TECHNICAL REPORT

ISO/TR 22442-4

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Medical devices utilizing animal tissues and their derivatives —

Part 4: Principles for elimination and/or inactivation of transmissible spongiform encephalopathy (TSE) agents and validation assays for those processes

Dispositifs médicaux utilisant des tissus animaux et leurs dérivés —

Partie 4: Principes d'inactivation et/ou d'élimination des agents transmissibles de l'encéphalopathie spongiforme bovine (ESB) et essais de validation de ces procédés

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

In exceptional circumstances, when a technical committee has collected data of a different kind from that which is normally published as an International Standard ("state of the art", for example), it may decide by a simple majority vote of its participating members to publish a Technical Report. A Technical Report is entirely informative in nature and does not have to be reviewed until the data it provides are considered to be no longer valid or useful.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

ISO/TR 22442-4 was prepared by Technical Committee ISO/TC 194, *Biological evaluation of medical devices*, Subcommittee SC 1, *Tissue product safety*.

ISO 22442 consists of the following parts, under the general title *Medical devices utilizing animal tissues and their derivatives*:

— Part 1: *Application of risk management*

— Part 2: *Controls on sourcing, collection and handling*

— Part 3: *Validation of the elimination and/or inactivation of viruses and transmissible spongiform encephalopathy (TSE) agents*

— Part 4: *Principles for elimination and/or inactivation of transmissible spongiform encephalopathy (TSE) agents and validation assays for those processes* [Technical Report]

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Introduction

Certain medical devices utilize materials of animal origin.

Animal tissues and their derivatives are used in the design and manufacture of medical devices to provide performance characteristics that were chosen for advantages over non-animal based materials. The range and quantities of materials of animal origin in medical devices vary. These materials can comprise a major part of the device (e.g. bovine/porcine heart valves, bone substitutes for use in dental or orthopaedic applications, haemostatic devices), can be a product coating or impregnation (e.g. collagen, gelatine, heparin), or can be used in the device manufacturing process (e.g. tallow derivatives such as oleates and stearates, fetal calf serum, enzymes, culture media).

This document is a Technical Report (TR) to offer suggestions for designing and conducting validation assays to help determine if processes used in the manufacture of medical devices derived from non-viable animal tissues might serve to reduce the risk of iatrogenic transmission of transmissible spongiform encephalopathies (TSEs). This document will refer to the infective vector as “TSE agent” rather than prion to remain consistent with the other Parts of ISO 22442. Some current information on human tissues and TSEs is also presented which may be applied by analogy to other animal tissues.

Iatrogenic transmission of the human TSE Creutzfeldt-Jakob disease (CJD) has been convincingly attributed to exposure to the human dura mater allograft (Hannah, E. L., E. D. Belay, et al. 2001) used in surgery as a patching material and to hormones extracted from human pituitary glands (Mills, J. L., L. B. Schonberger, et al. 2004)—both non-viable tissues; recently, sub-clinical infection with the vCJD agent was detected at autopsy in a patient with hemophilia and plausibly attributed to his treatment with processed human plasma-derived coagulation factor (UK Health Protection Agency 2009 at:

http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1234859690542?p=1231252394302

and

http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_100357).

In addition, corneal grafts have transmitted CJD (Kennedy, Hogan et al, 2001) and several transfused red blood cell concentrates have transmitted variant CJD (vCJD) (Llewelyn, Hewitt et al 2004; Peden, Head et al 2004; Peden, Ritchie and Ironside 2005).

Exposure to the agent of bovine spongiform encephalopathy (BSE) has been responsible for more than 210 cases of vCJD worldwide, most of them thought to have resulted from dietary exposure to infected beef products. Although, except for the iatrogenic vCJD infections just described, no transmissions of a BSE-derived agent via medical or veterinary products have been recognized, there is no reason to doubt that a medical device contaminated with BSE agent of ruminant origin could transmit infection to a susceptible subject. Indeed, two veterinary vaccines derived from non-viable ovine tissues transmitted the ovine/caprine TSE scrapie to sheep (World Health Organization 2006). Humans are not known to have been infected with the scrapie agent.

This Technical Report generally uses terminology suggested by the World Health Organization (WHO Guidelines on Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies, 2006 (World Health Organization 2006)), while recognizing that there is no international consensus regarding either preferred terminology, the probable molecular nature of the transmissible agents (the all-protein or “prion” theory (Prusiner 1982) currently most widely held) or the precise role of various forms of the host-coded prion protein in the replication of the infectious agents or pathogenesis of disease. The sole intent of the TR is to suggest strategies to validate the effectiveness of methods that might reduce the risk of accidentally transmitting TSEs by medical devices prepared using non-viable animal tissues.

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The following referenced documents are standards helpful for the proper interpretation of this document:

— ISO 22442-1, *Medical devices utilizing animal tissues and their derivatives — Part 1: Application of risk management*

— ISO 22442-2, *Medical devices utilizing animal tissues and their derivatives — Part 2: Controls on sourcing, collection and handling*

— ISO 22442-3, *Medical devices utilizing animal tissues and their derivatives — Part 3: Validation of the elimination and/or inactivation of viruses and transmissible spongiform encephalopathy (TSE) agents*

— ISO 14160, *Sterilization of health care products — Liquid chemical sterilizing agents for single-use medical devices utilizing animal tissues and their derivatives — Requirements for characterization, development, validation and routine control of a sterilization process for medical devices*

These documents include both normative and informative annexes also directly relevant to the topic of this ISO TR. All terms defined in those documents are used verbatim in this report.

Due to the lack of consistent process steps that can reliably eliminate TSEs, it is important that one must use low-risk source animals and tissues.

Although not directly applicable to validating methods purported to reduce the TSE risk from medical devices manufactured from non-viable animal tissues, UK and US competent authorities have solicited expert advice on desirable features of validation studies for devices intended to remove TSE infectivity from human blood potentially contaminated with TSE agents, and this advice may be helpful in evaluating methods for animal-derived tissues as well. These features included preliminary evaluation using TSE-spiked material with high titers of infectivity, selecting experimental agents relevant to the infection of concern, and accepting studies using assays for PrP^{TSE} as a preliminary screening strategy to dismiss unpromising methods. These methods were required to indicate significant reduction in infectivity demonstrated by bioassays in known susceptible experimental animals. To qualify a method as potentially useful, the assay needed to demonstrate similar results for the same candidate method with two TSE agent-bioassay combinations, whenever possible. These criteria should be met before concluding that the method offers sufficient promise to consider in practice. Demonstration that a method reduces TSE infectivity for tissues endogenously infected, and that the complete manufacturing process eliminates all detectable infectivity, while desirable, are not currently feasible. Very low titers of infectivity in most tissues outside the nervous system and limited animals known to be susceptible to naturally occurring TSE agents without adaptation to a new species are limiting factors. The lack of standard reference infected materials of known titer and biological properties from humans and animals with TSEs is thought to be an additional impediment to developing validation studies (World Health Organization (2006), Annex 2). Considering the extremely limited attempted validation efforts for methods for improving TSE safety of human blood-derived and other human tissue-derived medical products — products with demonstrated iatrogenic transmissions — care must be taken not to discourage new efforts to validate methods that might improve the TSE safety of medical devices derived from animal tissues.

It should be noted again that, as summarized above, animal tissues have not been directly implicated in causing any iatrogenic TSE infections of humans (Minor, Newham et al. 2004). However, experience with food-borne BSE and field transmissions of scrapie to sheep by ovine tissue-derived veterinary vaccines suggests that the risk of iatrogenic transmissions of TSEs (other than BSE) from animals to humans, while theoretical, remains worthy of continued attention.

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Medical devices utilizing animal tissues and their derivatives —

Part 4:
Principles for elimination and/or inactivation of transmissible spongiform encephalopathy (TSE) agents and validation assays for those processes

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1 Scope

This Technical Report offers suggestions for designing and conducting validation assays to help determine if processes used in the manufacture of medical devices derived from non-viable animal tissues might serve to reduce the risk of iatrogenic transmission of transmissible spongiform encephalopathies (TSEs).

The TSE-removal methods used to process animal tissues should also reduce the risk of transmitting TSE infections via non-viable tissues of human origin; this Technical Report does not address this issue. Some current information on human tissues and TSEs is presented which may be applied by analogy to other animal tissues.

This Technical Report does not intend to imply a need for validation of methods involving specific materials identified as having a “negligible risk” of contamination with TSE agents as listed in Annex C of ISO 22442-1:2007.

This Technical Report is intended to clarify final draft international standards included in the ISO 22442 series, as well as in ISO 14160.

This Technical Report builds upon the specific discussion in ISO 22442-3 relative to TSE agents and attempts to summarize the current state of the art in the arena of TSE agent elimination. As the understanding of inactivation and elimination of TSE agents evolves, this document will be revised when possible.

2 Normative references

The following referenced documents are indispensable for the application of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 22442-1, *Medical devices utilizing animal tissues and their derivatives — Part 1: Application of risk management*

ISO 22442-2, *Medical devices utilizing animal tissues and their derivatives — Part 2: Controls on sourcing, collection and handling*

ISO 22442-3, *Medical devices utilizing animal tissues and their derivatives — Part 3: Validation of the elimination and/or inactivation of viruses and transmissible spongiform encephalopathy (TSE) agents*

ISO 14160, *Sterilization of single-use medical devices incorporating materials of animal origin — Validation and routine control of sterilization by liquid chemical sterilant*s

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