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A practical guide to improving pharmaceutical and biotech manufacturing processes and production methods

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Table of contents

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Overview

Improving quality and productivity

From raw material identification through the pharmaceutical manufacturing process, to finished and packaged pharmaceutical product inspection, the next pages of this guide will discuss industry concerns and present an overview of solutions that help pharmaceutical and biotech manufacturers:

- save time
- improve processes
- protect brand integrity
- ensure patient safety

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Protect your brand

- Pharmaceutical formulations are complex, multicomponent mixtures. There is a need to identify and verify components, and also to evaluate the distribution of these components.
- The distribution of components within a product can affect the stability and functionality of the final product.
- With the wide variety of active pharmaceutical ingredients (API) that can be combined with numerous excipients, it is important to be able to analyze and provide accurate data on a variety of formulations.
- Ensuring that patients are not using falsified medicines keeps the consumer safe, and also protects pharmaceutical companies' brand.
- Identifying incomplete packages, checking weight requirements, and detecting metallic and non-metallic contamination before pharmaceuticals reach the consumer is important to brand integrity.
- Controlling manufacturing by testing and measuring during the processing of critical quality and performance attributes of raw and in-process materials helps ensure final product quality.

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Compliance

Regional compliance regulations

Pharmaceutical manufacturers are required to follow regional compliance regulations to verify the quality of their materials throughout the manufacturing process.

Federal Food, Drug and Cosmetic Act (FD&C Act) – requires conformity with Current Good Manufacturing Practice (cGMP)

- 21 CFR (Code of Federal Regulation) 210 & 211 – regulations which implement FD&C Act
  - Minimum requirements for the methods, facilities, and controls used in manufacturing, processing, and packing of a drug product. These regulations make sure that a product is safe for use, and that it has the ingredients and strength it claims to have.

Pharmaceutical Inspection Co-operation Scheme (PIC/S), Annex 8

- PIC/S is a non-binding, informal co-operative arrangement between Regulatory Authorities in the field of Good Manufacturing Practice (GMP) of medicinal products for humans or veterinary use. It is open to any Authority having a comparable GMP inspection system. PIC/S seeks to harmonize inspection procedures worldwide by developing common standards for GMP and providing training to inspectors.
- Requires that individual samples be taken from **all incoming containers** and an identity test be performed on each sample.
- This is a change from the traditional practice of allowing composite sampling of a statistical subset of the batch and identity testing of the single composited sample, in order to release the batch to manufacturing.

Regional compliance regulations

Pharmaceutical manufacturers look to improve efficiency and reduce costs while maintaining quality and regulatory compliance.

The Food and Drug Administration's (FDA) FD&C Act **requires conformity with cGMP** for manufacture of drugs and **makes no distinctions between API, excipients, and finished pharmaceuticals.**

Mandates:

- Testing of in-process materials for identity, strength, quality, and purity.
- Developing a well controlled, validated, and vigorous pharmaceutical manufacturing process, able to **reliably deliver** intended quality of product.

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Electronic signature and traceability

21 CFR Part 11 – electronic records, electronic signatures:

Electronic signature and traceability

- Protect the stored electronic data related to quality assurance within manufacturer's computer systems.
- Put controls in place to keep records authentic, incorruptible, and confidential.
- Electronic signatures signify that the user is taking responsibility for the electronic data in the system.
- Required in the data record: date and time of scan, name of the unique signer, and technological controls to ensure security (e.g. passwords).

NOTE: Many Process Mass Spectrometers and handheld Raman and NIR analyzers are 21 CFR Part 11 compliant with electronic signatures, complex password options, date and time stamps, and full audit trail features.

Inspection of packaged products

Adherence to Good Manufacturing Practices (GMPs) throughout the pharmaceutical production process is a must for manufacturers.

In response to increasing numbers of packaging defects, PIC/S issued PI 028-1 guidelines to enable a uniform interpretation of related GMPs.

Checking package weight with a high performance, qualified, and well maintained instrument is identified as part of a complete quality control system.

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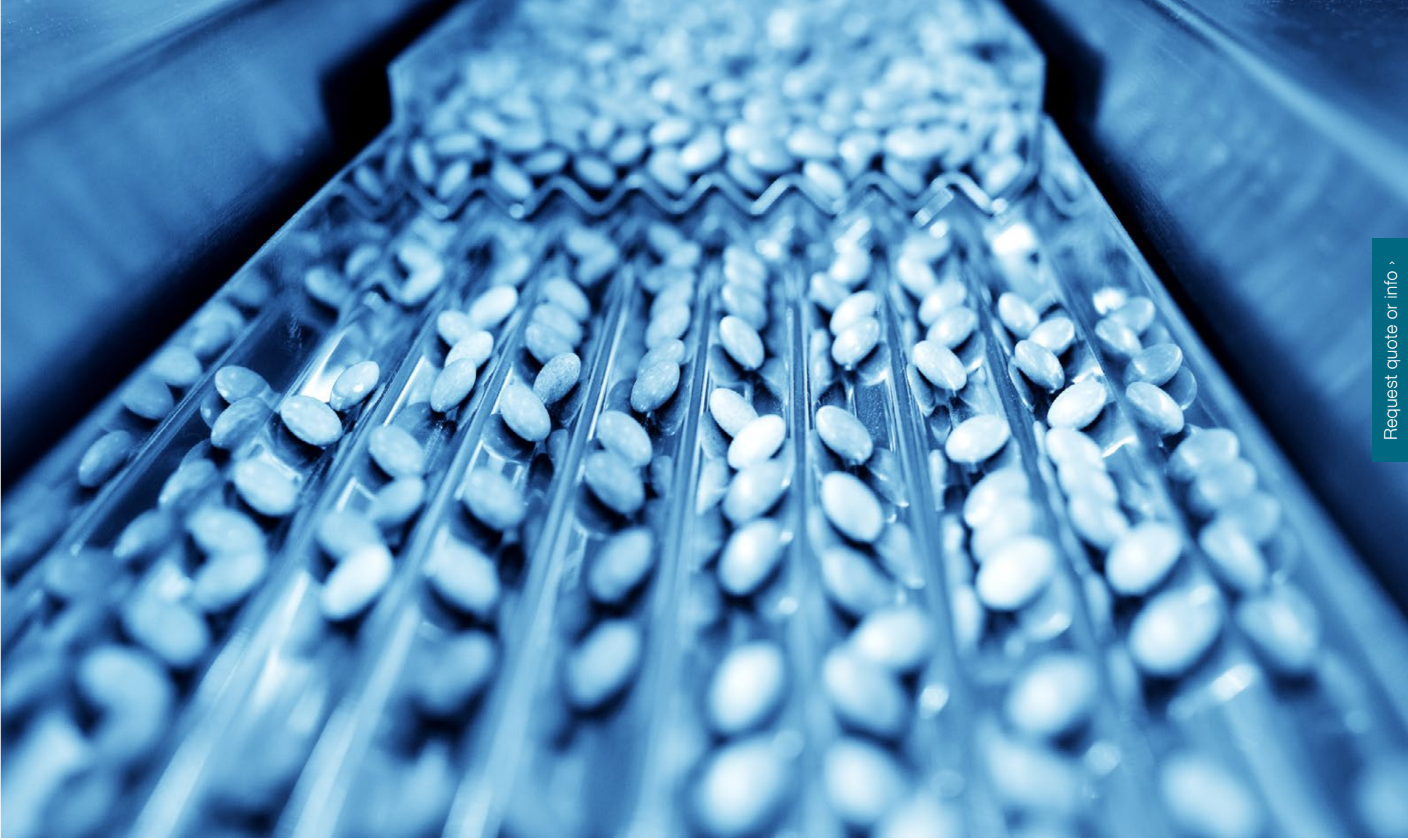

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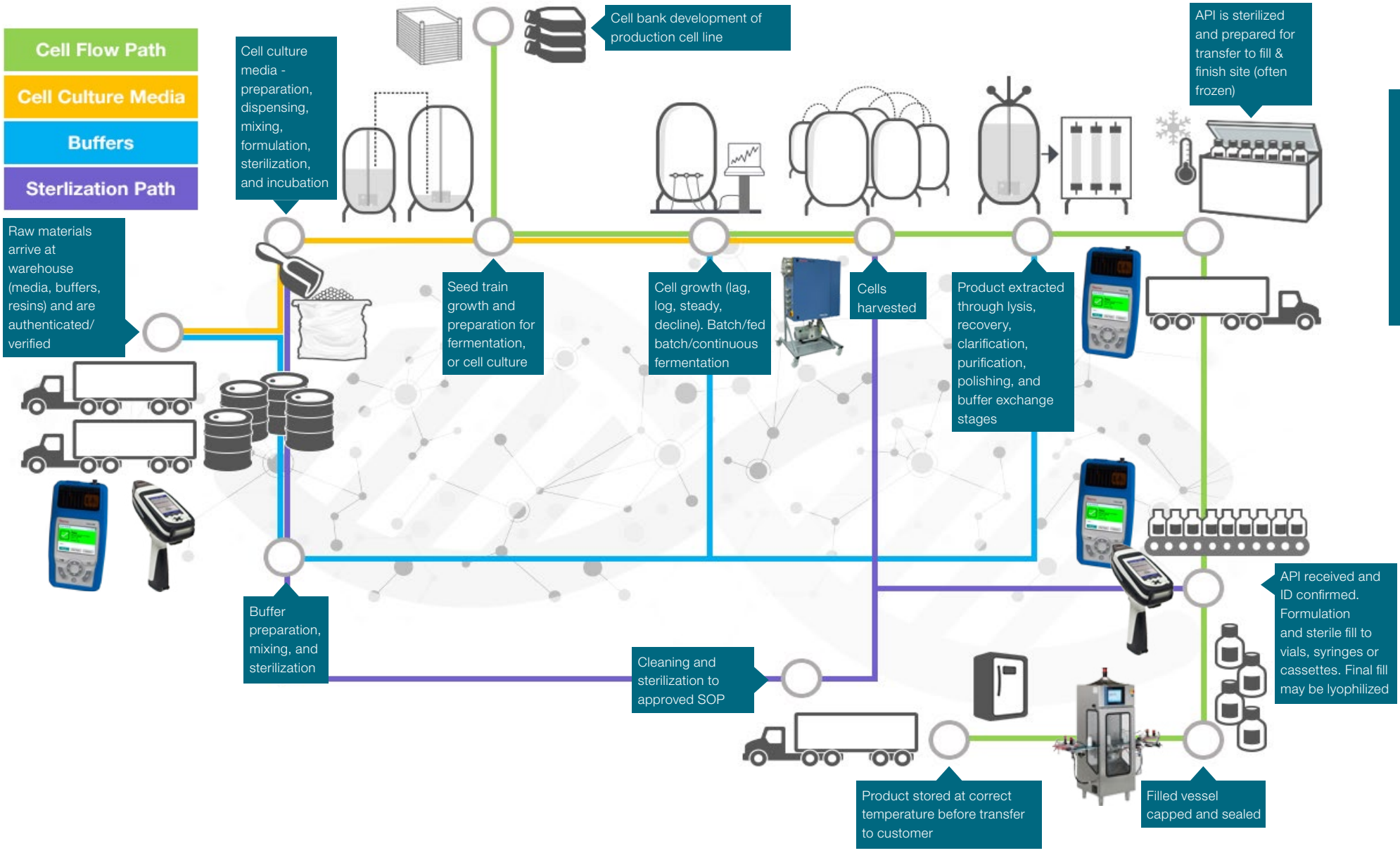
Process

Biologics process overview



Applications and technologies

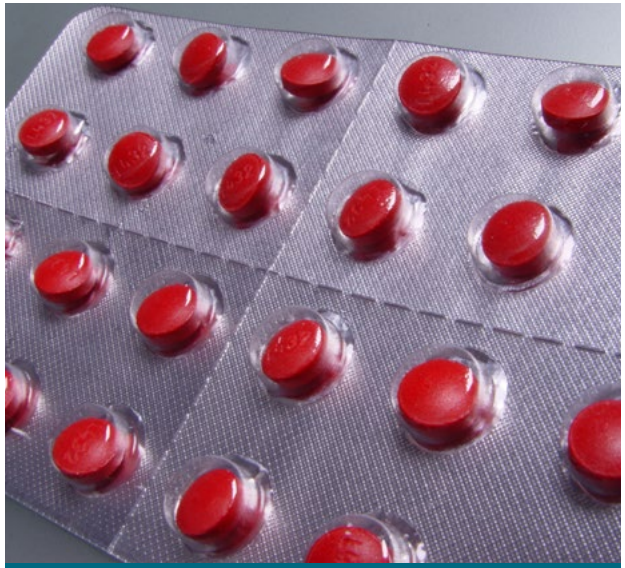
Improve pharmaceutical and biopharmaceutical manufacturing processes and production methods

Material ID

- Handheld Raman
- Handheld NIR

In process control & measurement

- Handheld Raman
- Handheld NIR
- Process mass spectrometer



Online product inspection

- Checkweighing
- X-Ray inspection
- Metal detection

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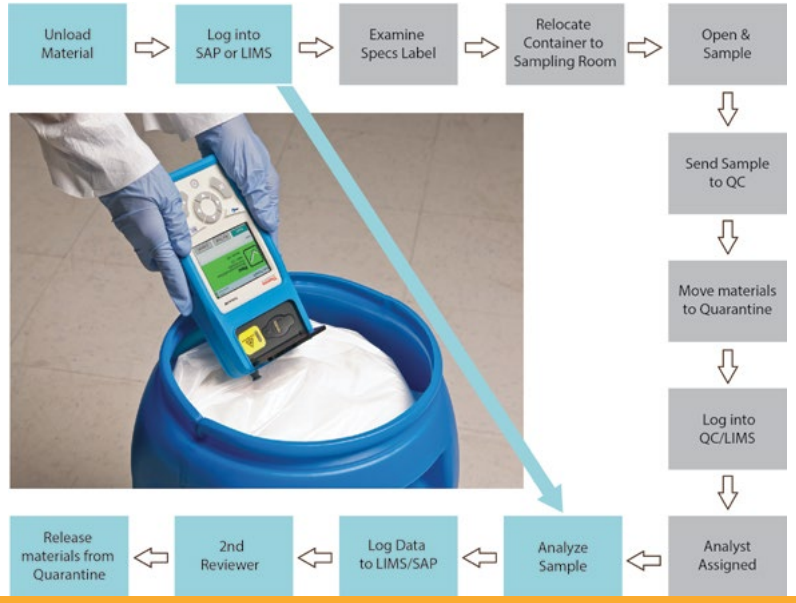
Material ID

Analyze, identify, and quantify raw materials

Traditional – send to lab



Handheld – at line

Raw material testing and identity verification are critical steps in the quality control process to ensure customer safety. **Portable pharmaceutical analyzers** can be used on the warehouse floor and at any inspection point throughout the QA/QC process to increase inspection intervals, improve inventory management, and reduce global supply chain risk.

Using handheld analyzers to move raw material authentication from the laboratory to the warehouse means fewer costly lab sample tests, faster release of raw materials, improved inventory management, and no risk of cross contamination by measuring through original packaging.

In process control & measurement

Process improvement

As part of **cGMP** many pharmaceutical manufacturers are adopting Process Analytical Technologies (**PAT**), Quality by Design (**QbD**), or Process Validation (**PV**).

cGMP and associated process monitoring necessitates continuous process verification and analysis. **Analytical instruments such as near-infrared and Raman spectroscopy and chemometric modeling software may be used to measure quality throughout the process.**

Online mass spectrometers deliver faster, more complete, lab quality online gas composition analysis, as well as help maximize product yield and increase profits.

In process control & measurement

Point of use solutions

Handheld Raman and NIR analyzers use lab-proven spectroscopy to perform:

- Accurate and reliable material identification.
- At-line process and quality checks.
- Quantitative and qualitative analysis.
- Intermediate and final product inspection.

For use anywhere in the manufacturing plant, Raman and NIR handheld analyzers utilize non-contact, non-destructive point-and-shoot sampling for rapid analysis of a broad range of compounds.

Thermo Scientific™ TruScan™ RM Analyzer with TruTools chemometric software and Thermo Scientific™ microPHAZIR™ RX analyzer allow users to bring rugged analytical instrumentation to the pharmaceutical/biopharmaceutical manufacturing floor for quick release of in-process materials.

For more information, download our microPHAZIR RX analyzer application note: **Determination of moisture in a protein sample using a portable NIR instrument** or our TruScan RM analyzer application note: **Biologic Drug Identification at Fill and Finish**

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Real-time monitoring of fermentation and cell cultures

Process mass spectrometers for continuous analysis of respiratory gases

- Characterise fermentation and cell culture processes
- Non invasive technique available for multiple sample points (up to 60)
- Track growth kinetics and substrate consumption
- Determine the end point for maximum product yield
- Precise measurement of Oxygen Uptake rate (OUR), CO2 Evolution rate (CER) and Respiratory Quotient (RQ)

The speed of MS makes it ideal for fermentation and cell culture applications but speed must not be at the expense of precision. It is equally important that precise data is acquired; otherwise, small changes in concentration will be lost.

Over 30 years of industrial experience have shown that magnetic sector analyzers offer the best performance for fermentation off-gas analysis. Key advantages include improved precision, accuracy, long intervals between calibration, and resistance to contamination.


Thermo Scientific™ Prima BT and Prima PRO Process Mass Spectrometers

Gas analysis mass spectrometer applications in fermentation and cell culture process

Click here to download our application note:
Gas analysis mass spectrometer applications in fermentation and cell culture process

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Generating reliable quantitative solvent drying process data in the pharmaceutical industry

Industrial process mass spectrometer for monitoring of multiple solvents from up to 10 dryers

- Monitor and improve drying stages
- Improve consistency and quality of the final product
- Reduce drying times, increase throughput and maximise profitability
- Avoid over-drying

A key production stage that has received a great deal of attention is the drying process, the complete or partial removal of a solvent or solvents from an Active Pharmaceutical Ingredient (API) or intermediate. Gas analysis mass spectrometry has been used extensively on a wide range of dryers, including filter dryers, vacuum dryers, tray dryers, rotary dryers and spray dryers.


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APPLICATION NOTE

Prima PRO Process Mass Spectrometer

Generating reliable quantitative solvent drying process data in the pharmaceutical industry

Click here to download the application note:
Generating reliable quantitative solvent drying process data in the pharmaceutical industry

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Online product inspection

Pharmaceutical applications demand the highest standards of performance, hygiene and reliability. Dynamic checkweighers can detect incomplete packages at high speed. Metal detection and x-ray inspection systems can identify contaminants in oral solid production and liquid vial filling.

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For more information about our checkweighers, click on our data sheets: **Versa Rx Pharma Checkweigher**, **Global VersaWeigh Pharma Checkweigher**, and **Global Versa GP Pharma Checkweigher**

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Technology

Analytical techniques

Spectroscopy = study of the interaction between matter and electromagnetic radiation

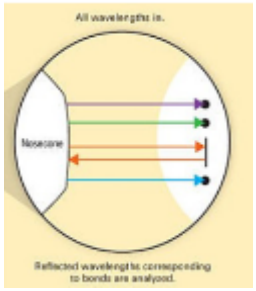
Vibrational spectroscopy = characterizes materials by the frequencies of their molecular vibrations

Learn about Raman spectroscopy

Raman spectroscopy

A spectroscopic technique that relies on light, usually from a laser, to observe vibrational, rotational, and other low-frequency modes in a system. **Raman spectroscopy** is commonly used in chemistry to provide a fingerprint by which molecules can be identified.*

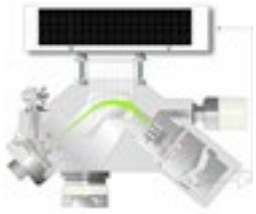
Named after Sir C. V. **Raman, an Indian physicist who carried out ground-breaking work in the field of light scattering (https://en.wikipedia.org/wiki/Raman_spectroscopy)*



Learn about NIR spectroscopy

Near-Infrared (NIR) spectroscopy

A spectroscopic method that uses the near-infrared region of the electromagnetic spectrum, and is based on overtones and combinations of bond vibrations in molecules.



Magnetic sector mass spectrometry

Neutral gas molecules are ionised and the resulting ions separated according to mass/charge in a scanning magnetic field. This method yields highly precise quantitative measurements of sample gas composition calibrated against known standards.

NIR and Raman: Complementary technologies

Gases, ionic salts, and some biologics excluded

TruScan RM's P-Value algorithm

	Patented P-value	HQI
phenol	0.45	0.9981
benzaldehyde	0.000000000000000000000000000015	0.9902
benzoic acid	0.00000000000000000000000000000011	0.9827
benzyl alcohol	0.000000000000000000000000000000012	0.9714
toluene	0.0000000000000000000000000000000000000054	0.9890

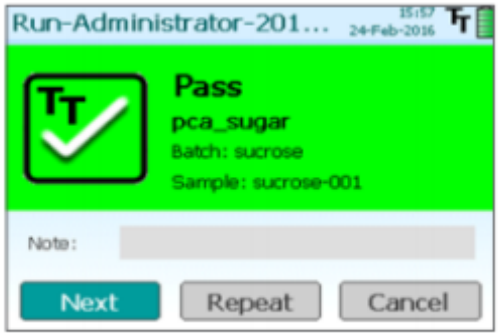
- **HQI** and other correlative techniques only measure the similarity between test materials.
  - Relatively insensitive to minor differences and make the validation of structural analogs challenging
- **P-value algorithm**
  - Doesn't simply measure the similarity between library spectra & test material - looks at the **differences** which strengthens ability to discriminate between 2 materials
  - Allows strong **discrimination of structural analogs**
  - Typically 1 single match result can be achieved
  - Doesn't require advanced validation as the threshold is fixed
- Multivariate analysis takes into account factors influencing the measurement know as **uncertainty characteristic** of a measurement:
  - Measurement settings – e.g. exposure time and number of scans or sweeps
  - Environmental properties – e.g. temperature, dark current
  - Properties of the sample itself – e.g. Raman cross section, absorbance, refractive index

TruScan RM analyzer with TruTools chemometric software

TruTools embedded chemometrics package is an on-board software that runs on the TruScan RM analyzer and allows manual control of acquisition parameters and development of models such as PCA, PLS, PCR, and PLSDA.

TruScan RM analyzer with TruTools chemometric software methods can:

- Support quantification of up to 10 chemicals
- Discriminate between materials with similar chemical compounds such as magnesium stearate, zinc stearate, and calcium stearate, or ethanol vs. methylated spirits
- Replace slower lab testing and run qualitative and quantitative methods at line
- Expand TruScan RM analyzer's raw materials verification capabilities – allows for finer discrimination of materials



A PCA TruTools method screen result

A PLS TruTools method screen result.

Meets cGMP and 21 CFR Part 11 requirements


Handheld Raman spectroscopy for qualitative and quantitative analysis

Click here to download the specification sheet:
Handheld Raman Spectroscopy for Qualitative and Quantitative Analysis

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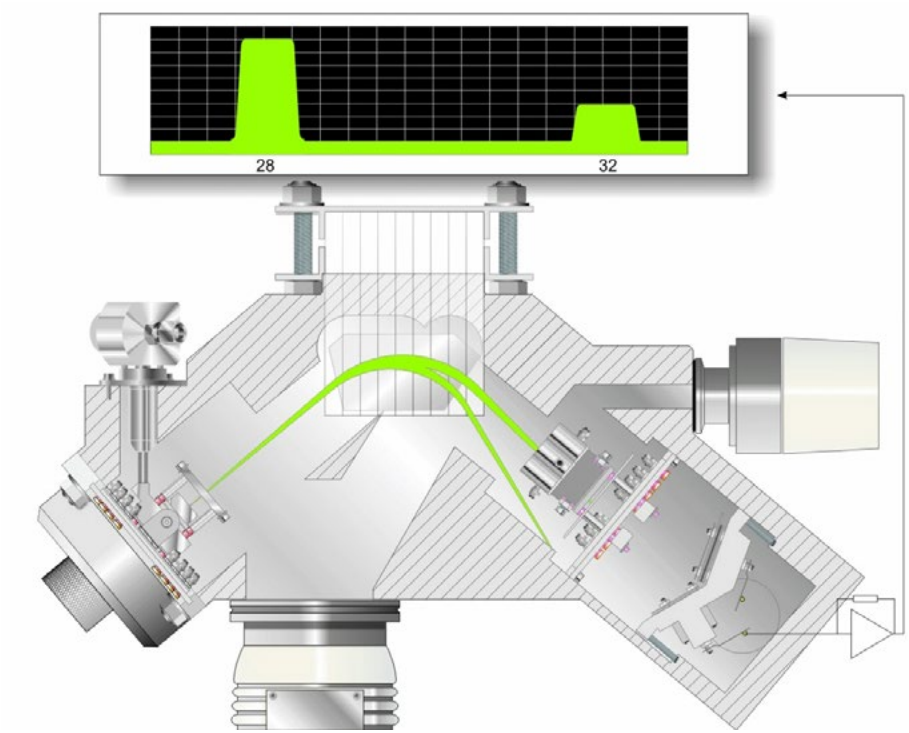
How mass spectrometers work



- Sample gas (here, N2 and O2) enters ion source and is converted to positive ions by collision with high energy electrons from filament.
  - *N_2 ionized to N_2^+, 28 AMU, O_2 ionized to O_2^+, 32 AMU.*
- Ions are accelerated into variable magnetic field and move in circular path.
- Radius depends on ion's mass, charge & energy and magnet field strength.
- Vary magnet field strength - bring ions sequentially onto a single detector.
- Peak height is directly proportional to concentration.
- Magnetic sector analyzer produces characteristic flat top peak – don't need to measure dead centre of peak.

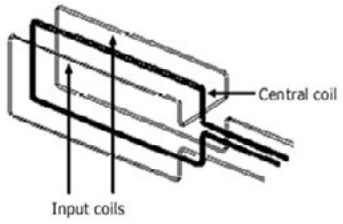
How metal detectors work

Metal detectors find small particles of ferrous, non-ferrous and stainless steel using coils wound on a non-metallic frame and connected to a high-frequency radio transmitter.

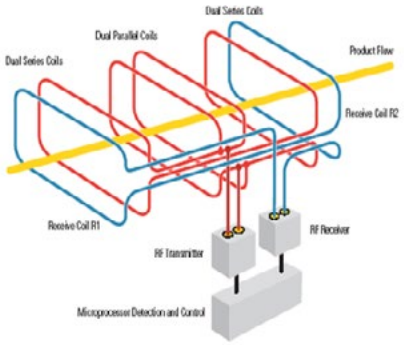
When a particle of metal passes through the coils, the high frequency field is disturbed under one coil, changing the voltage by a few microvolts.

The output is used to detect metal.

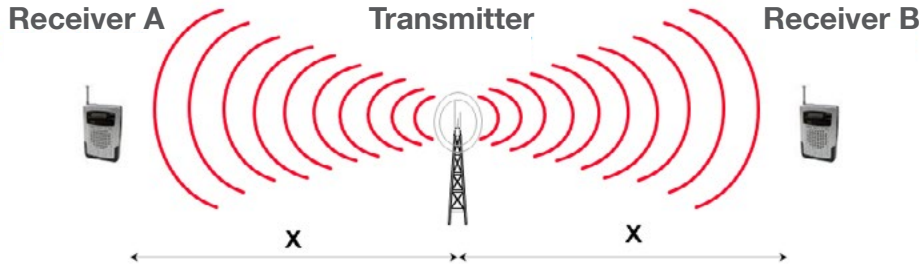
Metal detector coil systems



Traditional coil



Thermo Scientific™ APEX Metal Detector Multicoil



Multiscan technology

With multiscan technology, the critical control point (CCP) scans up to five completely adjustable frequencies to find metal types and sizes previously undetectable. It uses a true broad-spectrum approach to reduce the probability of an escape by many orders of magnitude.

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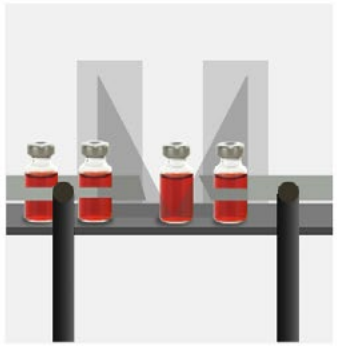
How x-ray inspection systems work

X-ray inspection systems are based on comparing the density of the product and the contaminant.

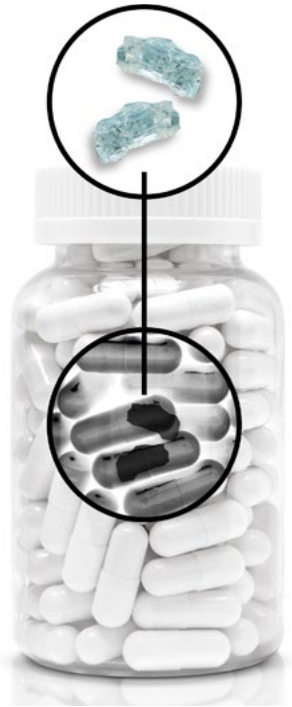
As an x-ray penetrates a product, it loses some of its energy. A dense area, such as a contaminant, will reduce the energy even further.

As the x-ray exits the product, it reaches a sensor. The sensor then converts the energy signal into an image of the interior of the product. Foreign matter appears as a darker shade of grey and helps identify foreign.



X-rays

X-rays are simply light waves that we can't see. Other light waves that we can't see include ultraviolet (UV) light (which gives you a sun tan), infrared light (which warms you up), and radio waves. X-rays have a very short wavelength, which corresponds to a very high energy.



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Equipment

Material identification and QA/QC

TruScan RM Handheld Raman Analyzer

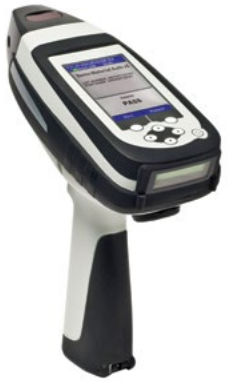
TruScan RM analyzer with TruTools chemometric software allows enhanced material ID of similar chemical compounds, multi-component discrimination, andutilization of custom quantitative and qualitative models such as PCA, PLS, and PLSDA.

Product details ›

TruScan GP Analyzer

The Thermo Scientific™ TruScan™ GP Analyzer provides quick, easy to use raw material identification and finished product inspection to screen out counterfeit substances and reduce supply chain risk.

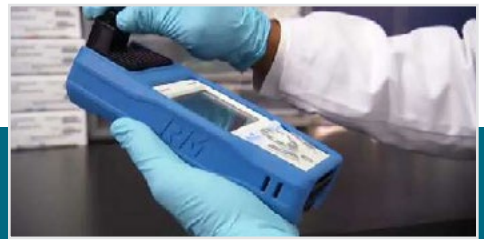
Product details ›



microPHAZIR RX Analyzer

With the microPHAZIR RX analyzer, pharmaceutical manufacturers can perform accurate determination of moisture levels during lyophilization and do so nondestructively, through glass for 100% of materials.

Product details ›



Click here to watch the video:
Achieve Quality Initiatives throughout the Manufacturing Process

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In process control & measurement

TruScan RM with TruTools Handheld Raman Analyzer

TruScan RM analyzer with TruTools chemometric software allows enhanced material ID of similar chemical compounds, multi-component discrimination, and utilization of custom quantitative and qualitative models such as PCA, PLS, and PLSDA.

Product details ›

Prima PRO Process Mass Spectrometer

Highly reliable and easy-to-own, the Thermo Scientific™ Prima PRO process mass spectrometer delivers faster, more complete, lab quality online gas composition analysis.

Product details ›

microPHAZIR RX Analyzer

With the microPHAZIR RX analyzer, pharmaceutical manufacturers can perform accurate determination of moisture levels during lyophilization and do so nondestructively, through glass for 100% of materials.

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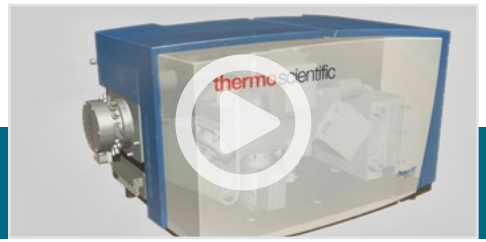

Click here to watch the video: Off-Gas Monitoring in Fermentations with Prima Mass Spectrometers

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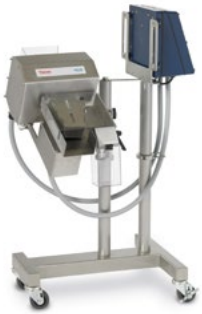
Online product inspection

Versa Rx Pharmaceutical Checkweigher

The Thermo Scientific™ Versa Rx Pharmaceutical Checkweigher ensures product content. With high accuracy performance it can detect the presence or absence of the lightweight descriptive pamphlet that is legally required within cartoned products.

Product details ›



APEX 500 Rx Pharmaceutical Metal Detector

Achieve cost-effective, industry-leading sensitivity in the most demanding pharmaceutical environments while meeting the U.S. Federal Drug Administration's (FDA) stringent requirements for validated production.

Product details ›

NextGuard X-Ray Detection Systems

Find metallic and non-metallic foreign objects and eliminate "wet" product effects common with metal detectors with the Thermo Scientific™ NextGuard™ X-ray Detection Systems.

Product details ›

POWERx X-Ray Inspection for Pharmaceutical Vials

Optimize detection probability and sensitivity using the Thermo Scientific™ POWERx X-Ray Inspection Systems which offer high x-ray power sideshoot inspection, or high speed production and patented dual beam, dual detector systems for pharma glass in glass detection.

Product details ›

Click here to watch the video: APEX 500 Rx Pharmaceutical Metal Detector for Pharmaceutical Applications

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Drug formulation and manufacturing

Hot melt extrusion

Pharmaceutical manufacturers are using conical and twin-screw extruders to mix drug molecules with bioactive polymers in situations where drug ingredients are poorly soluble or unstable during processing. Extruders are also useful in preparing enteric dosages, sustained release dosages, in taste-masking, and to create forms such as films.

Product details ›

Drug delivery systems

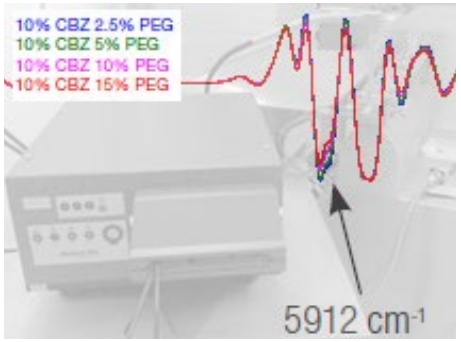
Hot melt extrusion (HME) is a key technology that can produce alternative drug delivery systems such as subcutaneous, solid implants for controlled-release treatment in ophthamology and cancer (e.g., hormone) as well as extrusion of biocompatible or biodegradable polymer/drug formulations.

Product details ›

Continuous granulation

Continuous granulation offers many opportunities to overcome the challenges of traditional batch production of tablets and capsules. It's efficient, inherently scalable and has advanced to a point of true reliability and flexibility. It can also be implemented all at once, or a little at a time.

Product details ›



Analytical instrumentation

Spectroscopic analytical instrumentation uses molecular vibrations to provide feedback in the form of a spectrum that identifies a material, or flags an unknown compound such as a contaminant or inclusion. Near-infrared spectroscopy can be used for inline monitoring of the extrusion process.

Product details ›

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Additional resources

For additional resources, including white papers, application notes, brochures, videos, comparison charts, and FAQs, visit our **Life Sciences Manufacturing Resource Library.**

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Thermo Fisher Scientific is the world leader in serving science. Our mission is to enable our customers to make the world healthier, cleaner and safer. We help our customers accelerate life sciences research, solve complex analytical challenges, improve patient diagnostics, deliver medicines to market and increase laboratory productivity. Through our premier brands – Thermo Scientific, Applied Biosystems, Invitrogen, Fisher Scientific and Unity Lab Services – we offer an unmatched combination of innovative technologies, purchasing convenience and comprehensive services.

For additional information or to request a quote, please click below.

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