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FEDERAL REGULATORY ISSUES: RECOMMENDED BIOCOMPATIILITY TESTING AND REGULTION OF TISSUE ENGINEERED PRODUCTS

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Required Biocompatibility Training and Toxicology Profiles for Evaluation of Medical Devices

http://www.fda.gov/cdrh/g951.html

- FDA-modified matrix that designates the type of testing needed for various medical devices.
- It also includes a flow chart entitled "Biocompatibility Flow Chart for the Selection of Toxicity Tests for 510(k)s."
- The guidance will be effective for all submissions that will be received on or after July 1, 1995. The former guidance, #G87- 1 entitled "Tripartite Biocompatibility Guidance," may continue to be applied until a final decision is reached on each submission received prior to July 1, 1995.

Required Biocompatibility Training and Toxicology Profiles for Evaluation of Medical Devices

- Biological evaluation of medical devices is performed to determine the potential toxicity resulting from contact of the component materials of the device with the body.
- The device materials should not, either directly or through the release of their material constituents:
  - (i) produce adverse local or systemic effects;
  - (ii) be carcinogenic; or
  - (iii) produce adverse reproductive and developmental effects.
- Therefore, evaluation of any new device intended for human use requires data from systematic testing to ensure that the benefits provided by the final product will exceed any potential risks produced by device materials.

Required Biocompatibility Training and Toxicology Profiles for Evaluation of Medical Devices

- When selecting the appropriate tests for biological evaluation of a medical device, one must consider the chemical characteristics of device materials and the nature, degree, frequency and duration of its exposure to the body.
- In general, the tests include:
  - acute, sub- chronic and chronic toxicity;
  - irritation to skin, eyes and mucosal surfaces;
  - sensitization;
  - hemocompatibility;
  - genotoxicity;
  - carcinogenicity; and
  - effects on reproduction including developmental effects.
- Additional tests for specific target organ toxicity, such as neurotoxicity and immunotoxicity may be necessary for some devices.
  - For example, a neurological device with direct contact with brain parenchyma and cerebrospinal fluid (CSF) may require an animal implant test to evaluate its effects on the brain parenchyma, susceptibility to seizure, and effects on the functional mechanism of choroid plexus and arachnoid villi to secrete and absorb (CSF).
- The specific clinical application and the materials used in the manufacture of the new device determines which tests are appropriate.

International Organization for Standards, ISO

http://www.iso.ch/iso/en/CatalogueListPage.CatalogueList?ICS1=11&ICS2=100&ICS3=

- ISO 10993-1:1997 Biological evaluation of medical devices -- Part 1: Evaluation and testing
- ISO 10993-2:1992 Biological evaluation of medical devices -- Part 2: Animal welfare requirements
- ISO 10993-3:1992 Biological evaluation of medical devices -- Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity
- ISO 10993-4:2002 Biological evaluation of medical devices -- Part 4: Selection of tests for interactions with blood
- ISO 10993-5:1999 Biological evaluation of medical devices -- Part 5: Tests for in vitro cytotoxicity
- ISO 10993-6:1994 Biological evaluation of medical devices -- Part 6: Tests for local effects after implantation

International Organization for Standards, ISO

http://www.iso.ch/iso/en/CatalogueListPage.CatalogueList?ICS1=11&ICS2=100&ICS3=

- ISO 10993-7:1995 Biological evaluation of medical devices -- Part 7: Ethylene oxide sterilization residuals
- ISO 10993-8:2000 Biological evaluation of medical devices -- Part 8: Selection and qualification of reference materials for biological tests
- ISO 10993-9:1999 Biological evaluation of medical devices -- Part 9: Framework for identification and quantification of potential degradation products
- ISO 10993-10:2002 Biological evaluation of medical devices -- Part 10: Tests for irritation and delayed-type hypersensitivity
- ISO 10993-11:1993 Biological evaluation of medical devices -- Part 11: Tests for systemic toxicity
- ISO 10993-12:2002 Biological evaluation of medical devices -- Part 12: Sample preparation and reference materials

International Organization for Standards, ISO

http://www.iso.ch/iso/en/CatalogueListPage.CatalogueList?ICS1=11&ICS2=100&ICS3=

- ISO 10993-13:1998 Biological evaluation of medical devices -- Part 13: Identification and quantification of degradation products from polymeric medical devices
- ISO 10993-14:2001 Biological evaluation of medical devices -- Part 14: Identification and quantification of degradation products from ceramics
- ISO 10993-15:2000 Biological evaluation of medical devices -- Part 15: Identification and quantification of degradation products from metals and alloys
- ISO 10993-16:1997 Biological evaluation of medical devices -- Part 16: Toxicokinetic study design for degradation products and leachables
- ISO 10993-17:2002 Biological evaluation of medical devices -- Part 17: Establishment of allowable limits for leachable substances

American Society for Testing and Materials

http://www.astm.org

Search "Biocompatibility"

FDA
TISSUE ENGINEERING PRODUCTS

FDA's Tissue Reference Group Workshop

August 29, 2001 - Slide Presentation

Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) Regulated as Devices

Mark N. Melkerson
CDRH / FDA

Tissue Reference Group (TRG)
"FDA's TRG Process"

http://www.fda.gov/cber/summaries/melkersontrg.htm

Premarket Review of Biological Products & Medical Devices

- Biological Products
- Medical Devices
- Combination Products

Definition of a Medical Device

- "...apparatus,…, implant, *in vitro* reagent, including any component…or accessory...
- intended for the diagnosis, mitigation, treatment, or prevention of disease...
- or intended to affect the structure or function of the body...
- and does not achieve its primary intended purposes through chemical action within or on the body…and which is not dependent upon being metabolized…"

Examples of Medical Devices & Combination Products

- Medical Devices - collagen, hyaluronic acid and synthetic implants
  - FocalSeal-L - aqueous PEG solutions modified to photo-polymerize *in situ*
  - Emdogain - porcine enamel matrix proteins
- Combination Products -
  - Apligraf - cells on bovine collagen

Marketing Applications

- Premarket Notification (Class II Devices)
  Section 510(k) of the FD&C Act (21 CFR 807)
- Premarket Approval Application (Class III Devices)
  Section 515 of the FD&C Act (21 CFR 814)
- Humanitarian Device Exemption (requires HUD Designation)
  Section 520(m) of the FD&C Act (21 CFR 814.100)

Premarket Notification Review

- Case-by-case approach, except if can demonstrate "equivalent" to predicate device
- Basic elements:
  - Same Intended Use(s)
  - Preclinical equivalence of Product Manufacture, *In vitro* and/or *in vivo* testing
  - May need to demonstrate equivalence of Clinical Performance, if seeking specific indication(s) for use under general intended use(s) or differences in technological characteristics

Food and Drug Administration Modernization Act of 1997

- Gave CDRH authority to recognize national and international standards in product reviews
  - Allows for "Declaration of Conformity"
  - Somewhat mirrors device marketing authorities used in Europe

CDRH Standards Program

www.fda.gov/cdrh/stdsprog.html

- Standards Participation
  - ASTM F04
    - Division IV - Tissue Engineered Medical Products (TEMPS)
  - ISO TC 150
    - Working Group 11 - Tissue Engineered Implants (Reviewing Other Standards Development Activities)

Premarket Approval Review

- Case-by-case approach
- Both safety and effectiveness evaluations
- Basic elements:
  - Product Manufacture
  - *In vitro* and *in vivo* testing
  - Clinical Performance
  - Product Labeling
- Product Manufacture
  - Cell, tissue & biomaterial sourcing
  - Product Processing
  - In-process and final product tests
  - Adventitious agents & co-purifying impurities
  - Lot - to - lot consistency
  - Quality control procedures

Premarket Approval Review

- *In vitro* and *in vivo* testing
  - Toxicity / Genotoxicity
  - Biomaterials biocompatibility
  - Immunogenicity /inflammatory responses
  - Models of product effectiveness
  - Product resorption/decomposition
- Investigating product safety and clinical benefit:
  - Patient population
  - Investigational and control treatments
  - Study endpoints
  - Study conduct
  - Data analysis
  - Labeling claims

Investigational Human Studies

- An exemption from marketing approval is required when unapproved products are studied in humans.
  - Investigational Device Exemption (IDE) 21 CFR 812
- For significant risk medical devices:
  - FDA approval of IDE
  - IRB approval

Humanitarian Device Exemption

- Requires HUD (maximum of 4000 cases/per year) and requires no alternatives be marketed
- Case-by-case approach
- Both safety and probable benefit evaluations
  - Product Manufacture
  - *In vitro* and *in vivo* testing
  - Clinical Perfor
  - Product Labeling

Internet Access to FDA Documents

- Proposed Approach to Regulation of Cellular and Tissue-Based Products - 2/28/97 - http://www.fda.gov/cber/gdlns/CELLTISSUE.txt
- Tissue Action Plan - http://www.fda.gov/cber/tissue/tissue.htm
- Intercenter Agreement Between The Center for Biologics Evaluation and Research and The Center for Devices and Radiological Health - http://www.fda.gov/oc/ombudsman/bio-dev.htm
- Guidance on Applications for Products Comprised of Living Autologous Cells Manipulated Ex Vivo and Intended for Structural Repair or Reconstruction (5/96) - http://www.fda.gov/cber/gdlns/GDEXV.TXT

Internet Access to FDA Documents

- Guidance For the Submission of Chemistry, Manufacturing and Controls Information and Establishment Description for Autologous Somatic Cell Therapy Products - 1/10/97 - http://www.fda.gov/cber/gdlns/xvcmc.txt
- Required Biocompatibility Training and Toxicology Profiles for Evaluation of Medical Devices 5/1/95 (G95-1) - http://www.fda.gov/cdrh/g951.html
- Public Health Service Guideline on Infectious Disease Issues in Xenotransplantation http://www.fda.gov/cber/gdlns/xenophs0101.htm
- FDA PMA Database Search Engine http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm

Tissue Related Documents

http://www.fda.gov/cber/tissue/docs.htm

- Guidance for Industry: Availability of Licensed Donor Screening Tests Labeled for Use with Cadaveric Blood Specimens - 6/23/2000
- Suitability Determination for Donors of Human Cellular and Tissue-Based Products; Proposed Rule; reopening of comment period - 4/18/2000
- Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products - 5/14/98
- Guidance for Industry - Screening and Testing of Donors of Human Tissue Intended for Transplantation - 7/29/97
- Guidance for the Preparation of a Premarket Notification Application for Processed Human Dura Mater - http://www.fda.gov/cdrh/ode/054.html

Specific Product Information

- FocalSeal-L Sealant- Focal - SSE
  - http://www.fda.gov/cdrh/pdf/p990028b.pdf
- Apligraf - Organogenesis - SSE
  - http://www.fda.gov/cdrh/pdf/p950032.pdf
- CCS - Ortec, Inc. - SSPB (H990013)
  - http://www.fda.gov/cdrh/pdf/h990013b.pdf

Multi-Agency Tissue Engineering Science (MATES) Working Group

The Multi-Agency Tissue Engineering Science (MATES) Working Group is proposed as a means for the various federal agencies involved in Tissue Engineering to stay informed of each other's activities and better coordinate their efforts.

http://www.tissueengineering.gov

Multi-Agency Tissue Engineering Science (MATES) Working Group

Five Year Plan; Subcommittee on Biotechnology

The term "Tissue Engineering" was coined at an NSF-sponsored meeting in 1987(1). At a subsequent NSF sponsored workshop, Tissue Engineering was defined as "the application of principles and methods of engineering and life sciences toward fundamental understanding of structure-function relationships in normal and pathological function" (2). This multidisciplinary technology involves the development of biological substitutes for the repair or regeneration of tissue or organ function and has led to a broad range of products.

1. Heineken FG and Skalak R. Tissue Engineering: A Brief Overview, Journal of Biomechanical Engineering 113, 111 (1991).
2. Skalak R and Fox CF, eds. Tissue Engineering, Proceedings for a Workshop held at Granlibakken, Lake Tahoe, California, February 26-29, 1988, Alan Liss, New York.

http://www.tissueengineering.gov

Multi-Agency Tissue Engineering Science (MATES) Working Group

To date, some of these products have been approved by the U.S. Food and Drug Administration while many are under either preclinical investigation or regulatory evaluation (3, 4). Since 1990, the Tissue Engineering industry has grown to become more than a $3.5 billion worldwide R&D effort by over seventy biotechnology start-ups and business units (5, 6). Less than ten percent of this effort is funded by the U.S. government, but this contribution is rapidly increasing.

3. Hellman KB, Knight E, and Durfor CN. Tissue Engineering: Product Applications and Regulatory Issues, pp. 341-366, Frontiers in Tissue Engineering, Charles W. Patrick, Antonio G. Mikos, and Larry V. McIntire (eds.), Amsterdam, Elsevier Science (1998).
4. Hellman KB., Solomon RR, Gaffey C, Durfor C and Bishop JG, III. Tissue Engineering: Regulatory Considerations, Principles of Tissue Engineering, 2nd Edition, Robert Lanza, Robert Langer, and Joseph P. Vacanti (eds.), Academic Press, San Diego, California (in press).
5. Lysaght MJ, Nguy AS, and Sullivan K. An Economic Survey of the Emerging Tissue Engineering Industry, Tissue Engineering: 4, 231 (1998).
6. Lysaght MJ, and Reyes J. The Growth of Tissue Engineering, Tissue Engr.

FDA APPROVAL PROCESS