21 CFR PART 11 COMPLIANCE

How machine vision technology helps control quality while speeding up delivery

COGNEX

21 CFR PART 11 COMPLIANCE

Deploy compliant vision-based systems

Pharmaceutical and medical device companies are modernizing their manufacturing practices by introducing more sophisticated and automated systems like machine vision technologies, including deep learning, barcode reading, and barcode verification. These systems perform quality control and ensure full track-and-trace capabilities and need to comply with regulations like 21 CFR Part 11.

Additionally, COVID-19 has accelerated the need for automation in pharma, life science, and medical device manufacturing. Manufacturing COVID-19 test kits and vaccines require full automation at scale while maintaining safety and compliance to serve the needs of human population.

Vision systems are essential for full automation. The issue of how to ensure vision system compliance with the requirements of 21 CFR Part 11 is a topic that has only been made more significant by the demands now being put on them.

In this whitepaper, we attempt to provide some considerations on thinking through the deployment of vision-based automation in pharma and medical device manufacturing while staying 21 CFR Part 11 compliant.

21 CFR PART 11 IN BRIEF

CFR stands for the Code of Federal Regulations and 21 CFR Part 11 deals primarily with the movement of paper-based records to electronic records. The FDA has provided guidance on how to manage this documentation movement for biotechnology, drug, and medical device businesses with a set of procedures and requirements that could guarantee that their choices would be secure and compliant, without imposing excessing costs. The specific section that applies to machine vision systems is Part 11, Subpart B titled 'controls for closed systems.'

21 CFR Part 11 deals primarily with the movement of paper-based records to electronic records.

It provides guidance in six main areas:

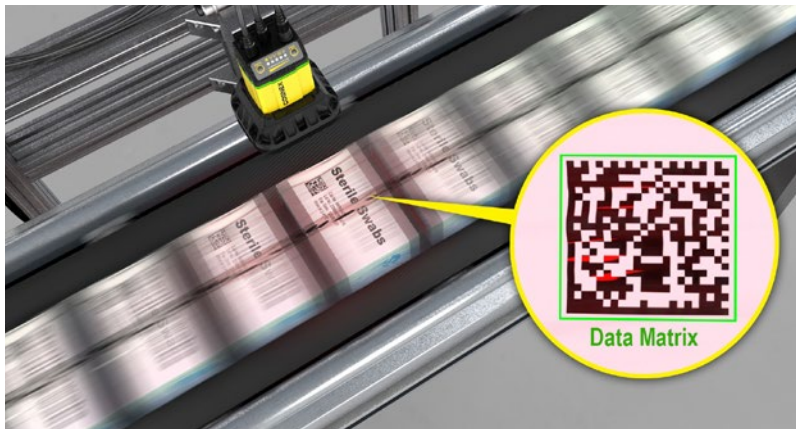
#	Rule	Description
11.10(a)	Validation	Validation of systems to ensure accuracy, reliability, consistency
11.10(b)(c)	Record copies and protection	Generate accurate copies of records suitable for inspection
11.10(d)	System access	Limit system access to authorized individuals only
11.10(e)	Audit trails	Time-stamped records of operator entries and changes for electronic records
11.10(f)	Operational checks	Enforcement of permitted sequencing of steps and events
11.10(g)	Authority checks	Ensure only authorized individuals can use the system and access the operation of the system

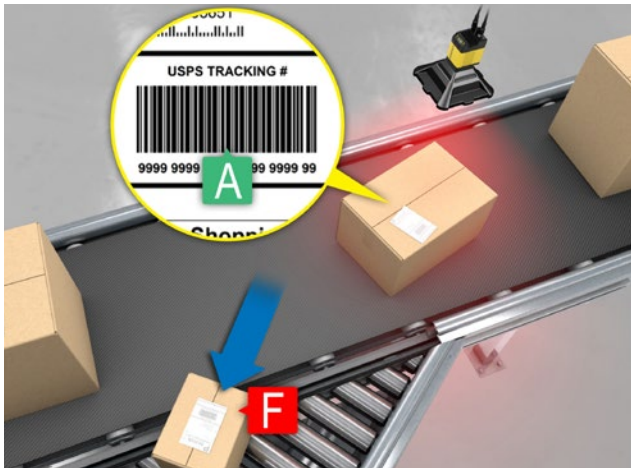
The EU's Annex 11 parallels Part 11, but while Part 11 is a requirement in the US, in the EU Annex 11 is intended as a guide. They have been harmonized, and systems that meet the requirements of one generally meet the requirements of the other.

HOW COVID-19 HAS ACCELERATED DEMAND FOR THE PHARMA INDUSTRY, AND HOW AUTOMATION HELPS

COVID-19 has revealed the lack of resiliency in lean, long supply chains that keep minimal inventory. In the future, more diversified supply chains with inherent redundancy mechanisms will increase resiliency and will be needed.

Flexible automation enabled by vision systems makes deploying and managing diversified supply chains easier by providing end-to-end visibility across supply and production.





Serialization and automated visual inspection of every product along the line provide the information and analytics necessary to operate multiple supply chains in a way that would have previously been very time consuming and labor-intensive.

Serialization and track-and-trace will provide visibility at every point along the supply chain and allow for a more rapid response to supply problems. All of this will also be important in the vast increase of capacity, both in production and in packaging and distribution, required for COVID vaccines.

VISION SYSTEMS AND 21 CFR PART 11 COMPLIANCE

Pharma manufacturers want to install vision systems on their lines to help with automation, but also want to stay compliant. Fortunately, automation and compliance work well together. There are a few considerations to keep in mind to meet both objectives.

At a minimum a vision system should, in addition to performing all of its required functions, be able to do the following to be 21 CFR Part 11 compliant:

- Limit system access to authorized individuals
- On request, efficiently locate the appropriate records and provide copies suitable for review
- Use audit trails that record the date and time of every operator action and entry that creates, changes, or deletes an electronic record
- Confirm the identity of any individual who electronically signs a record
- Ensure that no change obscures data previously recorded

A smart vision system that does not require a PC for these functions is significantly easier to maintain. Building 21 CFR Part 11 compliance in from the start guarantees that serialization, track-and-trace, defect detection and other processes can be fully automated while maintaining compliance.

It's worth looking at a few particular aspects of compliance in a bit more detail, with a specific focus on vision systems.

Audit trails

In a compliant vision system, every time someone changes something, such as the job or a parameter, a record is created. That creation, and every modification or deletion of a record, has to be logged automatically to an audit history which cannot itself be subject to modification. Such an audit trail provides proof of compliance and operational integrity, an example of how regulation and good practice go hand in hand. Automatically linking the audit trail application to a SQL database makes it much easier to maintain these records and retrieve them as needed.

Login credentials

A compliant vision system must have a secure authentication mechanism to prevent unauthorized access. The best solution is a link to the manufacturer's active directory account to verify users and issue the proper certificates. Any user or login changes must be logged and appear in the audit trail. Different users, such as those allowed to make changes to the application or inspection task, and those who can view the operator panel, should have different default views into the vision system.

Validation

A vision system needs to demonstrate that the results it generates are in fact those that it should, by validating against test samples with known results. This ensures that the system operates according to the intended specifications and that it is qualified per 21 CFR Part 11. This is called Performance Qualification (PQ).

The regulation also calls for Installation Qualification (IQ) and Operational Qualification (OQ), both typically the responsibility of the manufacturer, to complete the validation process. A manufacturer may choose to bring in third party integrator to help with the documentation around IQ and OQ while the vision system provider provides the features necessary in the SW to complete PQ.

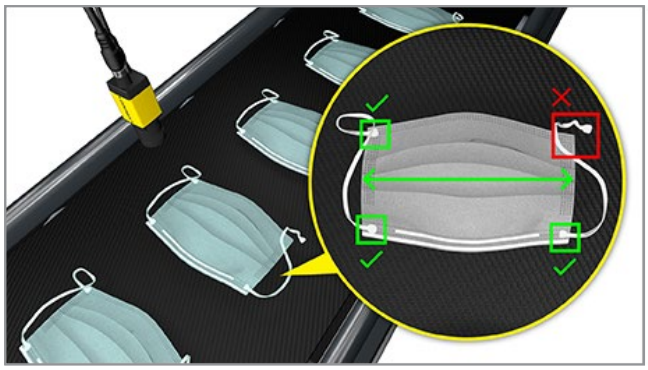
HOW MACHINE VISION TECHNOLOGY HELPS CONTROL QUALITY WHILE SPEEDING UP DELIVERY

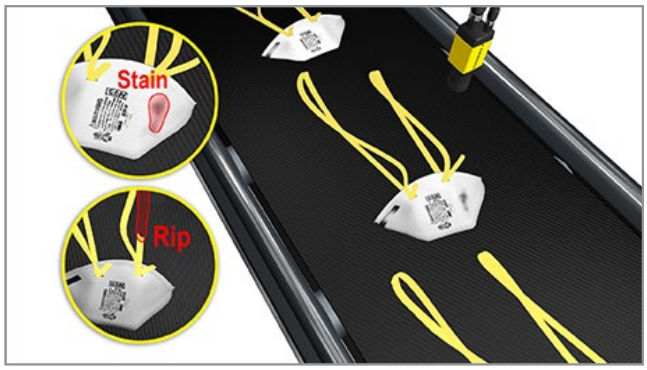
Vision systems have become an integral part of pharmaceutical and medical device supply chains. Automation of production and inspection, which speeds delivery while ensuring high quality, depends entirely on effective machine vision.

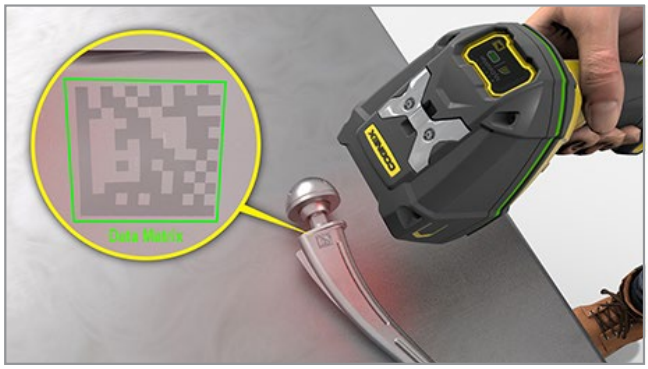
Machine vision performs a wide range of critical inspection processes in pharma manufacturing, detecting damage to products or containers, counting pills and vials, confirming fill levels and proper sealing, and detecting physical contaminants.

For devices, machine vision is widely applicable in a wide range of manufacturing operations, including confirming the presence and correct location of parts, detecting physical defects in components and wiring, and reading printed characters on circuit boards.

Vision systems are also essential for the track-and-trace that is the foundation of supply chain integrity.







HOW VISUAL INSPECTION HELPS WITH TRACK-AND-TRACE

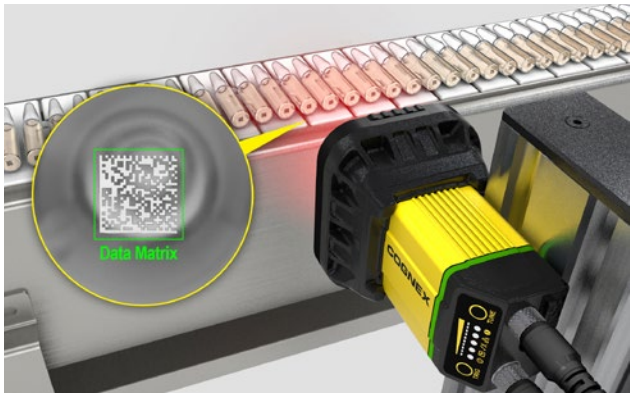
Pharmaceutical companies face increasing drug counterfeiting, unauthorized adulterations, and thefts and loss along their global supply chains. Verifying the location and identity of each drug has become a business imperative. The World Health Organization estimates that up to 10 percent of the global pharma drug supply is counterfeit.

The US Drug Supply Chain Security Act (DSCSA), passed in 2013 to protect the supply chain from counterfeit drugs, also makes it a compliance priority. It mandates a range of serialization, verification, and data exchange and storage guidelines for the industry. It requires the use of an electronic system to track drugs distributed within the US down to the unit level, a process called track-and-trace.

More specifically, track means you can know the current and past locations of a unit of a drug, while trace means you can know who came into contact with that unit anywhere along the supply chain. The ability to define and identify a specific unit is serialization, making sure that each unit is assigned a code, and that every code is unique.

Vision systems are key to track-and-trace. They check whether each unit has been properly assigned a code and detect and record that code at every step of the supply chain.

Barcode reading



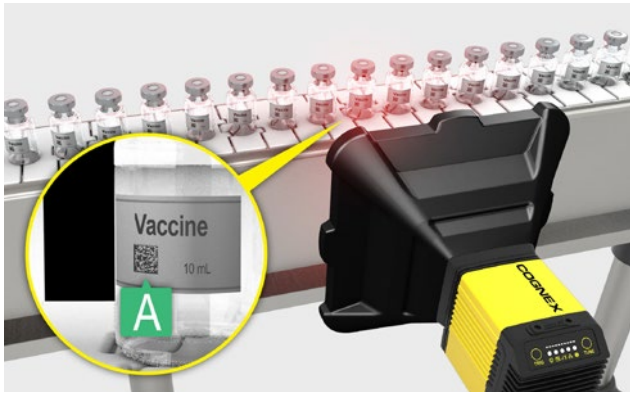
Serialization makes track-and-trace possible by requiring that every individual unit of a drug, in primary packaging, be identified with a unique serial and lot number and a matching GS-1 compliant barcode. Any secondary packaging has a corresponding serialized barcode that matches the codes on the primary packaging. Medical devices must also have a unique device identification (UDI) code.

These codes are used to authenticate and track each individual unit from production to final use. A dedicated image-based barcode reader is the best choice for reading and tracking product code, batch identification, expiration date, and serial number information. The unit is scanned by a reader at every step, maintaining a complete record of location and custody.

OCR/OCV

Reading and confirmation of printed labels and all of the required and optional information on pharmaceutical packaging are done by optical character recognition (OCR). The quality of mandatory or brand-related logos and other graphics is similarly done with optical character verification (OCV). Both of these can be accomplished at high speeds, minimizing the risk of error and recalls while maintaining the pace of production.

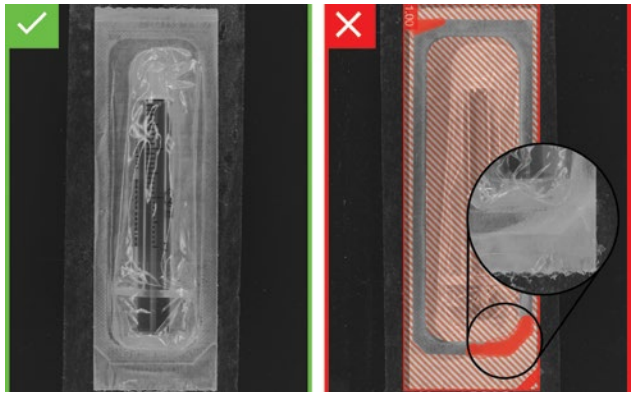
Barcode verification



Given the significance of barcodes in serialization and track-and-trace, their quality must be monitored to ensure readability across the entire supply chain, under a wide range of viewing conditions, with a variety of barcode readers. To guarantee readability, barcodes must be tested and graded. This is a process separate from scanning and reading.

Barcode grades are industry standards and are not up to the individual manufacturer. Codes are evaluated on seven basic attributes, with the final overall grade determined by the lowest score among these attributes. A barcode verifier can ensure that any degradation in barcode quality is detected long before it begins to affect track-and-trace effectiveness.

Deep Learning



Conventional machine vision is extremely capable when dealing with consistent features, such as precision alignment, gauging, and 1D and 2D barcode reading. Deep Learning can solve previously intractable inspection and identification problems that involve visual distortions, reflections, ambiguity, and defect unpredictability.

For example, deep learning trains on a set of image of glass vials or syringes and identify defects, particulate matter in the contents, and a variety of assembly defects without being confused by reflections, different alignments, or acceptable variations. It can OCR distorted characters, angled characters, direct part marked characters, and other text that is hard for conventional machine vision to recognize.

21 CFR Part 11 on the line

Senior quality managers at Life Sciences manufacturers are acutely aware that many of their production line operations are non-compliant with CFR-21 Part 11/Annex 11 regulations. However, remedial action to bring all lines and devices into a compliant state would be lengthy, require a costly and technically difficult rip and replacement of existing infrastructure, and negatively impact productivity.

Problem: non-compliant devices on the line

A review of vision systems and barcode readers on lines in a packaging hall at a major pharmaceutical manufacturer revealed many inconsistencies with 21 CFR Part 11 requirements.

The site's automation engineering management assessed the cost and downtime to upgrade or replace the vision systems and barcode readers. The estimated costs ran to hundreds of thousands of dollars.

A further problem lay in barcode verification. Barcodes are the foundation of supply chain management, track-and-trace, and asset management. Ideally, all barcodes should have their readability verified to International Organization for Standardization (ISO) grading standards when printed to ensure they can be read at machine speeds throughout the entire supply chain. This could only be accomplished by pulling samples offline and using a manual barcode verifier, delaying production while accepting that some low-quality codes may be missed.

Solution: wrapping all devices in compliance

This entire pharmaceutical packaging hall was brought into compliance by the installation of the CXV Global LineDirector product on all lines. LineDirector now provides full control of all production line peripherals from a central access point. Batch set-up steps, including recipes and batch variable data, are now managed from a central LineDirector interface and burst out to all devices, including Cognex's inline barcode verifier. Image feeds from all camera devices down the line are monitored on a single screen, with the ability to drill into a specific camera or call up individual image results as needed.

Cognex's recently introduced inline barcode verifier eliminated the need for offline sampling. The Cognex DataMan 475V series provides barcode verification to ISO standards

for 100 percent of barcodes with no impact on line speeds, improving both quality and throughput.

Both installation and validation on all lines were completed by CXV Global's professional services engineering team within a planned shut-down period, with zero impact on line production. The availability of full IQ/OQ/PQ documentation sets from CXV Global and a vendor validation team to execute the protocols was highly valued by the site Validation management.

The new installation guarantees compliance with all user authentication and audit trail requirements of 21 CFR Part 11/Annex 11.

Results: compliance and operational efficiency

In a regulated industry like Life Sciences, compliance and operations cannot be separated. Through LineDirector, the site's quality management is now assured that lines run by operations are 21 CFR Part 11 compliant and that they will be able to easily demonstrate this in case of an audit. Technicians and operators now monitor and manage devices and batch set-ups from a central point, making production both more reliable and more compliant. Robust inline barcode verification ensures tracking throughout the supply chain.

COGNEX VISION SYSTEMS AND GLOBAL PARTNERS

Cognex vision systems are uniquely suited to handle the track-and-trace requirements among global pharma supply chains and can do so while staying compliant with 21 CFR Part 11

Additionally, Cognex works with its global partners, such as CXV Global, to help manufacturers implement end-to-end compliant vision systems.

BUILD YOUR VISION

IMAGE-BASED BARCODE READERS

Cognex industrial barcode readers and mobile terminals with patented algorithms provide the highest read rates for 1-D, 2-D, and DPM codes regardless of the barcode symbology, size, quality, printing method, or surface.

- Reduce costs
- Increase throughput
- Control traceability

www.cognex.com/BarcodeReaders

2D VISION SYSTEMS

Cognex machine vision systems are unmatched in their ability to inspect, identify, and guide parts. They are easy to deploy and provide reliable, repeatable performance for the most challenging applications.

- Industrial grade with a library of advanced vision tools
- High speed image acquisition and processing
- Exceptional application and integration flexibility

www.cognex.com/machine-vision

3D LASER PROFILERS

Cognex In-Sight laser profilers and 3D vision systems provide ultimate ease of use, power, and flexibility to achieve reliable and accurate measurement results for the most challenging 3D applications.

- Factory calibrated sensors deliver fast scan rates
- Industry-leading vision software with powerful 2D and 3D tool sets
- Compact, IP65-rated design withstands harsh factory environments

www.cognex.com/3D-laser-profilers

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Companies around the world rely on Cognex vision and barcode reading solutions to optimize quality, drive down costs and control traceability.

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