a quantitative risk assessment based on a global geographic "risk ranking" model (Ref. 25) that estimated the contributions of donors potentially exposed to the BSE agent in various countries to total U.S. TTvCJD risk. The risk of exposure to the BSE agent was estimated either from the observed ("attributed") vCJD case rate of a country or from a rate "imputed" from probable exposure of the population to the BSE agent in beef products. The model then estimated potential person-years of potential BSE exposure by U.S. donors in the country (U.S. travelers visiting the country and immigrants to the U.S. from the country). FDA next used the model to evaluate both risk reduction and donor loss resulting from the current donor deferral policy compared with an alternative deferral option. FDA also evaluated a potential additional reduction in risk afforded by leukocyte reduction of RBC.

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The model estimated that current geographic donor deferrals for vCJD risk combined with leukocyte reduction of RBC voluntarily implemented by blood establishments have reduced risk of vCJD transmission via RBC transfusion by approximately 90%. The model also indicated that U.K., Ireland, and France, the three countries with the highest vCJD risks, contributed 95% of the total TTvCJD risk in the U.S. Thus, by deferring donors only for time spent in these three countries and incorporating an assumption that 95% of all RBC currently transfused in the U.S. are leukocyte reduced (Ref. 29), the model predicted that the modified policy would maintain a level of blood safety similar to that resulting from current policy. A similar estimate for reducing risk of TTvCJD is presented in Table 1 in section II.C.3 of this guidance, on the alternative assumption that only 71.3% of RBC units are leukocyte reduced, consistent with a recent national survey report (Ref. 30). Based on these results, FDA is proposing to recommend deferral only for donors who spent time in U.K., Ireland, and France (and donors exposed to U.K. beef on certain U.S. military bases in Europe) and no longer recommending deferrals for time spent in all other European countries. These revisions would simplify the donor screening process and potentially allow more donors to donate. The other CJD-related and vCJD-related recommended deferrals in the 2016 vCJD Guidance would remain unchanged.

### **2. Leukocyte Reduction of Cellular Blood Components**

Experience in the U.K. with universal leukocyte reduction of cellular blood components during the past 17 years has been far more encouraging than animal studies would have predicted (Refs. 27, 31). All four TTvCJD infections reported in the U.K. to date have been among a cohort of 27 persons transfused with non-leukocyte reduced RBC from donors who later developed symptomatic vCJD, while none of 25 transfusions of leukocyte reduced RBC from asymptomatic vCJD-infected donors have transmitted vCJD to recipients (Ref. 32). These compelling data indicate that leukocyte reduction reduces the risk of TTvCJD.

In addition to reducing the risk of TTvCJD, leukocyte reduction also provides other medical benefits. Leukocyte reduction is proven to reduce adverse effects attributed to leukocytes in transfused blood components including non-hemolytic febrile transfusion reactions, HLA alloimmunization and transmission of certain cell-associated blood-borne pathogens (e.g., cytomegalovirus, human T-cell lymphotropic viruses) (Refs. 33-36).

### **3. Risk Assessment Results**

Table 1 provides the results from the risk assessment model. The FDA risk assessment model estimated the probable contribution of leukocyte reduction to lowering TTvCJD risk. Currently U.S. blood establishments voluntarily leukocyte reduce approximately 71.3-95% of transfused RBC units (Refs. 29, 30). Additional reduction in TTvCJD risk might be achieved if all RBC products were leukocyte reduced. FDA estimated the additional decreased risk from leukocyte reduction and

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total risk reduction from combined donor deferral and leukocyte reduction. The estimated risk reduction by both the current 71.3-95% leukocyte reduction and universal leukocyte reduction of RBC, should that be implemented, were compared (see Table 1). Similar estimated reductions in total vCJD risk of close to 90% were achieved by both the current donor deferral policy and the proposed policy when either 71.3%, 95% or 100% of RBC were leukocyte reduced.

Table 1. Results from Risk Assessment Model

*Donor Deferral Strategy	Donor deferral only	Total percentage risk reduction (additional risk reduction)			Annual number of donors lost
		Donor deferral plus 71.3% RBC Leukocyte Reduction	Donor deferral plus 95% RBC Leukocyte Reduction	Donor deferral plus universal RBC Leukocyte Reduction	
<i>Model 1</i>	79.0%	87.1% (8.1%)	89.8% (10.8%)	90.4% (0.6%)	254,091
<i>Model 2</i>	78.0%	86.5% (8.5%)	89.3% (11.3%)	89.9% (0.6%)	156,021

\*Model 1. Current donor deferral policy (U.K. >3 months, 1980-1996; other countries in Europe: >5 years, 1980-present).

\*Model 2. Proposed donor deferral policy (U.K. >3 months, 1980-1996; France and Ireland: >5 years, 1980-2001).

Table 2 includes a summary of the proposed recommendations for geographical donor deferral changes. The proposed recommendations change the deferral for time spent in all European countries except for the U.K. Deferrals for time spent in the U.K. are unchanged because the risk assessment model results did not change the conclusions about U.K. risk of BSE exposure. Similarly, we are not changing the recommended deferral for individuals who spent time on military bases in Europe because their BSE exposure risk was from beef products sourced from the U.K. The risk assessment model also indicated that Ireland had a BSE risk similar to that of France. Therefore, we are recommending the same deferral period for time spent in France and Ireland and adding a deferral for individuals who had a blood transfusion in Ireland from 1980 to present.<sup>1</sup> The risk period for BSE exposure in Ireland and France is limited to 1980-2001 based on implementation of safeguards to the food chain by 2001 within the European countries (Ref. 37).

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<sup>1</sup> Some unknown number of persons may remain latently infected with the vCJD agent long after dietary exposure to the BSE agent ended; it is not known if their blood would transmit infection to recipients. Until the situation becomes better understood, FDA recommends deferring anyone transfused in the U.K., Ireland, or France from 1980 to the present.

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Table 2. Summary of Current Geographical vCJD Blood Donor Deferrals and the Proposed Deferrals

<b>Current deferrals</b>	<b>Proposed deferrals</b>
Donors who spent cumulatively $\geq 3$ months in the U.K. from 1980 to 1996	Unchanged
Donors who spent cumulatively $\geq 5$ years in France or other countries in Europe from 1980 to present	Donors who spent cumulatively $\geq 5$ years in France or Ireland from 1980 to 2001
Donors with a history of blood transfusion in the U.K. and France from 1980 to the present	Donors with a history of blood transfusion in the U.K., France, or Ireland from 1980 to the present
Donors based on time and duration of exposure at military bases in Europe during periods in which commissaries and mess halls were supplied with beef products from the U.K.	Unchanged

#### 4. 2015 TSEAC Meeting

FDA sought advice from TSEAC regarding revised geographic donor deferral policies to reduce the risk of TTvCJD. FDA presented results of the FDA risk assessment model predicting that deferral of donors who spent three months or longer in the U.K. from 1980 to the end of 1996 or five years or more in France or Ireland from 1980 through the end of 2001 plus leukocyte reduction of RBC (assumed to reduce risk of TTvCJD by about 54%) would maintain close to the current estimated level of risk reduction but allow a modest number of donors currently deferred to be reentered. FDA considered 2001 to be the year by which most European countries were to have implemented steps to protect food and animal feed from contamination with the BSE agent, steps similar to those adopted by 1996 in the U.K. Some TSEAC members disagreed with several assumptions used to develop the statistical model. FDA recognized the uncertainties of the risk assessment resulting from limitations of available information and agreed with the TSEAC members' concerns. Following the meeting, FDA investigated the issues raised by TSEAC and concluded that, although the TSEAC concerns were reasonable, none of the concerns changed the final results of the risk assessment or its final conclusion (Ref. 25).

At the meeting, the TSEAC also voted unanimously in favor of universal leukocyte reduction to reduce the risk of TTvCJD (Ref. 38).

### III. RECOMMENDATIONS

The recommendations set forth below, when finalized, will update the donor deferral recommendations in the 2016 vCJD Guidance at sections IV.A.3-6, and 8 and IV.D.2.b. questions 1-4. All other recommendations in the guidance related to risk of CJD and familial TSEs will remain unchanged.



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The following recommendations apply to the collection of Whole Blood and blood components intended for transfusion or for use in further manufacturing into injectable and non-injectable products, including recovered plasma, Source Leukocytes and Source Plasma.

#### **A. Recommendations for Donor Deferral**

We recommend that you defer donors for geographic risk of BSE exposure as follows:

1. Defer indefinitely a donor who has spent three months or more cumulatively in the U.K. from 1980 to 1996.
2. Defer indefinitely a donor who has spent five years or more cumulatively in France or Ireland<sup>2</sup> from 1980 to 2001.
3. Defer indefinitely former or current U.S. military personnel, civilian military personnel, and their dependents as follows:
  - a. Individuals who resided at U.S. military bases in Northern Europe (Germany, U.K., Belgium, and the Netherlands) for six months or more from 1980 through 1990, or
  - b. Individuals who resided at U.S. military bases elsewhere in Europe (Greece, Turkey, Spain, Portugal, and Italy) for six months or more from 1980 through 1996.
4. Defer indefinitely a donor with a history of blood transfusion in the U.K., France, or Ireland from 1980 to the present.

Appendix Table 1 in this guidance provides a summary of the current and revised recommendations for geographic risk of BSE exposure (see Appendix).

#### **B. Recommendations for Donor History Questionnaire**

We recommend that blood collection establishments update their donor history questionnaires (DHQ), including full-length and abbreviated DHQs and accompanying materials (e.g., flow charts) and processes to incorporate the recommendations provided in this guidance.

We recommend that the updated DHQ and accompanying materials include the following elements to assess donors for geographic risk of BSE exposure:

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<sup>2</sup> Note that Northern Ireland is part of the U.K.

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1. A history of travel or residence between 1980 through 1996 that adds up to three months or more in the U.K. (England, Northern Ireland, Scotland, Wales, the Isle of Man, the Channel Islands, Gibraltar, or the Falkland Islands).
2. A history of receiving a transfusion of blood, platelets, plasma, cryoprecipitate, or granulocytes since 1980 in the U.K. (England, Northern Ireland, Scotland, Wales, the Isle of Man, the Channel Islands, Gibraltar, or the Falkland Islands), Ireland, or France.
3. A history of serving as a member of the military, a civilian military employee, or a dependent of a member of the U.S. military between 1980 and 1996 and spending a total time of six months or more associated with a military base in any of the following countries:
  - From 1980 through 1990 in Belgium, the Netherlands, or Germany, or
  - From 1980 through 1996 in Spain, Portugal, Turkey, Italy, or Greece.
4. A history of travel or residence that adds up to five years or more in France or Ireland from 1980 through 2001 (including time spent in the U.K. from 1980 through 1996).

Appendix Table 2 in this guidance provides a summary of the current and revised recommendations for DHQ (see Appendix).

### **C. Donor Requalification**

Under 21 CFR 630.35, you may determine a deferred donor to be eligible if, at the time of the current collection, the criteria that were the basis for the previous deferral are no longer applicable. For donors deferred for reasons other than under 21 CFR 610.41(a), you must determine that the donor has met criteria for requalification by a method or process found acceptable for such purposes by FDA (21 CFR 630.35(b)).

Accordingly, donors who were previously deferred because they spent five years or more in France or other countries in Europe since 1980 may be eligible to donate provided that they would not be deferred under section III.A of this guidance and they meet all other donor eligibility criteria.

## **IV. IMPLEMENTATION**

Note: This guidance is being issued for comment purposes only. Implementation of the recommendations contained herein is not recommended at this time.

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When this guidance is finalized, you may implement any revised recommendations once you have revised your DHQs, including the full-length and abbreviated DHQs, and accompanying materials to reflect the new donor deferral recommendations.

Licensed blood establishments must report the revisions to FDA in the following manner (21 CFR 601.12):

1. Revision of your own DHQs and accompanying materials must be submitted to FDA as a prior approval supplement (PAS) under 21 CFR 601.12(b).
2. Revision of a previously FDA accepted DHQ and accompanying materials must be reported as a major change if you are revising the FDA accepted DHQ and accompanying materials to implement these new recommendations. Report such a change to FDA as a PAS under 21 CFR 601.12(b).

We recommend that you include the following in the PAS submission:

- a. Form FDA 356h “Application to Market a New or Abbreviated New Drug or Biologic for Human Use” which may be obtained at <https://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm>;
  - b. A cover letter describing the request and the contents of the submission;
  - c. The DHQ and accompanying document(s). Please highlight the modifications.
3. If the current version of the DHQs and accompanying materials prepared by the AABB Donor History Task Force or Plasma Protein Therapeutics Association are revised to contain the recommendations in this guidance and are found acceptable by FDA, we would consider the implementation of the DHQ and accompanying materials to be minor changes, if implemented without modification and in their entirety as a complete process for administering questions to donors. Report such a change to FDA in your annual report under 21 CFR 601.12(d), noting the date the process was implemented (see 21 CFR 601.12(a)(3)).

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### V. REFERENCES

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### APPENDIX

Appendix Table 1. Summary of Current and Revised Recommendations for Geographic Risk of BSE Exposure

Section of the 2016 vCJD Guidance	Current Recommendation	Proposed Recommendation
IV.A.	Donor deferral criteria 1-7 apply to all donors.  Donor deferral criterion 8 (residence in Europe for 5 years or more between 1980 and the present) applies to all donors <i>with the exception of</i> donors of Source Plasma.	Donor deferral criteria 1-7 apply to all donors.  Donor deferral criterion 8 is deleted.
IV.A.3	You should indefinitely defer donors who have spent 3 months or more cumulatively in the U.K. from the beginning of 1980 through the end of 1996.	Unchanged
IV.A.4	You should indefinitely defer donors who have spent 5 years or more cumulatively in France from the beginning of 1980 to the present.	You should indefinitely defer donors who have spent 5 years or more cumulatively in France or Ireland (but not Northern Ireland, which is part of the U.K.) from 1980 through 2001.
IV.A.5	You should indefinitely defer former or current U.S. military personnel, civilian military personnel, and their dependents as follows: a. Individuals who resided at U.S. military bases in Northern Europe (Germany, U.K., Belgium, and the Netherlands) for 6 months or more from 1980 through 1990, or b. Individuals who resided at U.S. military bases elsewhere in Europe (Greece, Turkey, Spain, Portugal, and Italy) for 6 months or more from 1980 through 1996.	Unchanged
IV.A.6	You should indefinitely defer donors who have received a transfusion of blood or blood components in the U.K. or in France between the beginning of 1980 and the present.	You should indefinitely defer donors who have received a transfusion of blood or blood components in the U.K. or in France or <u>in Ireland</u> from the beginning of 1980 to the present.
IV.A.8	You should indefinitely defer donors of Whole Blood, blood components for transfusion, and Source Leukocytes, who have lived cumulatively for 5 years or more in Europe from the beginning of 1980 until the present. (Note this criterion includes time spent in the U.K. from 1980 through 1996 and time spent in France from 1980 to the present.) Unless otherwise unsuitable (for example, because they lived in the U.K. or France or on U.S. military bases for the periods of time noted previously), these donors remain eligible for Source Plasma donation.	Deleted

## Contains Nonbinding Recommendations

*Draft – Not for Implementation*

Appendix Table 2. Summary of Current and Revised Recommendations for DHQ

Section of the 2016 vCJD Guidance	Current Recommendation	Proposed Recommendation
IV.D.2	<p>Since the beginning of 1980, have you ever lived in or traveled to Europe?</p> <p>a. If the donor answers “No”, you need not take any further action</p> <p>b. If the donor answers “Yes”, then ask the following questions;</p>	Delete
IV.D.2. question 1	Between 1980 through 1996 did you spend time that adds up to 3 months or more in the U.K. (England, Northern Ireland, Scotland, Wales, the Isle of Man, the Channel Islands, Gibraltar, or the Falkland Islands)?	Unchanged*
IV.D.2. question 2	Since 1980 have you received a transfusion of blood, platelets, plasma, cryoprecipitate, or granulocytes in the U.K. (England, Northern Ireland, Scotland, Wales, the Isle of Man, the Channel Islands, Gibraltar, or the Falkland Islands) or in France?	Assess donors for a history of receiving a transfusion of blood, platelets, plasma, cryoprecipitate, or granulocytes since 1980 in the U.K. (England, Northern Ireland, Scotland, Wales, the Isle of Man, the Channel Islands, Gibraltar, or the Falkland Islands), <u>Ireland</u> or France.
IV.D.2. question 3	<p>Between 1980 through 1996, were you a member of the military, a civilian military employee, or a dependent of a member of the U.S. military?</p> <p>If the donor answers “No,” you need not take any further action.</p> <p>If the donor answers “Yes,” ask the following question:</p> <p>Did you spend a total time of 6 months or more associated with a military base in any of the following countries:</p> <ul style="list-style-type: none"> <li>• From 1980 through 1990 in Belgium, the Netherlands, or Germany, or</li> <li>• From 1980 through 1996 in Spain, Portugal, Turkey, Italy, or Greece?</li> </ul> <p>4) From 1980 to 2001, have you spent time that adds up to 5 years or more in France or in Ireland?</p>	Unchanged*
IV.D.2. question 4	Since 1980, have you spent time that adds up to 5 years or more in France?	Assess donors for a history of travel or residence that adds up to 5 years or more in France or Ireland from 1980 through 2001 (including time spent in the U.K. from 1980 through 1996).
IV.D.2. question 4 (alternative)	Since 1980, have you spent time that adds up to 5 years or more in Europe (including time spent in the U.K. from 1980 through 1996)?	Deleted

\* Note that Section III.B. of this guidance does not recommend specific questions for inclusion on the DHQ.