Title:	Conversion to Animal Free or TSE Risk Free API Processing				
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Introduction

An "animal-free" process does not contain any raw materials, starting materials, components or agents derived from animals. A "TSE-risk-free" process does not contain any raw materials, starting materials, components or agents derived from animals known to be susceptible to Transmissible Spongiform Encephalopathy (TSE) agents.

When an API process or processing work centre is converted to animal-free or TSE-risk-free status, the following process elements should be assessed and shown to be consistent with these definitions: master and working cell banks or biologic seeds, process materials and recycle streams, equipment cleaning, process aides (e.g resins), process seeding and solvent recovery.

Practice:

For a process, process work center or process product to be considered "animal-free" or "TSE-risk-free" all elements of the process must be animal-free or TSE-risk-free according to the following definitions and requirements:

- Master and Working Cell Banks and Biologic Seeds – For master and working cell banks and biologic seeds to be animal-free or TSE-risk-free, those containing animal-derived materials should be recreated such that all animal-derived or all TSE-risk materials either are removed or are replaced with non-animal or non-TSE-risk counterparts.

  Alternatively, the master and working cell banks and biologic seeds can be considered to have minimal TSE-risk if they are compliant with the European Medicine Agency's "Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01 Rev.2 – October 2003)" or its current equivalent. Compliant cell banks and seeds must have been created and described in a marketing authorization that was approved prior to 1 July 2000 for human health products or prior to 1 October 2000 for animal health products.

  Alternatively, a marketing authorization holder can demonstrate compliance to the note for guidance by updating affected EU marketing authorizations individually with TSE-risk information or with an EP Certificate of Suitability for TSE compliance (TSE-CEP).

- Process Materials and Recycle Streams – All starting materials, raw materials, solvents, recycle streams, process aides, enzymes, cells or cell extracts, heels, tag ends, crystallization seeds, etc., must be defined to be of animal-free or TSE-risk free origin for an intermediate or API lot to be considered animal-free or TSE risk-free.

dedicate and segregate such materials between legacy animal-containing and animal-free or TSE-risk-free processes.

- When a change-out between the legacy animal-containing and the animal free or TSE-risk-free materials occurs, the product contact surfaces of the vessel, column, or apparatus that holds the aide or component must be cleaned to appropriate levels of residual product before introducing the animal-free or TSE-risk-free component or aide.

- Process Seeding – Crystal seed stocks used in animal-free or TSE-risk-free processes must be of animal-free or TSE-risk-free origin, respectively.

- For processes where seeding is optional, it should be omitted from use in the first lot of an animal-free or TSE-risk-free campaign. A portion of this first lot should be retained for future use as an animal-free or TSE-risk free seed.

- For processes requiring seeding, the first consideration should be to produce an animal-free or TSE-risk-free seed in a GLP laboratory or GMP pilot plant.

- If it is impractical to produce an animal-free or TSE-risk-free seed outside of the commercial process environment, it is acceptable to use a serial dilution approach in which seed stocks of ever decreasing content of legacy animal-derived or TSE-risk materials are produced from successive lots of an otherwise animal-free or TSE-risk-free manufacturing campaign. At the point a manufacturing lot is calculated to have NMT 25ppm of the original animal-derived seed, an animal-free or TSE-risk-free seed can be generated. The next lot produced using the animal-free or TSE-risk-free seed may be identified as animal-free or TSE-risk-free.

– Recovered Solvents – Solvent recovery methods to produce solvents for process specific or general reuse must be robust to separate other solvent components and solids from the recovery stream (e.g. multiple plate or packed distillation columns). The recovered solvent should contain NMT 25ppm dissolved solids to be considered animal-free or TSE-risk-free. This requirement should also be applied to solvents recovered off-site or obtained from suppliers who use waste solvents as feed stocks.

Discussion and Recommendations

Animal-derived materials are used in the manufacture of many Site APIs intermediates, and drug products. Many of these animal-derived materials are of ruminant origin. Ruminants and several other species have been shown to be susceptible to a number of transmissible spongiform encephalopathies (TSE) agents that include scrapie in sheep, bovine spongiform encephalopathy (BSE) in cattle, and chronic wasting disease (CWD) in deer, elk and other cervids. Humans are also susceptible to certain TSE agents including sporadic Creuzfeldt-Jakob Disease (sCJD) and variant Creuzfeldt-Jakob Disease (vCJD). There is convincing evidence that vCJD in humans is caused by the same agent responsible for BSE in cattle. Cases of BSE in cattle have been documented in Europe, Asia, and North America, including a case in the US. Consequently, world health authorities have placed ever more stringent control on the sourcing of food and drugs produced from bovine tissues or bovine-derived materials.

processing, only animal-free or TSE-risk-free starting materials, raw materials, solvents, recycle streams, process aides, enzymes, cells or cell extracts, heels, tag ends, crystallization seeds, etc. are to be used. Because many API processes recycle mother liquors, filtrates, distillates, filter-heels, or tag-ends of lots, upon conversion to animal free or TSE-risk-free processing, such legacy process materials must be strictly controlled and prevented from commingling with their counterparts in the animal-free or TSE-risk free process. If an animal-containing material is used in an otherwise animal-free lot, the resulting lot is considered to be animal-derived. Such legacy materials cannot be used into animal-free processes by applying a dilution strategy. To do so would be considered adulteration; the intent is clearly different than the applications of dilution strategies described elsewhere in this bulletin. It is recommended that legacy process recycle materials be tightly controlled to prevent unplanned commingling with otherwise animal free materials. Alternatively the legacy process materials should be destroyed unless it is planned to maintain both the legacy and the animal-free or TSE-risk-free processes.

Animal-free or TSE-risk-free lots may be reprocessed or reworked without jeopardizing their status so long as all elements of the reprocess or rework procedure meet the animal free or TSE-risk-free criteria described in this bulletin. However, it is not possible to reprocess or rework a non-animal-free lot or a non-TSE-risk-free lot to achieve animal free or TSE-risk-free status

Equipment Cleaning – The equipment cleaning requirements and limits defined in the site procedure should be applied as long as there is no "documented risk of TSE contamination." If a "documented risk of TSE contamination" situation were to occur, it should be addressed independently to define cleaning requirements.

Normal or routine cleaning used for process changeovers of multi-process product contact equipment or work centres are adequate to support the next lot to be animal-free or TSE-risk-free.

For dedicated equipment or work centers, the normal cleaning requirements between lots or between grades (e.g. Ag Grade to Rx Grade) define "clean." Equipment, piping, tanks etc. that are not product contact surfaces, but may be used to stage, transport or store animal-derived materials, need to be assessed for removal of the animal-derived materials before they can participate in animal-free or TSE-risk-free processing. In the absence of a "documented risk of TSE contamination" normal cleaning practices should be used.

For dedicated storage tanks or silos that are difficult to clean or contain hazardous materials, an assessment of the serial dilution of existing animal-containing materials with incoming animal-free or TSE-risk-free materials should be made. The storage tank or silo can be declared "animal-free" or "TSE-risk-free" when the legacy animal-derived component is below 25 ppm. If all other inputs into the process are animal-free, the first intermediate or API lot manufactured with this material may also be considered animal free or TSE-risk-free.

Processing Aides or Components – This grouping refers to ion-exchange and chromatography resins, carbon beds, filtration membranes or other elements that may be cleaned or regenerated for use in the next batch of intermediate or API. Generally, these types of materials are either dedicated to a particular process (e.g. ion-exchange and chromatography resins and filtration membranes) or are discarded as single use materials (e.g. carbon, celite, and other filtration and purification aids).

