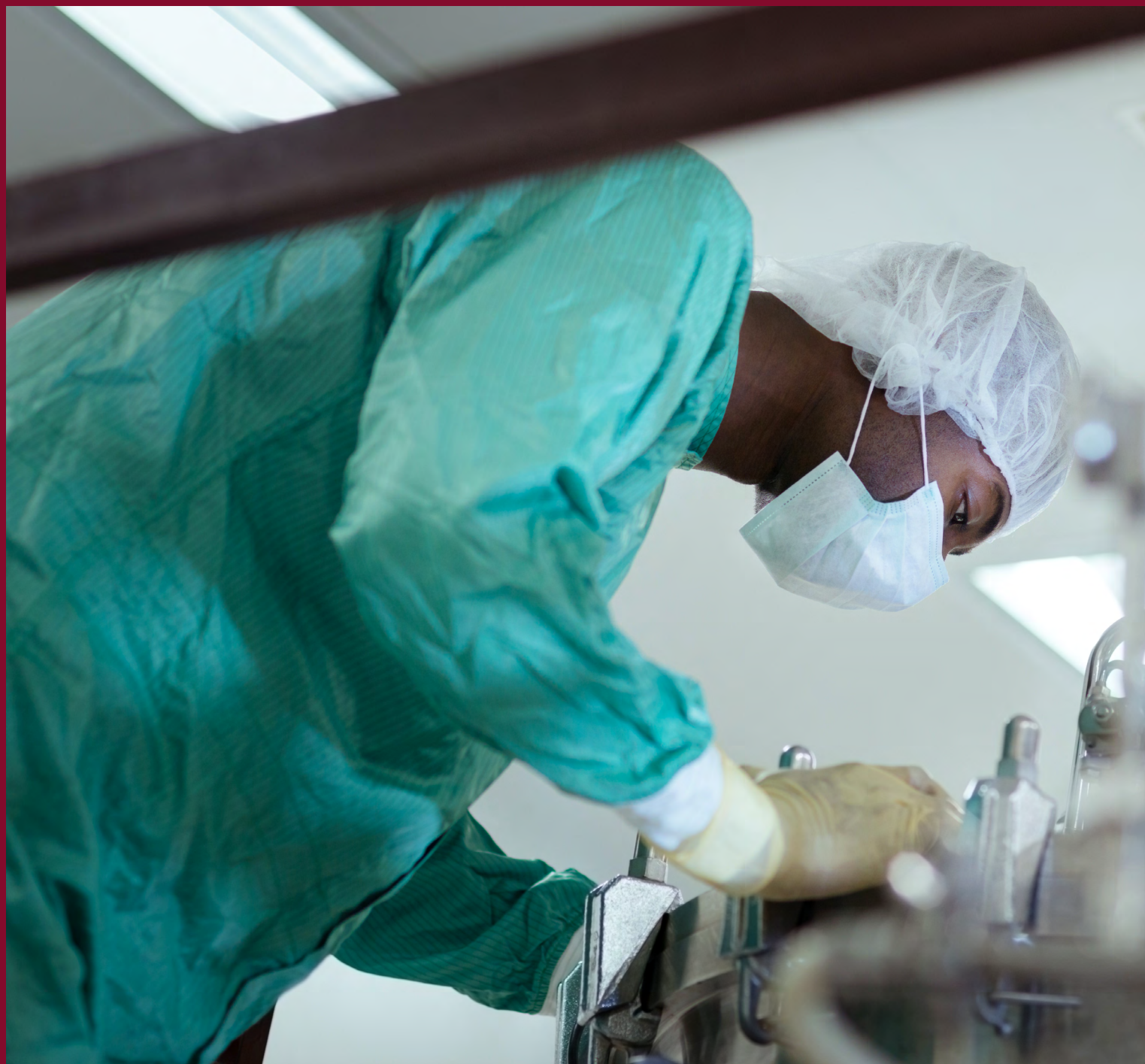
Medical Device Communiqué

Q4 2016



MEDICAL DEVICE REGULATIONS IN THE EU - A NEW ERA

The experts at Compliance Insight (www.compliance-insight.com) maintain our EU-focused medical device courses, including a new course on EU MDR. This course, CE Certification for Medical Devices (MDR03), is available to subscribers of our Medical Device GMP Library.

In this current environment of continuous improvement, the medical device industry has been playing catch-up by tirelessly revising processes and documentation to meet quality standards and keep up with technological advancements. Governments and regulatory agencies are no exception. Just as FDA updates are published annually for the Code of Federal Regulations, international agencies are focused on advancements in scientific understanding and higher quality standards and controls must follow. The European Union (EU) is working to harmonize standards for manufacturers, importers and distributors of medical devices, implantable devices, and in vitro diagnostic medical devices among its member states. The following paragraphs provide an outline of the coming changes.

Implementation of Revised Regulations

Expected in late 2016/early 2017, the EU is finalizing their revised Medical Device Regulations (MDR) published in June of this year. Among the many updates are a centralized review system for submissions, improved clinical oversight, and pharmacovigilance and supply chain management, post-marketing assessment and facility inspection activities.

These new regulations, found in EUR-Lex - 52012SC0274 – EN, EUR-Lex - 52012SC0273 – EN, European Commission Part II - Annex I, European Commission Part III - Annex 2 and European Commission Part IV - Appendices, are intended to incorporate, advance and supersede the EU medical device directives implemented in 2007.

These directives incorporated within the MDR include MDD 2007/47/EC and all associated amendments which consolidated the original directives from the EC. For additional details on the current EU regulations, refer to the European Commission website, which also includes a list of all current amendments.

Anticipated Compliance Schedule

As with most major regulation updates, implementation dates for industry can be tricky.

EU regulators have given consideration to the impact of these revisions and have defined the compliance schedule accordingly. Specifically, these regulations have compliance dates as follows:

- Class I medical devices: deadline at the date of application, expected in Q1 of 2020 or before.
- Higher-risk devices: switch to MDR certification once Notified Bodies (NBs, certified oversight entities similar to Institutional Review Boards [IRB]) have been designated for the MDR. Approved Medical Device Directive (MDD) certificates are valid through expiration. Expiration for certificates issued before the MDR date of application should not exceed four years; marketing may continue potentially until Q1 2024[2,3].

Potential Impact on the Global Medical Device Industry

While the impact on medical device manufacturing and distribution within the member states is direct, the impact on industry in partner countries has yet to be seen. As FDA compliance is required for any medical device industry contributors intending on marketing within the US, the same stands for those intending on marketing and exporting to the EU and compliance is mandatory.

For US manufacturers and exporters, much of what may be required for compliance is evaluation of the regulatory terms

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MEDICAL DEVICE REGULATIONS IN THE EU - A NEW ERA
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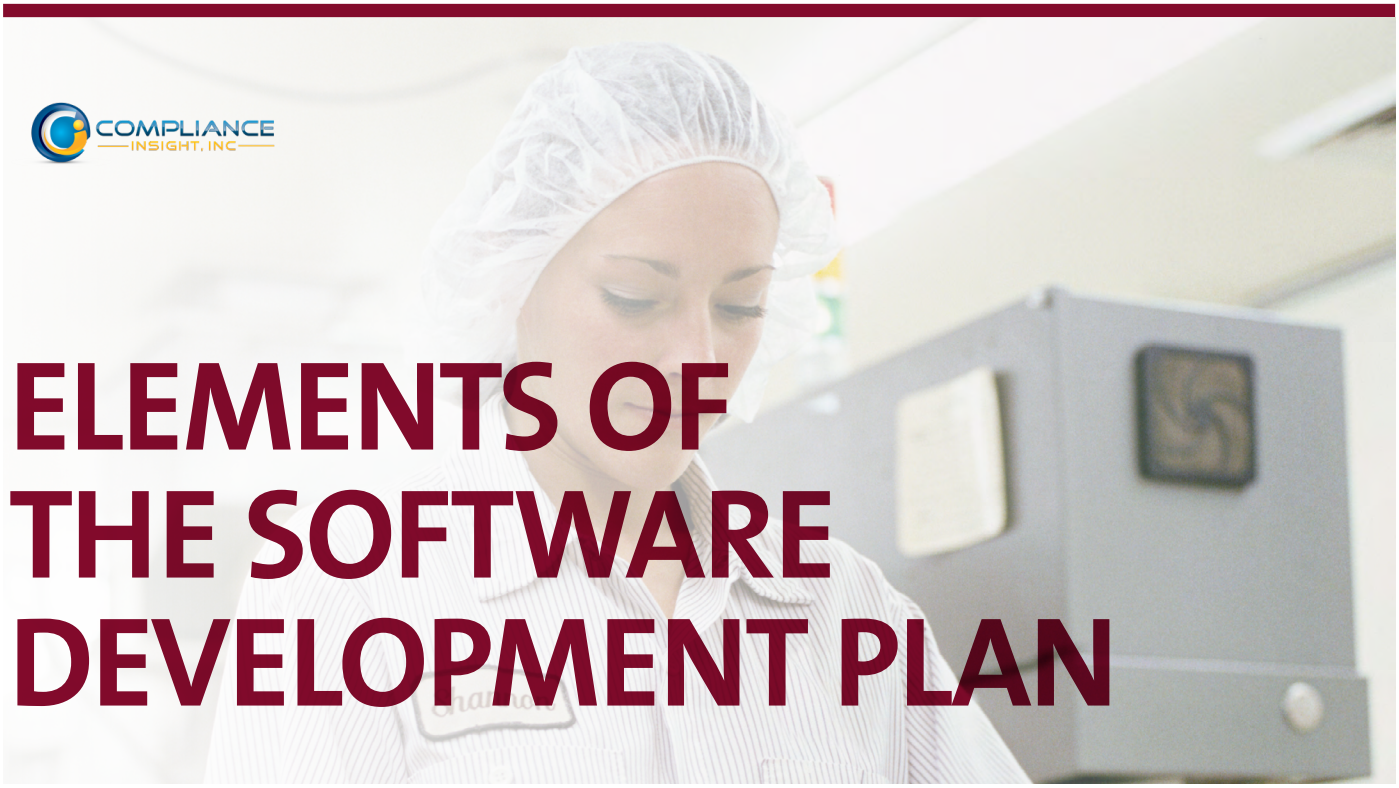
used by the MDR and consolidation with those used in FDA regulations, if not performed already. Globally, government regulatory agencies are preparing for these revisions through discussions with the EC and commitments to compliance based on international cooperation initiatives. Per EC dialogues with key trade partner:

"Discussions and exchanges of ideas have been pursued mainly with the US Food and Drug Administration (FDA), Japan Ministry of Health, Labour and Welfare (MHLW), Health/Santé Canada, Australia Therapeutic Goods Administration (TGA), China Food and Drug Administration (SFDA) and China Quality Supervision, Inspection and Quarantine (AQSIQ). The regulatory dialogues on health technology is also active under political umbrellas such as the Transatlantic and Trade Agreement (T-TIP) with the USA, the Free Trade Agreement (FTA) with Japan or the Revised Mutual Recognition Agreement with Australia (Revised MRA)."[1]

It is clear that the strengthening of the EU regulations is intended to elevate quality by ensuring performance and safety for medical devices marketed within the member states, in turn minimizing unacceptable risks that the use of these devices may pose.

References:

1. www.ec.europa.eu
2. Emergo Group White Paper, Understanding Europe's New Medical Devices Regulation (MDR); Boumans, Ronald and Eisenhart, Stewart; July 2016.
3. UL Compliance to Performance Course (Code: MDR03): CE Certification for Medical Devices, December 2016, www.ComplianceToPerformance.com



ELEMENTS OF THE SOFTWARE DEVELOPMENT PLAN

This is an article based on a new course authored by experts at Compliance-Insight (www.compliance-insight.com). The course, IEC 62304: Medical Device Software Development Process and Risk Management (code: MDSafety_10), is part of our new Medical Device Safety Library.

Software as a Medical Device

As more and more medical devices include sensors, controls, wireless connectivity, firmware, and remote monitoring, QA teams are adhering to best practices found in the standard IEC 62304.

This standard provides the framework of lifecycle processes with activities and tasks necessary for the design and maintenance of the medical device software. The standard also focuses on software development and the practices, policies, and procedures used to analyze and evaluate risk.

For manufacturers, the establishment of a device's safety and effectiveness requires that the manufacturer be aware of what the software is intended to do and demonstrate that the software fulfills those intentions over the lifetime of the medical device - without causing unacceptable risks.

In August 2016, the IMDRF, a group of regulatory agencies that includes US FDA, released guidance on "Software as a Medical Device: Clinical Evaluation." In the document, IMDRF states:

"SaMD, a type of medical device, has significant patient and public health impact and therefore requires reasonable assurance of safety, effectiveness and performance." Rather than have contact with a patient, most SaMDs, according to the report, "perform computation on data input and provide data output to a user to inform clinical management, drive clinical management, or in the diagnosis or treatment of the patient."

The report also notes that a "SaMD manufacturer is expected to gather, analyze, and evaluate data, and develop evidence to demonstrate the assurance of safety, effectiveness and performance of the SaMD."

When establishing a software development plan for conducting the activities of the software development process, you must consider the scope, magnitude, and software safety classifications of the software system to be developed.

The software development process must meet certain standards within IEC 62304 to ensure the software fulfills its intentions without causing unacceptable risks. The use of a risk management process that complies with ISO 14971 is required for all safety classes. In order for the software to achieve safety and

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ELEMENTS OF THE SOFTWARE DEVELOPMENT PLAN *(Continued)*

effectiveness, it must be proven that the software fulfills the specifications without causing unacceptable risks.

The software development plan must specify the required activities and tasks of the software risk management process, including the management of risks relating to Software of Unknown Provenance (SOUP). Here are those activities and tasks:

Coordination procedures

The software development plan includes or references procedures for coordinating the software development with applicable system developments necessary to satisfy Clause 4.1 of IEC 62304 (e.g., system integration and verification activities).

The term and activity "software validation" is not covered by IEC 62304. It is purposely left out of the scope of the standard. The US Food and Drug Administration guidance on General Principles of Software Validation for product software uses the term "validation" to mean the sum total of verification activities.

Verification information

Requirements of the software development plan include the following verification information:

- deliverables requiring verification.
- the required verification tasks for each life cycle activity.
- milestones at which the deliverables are verified.
- the acceptance criteria for verification of the deliverables.

Required documents

For each document or type of document, the software development plan references the following information:

- title, name, or naming convention.
- purpose.
- procedures and responsibilities for development, review, approval, and modification.

Configuration management

The software development plan must include software configuration management information. The information shall include or reference:

- the classes, types, categories, or lists of items to be controlled.
- the software configuration management activities and tasks.
- the organization(s) responsible for performing software configuration management activities.
- their relationship with other organizations, such as software development or maintenance.
- when the items are to be placed under configuration control.
- when the problem resolution process is to be used.

Defect management

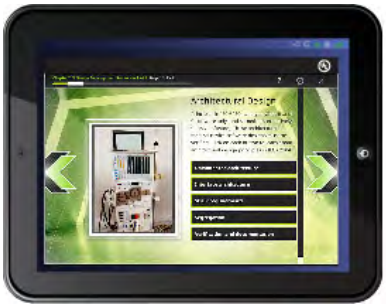
The software development plan requires procedures for:

- identifying categories of defects that may be introduced based on the selected programming technology that are relevant to their software system.
- documenting evidence that demonstrates that these defects do not contribute to unacceptable risks.

New Course on IEC 62304

UL certifies software for IEC 62304, and the UL Compliance to Performance team has developed a new course that describes IEC 62304's requirements for any software development process involving medical devices.

Contact Pat Thunell at pat.thunell@ul.com to take a demo of this course.



BUILDING A SKILLS DEVELOPMENT FRAMEWORK

The following article is an excerpt from a piece written by our Aseptic Processing expert, Ann Early, published in September 2016.

If your company manufactures sterile products, it would seem unimaginable for these events to happen:

- Operators on all fours crawling on the floor under the filling line during routine aseptic filling operations adjusting or removing vials from the line wearing gloved hands rather than restricted access barrier system gloves
- Poor facility and equipment design inadequately protecting the sterile product during manual manipulations, posing a substantial hazard to product sterility and an unreasonable risk to patient safety
- Failure to follow appropriate written procedures specifically designed to prevent microbiological contamination of drug products purporting to be sterile, and that require validation of all aseptic and sterilization processes

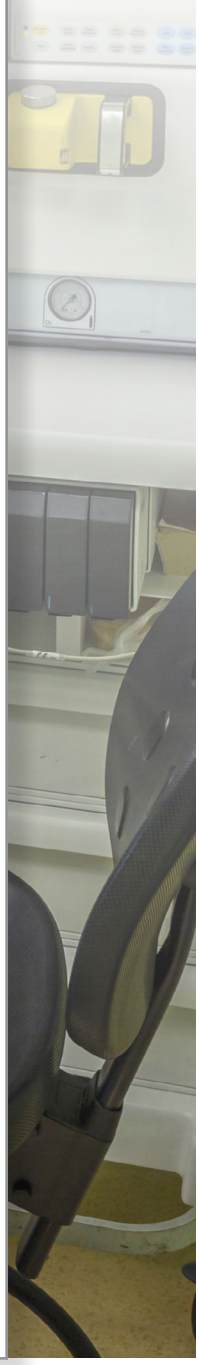
The events represent actual US FDA investigator citations typical of what companies operating in a sterile manufacturing environment would see as 483 observations during a routine FDA inspection.

The FDA expects sterile drug and device manufacturers to maintain a keen awareness of the public health implications of distributing non-sterile products. Poor and lax current Good Manufacturing Practice (cGMP) conditions at a manufacturing facility can ultimately pose a life-threatening health risk to patients. As a result, the Agency provides guidance to help companies meet the requirements in its cGMP regulations (21 CFR parts 210 and 211) when producing sterile products using aseptic processing.

It's no coincidence that aseptic processing, along with environmental monitoring and sterilization, represent three of the FDA's top 10 areas of ongoing scrutiny for organizations operating cleanrooms. Training ranks a close fourth. Yet, despite its relative importance for building and sustaining the competencies that support regulatory compliance and risk mitigation, training is often a topic that suffers from a low priority among the executive team and the resource allocation pecking order.

This could be attributed to perceptual and operational hesitancy in the sterile manufacturing space, since developing an effective skills training program takes time, funding, and:

- Requires indirect human capital to develop the course curriculum and analytics
- Can be more complicated than originally projected
- Suffers from a misperception about the value of the skill sets needed
- Is impacted by an institutionalized "re-train" mentality that offsets investing in a long-term development solution that elevates learning, engagement, and performance



BUILDING A SKILLS DEVELOPMENT FRAMEWORK *(Continued)*

With regulatory enforcement becoming more stringent, the days of cleanroom operators performing tasks by rote, or executing them incorrectly because that's how their predecessors did it, are over.

More organizations are concluding that it's time to drill down deeper – beyond SOP training and OJT checklists – and define more formal competency mapping.

Skills development programs serve as foundational elements of these "critical to quality" initiatives. In addition to helping organizations remain compliant with the FDA and other regulatory agencies, a well-designed competency-based aseptic training program addresses business issues, such as reducing work stoppages, compromised product sterility, and risk exposure from global agency observations.

In addition, a skills development program can improve performance, productivity, and quality for competitive advantage, and also raise workforce morale and motivate the pursuit of excellence.

Here are the seven steps of a skills development framework:

1. Assess each role within the area, and walk through the processes that each role interacts with.
2. Define the skill levels and competency levels for each job function.
3. Align similar roles, similar competencies, roles to competencies, and other relevant company scales.
4. Develop role-based training programs, curricula, and technical competency models.
5. Implement and deliver both training programs and technical competency programs.
6. Track and report qualifications to these programs, identify skill and competency gaps, and drive training that closes these gaps.
7. Monitor skill and competency development, evaluate if progress is on track, and adjust accordingly for each employee, team, unit, department, and physical location.

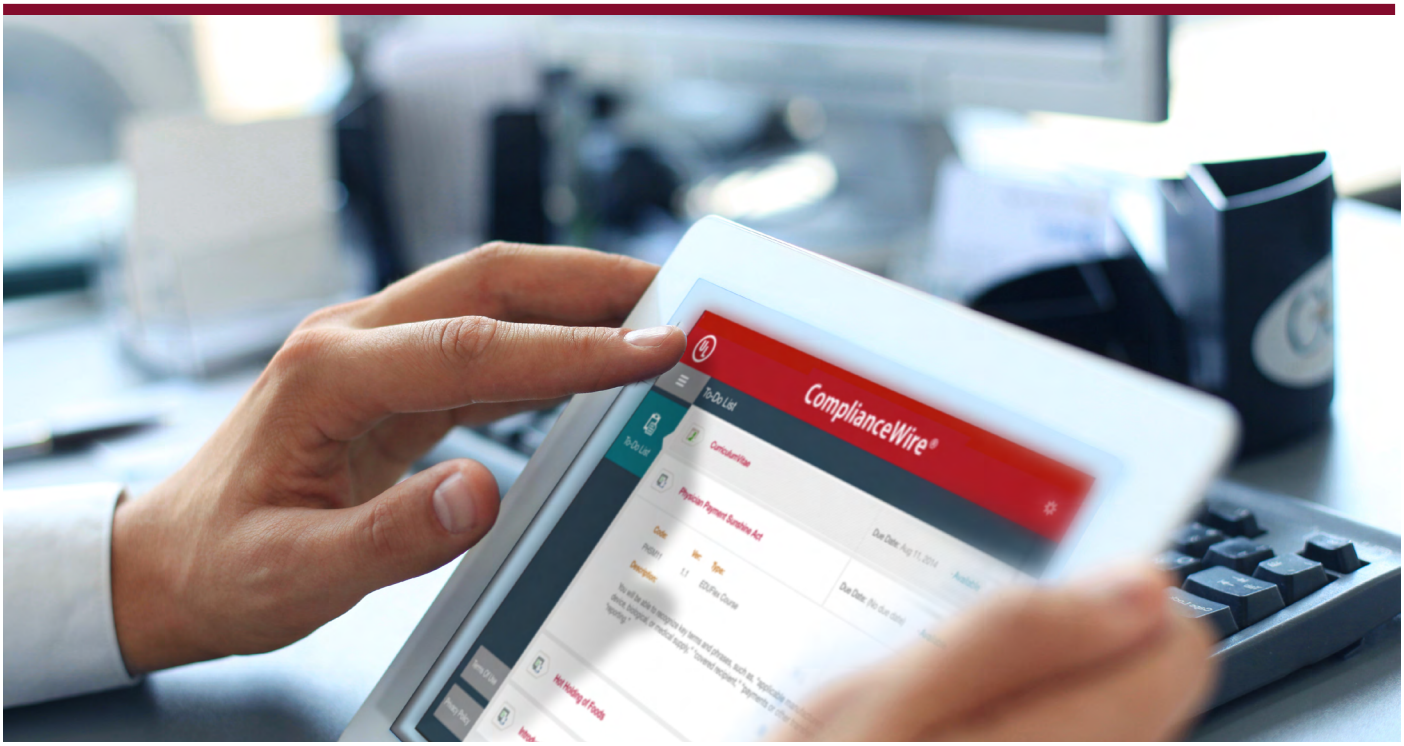
UL Aseptic Processing Competency Solution

UL's Aseptic Processing Competency solution includes hands-on GMP consulting expert Ann Early to work alongside your QA, Training, HR and Operations team to build a program that's based on proven best practices.

These steps map relevant, competency-based actions that need to be conducted for each job function. Companies can achieve compliance while improving business performance, and also drive these improvements:

- Greater employee knowledge related to the basics of microbiology, aseptic gowning, and aseptic behavior
- Increased employee engagement through well-defined roles and job functions
- Understanding of measurement best practices, such as incidence rate of personnel monitoring and production line environmental monitoring failures, deviation reports, and lot rejection rates
- Improved gowning and aseptic behavior

To learn more about our Aseptic Processing Competency solution, contact Pat Thunell at pat.thunell@ul.com.



About UL Compliance to Performance

UL Compliance to Performance provides knowledge and expertise that empowers Life Sciences organizations globally to accelerate growth and move from compliance to performance. Our solutions help companies enter new markets, manage compliance, optimize quality and elevate performance by supporting processes at every stage of a company's evolution. UL provides a powerful combination of advisory solutions with a strong modular SaaS backbone that features ComplianceWire®, our award-winning learning and performance platform.

UL is a premier global independent safety science company that has championed progress for 120 years. It's more than 12,000 professionals are guided by the UL mission to promote safe working and living environments for all people.