

BEC GLOBAL Services Catalog

Passion for Quality



Our Value Proposition

- * **Our focus is the U.S. FDA regulated market**
- * **Experience, Knowledge, and Expertise**
- * **Proven Results**
- * **Cost-effective and Affordable Services**

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Welcome to the 2017 BEC-GLOBAL Services Catalog

Founded in 2005, Business Excellence Consulting Inc. (BEC) offers consulting, remediation, auditing, regulatory affairs, and training services for the FDA-regulated industry. As a worldwide leading company, BEC covers all your compliance and regulatory needs for the pharmaceutical, biotech, medical devices, combination products, APIs, and food industries.

In these pages you will find what is needed to improve your compliance and quality system in a very cost-effective and affordable way.



Our services are tailored to your specific needs. Our team of experienced FDA industry professionals (more than 100 resources, averaging 20+ years of experience) will assist you with the implementation of risk-based, robust and sustainable solutions. We will support your efforts to achieve and maintain a compliant quality system as well as educate and develop your staff to maximize their contribution to the business.

BEC provides the following:

Industries we assist

Pharma – Biotech – OTC
Medical Devices
Combination Products
Food and Dietary Supplements
API
Excipient
Cosmetics

Type of Services

FDA Inspection Support
Training and Education
Auditing and Assessment
Remediation and Quality Systems Compliance
Data Integrity
Quality Systems Implementation for FDA industries
Risk Management
Investigation and CAPA System Support
Human Error Prevention and Reduction
Supplier Control Programs
U.S. Agent
Submissions: DMF, ANDA, NADA, 510K
U.S. Registration and Listing
ISO Certification Consulting and Support
Validation Life-Cycle
Temporary Support: backlog elimination of Investigations, CAPAs, Complaints, and Change Controls

Our value proposition is based on four elements:

- Our focus is the U.S. FDA regulated market
- Experience, Knowledge, and Expertise
- Proven Results
- Cost-effective and Affordable Services

About Us—History of BEC-GLOBAL

Passion for quality, sharing our knowledge, and working as partners with our clients in their pursuit of excellence best describes **Business Excellence Consulting, Inc. (BEC)** and our global trademark, **BEC GLOBAL**.

Since May 2005, our company has grown to provide a wide array of regulatory remediation and support services, including the placement of highly qualified professionals at client sites. Our people are our most important asset. Their average hands-on experience working in the FDA-regulated environment exceeds 20 years. Currently, we have more than one hundred highly skilled and experienced professionals including engineers, chemists, biochemists, and biologists, serving clients worldwide.

Accreditations and Certifications

Since May 2015, our company has been accredited under the *ANSI/IACET 2013-1 Standard for Continuing Education and Training* which is recognized internationally as a standard of excellence in instructional practices. The ANSI/IACET Standard for Continuing Education and Training is a universal model for learning process excellence. It defines a *proven model* for developing effective and valuable continuing education and training (CE/T) programs by measuring a CE/T provider's training program from procedure to process to result. As a result of this accreditation, BEC is authorized to issue the IACET CEU.



During the first quarter of 2018, our company will be completing the steps needed to become accredited under the international standard *ISO/IEC 17020:2012 Conformity assessment – Requirements for the operation of various types of bodies performing inspection*. This standard specifies requirements for the competence of bodies performing inspections and for the impartiality and consistency of their inspection activities.



Our Clients

Major pharmaceutical, medical device, biotech, API, and food companies are part of our broad client portfolio in four continents. In addition to Puerto Rico and the continental USA, we currently provide services in the Bahamas, Belgium, China, Canada, Colombia, Costa Rica, Czech Republic, Dominican Republic, Ecuador, Germany, Malaysia, Mexico, India, Indonesia, Ireland, Italy, Singapore, Spain, Switzerland, and the UK.

Among our clients: Akorn, Actavis, Amgen, AstraZeneca, Abbott, Abbvie, Baxter, Bristol Myers Squibb, Coca Cola, Cooper Vision, Cyndea Pharma, Edwards, Ferring, Fresenius-Kabi, Grunenthal, Hebei Jiheng Pharmaceutical, Hewlett Packard, Invacare, Johnson & Johnson (Ethicon, Janssen, LifeScan, McNeil), KernPharma, Medtronic, Merck Sharp & Dohme, Mylan, Neolpharma, Normon, Novartis, Pfizer, Sartorius, Shauguang Fukang Pharmaceutical, Smith & Nephew, Smiths Medical, U.S. Pharmalabs, WellSpring, and Zimmer among others.

About Us—Our People

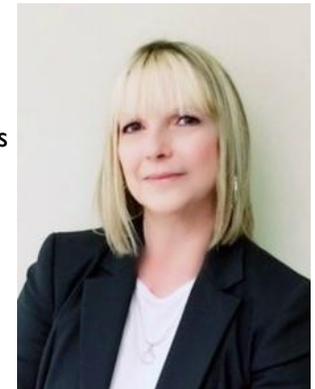
Our founders

José (Pepe) Rodríguez-Pérez, President and founder holds a bachelor's degree in biology and a PhD in immunology, both from the University of Granada, Spain, with post-graduate studies in medical sciences. During his 25+ year of career, he spent over 15 years working in a manufacturing plant (Abbott Laboratories). He also was a Science Advisor for the U.S. FDA from 2009 to 2012. He founded Business Excellence Consulting in May 2005 and since then has been leading its operation and expansion to a global consulting firm. He served as a senior member of the American Society of Quality and Chair of the Puerto Rico section during the period 2003-05. He was secretary from 2005 to 2012. Pepe holds seven American Society of Quality (ASQ) certifications: Certified Six Sigma Black Belt, Manager of Quality & Organizational Excellence, Quality Engineer, Quality Auditor, HACCP Auditor, Pharmaceutical GMP Professional, and Biomedical Auditor. He is also a member of RAPS, ISPE, AAMI, and PDA.



He is the author of five best-selling books (published by ASQ-Quality Press) covering FDA topics: CAPA for the FDA - Regulated Industry (2010), Quality Risk Management in the FDA-Regulated Industry (2012), The FDA & Worldwide Current Good Manufacturing Practices and Quality System Requirements Guidebook for Finished Pharmaceuticals (2014), the Handbook of Investigation and Effective CAPA Systems (2016), and Quality Risk Management in the FDA-Regulated Industry 2nd edition (2017). He is also author of several peer-review articles covering topics such as risk management, CAPA system, and data integrity.

Norma L. Copeland, Vice-President and co-owner of BEC Inc. She has a bachelor's degree in business administration, major in accounting from the University of Puerto Rico. Prior of founding BEC Inc. she worked in the advertisement industry. She oversees human resources and all administrative aspects of the company.



About Us—Our People

Our Leaders

Manuel E. Peña-Rodríguez is a process improvement and training consultant with more than 20 years of experience. He also serves as professor in the graduate program in biochemistry at the University of Puerto Rico, Medical Sciences Campus, in San Juan. Manuel is a licensed Professional Engineer with a master degree in Engineering Management from Cornell University, and a J.D. He is an ASQ Certified Six Sigma Black Belt, Manager of Quality & Organizational Excellence, Quality Engineer, Quality Auditor, HACCP Auditor, Biomedical Auditor, and an ISO 13485:2003 lead auditor. Also a senior member of ASQ and former Chair of the Puerto Rico section. He is the author of the book “*Statistical Process Control for the FDA-Regulated Industry*”, published by ASQ Quality Press in April 2013 and author of several peer-review articles covering topics such as risk management and sampling. He has been part of BEC Inc. since 2006.



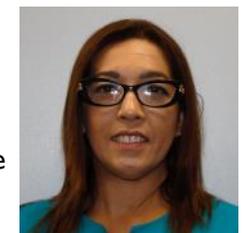
Genoveva Cruz-Malavé is a strategic, process improvement, managerial and training consultant. She has more than 30 years of experience in pharmaceutical plant operations. She acted as VP of worldwide operations (material and logistics) for a large pharmaceutical company. Genoveva holds a master degree in Industrial Engineering from Georgia Institute of Technology, and a bachelor degree in Industrial Engineering from University of Puerto Rico. She is ASQ Green Belt certified. Since 2013 Genoveva is fully devoted to business development, training of soft skills and managerial consulting services for BEC Inc.



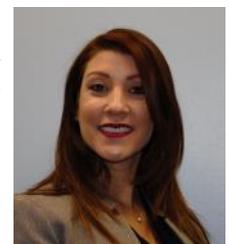
Madeline Muñoz has over 20 years of experience in the pharmaceutical industry. She has held leading positions as Production Manager, QA Director and Quality Systems Director for a major pharmaceutical company. Her areas of expertise are warning letter remediation, complaint and manufacturing investigations, CAPA, change control, product disposition, gap assessments and FDA PAI readiness. Mrs. Muñoz has worked as a consultant, leading international projects helping clients pass FDA inspections with zero observations. She is an ISO 13485:2003 Lead Auditor and has been part of BEC Inc. since 2012.



Leslie Orama is a management system implementation and training consultant within the FDA-regulated industries with over 22 years of experience. She has a bachelor degree in Chemistry from the University of Puerto Rico. She also has a master degree in Environmental Planning from Metropolitan University, Puerto Rico. Since year 2017, she is fully devoted to consulting under BEC Inc, focusing on training of food, internal audit, quality system regulations, root cause and effective CAPA, and management systems implementation. She is a Certified Planner, ISO 9001 and ISO 22000 Lead Assessor.



Frances Cartagena is a consultant within the FDA-regulated industries with over 20 years of experience in operations and quality; managing areas such as Operational Excellence and CAPA. She has a bachelor degree in Chemistry from Interamerican University of Puerto Rico. She also has a master degree in Business Administration from University of Phoenix with a major in Technology Management. Her work covers training in root cause and effective CAPA, and Human Error workshops. She has working experience in consent decrees. She is an ASQ Certified Six Sigma Green Belt and Certified Quality Auditor, and ISO 13485:2003 Certified Lead Auditor, and part of BEC Inc. since 2013.



Remediation and Quality System Compliance

BEC provides an affordable and comprehensive range of quality system remediation services for the FDA regulated industry. Our core expertise allows us to assist you in implementing risk-based, robust and sustainable solutions for your quality system. Regulatory inspections and compliance assessments frequently require regulated companies to respond to specific enforcement actions. We have comprehensive experience in developing, implementing, reviewing, and remediating all aspects of cGMP and quality systems for the FDA regulated sectors. Making your quality system compliant and sustainable while maximizing your investment is our main goal.

We provide expert compliance solutions to regulated companies including remediation strategy, planning and execution. Our expertise covers fixing your CAPA system (we wrote the best-selling book on this topic), validations, reviewing and writing technical documentation, SOPs, conducting failure investigations and preparing effective CAPAs. We also prepare our clients for successful FDA pre-approval and surveillance inspections (including mock inspections), providing support during inspections, in 483s and warning letters responses.

We also specialize in supporting foreign companies willing to market their regulated products in the U.S. We have a proven track assisting companies to introduce generic and OTC drugs, APIs, dietary supplements, food, medical devices and combination products into the U.S. In addition we also provide regulatory support to those companies, and we also prepare their quality systems to meet the FDA specific requirements.

We offer the following services:

Implementation of FDA cGMP/compliant quality system

FDA Inspections

- Pre-inspection readiness
- War-room handling/support during inspections
- Form 483 and warning letter response support
- Regulatory meeting preparation and support

FDA Pre-Approval Inspections (PAI)

Mock Inspections and cGMP assessments

Investigation and CAPA System

- Laboratory, manufacturing and complaint (including FAR) support and backlog reduction
- Retrospective/prospective review
- Investigations/complaints handling outsourcing

Human Error Reduction and Prevention Programs

Implementation and enhancement of Quality Risk Management programs

Quality by Design and Pharmaceutical Development Support

Annual Product Review/Product Quality Review Support and Outsourcing

Computer System Validation and 21 CFR Part 11

Data Integrity audit and assessment, remediation and training

Operational support

- QC laboratory analysts
- QA documentation and change control
- Documentation simplification and enhancement
- Batch record enhancement

Remediation and Quality System Compliance *cont.*

Validation Life-cycle Services

- Risk-based validation master plan development and management
- Equipment commissioning/qualification: manufacturing, packaging, laboratory, facilities/ utilities
- Cleaning validations
- Sterilization method validations
- Computer system validation for cGMP applications: SCADA, LIMS, BMS, ERP, TRACK-WISE, MES, Laboratory electronic notebook
- Computerized system validation life cycle: concept, requirements, design, vendor management, procurement, commissioning, qualification/validation, operation/maintenance, retirement
- 21 CFR 11 assessment and remediation
- Quality control laboratory: analytical test method validation, computer system validation, qualification of analytical equipment
- Qualification/validation package assessments
- Development of continuous process verification programs aligned with the new FDA guidance
- Full statistical support (SPC, DOE, data analysis, sampling assessment)

Training and Education Services

With more than 100 courses and workshops, BEC is well known for the high quality of our regulatory and compliance training and education. Since 2005, we have been leaders in providing education and training to thousands of professionals every year. And since May 2015, BEC educational program has been accredited under the *ANSI/IACET 2013-1 Standard for Continuing Education and Training* which is recognized internationally as a standard of excellence in instructional practices. The ANSI/IACET Standard for Continuing Education and Training is a universal model for learning process excellence. It defines a *proven model* for developing effective and valuable continuing education and training (CE/T) programs by measuring a CE/T provider's training program from procedure to process to result. As a result of this accreditation, BEC is authorized to issue the IACET CEU.



We believe in providing education, not just training. As Albert Einstein said: “Education is that which remains, if one has forgotten everything he learned”. Our courses focus not only on the “what” and the “how”, but also on the “WHY”. FDA-regulated companies must make sure their employees, at all levels, receive comprehensive regulatory and compliance training and education. With BEC’s effective training and educational programs, you will see immediate returns. And, as a bonus, all our IACET accredited courses include an evaluation of the training effectiveness.

We offer comprehensive training and educational programs designed to develop the knowledge and skills needed to meet the many challenges of the FDA-regulated industry. A robust and sustainable regulatory educational program is one of the best preventive actions a regulated company can take. Also, it is the perfect complement to any remediation efforts.

Our instructors are experts in their field and they are supported through a strong Train the Trainer program. Our IACET accreditation demonstrates the excellence of our educational process.

We offer a wide range of courses covering all areas of pharmaceutical, medical devices, combination, food and dietary supplements and API’s cGMP. All our courses can be offered in the following formats:

- Public courses
- On-site courses with on-site instructor(s)
- On-site courses with remote (via webex) instructor(s)
- Online courses (available 2018)

The following three pages contain a list of our courses.

Training and Education Courses Catalog

ASQ Certification Academies

- ASQ Certified Quality Auditor
- ASQ Certified Six Sigma Yellow Belt
- ASQ Certified Six Sigma Green
- ASQ Certified Six Sigma Black Belt
- ASQ Certified Manager of Quality & Organizational Excellence
- ASQ Certified Quality Improvement Associate
- ASQ Certified GMP Professional
- ASQ Certified Biomedical Auditor
- ASQ Certified HACCP Auditor
- ASQ Certified Quality Technician
- ASQ Certified Quality Inspector Academia
- ASQ Certified Quality Engineer
- ASQ Certified Supplier Quality Professional

Investigations and Effective CAPA Systems

- Investigation and Effective CAPA Systems Certification
- CAPA Effectiveness
- Root Cause Analysis, CAPA, and Compliance Writing
- Effective CAPA Systems Management Overview
- Effective OOS Investigations and CAPA for QC Analytical Laboratory

Human Error Investigation and Prevention

- Human Error Certification
- Overview of Human Error

Regulations and Standards

- Medical Device Quality System Expert Certification
- 21 CFR 111: cGMP for Dietary Supplements
- 21 CFR 117: cGMP for Food
- 21 CFR 210/211: cGMP for Finished Drugs
- 21 CFR 820: QSR for Medical Devices
- Food Safety Modernization Act Certification
- Q7: cGMP for API
- Excipients cGMP
- Cosmetics cGMP
- Understanding Combination Products for Pharmaceutical Manufacturers
- Understanding Combination Products for Medical Device Manufacturers
- MHRA/EMA Rules and Guidance
- Quality by Design - Pharmaceutical Development
- ISO 9001:2015
- ISO 13485:2016
- ISO 14001:2015
- ISO 17025:2017

Technical and Compliance Writing

- How to Write Effective CAPA Investigation Reports

Training and Education Courses Catalog cont.

Auditing Techniques

- Internal Auditing Workshop
- FDA Inspection Readiness for Pharma/Biotech
- FDA Inspection Readiness for Medical Device
- FDA Readiness Inspection for Combination Products
- FDA Inspection Readiness for API
- FDA Inspection Readiness for FSMA
- Prerequisite program for Food Safety Systems
- FDA Inspection Readiness for Dietary Supplements
- Auditing FDA Food and Dietary Supplements
- Auditing Pharma/Biotech
- Auditing Medical Devices
- Auditing Combination Products
- Auditing APIs
- Auditing Cosmetics
- Auditing Excipients
- Auditing ISO 9001:2015
- Auditing ISO 13485:2016
- Auditing ISO 14001:2015
- Auditing ISO 22000:2005
- Auditing ISO 17025:2017

Risk Management

- Quality Risk Management Certification
- Practical FMEA for the FDA-Regulated Industry

Statistics

- Analyzing and Trending Data
- Basic Applied Statistics with Minitab
- Sampling Best Practices for the FDA-Regulated Industry
- Design of Experiments

Lean and Six Sigma

- Poka-Yoke
- 5S
- Six Sigma Green Belt certification

Validations

- Computer System Validation for the FDA-Regulated Industry
- Validation Overview
- Cleaning Validation Lifecycle
- Essential Elements for the Manufacture for Aseptically Produced Sterile Products
- Facilities and Critical Utilities Systems Qualification
- Laboratory Equipment Qualification
- General Concepts of Thermal, Radiation, Chemical and Filtration Sterilization Validation
- Test Method Validation
- Process Validation for Medical Devices

Training and Education Courses Catalog cont.

Compliance

- Data Integrity Certification
- How to Write Procedures and Work Instructions to Reduce Human Errors
- Effective Handling of FDA Food and Dietary Supplements Recalls
- Medical Device Design Controls
- Change Control Systems
- Overview of Stability Programs for Drug, Biotech, and Combination Products
- Stability Program for APIs
- APR/PQR
- FDA's Quality Metrics
- Best practices on complaint handling for pharma/biotech
- Best practices on complaint handling for medical devices
- Best practices on complaint handling for food/DS
- Best practices on complaint handling for APIs

Training Program

- Train the Trainer
- How to Measure Training Effectiveness

Organizational Behavior

- Decision Making
- Critical Thinking
- Employee Motivation
- Hiring Strategies/ Interviewing Skills
- Generation Gaps
- Goal Setting
- Motivation
- Leadership Skills
- Supervisory Skills
- Meeting Management
- Safety in the Workplace
- Teamwork and Teambuilding
- Time Management
- Assertiveness and Self-Confidence
- Conflict Management
- Emotional Intelligence

Employee Development

- Certification Pharmaceutical Operators
- Certification Pharmaceutical Managers and Supervisors
- Certification Medical Devices Operators
- Certification Medical Devices Managers and Supervisors
- Certification for Dietary Supplements Operators
- Certification for Dietary Supplements Managers and Supervisors
- Certification API Plant Operators
- Certification API Plant Managers and Supervisors

Audit and Assessment

If your company needs an in-depth, expert assessment of a specific issue, to outsource your entire internal or supplier audit program or anything in between, BEC can support you through our team of experts covering all FDA-regulated areas.

Our auditing and assessment division is currently finishing (estimated 1st Quarter 2018) the process of accreditation under the international standard **ISO/IEC 17020:2012 Conformity assessment -- Requirements for the operation of various types of bodies performing inspection**. This standard specifies requirements for the competence of bodies performing inspection and for the impartiality and consistency of their inspection activities. We are servicing several major global companies auditing their critical suppliers worldwide. During 2016, we performed more than one hundred audits in 15 countries, covering Asia, North America, Central and South America and Europe.

We offer the following services:

Preparation for FDA Regulatory Inspection

BEC has provided FDA inspection readiness services for the last twelve years with an excellent success rate. Our expert service includes the following activities:

- * Initial gap assessment to identify opportunity areas, including comprehensive data integrity assessment
- * Development of a detailed and comprehensive remediation plan to address weak or noncompliance areas
- * Training your staff to prepare for an FDA inspection and how to interact with the inspector
- * Formal mock inspection to practice and to challenge staff and quality systems prior to the inspection
- * War-room handling/support during the inspection, with both onsite and remote expert support
- * Post-inspection support preparing formal responses and managing interactions with the FDA, including regulatory meeting preparation and support

We have extensive experience helping companies to address critical agency findings, as well as untitled and warning letters. We have a proven, demonstrable track record addressing complex regulatory problems and compliance issues.

Preparation for FDA Pre-Approval Inspection (PAI)

The inspection focus and methodologies used by FDA inspectors during pre-approval inspections (PAI) are different to those used for regular, surveillance, postmarket inspections. Before approval, the FDA typically evaluates the manufacturer by on-site inspections when the company is named in the Chemistry, Manufacturing, and Controls (CMC) section of a New Drug Application (NDA), Abbreviated New Drug Application (ANDA) or Biologic License Application (BLA). The pre-approval inspection (PAI) is performed to contribute to the FDA's assurance that a manufacturing establishment named in a drug application is capable of manufacturing a drug, and that submitted data is accurate and complete.

Our company has extensive experience helping companies with NDA and ANDA preapproval inspections. In this case, in addition to all preparation activities mentioned for regular FDA inspections, our experts will perform an intensive assessment of the following three elements:

- Readiness for Commercial Manufacturing*
- Conformance to Application*
- Data Integrity Audit*

Audit and Assessment *cont.*

Mock FDA Regulatory Inspections / FDA Readiness

We assist your company with the best possible preparation for your next FDA inspection. After hundreds of FDA inspections, we know very well how inspections are performed, and what inspectors look for. We can even mimic the FDA inspection atmosphere when more than one inspector is expected. Our mock inspections can include one-day education on FDA readiness and how to interact with the FDA inspector. We will advise your company on which documentation needs to be ready, how to establish an effective war-room to attend the inspection and how to effectively manage all aspect of the inspection, from logistics to record-keeping.

Quality System Assessment/GMP Compliance

Our team of experienced professionals can perform a thorough, in-depth assessment of your quality system against regulatory requirements and guidances, industry best practices and other standards such as USP and ICH. Our detailed risk-based audit report will include recommendations to enhance your weaknesses and can be used as the basis for a remediation/corrective action plan.

Often our clients request us to audit specific elements of their quality system. Some examples of recently performed audits are:

Data Integrity	QC Microbiology laboratory
Pest control	CAPA Systems
Incoming Process Control	Change Control
Manufacturing Processes	Internal Audit Program
Packaging Processes	Supplier Certification Program
Warehouse and Distribution Centers	Training Program and Learning Verification
Sterilization Process	Facilities and Critical Utility Systems
QC Analytical laboratory	Validation Program
LIMS	

Internal Audit/Self Inspection

The internal audit program is a regulatory requirement of the FDA and worldwide regulators. This program, when well executed, is your primary line of defense against regulatory inspection findings. However, many FDA regulated companies have weak internal audit programs. This is due to:

- Internal auditors are inherently non-independent
- Internal auditors often lack the education and experience necessary in many areas such as data integrity, computer system validation, laboratory test methods, equipment validation, etc
- Many internal audit programs are not risk-based

We established a very successful internal audit outsourcing model where we perform, twice a year, an in-depth assessment of the different elements of the applicable quality system, with a team of experts covering all the critical areas and elements. This model guarantees you a much more robust internal audit program that saves your company money. Typically you can save up to 50% of your current in-

Audit and Assessment cont.

Supplier Control Programs

We can design, implement and/or support a risk-based efficient supplier control program. Each year, our experts perform more than one hundred third party audits worldwide. We are servicing several major global companies auditing their critical suppliers worldwide. During 2016, we performed audits in 15 countries, covering Asia, North America, Central and South America and Europe. To learn how you can implement a compliant, risk-based supplier control program at a very reasonable cost, contact us.

Regulatory Affairs

We offer expert regulatory support and consulting services related to U.S. FDA regulated products. We prepare and/or review regulatory documentation and dossiers, or we can also act as your U.S. Agent representative for regulatory purposes. Our company also provides advice on product manufacturing, product specification development, and training on U.S. regulatory processes.

We provide the following services:

- U.S. Agent
- Drug Establishment Registration and Drug Listing
- Establishment Registration and Device Listing
- Registration of Food facilities
- Advice on product manufacturing and product specification development.
- Training on U.S. regulatory processes
- Review and preparation of IND, NDA, BLA, ANDA, NADA, and prior approval supplement (PAS) all with eCTD format
- Review and preparation of 510k and PMA dossiers, including prior approval supplement (PAS)
- Review and preparation of DMF dossiers with eCTD format

FDA Inspection Support

Preparation for FDA Regulatory Inspection

BEC has provided FDA inspection support services for the last twelve years with an excellent success rate. Our expert service includes the following activities:

- Initial gap assessment to identify opportunities areas, including comprehensive data integrity assessment
- Development of a detailed and comprehensive remediation plan to address weak or non-compliance areas
- Training your staff to prepare for an FDA inspection and how to interact with the inspector
- Formal mock inspection to practice and to challenge staff and quality systems prior to the inspection
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Conformance to Application
Data Integrity Audit

Mock FDA Regulatory Inspections / FDA Readiness

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Data Integrity

Data Integrity is a global mandatory requirement for the regulated healthcare industry. Developing a medical product and bringing it to market involves different players and activities. A fundamental step is linked to the robustness and accuracy of the data submitted by manufacturers to regulatory authorities. That data must be comprehensive, complete, accurate and, true to assure the quality of studies supporting applications for medical products to be placed on the market. Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA). It also must comply with good manufacturing practices (GMP), good clinical practices (GCP), and good laboratory practices (GLP).

Data Integrity is a basic element of good documentation practices, one of the most fundamental pillars of any quality management system, including current good manufacturing practices. There has been a dramatic increase in the number of U.S. Food and Drug Administration (FDA) warning letters, World Health Organization (WHO) notices of concern, and EU statements of noncompliance in which false or misleading information has been identified during inspections. Failure to properly manage data integrity applies equally to paper and electronic data. It can arise either from poor systematic control of the data management systems due to a lack of knowledge, human error or from intentionally hidden, falsified or misleading data. Recently, a string of FDA-issued warning letters for data integrity violations has been published on the agency’s website. Between 2015 and 2016, major regulatory bodies, such as the European Medicines Agency (EMA), the FDA, the WHO, and the Pharmaceutical Inspection Cooperation Scheme (PIC/S), published guidance documents on the topic of data integrity and data management.

Our company can offer you the following services related to data integrity:

- **Comprehensive Audits and Assessments** to identify system weaknesses regarding your manual, electronic and hybrid data feed. We cover all aspects of your records and data recording practices specially laboratory systems and electronic storage.
- **FDA inspection preparedness** for Data Integrity including mock inspection.
- **Remediation Consulting** focused on FDA recommended best practices.
- **Training** for your personnel at all levels including a very comprehensive 3-day certification for managers and subject matter experts. Participants learn how to detect data integrity problems.

Field Notes
Zooming in on industry-specific issues

Maintaining Data Integrity
Avoiding regulator scrutiny in the medical products industry

By José Rodríguez Pérez

In August 2015, the European Union (EU) banned the marketing of about 700 Indian-made generic drugs for alleged manipulation of clinical trials data. The largest-ever EU-wide suspension of sales and distribution of generic drugs ordered by the European Commission was applicable to all 28 member nations.¹ Recently, there has been a dramatic escalation in the number of U.S. Food and Drug Administration (FDA) warning letters, World Health Organization (WHO) notices of concern, and EU statements of noncompliance in which false or misleading information has been identified during inspections. Failure to properly manage data integrity applies equally to paper and electronic data. It can arise either from poor systematic control of the data management systems due to a lack of knowledge, human error or from intentionally hidden, falsified or misleading data.

What is data integrity?
Data integrity is a global mandatory requirement for the regulated healthcare industry. Developing and bringing a medical product to market involves different players and activities; therefore, robustness and accuracy of the data submitted by manufacturers to regulatory authorities is crucial. The data must be comprehensive, complete, accurate and true to ensure the quality of studies supporting applications for medical products to be placed on the market. Complete, consistent, and accurate data must be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA).¹ See Table 1.

Data integrity also must comply with good manufacturing practices (GMP), good clinical practices (GCP), and good laboratory practices (GLP). In recent years, however, data integrity issues are jeopardizing the regulatory compliance status of organizations. In many instances, data integrity problems are created by sloppy documentation practices or incidents that cause the loss of data, but regulators tend to label those situations as fraud. Moreover, it demonstrates a lack of commitment

Characteristics	Meaning
Attributable	Establishes who performed an action and when. Traceable to an individual.
Legible	Data must be recorded permanently in a durable medium and be readable by others. Traceable changes.
Contemporaneous	Activities must be recorded at the time they occur (when activity is performed or the information is obtained).
Original	The information must be the original record (first capture of the data) or a certified true copy. Not the transcribed data.
Accurate	Data reflect true information.

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Investigation and CAPA System Support

Root causes identification and effective corrective and preventive actions is a critical expectation of the FDA and other regulatory agencies worldwide. Indeed, this area represents one of the most frequently cited problems during regulatory inspections. As an example, almost 90% of medical device's warning letters issued by U.S. FDA include CAPA citations. Weak investigations and ineffective CAPAs are at the center of most regulatory enforcement actions.

Requirements for compliant deviation and CAPA systems are well established by regulatory agencies. Each organization must conduct focused investigations, identify true root causes, and implement effective corrective action and preventive action in a timely manner, including measuring their effectiveness.

BEC has provided investigations and CAPA system support since 2005 to major pharmaceutical, medical device, and food companies located worldwide. Among the services that our company can provide are:

TRAINING – To improve the capability of your personnel to make better investigations and to implement effective corrective and preventive actions. We have different courses and certifications that can be tailored to your specific needs. Our trainings explore the deviation and CAPA processes and best practices for both. Your participants learn how to avoid pitfalls and minimize regulatory scrutiny by having thorough investigations and a robust and a compliant deviation/CAPA system. Among our courses are:

- Four-day Investigator and CAPA Expert Certification for investigators, CAPA owners and approvers
- One-day CAPA System Management Overview for managers and directors

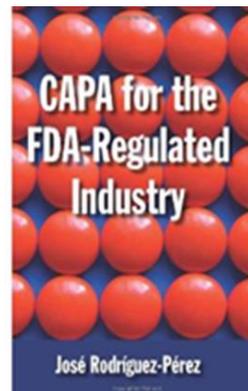
TEMPORARY SUPPORT – We can assist your company with temporary expert support to:

- Reduce backlog of laboratory, production or customer complaint investigations
- Fix and enhance your deviation/CAPA system. Our expert resources will design a compliant and sustainable deviation/NCR and CAPA system. After all, we wrote the best-selling book in this topic.

MONITOR – BEC can provide your company with affordable ways to monitor the effectiveness of your deviation/CAPA system. Our service of independent reviews of deviation and CAPA documents will provide you peace of mind about this critical system. Dozens of companies that went through a CAPA warning letter hired us to provide an independent verification of their deviations and CAPA documents.

OUTSOURCING – Our company offers full outsourcing possibilities for the above mentioned activities related to deviation and CAPA system activities.

Our best-selling books on this topic are used by companies around the globe to enhance their investigation and CAPA systems.



Human Error Investigation and Reduction

The cost of human errors to the manufacturing industry is estimated to be in the \$ billions. Recent statistics show that human error is the cause of nearly 80% of failures and deviations in the manufacturing sector. This poses a tremendous challenge to regulated companies as it translates to a significant loss of time, money, and consumer confidence each year, including regulatory enforcement activities.

Global regulators have increased their focus on deviations and root cause analysis (RCA), and this process is one of the largest sources of inspection observations. Frequently identifying “human error” as a root cause and “retraining” as a CAPA is a clear indication to the regulatory authorities that you’re not solving the problems that exist in your organization. Worse, it can give regulators the impression that your staff is ill-prepared, error prone, and you don’t have a handle on the real causes of your deviations. Human failure (voluntary and involuntary) is more a symptom than a cause. Current theories see human failures as the symptoms of deeper causes. In other words, human failures are consequences, not causes.

BEC has provided human error reduction expertise support since 2005 to major pharmaceutical, medical device, and food companies located worldwide. Among the services that our company can provide are:

ERROR REDUCTION PROGRAM - We can assist you with human reliability experts who can help with procedures and process simplification to reduce human errors and mistakes by:

- Evaluating your current situation (human error deviations and CAPAs)
- Investigating the *real* root causes of the above
- Suggesting comprehensive, sustainable and affordable actions to minimize the occurrence of human error(s) at your facilities

HUMAN RELIABILITY TRAINING – We can help your company to better understand why human errors occur, and this will enable your staff at all levels to move the organization from “error prone” to “error free” resulting in fewer enforcement observations/actions from global regulatory agencies. We have a comprehensive 3-days certification for quality assurance, production, regulatory affairs, supplier quality and quality control personnel. Participants will learn and practice how to:

- Investigate error incidents properly
- Evaluate the CAPA investigation process to identify all the root cause(s)
- Identify the root causes that lead to human error
- Identify the controls that could avoid human error

MONITOR – BEC can help your company with affordable ways to monitor the effectiveness of your human error reduction program. After implementation of the program, we can independently review your human error deviation and CAPA documents to ensure they are adequate in terms of root cause investigation and appropriate CAPA plans.

Our newest book on this topic will be published by the American Society for Quality in 2018.

Outsourcing Activities

BEC is providing support in the form of outsourced programs to regulated companies for the following elements of their quality system:

- Training Program
- Internal Audit
- Supplier Audit Program
- Complaint Investigation
- Investigation of Deviations/NCR/CAPA
- APR/PQR

Every day more companies are discovering the value and benefit derived from outsourcing specific critical activities to specialized providers such as our company. We provide our outsourcing clients with real and proven expertise in the FDA-regulated industry, 24/7 support, very affordable and cost-effective fees.

As an example, our outsourcing value model for the self-inspection program of a typical pharmaceutical plant includes the following elements:

- Developing and maintaining a risk-based and compliant internal audit program for the site
- Subject matter expert auditors with an average of 25+ year in the FDA-regulated industry
- Our audit process is becoming accredited under ISO 17020:2012
- Full support during external audits/inspections regarding internal audit function
- Follow-up of CAPAs generated after internal audit findings
- In total, we provide 50-days of audit during a calendar year covering all the elements of the quality system:
 - * Data Integrity (manual, electronic, and hybrid systems)
 - * CSV
 - * QC analytical lab
 - * QC microbiological lab
 - * Critical systems and utilities
 - * Calibration and PM program
 - * Stability program
 - * Master validation program
 - * Quality system
 - * Production system
 - * Investigation and CAPA system
 - * Complaint handling
 - * Management controls

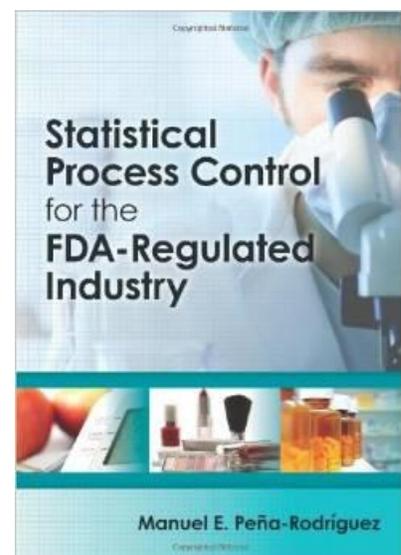
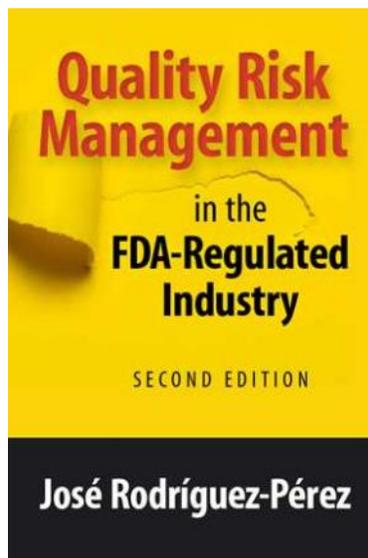
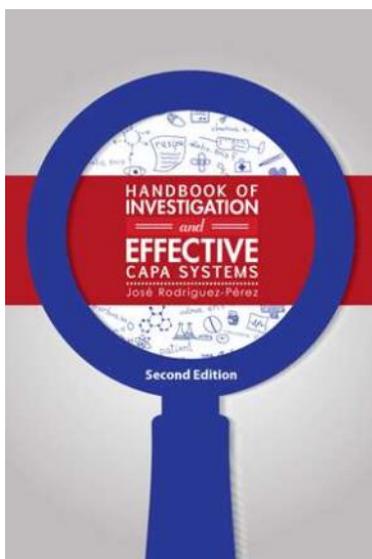
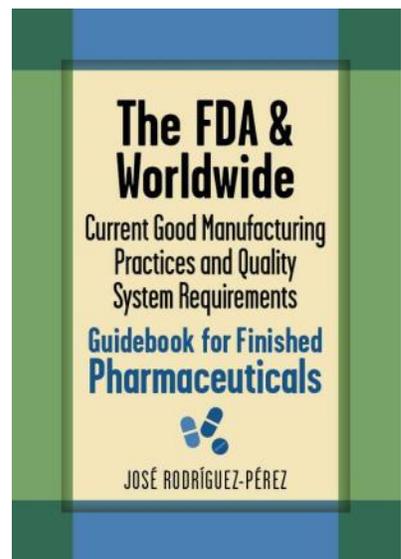
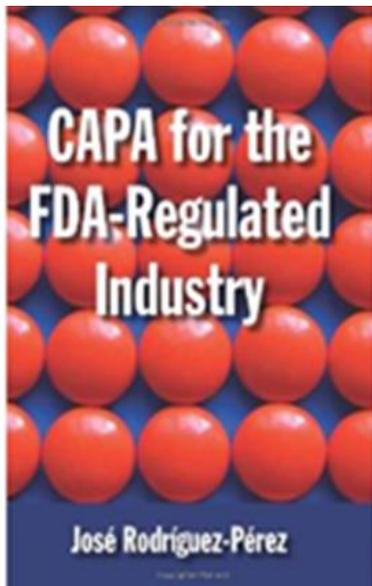
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Books

The authors of these books, published by the American Society of Quality, are part of our staff. Our first book, *CAPA for the FDA-Regulated Industry* became a best-seller since its publication in 2010 and was updated with a second edition in 2016 under the title of *Handbook of Investigation and Effective CAPA System*. Our second book, *Quality Risk Management in the FDA-Regulated Industry* was published in 2012 and also became a best seller with an updated second edition published in February 2017.

Our focus on the FDA regulated industry was also showed by the title of the other two books: *Statistical Process Control for the FDA-Regulated Industry* (2013) and *The FDA and Worldwide GMP for Finished Pharmaceuticals* published in 2014.

Under preparation we have books on topics such as Human Error, APIs, and Data Integrity.



Technical Articles published by our staff

Field Notes

Zooming In on Industry-specific Issues

FDA REGULATION

Maintaining Data Integrity

Avoiding regulator scrutiny in the medical products industry

By José Rodríguez Pérez

In August 2015, the European Union (EU) banned the marketing of about 700 Indian-made generic drugs for alleged manipulation of clinical trials data. The largest-ever EU-wide suspension of sales and distribution of generic drugs ordered by the European Commission was applicable to all 28 member nations.¹ Recently, there has been a dramatic escalation in the number of U.S. Food and Drug Administration (FDA) warning letters, World Health Organization (WHO) notices of concern, and EU statements of noncompliance in which false or misleading information has been identified during inspections. Failure to properly manage data integrity applies equally to paper and electronic data. It can arise either from poor systematic control of the data management systems due to a lack of knowledge, human error or from intentionally hidden, falsified or misleading data.

What is data integrity? Data integrity is a global mandatory requirement for the regulated healthcare industry. Developing and bringing a medical product to market involves different players and activities; therefore, robustness and accuracy of the data submitted by manufacturers to regulatory authorities is crucial. The data must be comprehensive, complete, accurate and true to ensure the quality of studies supporting applications for medical products to be placed on the market. Complete, consistent, and accurate data must be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA).² See Table 1.

Data integrity also must comply with good manufacturing practices (GMP), good clinical practices (GCP), and good laboratory practices (GLP). In recent years, however, data integrity issues are occurring during the regulatory compliance status of organizations. In many instances, data integrity problems are created by sloppy documentation practices or incidents that cause the loss of data, but regulators tend to label these situations as fraud. Moreover, it demonstrates a lack of commitment

Field Notes

chromatography (HPLC) testing sequence versus recording only at the end of the day).

Commitment from all Data integrity enables good decision-making by manufacturers and regulatory authorities. It is a fundamental mandatory requirement of the medical products quality system, applying equally to manual (paper) and electronic systems. To ensure data integrity, senior management must engage in the promotion of a quality culture along with the implementation of appropriate organizational and technical controls. It requires participation and commitment by staff at all levels within the organization, by the organization's suppliers and by its distributors.

Data integrity is a basic element of good documentation practices, one of the most fundamental pillars of any quality management system, including GMP. Upper management, and especially quality leaders at every regulated organization must ensure that everyone is accountable for their actions, including having proper documentation of activities performed. Unfortunately, most regulated organizations only react to data integrity issues after regulators discover them.

An outrageous example of this can be found in a warning letter³ issued in July 2014 in which the FDA required an organization to "identify the specific manager in place who participated in, facilitated, encouraged or failed to stop subordinates from falsifying data in CGMP records, and determine the extent of top and middle management's involvement, or awareness of data manipulation." In the same inspection, the FDA also discovered that "your firm falsified documents designed to demonstrate the effectiveness of CGMP training... That a senior manager was engaged in the falsification of documents is troubling and raises questions about validity of documents generated by your firm."⁴

Senior management, especially those with quality management responsibilities, should ensure that data integrity risk is assessed, mitigated and communicated in accordance with the principles of quality risk management. The effort and resources assigned to data integrity measures should be commensurate with the risk to product quality, and balanced with other QA resource demands. Where long-term measures are identified to achieve the desired state of control, interim measures should be implemented to mitigate risk and should be monitored for effectiveness.

Data integrity and human error Finally, remember that regulators do not distinguish between human error or stoppages, and data falsifications and fraud when assessing the impact of data integrity failures, as demonstrated in the following excerpt from a 2015 FDA warning letter⁵:

"In correspondence with the agency, you indicate that no malicious data integrity patterns and practices were found. Also, you state that no intentional activity to disguise, misrepresent or replace falsifying data with passing data was identified and no evidence of file deletion or manipulation was found. Your response and comments focus primarily on the issue of intent, and do not adequately address the seriousness of the CGMP violations found during the inspection."⁶

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Fail-Safe FMEA

Combination of quality tools keeps risk in check

by José Rodríguez-Pérez and Manuel E. Peña-Rodríguez

In 50 Words Or Less

- Failing to manage risk puts customers and entire organizations in jeopardy.
- Using failure mode and effects analysis (FMEA) can help identify risk but isn't enough to avoid potential disaster.
- By combining FMEA with other tools, organizations can ensure their products aren't harmed the way they're supposed to help.

QUALITY RISK MANAGEMENT principles are used effectively in many areas of business and government—including finance, insurance, occupational safety and public health—and by the agencies regulating these industries.

Risk management's widespread use isn't a surprise because every product and every process has an associated risk. But while there are some examples of the use of quality risk management in the medical product manufacturing industry, they are limited and do not take full advantage of what risk management has to offer. After all, inadequate or ineffective quality risk management can harm patients, product users and company value.



RISK MANAGEMENT

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