

**QUALITY BIOPHARMACEUTICAL AND
MEDICAL DEVICE CONSULTING &
LABORATORY TESTING SERVICES**

LEXAMED

Compliancedriven
Educationdriven
Analysisdriven
Clientdriven
Knowledgedriven

LexaMed, Ltd. (**LexaMed**), headquartered in Toledo, Ohio, is a company focused on providing the pharmaceutical and medical device industries with quality, compliant, state-of-the-art services in consulting, laboratory, and packaging services.

Our team of experienced, professional consultants has over two centuries of combined experience; these skill-sets allow us to address situations of any size and subject with technically competent, practical and comprehensive solutions. Our consultants are experienced in:

Quality Systems
Validation (product, process, equipment, methods)
Sterilization (EO, steam, radiation, VHP, liquid, novel processes)
Microbiology and Chemistry
Environmental Monitoring
Information Technology
Regulatory Affairs
Auditing
Engineering

Inside

| | |
|-----------------------------------|-------|
| Introduction | 1 |
| Quality Policy | 2 |
| Quality Management Systems | 3-6 |
| Microbiology | 7-12 |
| Chemistry | 13-14 |
| Medical Device Services | 14 |
| Biological Indicators | 15 |
| Validation Services | 16 |
| Hospital Stability Studies | 17 |
| Dietary Supplements | 18 |
| Auditing | 19 |
| Operational Effectiveness Program | 20-21 |
| Training | 22 |
| BEC Growth-Chek™ | 23 |
| Contact Us | 24 |

Our laboratories are ISO certified and have been in operation for more than 25 years, initially as BEC Laboratories, and now as **LexaMed**, providing quality services in microbiology, chemistry, and packaging. The laboratories have been expanded to include many offerings including BIER (EO and steam) testing, disinfectant efficacy, D-value and z-value determinations, package integrity, container-closure studies, and stability and accelerated aging under ICH specified conditions. We also offer tests to support routine lot release such as sterility tests (product and biological indicator) and LAL endotoxin testing. We also provide testing to support sterilization cycle validations such as bioburden quantitation, sterilant resistance, ethylene oxide residues and microbial identifications.

Ample available laboratory space and support resources can accommodate projects of nearly any size and scope. Optimal for customized client-specific Research and Development projects and proprietary product or process evaluations.

LexaMed also manufactures BEC Growth-Chek™ Microbial Suspensions for performing USP Growth Promotion, Monograph <71>, and Bacteriostasis/Fungistasis Test and other quality control measures for growth media.

Our microbial suspensions are derived from cultures traceable to a recognized culture collection identified in USP and ISO 11138:

Aspergillus brasiliensis formerly *Aspergillus niger*
Bacillus subtilis
Candida albicans
Clostridium sporogenes
Escherichia coli
Geobacillus stearothermophilus
Kocuria rhizophila formerly *Micrococcus luteus*
Staphylococcus aureus

LexaMed is ISO 13485 Certified, holds a State of Ohio Drug license and DEA registration, and maintains active memberships in the following associations:

AAMI • ACS • ASM • ISPE • PDA • RAPS

LexaMed QUALITY POLICY

LexaMed is committed to providing the medical device and pharmaceutical industries with the highest quality services and setting the standard for exceptional customer satisfaction. The quality of the service we deliver and the products we provide must always be of the highest quality.

We as a company and as individuals are committed to continually exploring ways to improve our business and to exceed our client's expectations. We will accomplish these goals by:

- ◆ Continually monitoring turn around times to ensure on time delivery of our products and services.
- ◆ Providing accurate, error free work.
- ◆ Conducting testing using state of the art methods and equipment that meets or exceeds regulatory requirements.
- ◆ Offering consulting services that provide competent assistance and timely solutions.
- ◆ Maintaining a professionally trained staff and providing on-going training programs to ensure that our scientists are experts in their fields.

Quality is the responsibility of all employees and in order for *LexaMed* to succeed it will be the priority of all to meet the quality expectations of this policy.

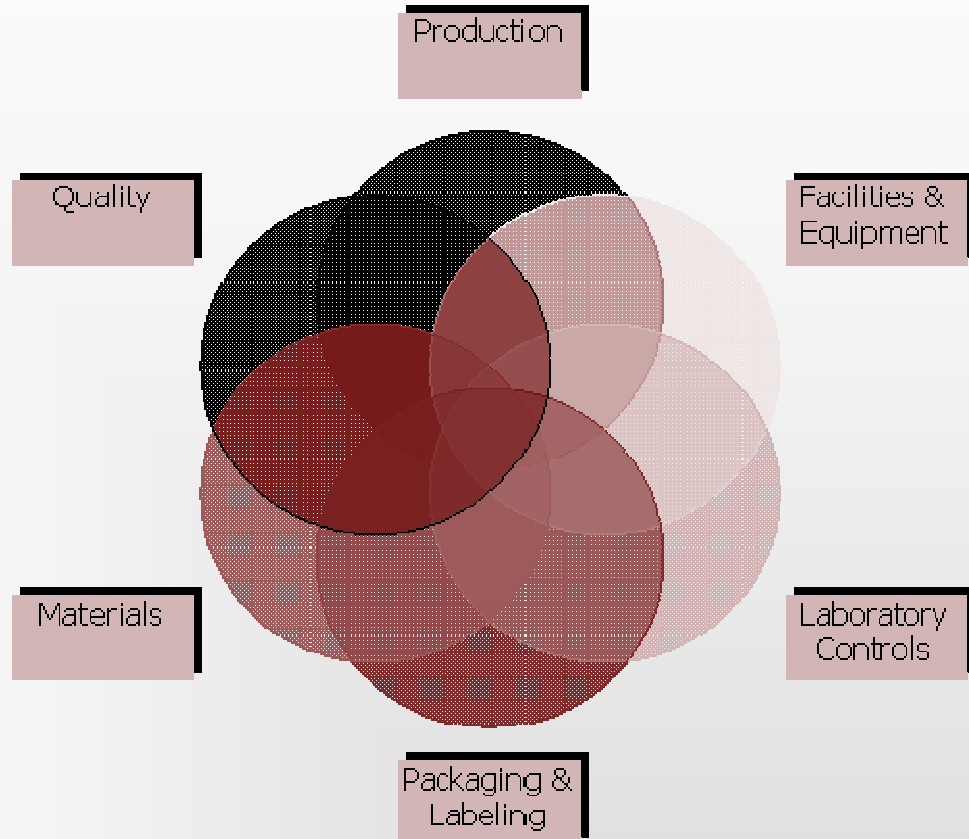
LexaMed's mission is to offer Quality, compliant value-added services and products to our clients in a courteous and expeditious manner at a fair price."

- *LexaMed* President, Robert R. Reich

QUALITY MANAGEMENT SYSTEMS

Quality System

LexaMed can build a robust quality system encompassing the six specific elements of the quality system to ensure each system is in a state of constant control.



Quality Compliance

LexaMed's concept of quality systems involves the synchronization of procedures and processes thus yielding a quality product or device intended for human use. This approach allows us to ensure compliance with cGMP regulations related to drug safety, identity, strength, quality, and purity.

Quality Services

LexaMed offers services in all aspects of the pharmaceutical and medical device industries including any niche markets. More specifically, **LexaMed** has experience in dealing with pharmaceutical companies that produce a variety of drugs in varied formulations which may include tablets, capsules, injectables, suppositories, sprays, steriles, powders, oral liquids, and semi-solids. For device manufacturers, **LexaMed** has experience in dealing with companies that produce a variety of devices from the design phase through the development stages. We have executed projects scoped at implementation of only one system to all six quality systems for facilities located both domestically and internationally. Geographically, we have previous services in the United States, Puerto Rico, India, Australia, Ireland, Denmark and Korea.

QUALITY MANAGEMENT SYSTEMS: DRUG AND PHARMACEUTICALS 21 CFR PART 210 & 211

Quality should be built into the product; testing alone cannot be relied upon to ensure product quality.

LexaMed demonstrates expertise in the following quality areas:

Quality

- ◆ Effective controls and monitoring tools
- ◆ Integrated Systems
- ◆ Quality by Design

Production

- ◆ Equipment validation and qualification
- ◆ Process Controls
- ◆ Cleaning validation

Facilities & Equipment

- ◆ Critical utilities system qualification
- ◆ Validation of compressed air and gases
- ◆ Clean room qualification
- ◆ Sterilization techniques

Laboratory Controls

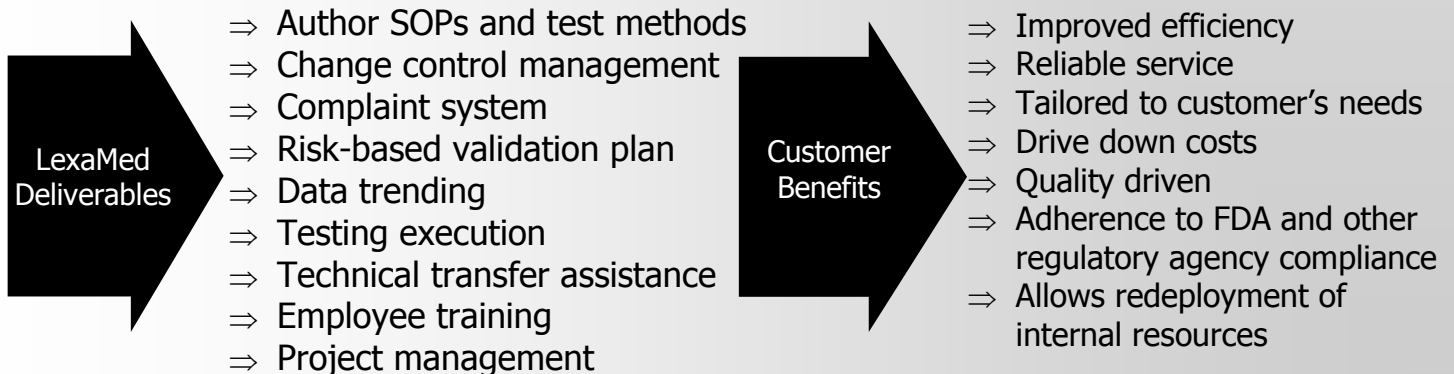
- ◆ Laboratory investigations
- ◆ SOPs and Test Method Generation
- ◆ CAPA plans
- ◆ Stability Program
- ◆ IQ/OQ/PQ
- ◆ Specification generation

Packaging & Labeling

- ◆ Specification generation
- ◆ Label control system
- ◆ Contamination prevention
- ◆ Product inspection process

Materials

- ◆ Incoming inspection program
- ◆ Supplier qualification
- ◆ Supplier audits
- ◆ Warehousing procedures



QUALITY SYSTEM REGULATIONS: MEDICAL DEVICES 21 CFR PART 820

LexaMed offers services in all Quality System Regulation areas:

SubPart B

Quality Audits

- ◆ Conduct internal audits
- ◆ Provide quality audit reports

Personnel Training

- ◆ Perform training in all areas

SubPart C

Design Controls

- ◆ Create design requirements for intended use
- ◆ Conduct design validation
- ◆ Develop applicable procedures

SubPart D

Document Controls

- ◆ Create a change control system
- ◆ Create an SOP system for approval and distribution
- ◆ Author department specific SOPs

SubPart E

Purchasing Controls

- ◆ Conduct supplier audits
- ◆ Develop a supplier qualification program
- ◆ Create supplier checklists and surveys

SubPart F

Identification and Traceability

- ◆ Create an incoming inspection program
- ◆ Develop a system for lot tracking

SubPart G

Production and Process Controls

- ◆ Establish process controls and process validation
- ◆ Develop an equipment calibration and maintenance program

SubPart H

Acceptance Activities

- ◆ Create in-process and finished device specifications

SubPart I

Nonconforming Product

- ◆ Develop device release procedures
- ◆ Establish rework procedures

QUALITY SYSTEM REGULATIONS: MEDICAL DEVICES 21 CFR PART 820

LexaMed offers services in all Quality System Regulation areas:

SubPart J

Corrective and Preventive Action

- ◆ Create a deviation management system
- ◆ Conduct failure investigations
- ◆ Create a monitoring system

SubPart K

Labeling and Packaging Control

- ◆ Create a label control system
- ◆ Develop a product inspection process

SubPart L

Handling, Storage, Distribution, and Installation

- ◆ Create a system for contamination prevention
- ◆ Create warehousing procedures

SubPart M

Records

- ◆ Create a program for record initiation, retention, and archival
- ◆ Develop device master records (DMR)
- ◆ Establish a customer complaint program

SubPart N

Servicing

- ◆ Create applicable service reports
- ◆ Analyze reports using varied statistical applications

SubPart O

Statistical Techniques

- ◆ Create procedures to identify the use of various statistical applications
- ◆ Develop sample plans



MICROBIOLOGY

Bioburden Validation

Bioburden quantitation does not always capture 100% of the viable population on a medical device or pharmaceutical article. There are a number of reasons for this, including extraction effectiveness and media variations. It is therefore imperative that a bioburden validation be performed to define the recovery efficiency. One of two methods is generally used: 1) inoculation, or 2) exhaustive extraction. This recovery efficiency is then applied to routine analyses to provide a more accurate estimation of the original product bioburden. Methods are consistent with ANSI/AAMI/ISO 11737-1.

Bioburden Determination

Bioburden testing is performed to determine the total microbiological population on a medical device or pharmaceutical article prior to sterilization. Available test methods permit the determination of aerobic (vegetative or spore-formers) organisms, anaerobic organisms (vegetative or spore-formers), and/or fungi (yeast and molds) present. These data can be utilized in the development of product sterilization cycles and further, monitoring the continued effectiveness of GMP controls in place. Methods are consistent with ANSI/AAMI/ISO 11737-1 and ANSI/AAMI/ISO 11737-3.

Total Viable Plate Count

USP <61>

The total aerobic count indicates the level of microorganism on a sample. The sample may be directly plated, or run through a filter which is then plated, and the colony forming units (CFU) enumerated. Dilutions may be necessary to obtain counts within the acceptable countable range.

Microbial Identification

The Biolog® microbial identification system identifies and characterizes aerobic and anaerobic bacteria based on reactions to a variety of carbon sources. The results of these reactions produce a "fingerprint" which is then compared to a database of such "fingerprints". Turn-around time for results is rapid – identifications can be obtained in as little as four hours.

Microbial Limit Test

USP <61>

This test determines the total aerobic bacteria and fungi present in/on non-sterile medical devices and pharmaceutical articles. The test also demonstrates freedom from specific pathogens, *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella* species, and *Staphylococcus aureus*.

MICROBIOLOGY

Particulate Analysis, Microscopic

USP <788>

Particulate counts are determined by microscopically examining a filtered sample of medical device rinsate or pharmaceutical article. Particulates are classified into two groups – those greater than 10µm but less than 25µm and those 25µm or greater. Alternative size ranges can be defined, if required.

Disinfectant Efficacy Testing

Known population concentrations of selected organisms are inoculated onto substrates representative of the surfaces to be disinfected. Challenge organisms are typically a combination of those derived from a recognized culture collection identified in USP and ISO 11138 and those obtained from the client's manufacturing environment. Selected disinfectant agents are applied to the test surfaces to demonstrate microbial reduction via predetermined cleaning regimens. The results of these studies are utilized to support medical device and pharmaceutical disinfectant use practices.

A disinfectant kill-time evaluation can also be performed to determine the effectiveness of a disinfecting agent against a selected microorganism(s). This test is generally performed in solution and as an initial screening of a disinfectant's effectiveness.

Antimicrobial Effectiveness Testing

USP <51>

The Antimicrobial Effectiveness test is designed to verify the efficacy of a preservative system in a product. A sample of a preserved product inoculated with a known concentration of a challenge organism (*Aspergillus brasiliensis*, *Candida albicans*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, or a client supplied isolate) is compared to a sample control. Sufficient reduction and/or inhibition of the growth microorganism within the test sample yields an acceptable result.

Sterility Tests

USP <71>

Medical devices and pharmaceutical articles labeled as sterile must be tested accordingly. Samples are filtered, when feasible, or directly inoculated into growth medium, incubated, and examined for microbial growth. Biological indicators previously exposed to sterilization processes can also be tested for sterility to assist in the verification of a successful sterilization cycle.

All sterility testing is performed in an ISO Class 5 cleanroom consistent with USP and ISO 11737-2 guidelines.

MICROBIOLOGY

Biological Indicator Performance Testing

In-house **B**iological **I**ndicator **E**valuator **R**esistometer (BIER) units and sterilizers can be utilized to determine/verify the resistance of a biological indicator. By exposing biological indicators to a known dose of sterilant for a range of times, the indicator's D-value (time required to reduce a population by 1 log, or 90%) and z-value (change in temperature required for a 1 log change in D-value) can be determined. Survivor/kill times can also be similarly determined. This information can be utilized to confirm a biological indicator manufacturer's label claim or certify a biological indicator's performance. The information can be further used in cycle development to calculate the sterilization time required to provide a desired safety factor.

Determination/verification of a biological indicator population consists of effectively removing the organisms from their substrate (i.e. maceration of paper carriers) and plating appropriate dilutions to enumerate the resistant population of the indicator organism.

All testing is performed according to USP, ANSI/AAMI/ISO/EN 11138 and 14161 guidelines or utilizing client or biological indicator manufacturer-specific procedures.

Sterilization Validation Studies

Sterilization validation studies can be performed for all methods of sterilization including radiation, ethylene oxide (EO), steam, VHP, dry heat and any novel process.

Radiation Dose Setting Studies

ANSI/AAMI/ISO 11137 Method 1, Bioburden: This method consists of performing a bioburden test on selected medical device or pharmaceutical articles, using this result to determine the required verification radiation dose, and then exposing samples to this dose. Each sample is then tested for sterility. Upon a successful sterility test, the minimum sterilization dose necessary to provide the desired safety factor is determined.

ANSI/AAMI/ISO 11137 Method 2, Fraction Positive: Selected medical device or pharmaceutical article samples are subjected to a series of radiation exposures over a range of doses. Following exposure, samples are tested for sterility. The sterility test results (number of samples positive) are used to calculate the dose necessary to obtain the required sterility assurance level.

MICROBIOLOGY

Sterilization Validation Studies, *continued*

Radiation Dose Setting Studies, *continued*

ANSI/AAMI/ISO 11137 Substantiation of VD_{max} : Similar to Method 1, this method requires determining the bioburden level on selected medical device or pharmaceutical article samples. Based on bioburden results and desired routine exposure dosage (VD_{max}), the verification dose is selected. Samples are exposed to the verification dose and subsequently tested for sterility. Acceptable sterility results substantiate the routine sterilization dose. There are VD_{max} protocols for both 25 and 15 kGy.

EO Dose Validation

Studies following ANSI/AAMI/ISO 11135 can be executed utilizing the 3M 5XL 100% EO sterilizer, available in-house. Most commonly, an overkill half-cycle approach to validation is employed. Medical device or pharmaceutical article samples are seeded with appropriate biological indicators (more resistant than indigenous product bioburden) and exposed to a defined EO cycle. Biological indicators are then removed from the samples and tested for sterility. The minimum exposure time at which all biological indicators are negative for growth equates to one-half the cycle duration to be employed for routine use. The full cycle then provides for the minimum desired sterility assurance level. Alternatively bioburden-based or bioburden-based BI validation approaches can also be employed.

Steam Cycle Validation

Similar to EO validation studies, appropriate biological indicators can be seeded within medical device or pharmaceutical article samples and exposed to steam for a period of time one-half that which is expected to be used for routine processing. Biological indicators are removed from the samples following exposure and tested for sterility. Negative sterility test results (no survivors) indicate an acceptable routine (full) sterilization cycle with a defined sterility assurance level. Bioburden and F_0 -based cycle validation approaches can also be utilized. These Studies are consistent with ISO 11134 and ISO draft standard 17665.

Novel Sterilization Methods

Study protocols for any other method of sterilization can be developed. Protocols are consistent with the ANSI/AAMI/ISO/EN 14937 guidance. With ample laboratory space available, experimental or developmental sterilizing units can be located in-house to accommodate testing.

MICROBIOLOGY

Post Sterilization Testing

Ethylene Oxide (EO) Residual Testing

Medical devices or pharmaceutical articles that have been sterilized with EO must routinely be tested for residuals to ensure residual EO does not exceed the limits set forth by the FDA and ISO. A product extract or sample is analyzed by gas chromatography for Ethylene Oxide (EO), Ethylene Chlorohydrin (ECH) residuals consistent with ANSI/AAMI/ISO 10993-7 and AAMI TIR 19 guidance. Product Ethylene Glycol (EG) residual can also be quantitated.

ICH Stability Services

Stability storage and testing is required for sterilized finished products to determine acceptable expiration dating and stability profiles. Samples are stored in controlled conditions, as required by ICH guidelines, for an extended period of time. Storage conditions represent both real time and accelerated aging conditions. Periodically, samples are pulled from storage and tested for a variety of factors as required by USP, ISO or client-specific procedures. This testing can include – among others – sterility, potency, and package integrity. Real-time storage is required for all products; however, accelerated aging storage may also be performed at the client's request. Accelerated aging samples are stored at an elevated temperature and relative humidity, when applicable, which allows a manufacturer to predict the effect of real-time storage on a product. SAS statistical evaluation, interpretation and extrapolation of data is also available.

Aerosol Microbial Challenge

Evaluating the microbial barrier properties of intact packages is critical in ensuring that sterilized product maintains its microbial barrier properties or remains consistent with its label claims. Subjecting post-sterilized packages to a microbial aerosol is one such method. Following exposure of packages to a controlled microbial challenge, the enclosed product is tested for the presence of the indicator organism, *Bacillus atrophaeus*. Absence of indicator organism recovery indicates microbial barrier integrity, whereas organism recovery signifies a breach in the package. This testing is often performed in association with exposing the product to simulated shipping and distribution tests per ASTM 4169 or equivalent in order to mimic the stresses on the package associated with distribution and handling. Package integrity can also be assessed by performing a dye ingress physical test consistent with ASTM F1929.

MICROBIOLOGY

In vitro Toxicology & Biocompati- bility

Cytotoxicity

Cytotoxicity, or cell culture, methods provide a rapid, economical, *in vitro* approach for screening biocompatibility of materials intended for use in medical devices. The mammalian cell culture systems employed are sensitive and can therefore be used in screening programs as well as in quality control and audit programs.

Cytotoxicity testing is recommended for all device types listed in FDA Memorandum G-95 and ISO 10993-1 for biocompatibility testing of devices. Methods are consistent with USP <87> and ANSI/AAMI/ISO 10993-5.

***In vitro* Hemolysis**

Medical device components that come in direct or indirect contact with human blood must be evaluated for hemolytic effect (lysis of red blood cells) per ISO 10993-4. Either the component itself or its fluid extractant is exposed to blood, incubated, and the blood evaluated for lysis. Samples are placed on a spectrophotometer and absorbance measured at 545nm, the result of which is correlated to a percentage of hemolytic activity.

SPECIAL MICROBIAL SUSPENSIONS

Bacillus subtilis "5230"

LexaMed produces highly concentrated *Bacillus subtilis* "5230" suspensions for validation of heat sensitive products.

Various Concentra- tions of Suspensions

LexaMed can also produce special microbial suspensions, as listed below, of various concentrations:

Aspergillus brasiliensis (formerly *Aspergillus niger*)

Bacillus subtilis

Candida albicans

Clostridium sporogenes

Escherichia coli

Geobacillus stearothermophilus

Kocuria rhizophila (formerly *Micrococcus luteus*)

Staphylococcus aureus

CHEMISTRY

Bacterial Endotoxin Testing

Bacterial Endotoxin Testing (BET)

Endotoxins are compounds derived from the cell walls of Gram-negative bacteria which stimulate a fever response, and are harmful to humans. Endotoxin levels are determined using the Limulus Amebocyte Lysate (LAL) assay, of which there are several methods. The LAL assay utilizes cells obtained from the circulatory system of the horseshoe crab (*Limulus polyphemus*) which react quantitatively and selectively with endotoxins. We conduct the Gel-Clot Method which is consistent with the FDA guidance document, AAMI/ST72, and the USP <85>.

Materials Characterization

USP Physiochemical Test-Plastics or Elastomeric Materials

It is important that medical device manufacturers demonstrate that their devices are safe for their intended use. This test is useful in characterizing extractables, a potential source of contaminants, from devices. A battery of tests are conducted and provide basic information about the presence and nature of water-soluble extractables. The four tests conducted for plastic materials are, Buffering Capacity, Heavy Metals as Lead, Non-Volatile Residue and Residue on Ignition. The five tests conducted for elastomeric materials are Heavy Metals, pH Change, Reducing Agents, Total Extractables and Turbidity.

Analysis & Determinations

pH Determination

The chemical activity of many aqueous solutions depends upon their hydrogen ion (acid) or hydroxyl ion (alkaline) concentrations. The degree of acidity or alkalinity of a solution is expressed as its pH value. This test determines electrometrically using a hydrogen ion electrode calibrated over a range of pH buffer solutions.

Conductivity

An assay to measure a material's ability to conduct an electric current. A measure of Conductivity is one of the USP requirements for Purified Water.

CHEMISTRY

EO Residuals **Ethylene Oxide (EO) Residuals**

EO is considered a processing material that must be removed or reduced to acceptable levels as prescribed in the Good Manufacturing Process (GMP) and ISO regulations. Products sterilized using ethylene oxide (EO) may retain residuals of sterilant gas for varying periods of time. Retention is influenced by product size, design, materials and packaging.

Following the AAMI/ISO 10993-7 guideline, an extract of a sample is prepared and analyzed by gas chromatography for Ethylene Oxide (EO), Ethylene Chlorohydrin (EC) and Ethylene Glycol (EG) (or any combination of these) residuals. Analytical results are expressed as concentration (ppm) of residuals recovered from the test sample or as weight (micrograms or milligrams) of residuals recovered from the entire test article.

MEDICAL DEVICE SERVICES

Medical Device Services

With our integrated consulting, and laboratory capabilities we are uniquely organized to meet the requirements of the Medical Device Industry. Some of the services we are currently providing include, but not limited to, the following:

- ◆ Routine product release testing: sterility, LAL (endotoxin), bioburden, cytotoxicity
- ◆ Validation of gamma and e-beam irradiation sterilization processes
- ◆ Environmental monitoring: viable, non-viable, bioburden
- ◆ Customized training
- ◆ Custom R&D projects: product performance evaluations, microbiology, and product/process development
- ◆ Biological indicator testing - EO, steam, custom: Performance verifications, D-value, z-value, survivor/kill, custom production

BIOLOGICAL INDICATORS

BIs are an integral component of a product sterility assurance program. As such, their performance parameters such as population and resistance, must be known and understood in order to utilize them effectively. **LexaMed** has a defined program to perform these analyses, according to consensus domestic and international standards and guidelines.

Biological Indicator Population Assays

Population assays are performed according to approved **LexaMed** SOPs. Population verification assays can be performed in accordance with ISO/EN 14161, ISO 11138 (series), USP or client requirements, depending on specific client requests.

Resistometer Vessel Resistance Testing

LexaMed performs resistance studies in **Biological Indicator Evaluator Resistometers (BIER)** that conform with the requirements of ANSI/AAMI/ISO/EN18472. D-value and survivor/kill confirmation studies are performed according to ISO 11138/ISO 14161 and USP standards guidelines. Moist and dry heat z-values can be performed as required.

LexaMed Consultants Lead Sterilization Committees

LexaMed consultants routinely provide resolution to sterility issues, and have a proven record in this area. Our consultants have served as members of AAMI/ISO BI committees for the last 20 years and do so currently. **LexaMed** consultants have served as co-chairs of the AAMI ISO Industrial EO Sterilization committee and remain members. They also currently serve on the Microbiological Methods, Aseptic Process, Radiation, Industrial Steam and Packaging AAMI committees. Moreover, many BI articles, authored by **LexaMed** scientists, have been published over the past three decades.

PUBLICATIONS

1. Reich, R.R., J.E. Whitbourne, and L.L. Morien. "Critical Evaluation of Ethylene Oxide Biological Indicator Performance Characteristics." Abst. ASM Meeting, 1978.
2. Whitbourne, J.E., and R.R. Reich, 1979. "Ethylene Oxide Biological Indicators: Need for Stricter Qualification Testing Control." *J. Parenteral Drug Assoc.* Vol. 33, Pp 132-143.
3. Reich, R.R., J.E. Whitbourne, and A. McDaniel, 1979. "Effect of Storage Conditions on the Performance of *Bacillus stearothermophilus* Biological Indicators." *J. Parenteral Drug Assoc.* Vol. 33, Pp 228-234.
4. Reich, R.R. 1980. "Effect of Sublethal Ethylene Oxide Exposure on *Bacillus Subtilis* Spores and Biological Indicators." *J. Parenteral Drug Assoc.* Vol. 34, Pp 200-211.
5. Reich, R.R. 1980. "Storage Stability of *Bacillus subtilis* Ethylene Oxide Biological Indicators." *Appl. and Environmental Microbial.* Vol. 39, Pp 227-229.
6. Reich, R.R. and L.L. Morien, 1980. "Storage Stability of *Bacillus stearothermophilus* and *Bacillus subtilis* Biological Indicators." In proceedings of the Third Pharmaceutical Manufacturers Assoc. Seminar on Validation of Sterile Manufacturing Processes: Biological Indicators. Chicago, IL. Pp. 54-67.
7. Reich, R.R., L.L. Morien, and J. Scoville, 1981. "A Manufacturer's Response to Biological Indicator Questions." *Med. Device and Diagnostic Industry.* Vol. 3, No. 9.
8. Reich, R.R. and L.L. Morien, 1982. "Influence of Environmental Storage Relative Humidity on Biological Indicator Resistance, Viability, and Moisture Content." *Appl. and Environmental Microbial.* Vol. 43, Pp 609-614.
9. Reich, R.R. and G.T. Frederick, 1982. "Microbial Barrier Properties of Sterilizable Glassine paper Used for BI Packaging." *Particulate and Microbial Control.* No. 2, Vol. 1, Pp 71-74.
10. Reich, R.R. 1984. "Indicator Tapes; A Word of Caution." *Med. Device and Diagnostic Industry*, No.1, 614-15.
11. Reich, R.R. and B.G. Fitzpatrick, 1985. "Evaluation of Sterilization Indicators in Gravity Steam Sterilization Cycles." *J. Hosp. Supply, Processing, Distribution.* May/June, Pp 60-63.
12. Reich, R.R. and G.S. Graham, 1986. "Performance Requirements for Biological Indicators in the USA." Proceedings EUCOMED Conference on Biological Monitoring of Sterilization. *Kerkraade the Netherlands.* Pp 30-42. EUCOMED, London, England.
13. Burgess, D.J. and R.R. Reich, 1993. "Industrial Ethylene Oxide Sterilization." *Industrial Sterilization*, Pp. 152-195. R. Morrissey and G.B. Phillips (eds). Van Nostrand Reinhold, New York City, New York.
14. Reich, R.R., 1999. "The Secrets of the Bacterial Spore: Applications for Steam Sterilization". PDA European Forum. Basel, Switzerland.

VALIDATION SERVICES

Expertise

LexaMed offers professional validation services in all aspects of the **Pharmaceutical, Bio-tech, and Medical Device** industries. Our expert validation team leaders are authorities in their fields—over two centuries of accumulated experience. Many are involved with the development of standards and guidelines for professional quality organizations such as AAMI, PDA, ISPE and ISO.

“Our concept of validation involves the integration of individuals with varied skill-sets into multifunctional problem solving teams. This approach allows **LexaMed** to capitalize on the broad-based industrial experience of our staff and to provide the most appropriate and cost-effective practical solutions to a particular validation situation.”

- Robert R. Reich, **LexaMed** President

Services

LexaMed has unique experience and expertise to provide your company with guaranteed results and proven solutions to all of your validation needs which include, but not limited to:

- Process and Equipment Validation
- Analytical Method Validation and Transfer
- Isolator Technology
- Sterilization Process Validation (EO, Steam, VHP, Radiation, UV, Ozone, Pulsed-Light, Dry Heat, Low Temperature)
- Aseptic Processing / Clean Room Qualification
- Microbiology / Chemistry / Engineering
- Environmental and Critical Utility Qualification
- GAP Analysis to gain compliance with sterilization standards
- Cleaning Validation
- Laboratory Support

LexaMed routinely provides quick and reliable resolution to many manufacturing process, raw material, analytical and sterility issues. We also provide authoritative training to many world class companies and regulatory employees on a routine basis.

LexaMed provides cutting-edge, dependable and sustainable solutions to your most challenging qualification requirements.

SIMULATED USE HEALTH CARE FACILITY PRODUCT EVALUATIONS

LexaMed Health Care Facility Compliance

Health Care Facilities (HCF) and medical device suppliers to HCF must have data to support expiration dates/stability dates assigned to sterile products produced in and/or supplied to their facilities. This includes, among other things procedural trays and products wrapped and stored in the Central Supply. This is a JCAHO (Joint Commission for the Accreditation of Health Care Organizations) requirement.

HCF Program

LexaMed has developed a unique program in this area to assist both medical device suppliers and the HCF to meet this requirement. The primary elements of our program include:

Expert Project Staff

- ◆ Competent staff of experienced scientists and regulatory affairs professionals to assist with project design, execution and final report generation. Our staff can also assist with any regulatory submissions to be supported by the generated data. Our staff has been and is currently involved with many of the AAMI and ISO task teams charged with the production of revised and new industry guidelines and standards in this area.

Certified Laboratory Operation

- ◆ We offer an FDA-registered and ISO certified laboratory operation to perform any associated testing required during program execution, including: bioburden quantitation, sterility testing, endotoxin (pyrogen testing), product EO residual testing, etc.

EO and Steam Expertise

- ◆ We offer both ethylene oxide and steam sterilization capabilities in-house and can duplicate typical hospital sterilization cycles as define in AAMI standards. We can also coordinate product exposures in the STERRAD system.

Packaging Solutions

- ◆ We offer a packaging operation and have dedicated controlled environmental space to conduct these operations. We have validated heat sealers for production of pouched product and have trained personnel that are familiar AAMI specified manual folding procedures for the assembly of wrapped product.

Simulated Hospital Storage

- ◆ We offer simulated hospital storage in a dedicated large, clean area that is temperature and humidity controlled and environmentally monitored for viable contamination.

Please **contact us** to discuss your specific requirements and determine how our staff can best support you.

DIETARY SUPPLEMENTS: 21 CFR PART 111

21 CFR Part 111

In August of 2007, the U.S. Food and Drug Administration (FDA) issued the final ruling: 21 CFR Part 111, "Current Good Manufacturing Practices for activities related to Manufacturing, Packaging, Labeling or Holding Dietary Supplements". This regulation establishes minimum controls necessary to ensure the Quality, Safety and Uniformity of Dietary Supplements.

Your Compliance Requirement

For manufacturers, packagers, warehouses and shippers of dietary supplements having 500 or more employees, compliance to 21 CFR Part 111 is now mandatory. Companies with fewer than 500 employees are required to comply by June 25, 2009 and companies with 20 or less employees must comply by June 25, 2010.

LexaMed Proven Compliance Solutions

LexaMed has unique experience and curriculum to show your company how to meet the requirements of 21 CFR Part 111. We provide "Hands On" solutions to quickly and efficiently safeguard your company against the negative impact of non-compliant practices.

LexaMed has been a leader in the field of Nutritional Supplement Quality in the areas of:

AUDITING against Part 111, GAP Assessment, Quality System Review, Facility evaluation

IDENTIFYING critical areas needing development, improvement or renovation

PLANNING compliance goals and projects

IMPLEMENTING proven solutions, programs, training and execution

ASSESSING the effectiveness and sustainability of your companies compliance program.

Let *LexaMed*, not the FDA, help you find your compliance problems.

Contact *LexaMed* today to discuss the impact of these new regulations on your business.

AUDITING

Authoritative Auditing

LexaMed is an internationally recognized industry leader at performing Medical Device and Pharmaceutical Manufacturing Operational Audits. Our experienced team of auditors and subject matter experts are eager work with your company to provide a comprehensive assessment of all aspects of your facilities, quality systems and suppliers. Your company will benefit from the safety and confidence gained by our comprehensive, "eye of the agency" evaluations.

Contact **LexaMed** to discuss our specialized auditing capabilities which include, but are not limited to:

| | |
|----------------------------------------------------------|--------------------------------------|
| Pharmaceutical cGMP: 21 CFR 210/211 | Dietary Supplement cGMP: 21 CFR 111 |
| Large and Small Volume Parenteral Terminal Sterilization | API cGMP: ICH Q7A |
| Aseptic Operations | Medical Device QSR: 21 CFR 820 |
| Isolator Technology | Quality Systems ISO 9001 and 13485 |
| Non-Sterile Solid Dosage | Laboratory GLP: 21 CFR 58, ISO 17025 |
| Computer Systems, Part 11 | Clinical Trials |
| Parametric Release | All Sterilization Technologies |
| Equipment, Process and Method Validation | IPEC-PQC Excipient cGMP |

Compliance

LexaMed offers a full spectrum of focused Domestic and International Compliance Solutions which include, but are not limited to:

- System GAP analyses for compliance with US and International statutory requirements, ISO standards and industry guidelines
- Pre-PAI Preparedness
- Pre-FDA GMP Preparedness
- Pre-ISO certification
- Vendor / Supplier Qualification / Re-Qualification
- Internal Corporate Compliance

Verification

LexaMed has state of the art, integrated Laboratory, Research and Consulting capabilities and are uniquely qualified to assist with post-audit verification activities which include, but are not limited to:

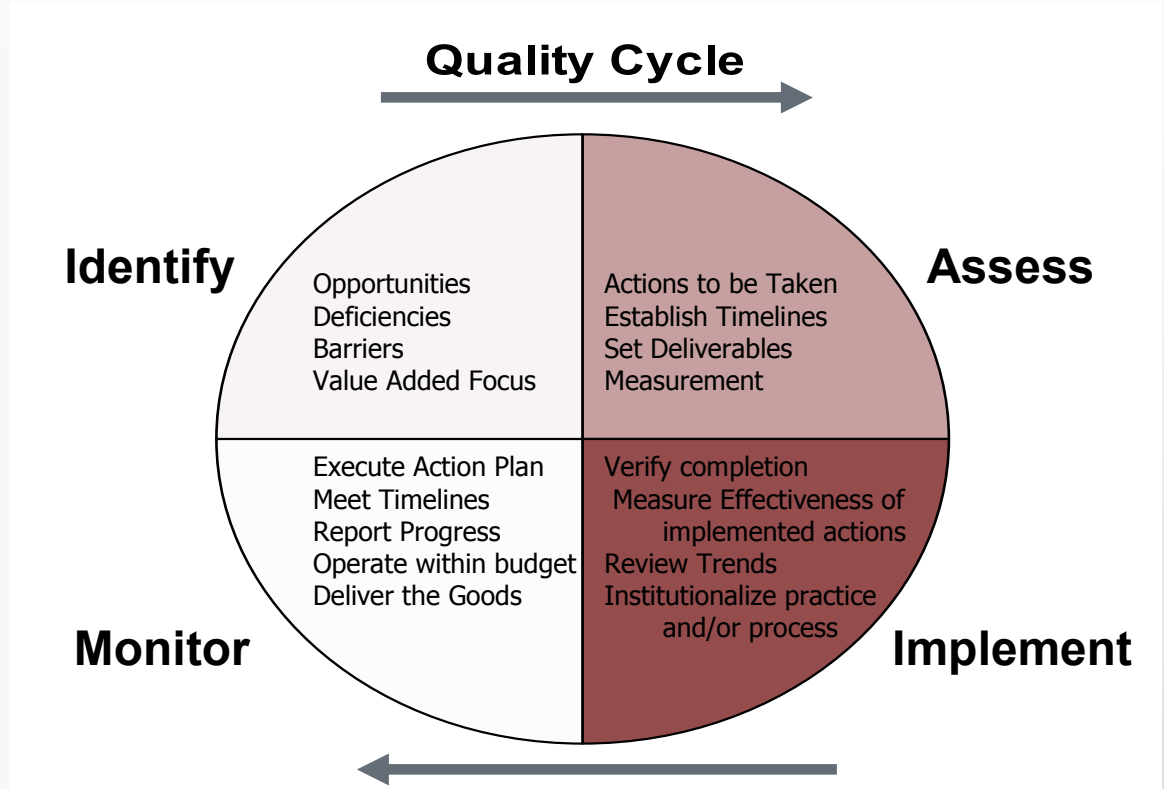
- Generation and Management of Compliance Action Plans
- Assistance with Execution of Remediation Activities
- 483 and Warning Letter Responses
- Post-Audit Sustainable Compliance Evaluations

OPERATIONAL EFFECTIVENESS PROCESS

Novel Process

- OEP is a unique process that is designed to assess operational capabilities:
- ◆ Model that is field tested with demonstrated positive results
 - ◆ Allows for participation at all levels across the organization
 - ◆ Disciplined approach towards continual improvement
 - ◆ Process design integrates key performance metrics and management reporting

Built on Quality Principles



4 Key Process Steps

Identification

- LexaMed Collects Information
- Appoint OEP Team Leaders
- Formation of OEP Teams
- Recommend opportunities for CHANGE

Monitoring

- Oversight By and Management Reporting
- Use of Metrics to Gauge Performance

Assessment

- Course Setting and Deliverables

Implementation

- Actioning against agreed upon objectives and areas of responsibility

The Approach

OEP is an interactive process and must include key decision makers at the site. This process is designed to be internally driven:

LexaMed resources utilized during the initiation of this process will be appropriately qualified and have the necessary experience and technical expertise with practical application, and working knowledge of pharmaceutical manufacturing operations.

OPERATIONAL EFFECTIVENESS PROCESS

The Approach (continued)

Communication channels need to remain open to ensure a steady flow of information to and from *LexaMed*.

LexaMed provides ongoing feedback to Site Management

The process is proactive, not reactive.

OEP utilizes **SWOT Analysis**.

Operational Effectiveness Model will facilitate:

- ◆ Focusing resources
- ◆ Understanding Business Goals
- ◆ Establishing Process Capabilities
- ◆ Disciplined Decision-Making
- ◆ Re-aligning Targeted Processes
- ◆ Focusing Manufacturing Unit on One Set of Objectives
- ◆ Defining KPIs
- ◆ Measuring, Monitoring and Actioning

Deliverables

The deliverable from this process will be set of well-defined initiatives prioritized based on operational improvements across:

- ◆ Manufacturing operations
- ◆ Laboratory operations (Chemistry, Microbiology and Environmental Monitoring)
- ◆ Quality Assurance systems
- ◆ Distribution operations
- ◆ Facility and equipment as related to GMP applications

As necessary, other resources may be utilized to further explore opportunities particularly around systems and/or processes that are identified or targeted for advancement.

Process Requirements

- ◆ Communication – Establish a network at the site for frequent reporting
- ◆ Trust – Believe in the process and stay open regarding suggestions and recommendations
- ◆ Schedule – *LexaMed* will provide a weekly schedule in advance to allow for proper planning and availability of resources
- ◆ Commitment of Resources – Maintain continuity and communication
- ◆ Work environment – Access to facility, processes, equipment and supplies to maintain focus and momentum

LexaMed is prepared to establish a long-term relationship and to provide qualified, senior technical resources to support SP business needs. We want to support the site expertise in achieving the stated business mission. We will participate in the process and we will deliver for your vision.

TRAINING

Customized Training

LexaMed's uniquely qualified experienced professional staff can offer customized training programs on a variety of subjects to meet any specific requirement. Our staff routinely provides training to field inspectors in sterilization technology and is frequent invited presenters at Quality, Regulatory, Engineering, and trade association conferences.

Training Services



LexaMed is your missing piece

LexaMed offers training services in all aspects of the medical device and pharmaceutical industries. Training sessions can be provided on client sites or coordinated in any convenient geographic location. Training topics are listed below:

GMP Compliance

- 21 CFR Part 820
- 21 CFR Parts 210 & 211
- 21 CFR Part 111

Regulatory Compliance

- CAPA
- Laboratory Investigations

Microbiology

- Basic microbiology
- Contamination control
- Bioburden
- Biological indicators

Aseptic Practices

- Aseptic operations

Environmental

- Environmental monitoring programs

Sterilization

- Ethylene oxide
- Radiation
- VHP
- Steam
- Isolator and Barrier technology
- Disinfectants

Other

- Calculation and application of D and z- value



- ⇒ Improved efficiency
- ⇒ Reliable service
- ⇒ Tailored to customer's needs
- ⇒ Drive down costs
- ⇒ Quality driven
- ⇒ Adherence to FDA and other regulatory agency compliance
- ⇒ Allows redeployment of internal resources

BEC GROWTH-CHEK™

Microbial suspensions specially prepared for simplifying the performance of USP Growth Promotion, Monograph <71>, and Bacteriostasis/Fungistasis testing are available for sale. **LexaMed** manufactures these suspensions, and ships them ready-to-use; they require no additional preparation or dilution prior to use. Each lot is derived from recognized culture collections identified in USP and ISO 11138, and certified for purity and population (<100 organisms per dose). The following organisms are currently available, with additional products in development:

**Growth-
Chek™**

**Microbial
Suspensions**

| ORGANISM | SHELF LIFE | 100 DOSE VIAL | 20 DOSE VIAL |
|----------------------------------------------------------------------|------------|--------------------------------|------------------------------|
| <i>Bacillus subtilis</i> | 365 Days | \$114.00/Vial P/N 6633-100 | \$42.00/Vial P/N 6633-20 |
| <i>Candida albicans</i> | 60 Days | \$145.00/Vial P/N 10231-100 | \$50.00/Vial P/N 10231-20 |
| <i>Clostridium sporogenes</i> | 365 Days | \$114.00/Vial P/N 11437-100 | \$42.00/Vial P/N 11437-20 |
| <i>Aspergillus brasiliensis</i> formerly <i>Aspergillus niger</i> | 180 Days | \$200.00/Vial P/N 16404-100 | \$57.00/Vial P/N 16404-20 |
| <i>Kocuria rhizophila</i> formerly <i>Micrococcus luteus</i> | 60 Days | \$145.00/Vial P/N 9341-100 | \$50.00/Vial P/N 9341-20 |
| <i>Escherichia coli</i> | 90 Days | \$145.00/Vial P/N 8739-100 | \$50.00/Vial P/N 8739-20 |
| <i>Geobacillus stearothermophilus</i> | 365 Days | \$145.00/Vial P/N 7953-100 | \$54.00/Vial P/N 7953-20 |
| <i>Staphylococcus aureus</i> | 90 Days | \$160.00/Vial P/N 6538-100 | \$56.00/Vial P/N 6538-20 |



100 Dose Vial—10 mL Volume, < 100 Organisms per 0.1 mL

20 Dose Vial—10 mL Volume, < 100 Organisms per 0.5 mL

To be used by Microbiologist trained to work with live microorganisms.

LexaMed, Ltd. 705 Front Street Toledo, OH 43605

Office (419) 693-5307 / (888) 232-5227

Fax (419) 691-0418

Web Site www.lexamed.net

Email info@lexamed.net

23

CONTACT US

LexaMed

Quality • Science • Innovation

705 Front Street

Toledo, OH 43605

Office (419) 693-5307 / (888) 232-5227

Fax (419) 691-0418

Web Site www.lexamed.net

Jan Koenker

Marketing Manager

jkoenker@lexamed.net