This guidance was written prior to the February 27, 1997 implementation of FDA's Good Guidance Practices, GGP's. It does not create or confer rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. This guidance will be updated in the next revision to include the standard elements of GGP's.

DRAFT GUIDANCE FOR PREPARATION OF PMA APPLICATIONS FOR THE IMPLANTED MECHANICAL/HYDRAULIC URINARY CONTINENCE DEVICE (ARTIFICIAL URINARY SPHINCTER)

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Division of Reproductive, Abdominal, Ear, Nose and Throat
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DRAFT GUIDANCE FOR THE PREPARATION OF PMA APPLICATIONS FOR THE ARTIFICIAL URINARY SPHINCTER

I. PREAMBLE

This guidance document addresses the preparation of premarket approval (PMA) applications for the Artificial Urinary Sphincter (AUS), a device intended for the treatment of urinary incontinence in males and females. It may also be useful for the preparation of investigational device exemption (IDE) applications and master files. Development of this guidance document is based upon scientific review and analysis by the FDA and by published and unpublished studies.

The intent of this document is to assist sponsors that are affected by the notice of proposed rule published in the February 15, 1995, Federal Register (60 FR 8595) which outlines FDA's intent to call for PMA applications for the Implanted Mechanical/Hydraulic Urinary Continence Device (a pre-Amendment class III device). This guidance document specifically addresses the AUS since it is the only device design in wide use at the time of the proposed rule. However, the manufacturing, preclinical, and clinical principles outlined in this document are applicable to multiple device designs and should prove useful to any sponsor wishing to market any design type of an Implanted Mechanical/Hydraulic Urinary Continence Device.

An AUS treats urinary incontinence by the application of intermittent pressure to occlude the urethra. The totally implanted device generally consists of the following components: (1) a container of saline or radiopaque fluid (typically implanted in the abdomen), (2) a manual pump and valve (typically implanted under the skin surface), (3) an adjustable pressure cuff (typically implanted around the urethra), and (4) tubing and connectors to connect all of the system's components. Fluid is pumped as needed from the container to inflate the cuff which compresses the urethra. The current devices consist mainly of silicone elastomers. FDA recognizes that other materials could also be used for this application, however this guidance focuses mainly on silicone materials since silicone is the primary material used for this device at the time that this draft document was prepared. Additional guidance on the information needed for other materials (i.e., polyurethanes and silicone gels) used in urogenital implants may be obtained from the draft guidances available on penile inflatable implants and testicular prostheses.

FDA welcomes comments on this draft guidance document and will consider scientifically valid alternatives to the requirements stated within. It is also highly recommended that the sponsor of an application for the proposed device contact the Urology and Lithotripsy Devices Branch (ULDB) within the Office of Device Evaluation (ODE) of the Center for Devices and Radiological Health (CDRH) prior to filing an original PMA application or other type of submission.

II. GENERAL PMA REQUIREMENTS

A PMA must be submitted by all distributors of Implanted Mechanical/Hydraulic Urinary Continence Devices. Any PMA submitted should meet the content requirements contained in Section 515(c)(1) of the Federal Food, Drug and Cosmetic Act (the act) and 21 CFR 814.20. In particular, the PMA should include a detailed discussion, with results of preclinical and clinical studies, of the:

- risks identified in this document, as well as all known or otherwise available data/information regarding risks known to the sponsor that have not been identified in this document; and

- effectiveness of the specific device that is the subject of the PMA application.

Valid scientific evidence, as defined in 21 CFR 860.7, addressing the safety and effectiveness of the device should be presented, evaluated, and summarized in a section or sections of the PMA, separate from known or otherwise available safety and effectiveness information that does not constitute valid scientific evidence (e.g., isolated case reports, random experiences, etc.). Although there is reasonable knowledge of the risks and benefits associated with the implanted mechanical/hydraulic urinary continence device, there is insufficient valid scientific evidence to permit FDA to perform a risk/benefit analysis. Each PMA application should address the following safety and effectiveness issues associated with the implanted mechanical/hydraulic urinary continence device:

- long-term safety and effectiveness data to address the incidence of implant failure and attendant causes, as well as the incidence of adverse events and reoperations (FDA believes that 5 year follow-up data are necessary in order to characterize the safety and effectiveness of the device over its expected lifetime; however, appropriately justified alternate follow-up schedules will be considered);

- for which subgroups of the population with urinary incontinence the benefits of the implanted device outweigh the attendant risks, especially since other voiding abnormalities, such as bladder dysfunction (detrusor instability and poor compliance) and reflux often coexist with sphincteric insufficiency;

- the required presurgical workup of patients prior to device implantation, including diagnostic tests, patient selection, and screening procedures;

- the long-term effects of devices implanted in pediatric patients if intended for pediatric use;

- the effects of the implanted device upon male sexual function;

- for women of childbearing age, the effects of the device upon sexual function, pregnancy, and delivery;

- the effect of device implantation upon future medical diagnoses and treatments;

- the potential risks associated with silicone particle shedding and the subsequent migration of the particles;

- the potential long-term adverse effects related to the device materials, such as cancer, immune related connective tissue disorders, and reproductive and teratogenic effects; and

- the malfunction rate and longevity reported for the implanted device.

The following sections provide specific requirements for addressing the concerns stated above.

III. MANUFACTURING INFORMATION

All manufacturing information should be completely described, including the methods, facilities, and controls used in the manufacturing, processing, packing, and storage of the device. Manufacturing should be in compliance with current good manufacturing practices (CGMPs).

Manufacturing guidance is available in the document entitled "Guidance for the Preparation of PMA Manufacturing Information" available upon request from the Division of Small Manufacturers Assistance (DSMA), HFZ-220, CDRH, FDA, 1350 Piccard Drive, Rockville, Maryland 20850.

In addition, the following specific chemical processing, sterilization, and quality assurance information is considered necessary to assess the safety and effectiveness of the AUS.

Manufacturing and process information tree shows how the components of a device are made from starting materials and identifies potentially leachable chemicals and immediate precursors of crosslinked polymers. Only a limited amount of chemical characterization can be done on highly crosslinked polymers. For such polymers, it is important to characterize the immediate precursors to assure the quality of the base polymers and crosslinking agents. The viscosity and molecular weight distribution are very basic characteristics of all polymers and greatly influence the mechanical and physical properties of the device. Determination of volatile content, extent of chemical crosslinking, and the solution fraction of components characterize the curing processes that are used. These determinations should be done on 10 or more lots of material to establish that control of the chemical processing exists. Chemical formulation and manufacturing information presented in a step-by-step manner

from the starting materials to the final products, including, but not limited to, all nonreactants (e.g., antioxidants, light stabilizers, and plasticizers) and reactants (e.g., catalysts, curing agents, and intermediate precursors), should be provided for all device components, including all adhesives, colorants, and filling agents (e.g., saline, contrast medium, etc.). On this process tree, any substance or material identified by any available company name or code should also be identified by a corresponding common chemical name.

A complete master list of common chemical names and alternate names (company, trade and code) for all nonreactants, reactants, additives, catalysts, adjuvants, and products should be provided. The same name for each specific compound should be utilized throughout the document.

Chemical characterization of the elastomer intermediates (i.e., network precursors) of the various components of the device sufficient to demonstrate control of chemical processing of the device materials should be provided. This should be based on lot-to-lot comparisons (10 consecutive lot minimum) of the following information:

- the molecular weight distribution expressed as weight average molecular weight (Mw), number average molecular weight (Mn), peak molecular weight (Mp), viscosity average molecular weight (Mv), and polydispersity (MWD) of these precursors;

- analyses for volatile and nonvolatile (if applicable) compounds (e.g., cyclic oligomers) to establish the upper limit of these compounds and to show that they are being controlled;

- if copolymers are being used, data to show that the composition of these copolymers is under control and that a consistent product is being made (usually such data would consist of analyses of the group content of the copolymer, for example, phenyl, fluoro, vinyl, hydroxyl number, acid number, peroxide, etc., as appropriate);
- when viscosity is used as the variable that is measured for production control, a comparison of viscosity, Mn, and volatile content should be given on a lot-by-lot basis to show that viscosity monitoring is sufficient to control the chemical processing;

- if composites or filled or reinforced polymers are being used, the fillers should be characterized. The particle size or surface area of any reinforcing and non-reinforcing filler should be given. If silica is being used, the percent crystallinity should be provided.

Sterilization information should be provided and should include standard operating procedures for sterilizing and qualifying the sterilization process and materials. This information should include the method of sterilization; detailed sterilization and packaging validation protocols/results; sterility assurance level; type of packaging; residual levels of ethylene oxide, ethylene glycol, and ethylene chlorhydrin remaining on the device after the sterilization quarantine period, if applicable; and radiation dose, if applicable.

Quality Assurance/Quality Control (QA/QC) information sufficient to demonstrate functional integrity and to detect any device flaws that could lead to short-term failure should be provided and should include:

- a plan that demonstrates how raw materials, components, subassemblies, and any filling agents will be received, stored, and handled in a manner designed to prevent damage, mix-up, contamination, and other adverse effects. This plan should specifically include, but not necessarily be limited to, a record of raw material, component/subassembly/filling agent acceptance and rejection, visual examination for damage, and inspection/sampling/testing for conformance to specifications.

- written procedures for finished device inspection to assure that device specifications are met. These procedures should require, but are not necessarily limited to, that each production run, lot, or batch be evaluated and, where necessary, tested for conformance with device specifications prior to release for distribution. A representative number of samples should be selected from a production run, lot, or batch and tested under simulated use conditions and to any extremes to which the device may be exposed.

- written procedures for appropriate visual testing of the packaging, packaging seal, and product. Sampling plans for checking, testing, and release of the device should be based on an acceptable statistical rationale (21 CFR 820.80 and 820.160).

IV. PRECLINICAL INFORMATION

Chemical Identification/Quantification, Leachables, and Surface Composition

All physical and chemical properties of the device should be completely characterized. Each item should be supported by complete reports (i.e., protocols with a full description of test methods and raw data). These reports should be from the testing of an adequate number of samples of final sterilized devices.

Laboratory test methods and animal experiments used in the characterization of the physical, chemical (other than exhaustive extraction), and mechanical properties of the device should be applicable to the intended use of the device in humans.

If fabrication of the device involves curing of polymeric components by chemical crosslinking, then data establishing the extent and reproducibility of the crosslinking should be provided. This may be done by various methods, for example:

- measurement of Young's modulus at low strain, as this is approximately proportional to crosslink density;

- measurement of equilibrium swelling of the polymeric component by an appropriate solvent; and

- determination of the amount of unreacted crosslinker from its concentration in the total extractables.

Determination of the extractable or releasable chemicals in an implant device are necessary for assessment of the safety of the device. Chemical identification and quantification of releasable chemicals (as described below) and migration rates from various device components are necessary to facilitate the determination of safe levels by dose-response toxicological methods. Migration rates of the releasable chemicals from various components of the device may also be evaluated when providing toxicology data. Knowledge of the levels of volatiles and residues in the device provides an upper limit to the amount of releasable chemicals from the various components as they are found in the final sterilized device. This is necessary to relate amounts of releasable chemicals back to device characteristics as these are factors that can and should be controlled in the manufacturing process.

Complete identification and quantification of all chemicals, such as:

- residual monomers, cyclics, and oligomers;

- known toxic residues, such as polychlorinated biphenyls (PCBs) if dichlorobenzoyl peroxides are used, heavy metals, and residues of transition metal catalysts;

- residues of ethylene oxide if that is used for sterilization; and

- additives and adjuvants used in the manufacture of the device, such as plasticizers, antioxidants, etc.;

below a molecular weight of 1500, exhaustively extracted from each of the individual structural components as they are found in the final sterilized device should be reported. The solvents used for extraction should have varying polarities and should include, but not be limited to dichloromethane and ethanol/saline (1:9). Other, more contemporary extraction techniques such as supercritical fluid extraction, may also be useful - at least for exhaustive extraction of the silicone materials.

Experimental evidence should be provided to show that exhaustive extraction has been achieved with one of the solvents, and the percent recovery, especially for the more volatile components, should be reported. Extracts that may contain oligomeric or polymeric species should have the molecular weight distribution provided, along with number and weight average molecular weights, and polydispersity.

Guidelines for extraction and a selected bibliography of analytical methodologies are included as Appendix I and II respectively.

All experimental methodologies should be described, and raw data (including instrument reports) provided along with all chromatograms, spectrograms, etc. The practical quantitation limit (PQL) (see Compilation of EPA's sampling and analysis methods, Lewis publishers 1992) should be provided when the analyte of interest is not detected.

Infrared measurements of the surface of device components as they occur in the final sterilized product should be provided to establish the major chemical characteristics of the surface which may differ from the bulk and also to provide baseline characterization for comparison with explants.

Toxicological Evaluation

The synthetic polymeric materials used in the AUS should not present any toxic risks upon long-term intimate contact with the body. The high molecular weight polymeric material used in silicone devices contains low molecular weight components, such as monomers, oligomers, and catalysts which can leach out into the body. Therefore, one important requirement of the preclinical toxicology testing of the device is to determine the potential toxicity of the previously identified releasable chemicals as they appear in the final sterilized device. These tests should reveal the potential for local as well as systemic toxicity (including genotoxicity, carcinogenicity, adverse reproductive effects, teratogenicity, and immunotoxicity) of any leachable substance. Thus, when appropriate, the chemicals recovered by extraction of the final sterilized device should be used as the test article in animal studies after they are separated, quantified, and identified.

In addition, a significant concern for any implanted device is its potential to cause cancer. This potential may arise not only from chemical leachables and degradation products from the device, but also from physical effects of the device at the implanted site. Therefore, adequate long-term studies with implantation of device materials should be conducted to evaluate the carcinogenic potential of the device.

Biocompatibility testing should be conducted in accordance with blue book memorandum # G95-1 entitled "Use of International Standard ISO -10993, Biological Evaluation of Medical Devices Part 1: Evaluation and Testing" (obtainable through DSMA), which includes an

FDA-modified matrix that designates the type of testing needed for various medical devices. For the AUS, these tests include:

- irritation tests,
- sensitization assay,
- cytotoxicity,
- acute systemic toxicity,
- hemocompatibility/hemolysis,
- pyrogenicity (material-mediated),
- implantation tests,
- mutagenicity (genotoxicity)
- pharmacokinetics studies,
- subchronic toxicity,
- chronic toxicity,
- carcinogenesis bioassay, and
- reproductive and developmental toxicity.

Mutagenicity testing Mutagenicity testing should, at minimum, consist of bacterial mutagenicity, mammalian mutagenicity, DNA damage, and cell transformation assays.

Of special concern in the pharmacokinetics/biodegradation studies are questions regarding the ultimate fate, quantities, sites/organs of deposition, routes of excretion, and potential clinical significance of silicone shedding, retention, and migration.

Acute, subchronic and chronic toxicity, carcinogenicity*, reproductive and teratological effects*, and immunotoxicity* studies should be conducted on the final sterilized device, using either device materials and/or appropriate extracts of the device materials. Dose response and time to response should be characterized. Complete reports from acute and subchronic toxicity testing of extractable chemicals contained in the final sterilized device should include gross and histopathological studies in appropriate tissues both surrounding and remote from the implanted site.

* For specific guidance on these studies, please contact the ULDB at (301) 594-2194.

General Performance Requirements

Physical, mechanical, and reliability tests should be conducted on components, subassemblies, and finished devices of each device model and examine all aspects of device design, construction, and operation. All tests should be performed on components and devices fabricated by representative manufacturing processes and subjected to the final validated sterilization procedures intended for the device.

An adequate number of samples of each model, based on relevant power calculations, should

be tested. If sample devices of each available size are not tested, it should be clearly indicated which device sizes were used for each test. The absence of testing on each size should be justified by an analysis demonstrating that the results from the tested devices will accurately predict results for the untested device sizes.

Copies of typical original data sheets from all tests should be included. For all tests that result in device failure, the failure mode should be completely described. The significance of all tests that result in failure of a device, component, or subassembly to meet specification should be rationalized. If the conditions under which the failed device, component, or subassembly was tested (loads, environments, etc.) are likely to occur *in vivo*, corrective actions should be taken to eliminate or minimize further occurrence and modified samples should be retested.

The performance specifications for all components, subassemblies, and finished devices, and test conditions and acceptance criteria for all tests should be completely explained and justified by comparison to expected *in vivo* conditions, whenever possible. All tests should be performed in an environment simulating the possible range of anticipated *in vivo* conditions (temperatures, pressures, forces, stresses, etc.), including capsular formation, where possible. All methods used to determine the condition of the device after testing (e.g., visual examination, electrical continuity, electron microscope examination, functional testing, etc.) should be discussed and justified.

If accelerated aging is used to demonstrate device durability and reliability, all processes used should be completely described, and the calculations validating the expected aging should be provided.

All data (collected from *in vitro* and animal testing) regarding the useful lifetime or long-term reliability of the device, should be compared to data from clinical studies (prospective and/or retrospective) where the useful lifetime of the device has been determined. This comparison should validate the ability of the *in vitro* and animal tests to accurately predict the useful lifetime of the implanted device.

A failure mode and effects analysis (FMEA) should be conducted and provided. Testing should demonstrate how the proposed device design and manufacturing processes are consistent with the FMEA.

Additionally, the effects of implantation, including the stresses of the biological environment, on device function and integrity should be determined by appropriate animal testing. Complete material, chemical and physical characterization, and device/component performance testing should be performed on devices explanted from animals after an appropriate implantation duration. Of special concern is the integrity of the cuff, reservoir, pump, tubing, joints, etc. Test results of explants should be compared to results of non-implanted devices and conclusions about degradation of materials or components should be

reported. The results of this testing should also be compared to failure rates determined in *in vitro* tests and clinical studies, in order to demonstrate when the animal model and study duration are appropriate.

Physical Material Characterization

Physical tests should include, but are not necessarily limited to, the following, as appropriate. Suggested methodologies are listed where available. The adequacy of all test results should be justified.

- tensile strength and ultimate elongation of material specimens (ASTM D412) taken from the components of the final sterilized product. The device materials should possess a level of mechanical strength necessary to withstand rupture from stresses and deformations applied to the components of the device. Tensile strength and ultimate elongation represent respectively the largest sustainable stress and stretching deformation on a test specimen before rupture occurs.

- energy to rupture (i.e., strain energy to failure) for material specimens taken from each component of the final sterilized device. Energy to rupture, determined from the total area under a generated stress-strain curve, represents the total trauma, in units of energy, that a test specimen can endure before rupturing.

- tear resistance for material specimens taken from each of the above listed device components of the finished, sterilized device (ASTM D624). The device materials should possess some minimum level of protection against the catastrophic propagation of a puncture or small tear. Tear resistance is a measure of this capability.

- integrity of fused or adhered joints. ASTM F703 contains a methodology, including geometries of test specimens. Unlike ASTM F703, however, the testing should be conducted to, and results reported for, the failure points of the specimens. The breaking force at failure, normalized to the joint thickness, should be reported for the test specimens. Failure of a fused or adhered joint represents a potential source for leakage of the filling agent from the device. This testing provides a measure of the resistance of the device to such failures.

- abrasion resistance and analysis of abraded surfaces of device components taken from the final sterilized device with particular attention directed at the folds in the cuff. Some elastomeric components (particularly silicone ones) can be relatively soft and prone to abrasive degradation at their surfaces. While being placed in a patient, the prosthesis is rubbed against tissue; when the patient moves, tissue or other anatomic structures move over the prosthesis; and folds or hernias in device components could cause device component surfaces to rub against one another. Rubbing actions such as these can abrade the surface of the device.

Abrasion can lead to weakening of the device component surface making it more prone to mechanically induced trauma. Abrasion can also release small particles of silicone or other elastomers into the body, leading to the formation of granulomas. In addition, abrasion of a silicone elastomer can expose the particles of silica added to reinforce the elastomer. Crystalline silica is recognized as a sclerogen (i.e., an agent which produces hard or sclerotic tissue, capable of causing adverse reactions when placed in the body). Amorphous fumed, rather than crystalline, silica is typically used to reinforce the silicone elastomers of these devices. However, there are still concerns over the presence of minute crystalline silica impurities in the reinforcer and whether there is any significant *in vivo* conversion of amorphous silica into crystalline silica.

The abrasion resistance of the surfaces of elastomeric components and the content and particle size distribution of the material abraded from the elastomeric components must be known in order to determine whether the implant is safe and effective. Reports on abrasion resistance testing should contain relevant information on the equipment and abrader used, identification and dimensions of specimens, and detailed protocols. In particular, a standard abrasion test machine, or equivalent specialized equipment, should be used to conduct the testing. A description of the test apparatus used, including the number of specimens that can be tested simultaneously, the dimensions (width and length) of both the maximum sample size and the maximum abrading area, and the manner in which specimens are held, should also be provided. The material used to abrade specimens should be identified along with a rationale for choosing this material. Properties of the abrading medium (e.g., hardness, roughness, etc.) and test parameters (e.g., load force, velocity, and cycling rates) that are pertinent to the abrasion process should also be identified and be representative of the *in vivo* situation.

Test specimens should be obtained from components of finished sterilized devices. Significant weight losses in the abraded material should be induced, and the total number of passes (by the abrasive medium) required to induce this observed weight loss should be reported. Averages, standard deviations, detailed protocols, and raw data should be reported. Examinations for exposed silica (particularly crystalline silica) of both the abraded surfaces and abraded particles from test specimens should be conducted and reported. Percentages of crystalline silica and the total content of crystalline silica in these abraded particles should be analyzed and reported. Particle size distributions of abraded particles should be reported.

The results of these tests should be compared to the energy, stresses, etc., that the device will encounter *in vivo*.

Device Performance Testing

Life testing should demonstrate that the device is sufficiently durable to withstand the

demands of use while maintaining operational characteristics sufficient for urethral compression throughout the expected operational lifetime of the device, as stated in the physician and patient labeling. Life testing should include:

- measurements of all component and material wear and bond strengths after the device is cycled between inflated and deflated conditions;

- a discussion comparing the rate of cycling performed in each test to the approximate maximum rate of cycling of the device *in vivo* and to the expected life of the device;

- appropriate "downtimes" at predetermined cyclical intervals to evaluate relevant performance characteristics and conformance to design specifications;

- a complete evaluation of material characteristics indicative of material degradation that could induce device malfunction; and

- cyclical testing beyond the expected longevity of the implant with identification of the failure mode.

The permeability of the filling agent through the reservoir and body of the device should be evaluated to demonstrate that fluid loss due to osmosis will be acceptable over the expected life of the device.

Testing to demonstrate the operational characteristics of the device should include but not necessarily be limited to the:

- amount of pressure generated in the cuff during inflation;

- rate of pressure rise during inflation and pressure drop during deflation;

- range of time and number of strokes required for full inflation;

- ability to maintain the cuff in a functional inflated condition for the specified duration (assessment of valve leakage);

- time to fully deflate the cuff from the fully inflated pressure;

- shear and tensile strength of all bonds between device components; and

- cyclic inflation/deflation tests to demonstrate appropriate functional durability.

Component Specific Performance Testing

Proper component operation, conformance to predetermined operational specifications, and reliability over the expected life of the device should be demonstrated. Resistance of each component to tears, crazing, fracture, material fatigue (including wear between mating components), change of position (e.g., valve seats), and permanent deformation should also be demonstrated. Component characterization and testing should include but not necessarily be limited to:

Cuff

- maximum pressure and expansion capability,
- measurement of stiffness, including resistance to buckling,
- resistance to aneurysms,
- ability of cuff closure to remain inflated under maximum loads expected *in vivo*,
- uniformity of inflated dimensions,
- inflation and deflation characteristics,
- wear characteristics at folds in the cuff,

Pump

- minimum force required to affect fluid displacement,
- range of volume displaced per stroke,
- squeeze force versus fluid displacement (volume),
- inflation effort, defined as pump force times the number of strokes required for full inflation,
- ability to maintain its set pressure after repeated punctures to the pressure adjustment port with both new devices and devices evaluated in the reliability tests,

Valves

- pump output pressure required to affect valve opening for device activation,
- tactile pressure/force required to affect valve opening, against fully inflated cuffs, for deflation,
- back pressure required for valve failure,
- maximum pressure differential across closed valve at full inflation and leakage rate at this pressure,
- prevention of spontaneous inflation and deflation under movements and loads simulating those expected to be sustained by the implanted device in both the inflated and deflated states,
- potential for valve failure which may result in an inability to inflate or deflate the cuff,

Reservoir

- capacity (volume),
- pressures experienced over the inflation/deflation cycle,
- rate of maximum fluid outflow and inflow,
- wear characteristics if a fold in the reservoir envelope occurs,
- durability tests demonstrating adequate resistance to fatigue caused by cyclic external compression applied radially to the inflated reservoir,

Tubing

- tensile characteristics (with and without tubing connectors, if any),
- tear or rupture resistance,
- kink resistance,
- wear characteristics if a fold in the tubing develops, and
- ability to remain intact under loads simulating and exceeding those expected *in vivo*.

Other components of the device or accessories such as tubing connectors and specialized tools used during the insertion procedure should be evaluated appropriately. Testing of these components or accessories should reflect the anticipated conditions of use (e.g., tubing connectors should be demonstrated to be able to maintain connection to the device for the expected life of the device).

V. CLINICAL INFORMATION

The clinical information should provide reasonable assurance of the safety and effectiveness of the device in the treatment of urinary incontinence and should constitute valid scientific evidence as defined in 21 CFR 860.7(c)(2). For the AUS, this should include:

- information from well-controlled clinical studies, whenever possible,
- a statistically justified sample size,
- detailed history and preoperative work-up, and
- detailed long-term (5 year) follow-up.

A detailed protocol for the clinical trial should be specified with:

- appropriately justified concurrent control/comparison groups,
- explicit patient inclusion/exclusion criteria,
- focused clear study objectives,
- step-by-step implant and follow-up procedures, and
- a well-defined follow-up schedule.

Full patient accounting should be reported, including:

- theoretical follow-up (the number of patients that would have been examined if all patients were examined according to their follow-up schedules);

- patients lost to follow-up with measures taken to minimize such events and all available information provided on patients lost to follow-up (loss to follow-up should not exceed 20% over the course of the study);

- specification of any deviations from the protocol with all deviations justified;

- time course of revisions, including all explant and repair data; and

- time-course of deaths (stating the cause of death, including the reports from any post-mortem examinations).

As part of this patient accounting, each clinical report should clearly state the date that the database was closed to the addition of new information. In addition, examples of a raw data spreadsheet and patient accountability tree can be obtained from ULDB which may assist in the organization and presentation of the clinical data.

A statistical demonstration, based on the number of patients who complete the required study period, should show that the sample size of the clinical study is adequate to provide accurate measures of the safety and effectiveness of this device. The statistical demonstration should identify:

- study definitions of success and failure,
- clinically reasonable levels for Type I (alpha) and Type II (beta) errors,
- anticipated variances of the response variables, and
- assumptions made and all statistical formulas used (with copies of any references).

A complete description of all patient randomization techniques used, and how these techniques were employed to exclude potential sources of bias, should be provided, where applicable.

Detailed patient demographic analyses and characterizations should be presented to show that the patients enrolled in the study are representative of the population for whom the device is intended.

If pooling is intended, statistical justifications for pooling across several variables should be provided, such as:

- the etiology and duration of incontinence,
- age,

- gender,
- concomitant medical conditions,
- various anatomical abnormalities,
- the type or model of the implanted device,
- the number and type of prior treatments attempted to restore continence,
- device usage (initial implantation versus revision),
- investigational site,
- degree of patient motivation and manual dexterity,
- surgeon experience and technique, and
- cuff placement site.

The data collected and reported should include all necessary variables in order to permit stratification and analysis of the study data required to evaluate the risk/benefit ratio for each clinically relevant subpopulation of patients. For each relevant subgroup, a sufficient number of patients need to be followed for a sufficient length of time to support all claims (explicit and implied) in any PMA submission.

FDA believes that 5 year follow-up data are necessary in order to characterize the safety and effectiveness of the device over its expected lifetime; however, appropriately justified alternate follow-up schedules will be considered.

Safety

To evaluate device safety, clinical studies should include time-course presentations of clinical data demonstrating the presence or absence of:

- tissue erosion,
- infection,
- pain/discomfort,
- injury to the upper urinary tract due to either urinary retention or hydronephrosis,
- continued or worsened incontinence,
- leakage,
- wear,
- tubing kinking/breaking or disconnection,
- pump failure,
- cuff failure,
- iatrogenic complications,
- hematoma,
- seroma,
- inguinal hernia formation,
- fibrous capsule formation,
- fistula formation from urethral erosion,
- urethral scarring,

- bleeding,
- urethral stricture,
- development of bladder hyperreflexia,
- reoperation,
- wound dehiscence,
- pelvic abscess,
- fistula to the skin, and
- any effects on the immune system[1] (both local to the device and systemic) and the reproductive system, without regard to the device relatedness of the event.

The diagnostic criteria for each type of immunological and allergic phenomenon should be defined at the beginning of the study, and all cases should be well documented utilizing these criteria. Patients should be regularly monitored for the occurrence of such adverse events

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[1]As yet, there are no tests or studies to show that autoimmune diseases are caused by the presence of silicone implanted in the body. However, preliminary clinical data have shown: (1) the presence of IgG antibodies to silicone in some individuals after implantation with silicone ventriculoperitoneal shunts (ref.1), and (2) antinuclear autoantibodies (as measured by immunofluorescence, immunodiffusion, western blot analysis, and immunoprecipitation of radiolabelled intracellular proteins) in some women with silicone breast implants (ref.2). Although additional confirmatory research studies are needed, these results suggest that anti-silicone antibodies and anti-nuclear autoantibodies of defined specificity may serve as early serological biomarkers prior to clinical symptoms of autoimmune disease. For this reason, it is suggested that blood samples from subjects with silicone implants be tested yearly for 10-15 years after implantation for anti-silicone antibodies and anti-nuclear autoantibody specificities as described in references 1 and 2, respectively. As a control, blood collected before implantation should also be tested. The suggested time period of 10-15 years is based on 9.8 years, the mean latent period from implantation to onset of clinical symptoms of defined autoimmune disorders (ref.2). However, it should be noted that Press et al. (1992; ref.2) did not examine sera from women who have silicone implants but have no clinical symptoms or from women who have no silicone implants but have clinical symptoms of defined autoimmune disorders. Thus, more studies are needed to determine whether antinuclear autoantibodies are associated with the development of autoimmune disorders in men or women with silicone artificial urinary sphincters, and whether anti-silicone antibodies are biomarkers of clinical symptoms of autoimmune disease.

References:

1. Goldblum, R.M., R.P. Pelley, A.A. O'Donell, D. Pyron and J.P. Heggers. 1992. Antibodies to silicone elastomers and reactions to ventriculoperitoneal shunts. Lancet 340: 510-512.
2. Press, R.I., C.L. Peebles, Y. Kumagai, R.L. Ochs and E.M. Tan. 1992. Antinuclear autoantibodies in women with silicone breast implants. Lancet 340: 1304-1307.

for a minimum of 5 years post-implantation.

In addition, the effect of the presence of the implant upon future medical diagnoses/treatments involving the lower pelvic region in recipients of the AUS should be evaluated.

Effectiveness

The effectiveness of the device may be assessed by an objective and standardized recording/measurement of the ability of the device *in vivo* to either restore or significantly improve urinary continence and the enhancement of a patient's quality of life following implantation of the device; both of which can be balanced against any risk of illness or injury from use of the device. In addition, any accessories sold with the device should be shown to have been effectively used in implant procedures without adverse effects.

Time-course presentations of restoration of continence (dryness) or significant improvement in continence, as well as other information on the anatomical and physiological effects of the device (including all adverse events) should be provided.

Documentation of the anatomical and physiologic outcomes of implantation of the device should include:

- regular postsurgical evaluations of the functional (i.e., inflation and deflation) characteristics of the device for at least 5 years post-implantation;

- periodic postsurgical urodynamic testing (such as measurements of leak point pressure and the volume of urine leaked into a pad after a standard set of maneuvers) during this follow-up period, with comparisons to baseline measurements;

- regular postsurgical assessments of incontinence grade (possibly obtained from periodic patient voiding diaries or the number of pads required per day to keep dry or some other standard assessment technique), as compared to baseline values; and

- patient assessments of the mechanical function of the implant (such as ease of activation) during this follow-up period (which may be influenced by the manual dexterity or motivation of the patient).

Documentation of the effect of the AUS upon the patient's quality of life should include:

- prospective research designs, including pre- and postsurgical repeated measures for at least 5 years post-implantation;

- standardized test questions rather than informal, yet-to-be-validated questionnaires,

whenever possible; and

- comparisons of the postsurgical scores to those measured prior to device implantation.

Separate Analyses

Any PMA for the device should separately analyze the degree of device safety and effectiveness by the following variables:

- etiology,
- duration and degree of urinary incontinence,
- the device type or model implanted,
- the number and type of treatments (if any) attempted to restore continence prior to device implantation,
- degree of manual dexterity,
- investigational site,
- gender,
- age,
- surgeon experience and technique, and
- incision site.

Furthermore, for each explantation procedure performed on the study subjects, the following information should be provided:

- the mode of failure of the removed device,
- whether or not the explanted device was replaced with a new device, and
- either the manufacturer, type, and model of the new device implanted, or the type of treatment that the patient received for his/her incontinence (if revision surgery was not performed).

Post Approval and Epidemiological Studies

The agency believes that insufficient time has elapsed to permit a direct evaluation of the risks of cancer, immune related connective tissue disorders, and reproductive/teratogenic effects of the device as well as the later effects on offspring posed by the presence of silicone in the human body and that sufficient epidemiological data or experimental animal data is not available to make a reasonable and fair judgement of these risks. Furthermore, the potential long-term risk of hydronephrosis and/or decreases in renal function in patients implanted with the device, due to the chronic elevation of urethral resistance experienced post-implantation, has yet to be quantified and is a concern of the agency. Therefore, the agency will require long-term post-approval follow-up for any AUS permitted to continue in commercial distribution.

Protocols to study the influence of the implanted device on the risks of developing cancer, immune related connective tissue disorders (especially scleroderma), and any other illness of interest that may be associated with the use of the device should be provided. More than one protocol may be necessary to satisfy this requirement.

The incidence of implantation and prevalence of users of the AUS is not available in the scientific literature. This information is crucial to determining whether any of the proposed studies are feasible. Therefore, sponsors should submit scientifically valid descriptions of implant recipients in terms of their distribution by age, race, number of previous implants, and whether the device is currently in place. Based on the descriptive data, the sponsor should either provide a study protocol, or explain why an epidemiologic study is not feasible.

The arguments should use scientific estimates of the usual frequency or incidence of the illness of interest (e.g., cancer, connective tissue disorders, etc.) and statistically-derived power calculations.

If a study is <u>feasible</u>:

The cancer study should allow sufficient time to elapse after implantation for a diagnosis of cancer to be reasonably attributable to the device, under a promotor or initiator model.

For each hypothesized adverse outcome (i.e., cancer, connective tissue disorders, etc.), the study population should include sufficient numbers of patients in the age groups for which the health outcome in question has significant incidence.

The study design(s) are expected to reflect the personal and sensitive nature of the device. Furthermore, the following and other relevant variables need to be recorded, where possible, and taken into account in the analysis:

- device usage (initial implantation versus revision),
- device type or model,
- surgeon experience and technique, and
- location of device placement.

For devices that have been marketed prior to the PMA submission, retrospective study designs (case control, retrospective cohort, etc.) using historical data are encouraged.

The following elements should be included in the protocol: study objectives, variables, and design (including study type, size, and duration). The sources and representativeness of patient and device data should be presented along with the data collection plan, forms, quality control measures, and analysis plans. The timing of the interim and final reports, and the background of the principle investigator should also be included.

VI. LABELING

Copies of all proposed labeling for the device including any information, literature, or advertising that constitutes labeling under Section 201(m) of the act should be provided. The general labeling requirements for medical devices are contained in 21 CFR part 801. These regulations specify the minimum requirements for all devices. Additional guidance regarding device labeling can be obtained from FDA's publication "Labeling: Regulatory Requirements for Medical Devices," and from ODE's "Device Labeling Guidance" (both documents are obtainable through DSMA). Highlighted below is additional guidance for some of the specific labeling requirements for the AUS.

The intended use statement should include the specific indications for use and identification of the target populations. Specific indications and target populations should be completely supported by the clinical data described in this guidance. For example, it may be necessary to restrict the intended use to patients who have failed prior, less invasive therapies and/or to patients with specific etiologies of incontinence in whom safety and effectiveness have been demonstrated.

The directions for use should contain comprehensive instructions regarding the preoperative, perioperative, and postoperative procedures to be followed. This information should include, but is not necessarily limited to:

- a description of any pre-implant training necessary for the surgical team;

- a description of how to prepare the patient (e.g., prophylactic antibiotics), operating room (e.g., what supplies should be on hand), and device (e.g., handling instructions, resterilization instructions) for device implantation;

- instructions for implantation, including possible surgical approaches, sizing, fluid adjustment (including what filling solutions may be used and how they should be prepared), device handling, and intraoperative test procedures to ensure implant functionality and proper placement;

- instructions to caregivers to specifically question patients prior to surgery for any history of allergic reaction to any of the device materials or filling agents.

- instructions for follow-up, including whether antibiotic prophylaxis is recommended during the post-implant period and/or during any subsequent dental or other surgical procedures, how to determine when patients are ready to activate the device, and how to evaluate, and how often to evaluate, proper functionality and placement;

- a brief summary of the clinical experience with the implant; and

- troubleshooting procedures.

The labeling should include both implant and explant forms to allow the sponsor to adequately monitor device experience. The explant form should allow collection of all relevant data, including the reason for the explant, any complications experienced and their resolution, and any action planned (e.g., replacement with another implant).

Patient labeling should be provided which includes the information needed to give prospective patients realistic expectations of the benefits and risks of device implantation. Such information should be written and formatted so as to be easily read and understood by most patients and should be provided to patients prior to scheduling implantation, so that each patient has sufficient time to review the information and discuss it with his or her physician(s). Technical terms should be kept to a minimum and should be defined if used. Patient information labeling should not exceed the seventh grade reading comprehension level and should provide the patient with the following information:

- the indications for use and relevant contraindications, warnings, precautions, and adverse effects/complications described using terminology well known and understood by the average layperson;

- the anticipated benefits and risks associated with the device to give patients realistic expectations of device performance and potential complications (the known, suspected, and potential risks of device implantation should be identified and the consequences, including possible methods of resolution, should be described);

- alternatives to the use of the device, including less invasive treatments, should be identified, along with a brief description of the associated benefits and risks of each (the patient should be advised to contact his or her physician for more information on which of these alternatives might be appropriate given his/her specific condition);
- instructions for how to use the device which include the expected length of recovery from surgery and when to attempt activation following implantation, warnings against certain actions that could damage the device, how to identify conditions that require physician intervention, who to contact if questions arise, and other relevant information; and

- emphasis of the fact that the implant may fail and should therefore, not be considered a "lifetime" implant. (Where possible, the patient labeling should provide information on the approximate number of revisions necessary for the average patient, and indicate the average longevity of each implant so patients are fully aware that additional surgery for device modification, replacement, or removal may be necessary. This information should be supported by the clinical experience (i.e., not merely bench studies) with the implant or by published reports of experience with similar devices.)

The physician's labeling should instruct the urologist or implanting surgeon to provide the implant candidate with the patient labeling prior to surgery to allow each patient sufficient time to review and discuss this information with his/her physician(s).

Each clinical investigation should validate the adequacy and appropriateness of the physician and patient instructions for use (labeling) that were used.

Appendix I Extraction Guidelines for Polymers

I. Leachables

Most polymeric materials contain, in addition to the relatively inert, high molecular weight polymer, other components such as residual monomers, oligomers, catalysts, processing aids, etc. These are present at varying levels depending on the raw material sources, the manufacturing processes, and intended function of additives. Also, additional chemical species may be generated during manufacturing processes such as heat sealing, welding, or sterilization of the device. All of these may migrate from the device into the human body and should be the subject of risk assessments.

The rate of migration of leachables from a device component will very likely be controlled by diffusion processes in the polymer itself unless there is partitioning in the external phase, in most cases, body fluids and tissues. The latter cannot hold if metabolic processes convert the migrant into another chemical species or if it is eliminated. In either case, the situation is equivalent to migration into infinite volume and corresponds to exhaustive extraction. The effect of the external phase is treated in a paper by R. C. Reid, K. R. Sidman, A. D. Schwope and D. E. Till, Ind. Eng. Chem. Prod. Res. Dev., 19(4), **1980**, p. 580-587.

The rates of migration may be very slow so that the levels of migrants in short term animal studies may not be high enough to elucidate any responses. Toxicological testing of migrants allows for determination of dose response curves and "no adverse effect levels." For device components, initial levels plus migration rates would allow calculation of dose rates. In order to carry out such risk assessments, the identity and levels of the potential migrants must be established. Presently, exhaustive extractive experiments are the best approach for accomplishing this.

II. Samples

Each of the individual structural components as they are found in the final sterilized device should be subjected to extractions. No additional processing or curing should be performed on these samples. A major fraction of each structural component as it is in the final device should be subjected to extractions. Two approaches are possible;

1. Several replicate samples can be taken from each of the structural components of the finished devices and these samples can be subjected to extractions.

2. Several replicate samples can be taken from the structural components before final assembly, but the components must have undergone all processing, curing and sterilization treatments that the finished device receives. This approach can be used provided that the content and chemical identity of the extracts is the same as (or closely represents) that found using approach 1.

Both of these approaches require that the ratio of the sample weight to the device structural component weight be known so that levels of extractants can be referred back to the entire device as implanted. That is, the grams of migrant per grams of the specific structural component is then multiplied by the total weight of the structural component to give the total amount per device.

III. Selection of Extracting Solvents

Solvents should be chosen that are expected to solubilize the low molecular weight migrants thus facilitating exhaustive extraction. Inasmuch as the chemical nature of all of the migrants

polarity, aromaticity, etc. Both polar and non-polar solvents should be used. Charged or

also migrate from the polymers and would not be soluble in non-polar solvents.

Initial experiments should use a solvent of mixed polarity such as
highly crosslinked polymers that may used, solvents which swell the polymer are desirable as

IV. Design of the Extraction Experiment

An extraction cell should be used in which a sample of known weight and known geometric surface area is extracted by a known volume of solvent. An example of such a cell is described in an article by Snyder, R. C. and Breder, C.V., J.Assoc. Off. Anal. Chem., 68(4) **1985**, p 770f. Such a cell may work for polymer plates such as cut from the shell. Mild agitation of the solvent is recommended. Although immersion of samples allows for two-sided extraction, calculation should be based on the sample weight or the area of one side when doing exhaustive extractions. Additional considerations and helpful comments are given in the section "Design of the Extraction Experiment, part D.1.a, Extraction Vessel" of the Recommendations for Chemistry Data for Indirect Food Additive Petitions obtainable from the Division of Food Chemistry and Technology, CFSAN, FDA, Washington, D. C. 20204.

B. Extraction Sample

General considerations on sampling are given above. Because migration is a diffusive process plate geometry is desirable; the experimental time can be further minimized by using thin samples. The sample geometry, thickness, weight and solvent volume must be reported. The ratio of volume of solvent to the area of the sample is not so important for exhaustive extraction as described below. However, if cloudy solutions or precipitation is noticed

during the first time interval, then the solvent volume to sample surface area may be too low.

C. Temperature and Time of Extractions

For the determination of residual levels of low-molecular weight components of polymeric materials, experiments can be accelerated since only the levels are of interest here and not the kinetics. Exhaustive extractions should be carried out as described below in order to determine residue levels. This will also provide the maximum amount of migrants per sample which should be used for further chemical characterization and for toxicological tests. Extractions can be done at 37°C or at elevated temperatures in order to accelerate the experiment. However, the petitioner is advised that elevated temperatures may cause chemical reactions to produce additional extractants. Also, if elevated temperatures are used they should be chosen so that no additional curing or crosslinking of the polymers takes place during the extraction experiment.

For exhaustive extractions, the duration of the extraction cannot be prescribed in advance but can be dealt with in the following manner. A series of successive extractions is carried out by exposing the sample to the solvent for a period of time, analyzing the solvent for extractants, replacing with fresh solvent and again exposing the sample for a period of time, analyzing and repeating the process. When the level of the analyte for the ith successive extraction is one-tenth (.1) of the level in the first extraction the extraction may be deemed complete. It is possible that this condition may not occur because of extremely slow migration of the higher molecular weight material. The test can be applied to the contents of the extract with molecular weights below 1500. All the separate analyte levels are added up to give the cumulative value and via the sample/solvent ratio referred back to sample levels and finally back to device levels.

In order to minimize experimental time and provide for analysis choosing unequal time periods is desirable. Intervals based on a log or half-log scale generally work out well and minimizes the number of chemical analyses. For shells, this should also allow determination of migration rates by log-log plots of cumulative migration against time.

V. Characterization of the Extracts

A. Analytical Methodology

Specific or non-specific analytical methods may be required depending on the situation. For example, size exclusion chromatography (SEC), high pressure liquid chromatography (HPLC) or some other chromatographic or separation methods may show that the extractants in a given solvent consist of several chemical species. Appropriate methodologies, such as atomic absorption (AA), ion chromatography, etc., should be employed to assess the presence of metallic, inorganic, organometallic, etc., leachables in polar solvents. For the purposes of performing the exhaustive extraction, determination of

the total concentration of extractants by gravimetric or some other method would suffice. A bibliography of representative analytical methodologies which may be useful is given in Appendix II.

It is necessary for the purposes of toxicological testing to identify the individual components in terms of their molecular composition and to determine the concentration of the individual components of the extract. Following separation and isolation, identification of the individual components in terms of chemical composition can be done by any number of chemical identification methods such as infrared, UV-visible (including diode array), NMR, or mass spectrometries (See Appendix II). Comparison to known structures will be beneficial. Determination of the individual concentrations may require a specific analytical method unless relative concentrations of the components can be determined and used together with the total concentration to give the individual concentrations.

B. Description of Analytical Methods

All analytical methods must be completely described. Calibration or standard curves should be supplied. The calibration curve should bracket the concentration of the migrant in the extract. All analytical methods should be validated. An excellent discussion of these points is given in the Section D.3 entitled "Analytical Methodology" in the Recommendations for Chemistry Data for Indirect Food Additive Petitions already cited above. Additional information with accompanying references concerning validation procedures can be found in papers by Vanderwielen and Hardwidge (Guidelines for Assay Validation, Pharmaceutical Technology, March 1982, pp 66-76) and by Ficarro and Shah (Validation of High-Performance Liquid Chromatography and Gas Chromatography Assays, Pharmaceutical Manufacturing, Sept 1984, pp 25-27). We agree with the recommendations given in those Guidelines.

GENERAL REFERENCES

Wheeler, D.A., "Determination of Antioxidants in Polymeric Materials", *Talanta*, 15, 1315-1334, (1968).

Majors, R.E., "High Speed Liquid Chromatography of Antioxidants and Plasticizers Using Solid Core Supports", *J. Chromatogr. Sci.*, 8, 338-345, (1970).

Schroeder, E., "The Development of Methods for Examining Stabilizers in Polymers and their Conversion Products", *Pure Appl. Chem.*, 36, 233-251, (1973).

Pacco, J., Mukherji, A.K., "Determination of Polychlorinated Biphenyls in a Polymer Matrix by Gel Permeation Chromatography using micro-Styragel® Columns", *J. Chromatogr.*, 144, 113-117, (1977).

Crompton, T.R. *Chemical Analysis of Additives in Plastics*; International Series in Analytical Chemistry, Pergamon Press: New York, 1977; Vol. 46.

Majors, R.E., Johnson, E.L., "High-Performance Exclusion Chromatography of Low-Molecular-Weight Additives", *J. Chromatogr.*, 167, 17-30, (1978).

Thompson, R.M., Howard, C.C., Crowley, J.P. DeRoos, F.L., Leininger, R.I., "Literature Review: Polymeric Material Leachables and their Biological Effects and Toxicology"; final report to Food and Drug Administration, Center for Devices and Radiological Health (formerly Bureau of Medical Devices) on Contract Number 233-77-5038; Battelle - Columbus Laboratories: Columbus, OH, 1979.

Walter, R.B., Johnson, J.F., "Analysis of Antioxidants in Polymers by Liquid Chromatography", *J. Polym. Sci.: Macromol. Rev.*, 15, 29-53, (1980).

Shepherd, M.J., Gilbert, J., "Analysis of Additives in Plastics by High-Performance Size-Exclusion Chromatography", *J. Chromatogr.*, 218, 703-713, (1981).

Squirrell, D.C.M., "Analysis of Additives and Process Residues in Plastics Materials", *Analyst*, 106, 1042-1056, (1981).

Low Molecular Weight Leachables from Medical Grade Polymers; U.S. Department of Commerce, National Institute of Science and Technology (formerly National Bureau of Standards). National Technical Information Service (NTIS), Springfield, VA, 1982; NBSIR 81-2436.

Krause, A., Lange, A., Erzin, M. *Plastics Analysis Guide: Chemical and Instrumental Methods;* Hanser: New York, 1983.

Crompton, T.R. *The Analysis of Plastics*; Pergamon Series in Analytical Chemistry, Pergamon Press: New York, 1984; Vol. 8.

Vargo, J.D., Olson, K.L., "Characterization of Additives in Plastics by Liquid Chromatography-Mass Spectrometry", *J. Chromatogr.*, 353, 215-224, (1986).

Gibbons, J.J., "An Evaluation of Plasticizers by Fourier Transform Infrared Spectroscopy", *American Laboratory*, November, 78-85, 1987.

Middleditch, B.S., Zlatkis, A., "Artifacts in Chromatography: An Overview", *J. Chromatogr. Sci.*, 25, 547-551, (1987).

Hopkins, J.L., Cohen, K.A., Hatch, F.W., Pitner, T.P., Stevenson, J.M., Hess, F.K., "Pharmaceuticals: Tracking Down an Unidentified Trace Level Constituent", *Anal. Chem.*, 59(11), 784-790, (1987).

McGorrin, R.J., Pofahl, T.R., Croasmun, W.R., "Identification of the Musty Component From an Off-Odor Packaging Film", *Anal. Chem.*, 59(18), 1109-1112, (1987).

Del Rios, J.K., "Polymer Characterization Using the Photodiode Array Detector", *American Laboratory*, January, 1988.

Multidimensional Chromatography; Cortes, H.J., Ed.; Chromatographic Science Series 50; Dekker, New York, 1990.

The Analytical Chemistry of Silicones, Smith, A. Lee, Ed.; Chemical Analysis: A Series of Monographs on Analytical Chemistry and Its Applications 112; Wiley-Interscience, New York, 1991.

Braybrook, J.H., Mackay, G.A., "Supercritical Fluid Extraction of Polymer Additives for Use in Biocompatibility Testing", *Polym. Int.*, 27, 157-164 (1992).

Erickson, M.D., *Analytical Chemistry of PCBs*;Lewis:Boca Raton,1992.

POLYOLEFINS

Spell, R.L., Eddy, R.D., "Determination of Additives in Polyethylene by Absorption Spectroscopy", *Anal. Chem.*, 32(13), 1811-1814, (1960).

Crompton, T.R., "Identification of Additives in Polyolefins and Polystyrenes", *Eur. Polym. J.*, 4, 473-496, (1968).

Howard, J.M., "Gel Permeation Chromatography and Polymer Additive Systems", *J. Chromatogr.*, 55, 15-24, (1971).

Couper, J., Pokorny, S., Protivova, J., Holcik, J., Karvas, M., Pospisil, J., "Antioxidants and Stabilizers. XXXIII. Analysis of Stabilizers of Isotactic Polypropylene: Application of Gel Permeation Chromatography", *J. Chromatogr*., 65, 279-286, (1972).

Wims, A.M., Swarin, S., "Determination of Antioxidants in Polypropylene by Liquid Chromatography", *J. Appl. Polym. Sci.*, 19, 1243-1256, (1975).

Lichenthaler, R.G., Ranfelt, F., "Determination of Antioxidants and their Transformation Products in Polyethylene by High-Performance Liquid Chromatography", *J. Chromatogr*., 149, 553-560, (1978).

Schabron, J.F., Fenska, L.E., "Determination of BHT, Irganox 1076, and Irganox 1010 Antioxidant Additives in Polyethylene by High Performance Liquid Chromatography", *Anal. Chem.*, 52, 1411-1415, (1980).

Haney, M.A., W.A. Dark, "A Reversed-Phase High Pressure Liquid Chromatographic Method for Analysis of Additives in Polyolefins", *J. Chromatogr. Sci*., 18, 655-659, (1980).

Lehotay, J., Danecek, J., Lisa, O., Lesko, J., Brandsteterova, E., "Analytical Study of the Additives System in Polyethylene", *J. Appl. Polym. Sci*., 25, 1943-1950, (1980).

Schabron, J.F., Bradfield, D.Z., "Determination of the Hindered Amine Additive CGL-144 in Polypropylene by High-Performance Liquid Chromatography, *J. Appl. Polym. Sci.*, 26, 2479-2483, (1981).

Francis, V.C., Sharma, Y.N., Bhardwaj, I.S., "Quantitative Determination of Antioxidants and Ultraviolet Stabilizers in Polymers by High Performance Liquid Chromatography", *Angew. Makromol. Chem.*, 113, 219-225, (1983).

Choudhary, V., Varshney, S., Varma, I.K., "Degradation of Polypropylene: Effect of Stabilizers", *Angew. Makromol. Chem.*, 150, 137-150, (1987).

Munteanu, D., Isfan, A., Isfan, C., Tincul, I., "High-Performance Liquid Chromatographic Separation of Polyolefin Antioxidants and Light-Stabilisers", *Chromatographia*, 23 (1), 7-14, (1987).

Padron, A.J.C., Colmenares, M.A., Rubinztain, Z., Albornoz, L.A., "Influence of Additives on

Some Physical Properties of High Density Polyethylene - I. Commercial Antioxidants", *Eur. Polym. J*., 23 (9), 723-727, (1987).

Padron, A.J.C., Rubinztain, Z., Colmenares, M.A., "Influence of Additives on Some Physical Properties of High Density Polyethylene - II. Commercial u.v. Stabilisers", *Eur. Polym. J*., 23 (9), 729-732, (1987).

Raynor, M.W., Bartle, K.D., Davies, I.L., Williams, A., Clifford, A.A., "Polymer Additive Characterization by Capillary Supercritical Fluid Chromatography/Fourier Transform Infrared Microspectrometry", *Anal. Chem.*, 60, 427-433, (1988).

"Deformulating Polypropylene by HPLC", *Polymer Notes*, Waters Chromatography Division, 2(2), 1988.

Neilson, R. C., "Extraction and Quantitation of Polyolefin Additives", *J. Liquid. Chromatogr.*, 14 (3), 503-519, (1991).

Waters Polymer Update, applications Brief No. RN101, "The Analysis of Additives in Polyolefins by Reverse Phase Gradient Chromatography", date unknown.

POLYVINYL CHLORIDE (PVC)

Pedersen, H.L., Lyngaae-Jorgensen, J., "Gel Permeation Chromatography Measurements on PVC Resins and Plasticisers", Br. Polym. J., 1, 138-141, (1969).

Howard, J.M., "Gel Permeation Chromatography and Polymer Additive Systems", *J. Chromatogr.*, 55, 15-24, (1971).

Liao, J.C., Browner, R.F., "Determination of Polynuclear Aromatic Hydrocarbons in Poly(vinyl chloride) Smoke Particulates by High Pressure Liquid Chromatography and Gas Chromatography-Mass Spectrometry", *Anal. Chem.*, 50,(12), 1683-1686, (1978).

Shepherd, M.J., Gilbert, "Simple and Inexpensive Application of Steric Exclusion Chromatography for the Isolation of Low-Molecular Weight Additives form Polymer Systems", *J. Chromatogr*., 435-441, (1979).

Perlstein, P., "The Determination of Light Stabilisers in Plastics by High-Performance Liquid Chromatography", *Anal. Chim. Acta*, 21-27, (1983).

Preussler, V., Slais, K., Hanus, J., "The Use of Micro-HPLC with Gradient Elution for the Characterization of Phenol-Formaldehyde Resins", *Angew. Makromol. Chem.*, 150, 179-187, (1987).

POLYMETHYLMETHACRYLATE (PMMA)

Pasteur, G.A., "Quantitative Determination of Stabilizers in Tetraethylene Glycol Dimethacrylate by High Pressure Liquid Chromatography", *Anal. Chem.*, 49(3), 363-364, (1977).

Brauer, G.M., Termini, D.J., Dickson, G., "Analysis of the Ingredients and Determination of the Residual Components of Acrylic Bone Cements", *J. Biomed. Mater. Res.*, 11, 577-607, (1977).

Schoenfeld, C.M., Conard, G.J., "Monomer Release from Methacrylate Bone Cements During Simulated *in vivo* Polymerization", *J. Biomed. Mater. Res.*, 13, 135-147, (1979).

Brynda, E., Stol, M., Chytry, V., Cifkova, I., "The Removal of Residuals and Oligomers from Poly(2-hydroxyethylmethacrylate)", *J. Biomed. Mater. Res.*, 19, 1169-1179, (1985).

Huribut, J.A., Cummins, J.D., "Analysis of 2-Hydroxyethyl Methacrylate in Soft Contact Lenses by High Performance Liquid Chromatography with UV Detection", *LC·GC*, 8(6), 478-479, (1990).

POLYURETHANES

Spagnolo, F., "Quantitative Determination of Small Amounts of Toluene Diisocyanate Monomer in Urethane Adhesives by Gel Permeation Chromatography", *J. Chromatogr. Sci.*, 14, 52-56, (1976).

McFadyen, P., "Determination of Free Toluene Diisocyanate in Polyurethane Prepolymers by High-Performance Liquid Chromatography", *J. Chromatogr.*, 123, 468-473, (1976).

Guthrie, J.L. and McKinney, R.W., "Determination of 2,4- and 2,6-Diaminotoluene in Flexible Urethane Foams", *Anal. Chem.*, 49(12), 1676-1680, (1977).

Bagon, D.A., Hardy, H.L., "Determination of Free Monomeric Toluene Diisocyanate (TDI) and 4,4′-diisocyanatodiphenylmethane (MDI) in TDI and MDI Prepolymers, Respectively, by High-Performance Liquid Chromatography", *J. Chromatogr.*, 152, 560-564, (1978).

Unger, P.D., Friedman, M.A., "High-Performance Liquid Chromatography of 2,6- and 2,4-Diaminotoluene, and its Application to the Determination of 2,4-Diaminotoluene in Urine and Plasma", *J. Chromatogr.*, 174, 379-384, (1979).

Snyder, R.C., Breder, C.V., "High-Performance Liquid Chromatographic Determination of 2,4- and 2,6-Toluenediamine in Aqueous Extracts", *J. Chromatogr.*, 236, 429-440, (1982).

Lattimer, R.P., Welch, K.R., "Direct Analysis of Polymer Chemical Mixtures by Field Desorption Mass Spectroscopy", *Rubber Chem. Technol.*, 53, 151-159, (19**).

Hepburn, C., *Polyurethane Elastomers,* Applied Sci. Publ.: New York, 1982, Chapter 11.

Owen, D.R., Zone, R., Armer, T., Kilpatrick, C., "Analytical Methods for the Determination of Biologically Derived Absorbed Species in Biomedical Elastomers", In *Biomaterials: Interfacial Phenomena and Applications*; Cooper, S.L., Peppas, N.A., Eds.; Advances in Chemistry 199; American Chemical Society: Washington, DC, 1982; pp 395-411.

Guise, G.B., Smith, G.C., "Liquid Chromatography of Some Polyurethane Polyols", *J. Chromatogr.*, 247, 369-373, (1982).

Kuo, C., Provder, T., Kah, A.F., "Application of HPGPC and HPLC to Characterise Oligomers and Small Molecules used in Environmentally Acceptable Coatings Systems", *Paint & Resin*, 53(2), 26-33, (1983).

Ernes, D.A., Hanshumaker, D.T., "Determination of Extractable Methylene (aniline) in Polyurethane Films by Liquid Chromatography", *Anal. Chem.*, 55, 408-409, (1983).

Ratner, B.D., "ESCA Studies of Extracted Polyurethanes and Polyurethane Extracts: Biomedical Implications", In *Physicochemical Aspects of Polymer Surfaces*, Mittal, K.L., Ed.; Plenum: New York, 1983; pp 969-983.

Mazzu, A.L., Smith, C.P., "Determination of Extractable Methylene Dianiline in Thermoplastic Polyurethanes by HPLC", *J. Biomed. Mater. Res.*, 18, 961-968, (1984).

O'Mara, M.M., Ernes, D.A., Hanshumaker, D.T., "Determination of Extractable Methylenebis(aniline) in Polyurethane Films by Liquid Chromatography", In *Polyurethanes in Biomedical Engineering*, H. Planck, G. Egbers, I. Syré, Eds.;Elsevier:Amsterdam,1984;pp. 83-92.

Ward, C.J.P., Radzik, D.M., Kissinger, P.T., "Detection of Toxic Compounds in Polyurethane Food Bags by Liquid Chromatography/Electrochemistry", *J. Liq. Chromatogr.*, 8(4), 677-690, (1985).

Rosenberg, C., Ainen, H.S., "Detection of Urinary Metabolites in Toluene Diisocyanate Exposed Rats", *J. Chromatogr.*, 323, 429-433, (1985).

Hirayama, T., Ono, M., Uchiyama, K., Nohara, M., *J. Assoc. Off. Anal. Chem.*, 68(4), 746-748, (1985).

Vimalasiri, P.A.D.T., Burford, R.P., Haken, J.K., "Chromatographic Analysis of Elastomeric Polyurethanes", *Rubber Chem. Tech.*, 60, 555-577, (1987).

Richards, J.M., McClennen, W.H., Meuzelaar, H.L.C., Shockcor, J.P., Lattimer, R.P., "Determination of the Structure and Composition of Clinically Important Polyurethanes by Mass Spectrometric Techniques", *J. Appl. Polym. Sci.*, 34, 1967-1975, (1987).

Noel, D., VanGheluwe, "High-Performance Liquid Chromatography of Industrial Polyurethane Polyols", *J. Chromatogr. Sci.*, 25, 231-236, (1987).

Marchant, R.E., Zhao, Q., Anderson, J.M., Hiltner, A., "Degradation of a Poly(ether urethane urea) Elastomer: Infra-red and XPS Studies", *Polymer*, 28, 2032-2039, (1987).

Grasel, T.G., Lee, D.C., Okkema, A.Z., Slowinski, T.J., Cooper, S.L., "Extraction of Polyurethane Block Copolymers: Effects on Bulk and Surface Properties and Biocompatibility", *Biomaterials*, 9, 383-392, (1988).

Hull, C.J., Guthrie, J.L., McKinney, R.W., Taylor, D.C., Mabud, Md.A., Prescott, S.R., "Determination of Toluenediamines in Polyurethane Foams by High-Pressure Liquid Chromatography with Electrochemical Detection", *J. Chromatogr.*, 477, 387-395, (1989).

Richards, J.M., Meuzelaar, H.L.C., Bunger, J.A., "Spectrometric and Chromatographic Methods for the Analysis of Polymeric Explant Materials", *J. Biomed. Mater. Res.*, 23, 321-335, (1989).

Richards, J.M., McClennen, W.H., Meuzelaar, H.L.C., "Determination of Additives in Biomer and Lycra Spandex by Pyrolysis Tandem Mass Spectrometry and Time Temperature Resolved Pyrolysis Mass Spectrometry", *J. Appl. Polym. Sci.*, 40, 1-12, (1990).

Belisle, J., Maier, S.K., Tucker, J.A., "Compositional Analysis of Biomer", *J. Biomed. Mater. Res.*, 24, 1585-1598, (1990).

Dillon, J.G., Hughes, M.K., "Determination of Cholesterol and Cortisone Absorption in Polyurethane I. Methodology Using Size-exclusion Chromatography and Dual Detection," *J. Chromatogr.*, 572, 41-49, (1991).

Shintani, H., "Solid-Phase Extraction and High-Performance Liquid Chromatographic Analysis of a Toxic Compound from γ-irradiated Polyurethane", *J. Chromatogr.*, 600, 93-97, (1992).

RUBBERS

Protivova, J., Pospîsil, J., "XLVII. Behavior of Amine Antioxidants and Antiozonants and Model Compounds in Gel Permeation Chromatography", *J. Chromatogr.*, 88, 99-107, (1974).

Protivova, J., Pospîsil, J., "XLVIII. Analysis of the Components of Stabilization and Vulcanization Mixtures for Rubbers by Gel Permeation Chromatography and Thin-Layer Chromatographic Methods", *J. Chromatogr.*, 92, 361-370, (1974).

Weston, R.J., "Volatile Nitrosamine Levels in Rubber Teats and Pacifiers Available in New Zealand", *J. Anal. Toxicol.*, 9, 95-96, (1985).

Zwickenpflug, W., Richter, E., "Rapid Method for the Detection and Quantification of N-Nitrosodibutylamine in Rubber Products", *J. Chromatogr. Sci.*, 25, 506-509, (1987).

NYLONS

Caldwell, J., Perenich, T., "Recovery and Analysis by HPLC of Benzoyl Peroxide Residues in Nylon Carpet Fibers", *Textile Res. J.*, June, 1987.

CELLULOSE ACETATE

Floyd, Th.R., "Use of Two-Dimensional Liquid Chromatography in the Analysis of Additives in Cellulose Acetate Polymer", *Chromatographia*, 25(9), 791-796, (1988).

SILICONES

Horner, H.J., Weiler, J.E., Angelotti, "Visible and Infrared Spectroscopic Determination of Trace Amounts of Silicones in Foods and Biological Materials", *Anal. Chem.*, 32(7), 858-861, (1960).

Estes, Z.E., Faust, R.M., "A Colorimetric Method for the Determination of Silicon in Biological Materials", *Anal. Biochem.*, 13, 518-522, (1965).

Neal, P., "Note on the Atomic Absorption Analysis of Dimethylpolysiloxanes in the Presence of Silicates", *J. Assoc. Off. Anal. Chem.*, 52(4), 875-876, (1969).

Neal, P., Campbell, A.D., Firestone, D., "Low Temperature Separation of Trace Amounts of Dimethylpolysiloxanes from Food", *J. Am. Oil Chemists Soc.*, 46, 561-562, (1969).

Sinclair, A., Hallam, T.R., "The Determination of Dimethylsiloxane in Beer and Yeast, *Analyst*, 96, 149-154, 1971.

Howard, J.W., "Report on Food Additives", *J. Assoc. Off. Anal. Chem.*, 55(2), 262, (1972).

Frick, R., Baudisch, H., "Physico-chemical Determination of Intravascular Silicone in Brain and Kidney", *Beitr. Path. Bd.*, 149, 39-46, (1973).

Cassidy, R.M., Hurteau, M.T., Mislan, J.P., Ashley, R.W., "Preconcentration of Organosilicons on Porous Polymers and Separation by Molecular-Seive and Reversed-Phase Chromatography with an Atomic Absorption Detection System", *J. Chromatog. Sci.*, 14, 444-447, (1976).

Vessman, J., Hammar, C., Lindeke, B., Stromberg, S., LeVier, R., Robinson, R., Spielvogel, D., Hanneman, L., "Analysis of Some Organosilicone Compounds in Biological Material", In *Biochemistry of Silicon and Related Problems*; Bendz, G, Lindquist, I., Eds.; Plenum: New York, 1977; pp 535-558.

Pellenbarg, R., "Environmental Poly(organosiloxanes) (Silicones)", *Environmental Science and Technology*, 13(5), 565-569, (1979).

Abraham, J.L., Etz, E.S., "Molecular Microanalysis of Pathological Specimens *in situ* with a Laser-Raman Microprobe", *Science*, 206, 716-718, (1979).

Buch, R.R., Ingebrightson, D.N., "Rearrangement of Poly(dimethylsiloxane) Fluids on Soil", *Environmental Science and Technology*, 13(6), 676-679, (1979).

Doeden, W.G., Kushibab, E.M., Ingala, A.C., "Determination of Dimethylpolysiloxanes in Fats and Oils", *J. Amer. Oil Chemists Soc.*, 57(2), 73-74, (1980).

Abe, Y., Butler, G.B., Hogen-Esch, T.E., "Photolytic Oxidative Degradation of Octamethylcyclotetrasiloxane and Related Compounds", *J. Macromol. Sci., Chem.*, A16(2), 461-471, (1981).

Leong, A.S.-Y., Disney, A.P.S., Grove, D.W., "Spallation and Migration of Silicone from Blood-Pump Tubing in Patients on Hemodialysis", *N. Engl. J. Med.*, 306(3), 135-140, (1982).

Baker, J.L., LeVier, R.R., Spielvogel, D.E., "Positive Identification of Silicone in Human Mammary Capsular Tissue", *Plast. Reconst. Surg.*, 69(1), 56-60, (1982).

Kacprzak, J.L., "Atomic Absorption Spectroscopic Determination of Dimethylpolysiloxane in Juices and Beer", *J. Assoc. Off. Anal. Chem.*, 65(1), 148-150, (1982).

Mahone, L.G., Garner, P.J., Buch, R.R., Lane, T.H., Tatera, J.F., Smith, R.C., Frye, C.L., "A Method for the Qualitative and Quantitative Characterization of Waterborne Organosilicon Substances", *Environ. Toxicol. Chem.*, 2, 307-313, (1983).

Buch, R.R., Lane, T.H., Annelin, R.B., Frye, C.L., "Photolytic Oxidative Demethylation of Aqueous Dimethylsiloxanols", *Environ. Toxicol. Chem.*, 3, 215-222, (1984).

Watanabe, N., Yasuda, Y., Kato, K., Nakamura, T., "Determination of Trace Amounts of Siloxanes in Water, Sediments and Fish Tissues by Inductively Coupled Plasma Emission Spectrometry", *The Science of the Total Environment*, 34, 169-176, (1984).

Bruggeman, W.A., Weber-Fung, D., Opperhuizen, A., Van der Steen, J., Wijbenga, A.,

Hutzinger, O., "Absorption and Retention of Polydimethylsiloxanes (Silicones) in Fish: Preliminary Experiments", *Toxicol. Environ. Chem.*, 7, 287-296, (1984).

McCamey, D.A., Iannelli, D.P., Bryson, L.J., Thorpe, T.M., "Determination of Silicone in Fats and Oils by Electrothermal Atomic Absorption Spectrometry with In-Furnace Air Oxidation", *Anal. Chim. Acta.*, 188, 119-126, (1986).

Anderson, C., Hochgeschwender, K., Weidemann, H., Wilmes, R., "Studies of the Oxidative Photoinduced Degradation of Silicones in the Aquatic Environment", *Chemosphere*, 16(10-12), 2567-2577, (1987).

Watanabe, N., Nagase, H., Ose, Y., "Distribution of Silicones in Water, Sediment and Fish in Japanese Rivers", *The Science of the Total Environment*, 73, 1-9, (1988).

Winding, O., Christensen, L., Thomsen, J.L., Nielsen, M., Breiting, V., Brandt, B., "Silicon in Human Breast Tissue Surrounding Silicone Gel Prostheses", *Scand. J. Plast. Reconstr. Surg.*, 22, 127-130, (1988).

Annelin, R.B., Frye, C.L., "The Piscine Bioconcentration Characteristics of Cyclic and Linear Oligomeric Permethylsiloxanes", *The Science of the Total Environment*, 83, 1-11, (1989).

Parker, R.D., "Atomic Absorption Spectrophotometric Method for Determination of Polydimethylsiloxane Residues in Pineapple Juice: Collaborative Study", *J. Assoc. Off. Anal. Chem.*, 73(5), 721-723, (1990).

Nakamura, K., Refojo, M.F., Crabtree, D.V., "Factors Contributing to the Emulsification of Intraocular Silicone and Fluorosilicone Oils", *Invest. Ophth. Vis. Sci.*, 31(4), 647-656, (1990).

Nakamura, K., Refojo, M.F., Crabtree, D.V., Leong, F., "Analysis and Fractionation of Silicone and Fluorosilicone Oils for Intraocular Use", *Invest. Ophth. Vis. Sci.*, 31(10), 2059-2069, (1990).

Gaboury, S.R., Urban, M.W., "Spectroscopic Evidence for Si-H Formation During Microwave Plasma Modification of Poly(dimethylsiloxane) Elastomer Surfaces", *Polym. Commun.*, 32(13), 390-392, (1991).

Israeli, Y., Philippart, J.-L., Cavezzan, J., Lacoste, J., Lemaire, J., "Photo-oxidation of Polydimethylsiloxane Oils: Part I - Effect of Silicon Hydride Groups", *Polym. Degradation. Stab.*, 36, 179-185, (1992).

"Selective Detection of Cyclic Silicon Compounds Extracted from Silicone Breast Implants"; DET Report No. 22, March, 1992; DETector Engineering & Technology, Inc., Walnut Creek, CA.