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Innovative Technologies in Pharmaceutical Industries

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ABSTRACT

The pharmaceutical industry is undergoing a major transformation. The sector, which has been slow to adopt technology in the past, is currently undergoing fast transformation as a result of the development of numerous technologies. Increased investments, the rise of technological start-ups, the expiration of many major patents, as well as growing inter-organizational partnerships and a favourable regulatory environment, are all driving innovation in the pharmaceutical sector. In research and development, marketing and advertising, and sales and distribution, technology is becoming increasingly important. Artificial intelligence, digital apps, block chains, and organ-on-chips are some of the technologies that are beginning to revolutionise the pharmaceutical business in the same way they have transformed other industries such as media, retail, finance, telecommunications, and education. This shift in research and development has been seen most strongly in the pharmaceutical industry in recent years, and it will be felt more strongly in other divisions during the coming decade. Here are a few themes that will shape the pharmaceutical business in the next few years.

INTRODUCTION

All regulatory agencies place an emphasis on the quality of pharmaceutical goods. The mission of Quality by Design is to "create a more systematic scientific and risk-based approach to pharmaceutical product development." "Quality cannot be tested into a product, but it should be built into it," according to Dr. Joseph M. Juran [1]. He thought that quality could be planned and that the majority of quality problems and crises stemmed from how quality was planned in the first place. The Quality by Design approach has shown amazing results in terms of improving product and process quality in industry [2].

The quality guidelines of the international conference on harmonisation, ICH Q8 Pharmaceutical Development, ICH Q9 Quality Risk Management, and ICH Q10 Pharmaceutical Quality System, explain the underlying principles of Quality by design, such as science- and risk-based product development, risk assessment, lifecycle approach, and method design. The basis of ICH Q8, Q9, and Q10 are the foundations of Quality by Design.

Advantages

1. It reduces the process variation.
2. It enables process control strategies
3. Science based risk assessment is carried.
4. Avoid regulatory compliance problems
5. It offers robust method or process
6. It reduces Batch failure.
7. Ensure better design of products with less problem in manufacturing [3].

Elements of QBD

Quality Target Product Profile (QTPP)

Critical Quality Attributes (CQAs)

Critical Material Attributes (CMAs)

1. Critical Process Parameters (CPP) [4]

Tools in Quality by Design

1. Risk assessment
2. Design of experiment
3. Process analytical technology [5]

Steps

Development of new molecular entity

1. Preclinical Study
2. Nonclinical Study
3. Clinical Study
4. Scale Up
5. Submission for Market Approval

Manufacturing

1. Design space
2. Process analytical technology

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3. Real time quality control

Control strategy

1. Risk based decision
2. Continuous improvement
3. Product performance

Seven steps of quality by design start up plan

1. Hire an independent Quality by design expert.
2. Audit your organization and process with the expert conducting a gape analysis.
3. Hold a basic quality by design workshop with all your personal.
4. Review the expert's report and recommendation.
5. Draft an implementation plan, timelines and estimated costs.
6. Assign the resources
7. Retain the independent expert as your "Project Assurance" advisor.

Applications of Quality by Design

1. *Cell propagation/substrate preparation*: Take the frozen, preserved cell culture from the WBC cell line and grow it at 37°C in an incubator. The cells are then cultured in a tiny volume of culture media, where they develop and multiply. After that, move to a much larger container.
2. *Virus propagation*: Once a large number of cells have been generated, add influenza seed virus from a WHO diagnostic laboratory to a cell-containing bioreactor (Fermenter), where the virus infects the cells, multiplies, and produces additional virus particles. Viruses in bioreactors kill the cells after a few days. The virus is collected and rendered non-infectious by eliminating the garbage produced by the cells.
3. *Purification*: The virus is isolated from the cells and removed from the solution using a centrifuge or chromatography.
4. *Inactivation and splitting*: A chemical procedure is utilised to inactivate the virus, removing its capacity to infect. Formaldehyde is employed in this process, which is referred to as splitting. The surface antigen is then isolated from the virus and removed.
5. *Blending, filling, and approval*: The non-infectious solution is mixed, concentrated, and put into a sterile syringe. During the vaccine production process, the following parameters should be managed using Quality by design.

SIX SIGMA

Many pharmaceutical companies have implemented six sigma to save costs and enhance quality and productivity by decreasing variance and errors. In statistical words, Lean Six Sigma assures that only 3.4 faults or less occur in every million actions. Six sigma simply refers to the product's quality. The most common use of the lean technique is to decrease product waste. Some of the world's most successful organisations have utilised Six Sigma to save billions of dollars, improve the speed and capacity of their operations, and build new, better customer connections. Many pharmaceutical firms have been able to eliminate waste and make successful changes to their manufacturing processes by implementing six sigma and lean manufacturing. Six sigma is a process that combines the 4Ms (man, machine, materials, and methods) in order to produce goods or services that satisfy customer expectations. These products or services are assessed using statistical techniques and must have intrinsic statistical variability [6].

Critical to Quality:

The customer is the start and what is important for the customer needs to be identified.

1. Defect: Anything that does not deliver exactly what the customer wants.
2. Process Capability: The processes need to be able to deliver what the customer wants.
3. Variation: As it is experienced by the customer.
4. Stable Operations: The goal is to secure reliable, robust processes that improve the customer's experience.
5. Design for Six Sigma: The design must meet all the customer requirements and the capability of the process.

Six sigma tools

This process uses a DMAIC framework to solve any problems. This framework contains five stages;

1. Define - In this stage, the problem is defined and project aims are listed
2. Measure – the process data, capabilities and variables are collected and measured at this stage
3. Analyse -The roots causes of a defect are analysed
4. Improve- solutions are bought up to fix the defect and improve the process
5. Control -A control system is put in place to assure that the improvements will hold [7].

Lean six sigma

In the drug development process, lean six sigma has the benefit of producing less waste. It also has the advantage of lowering production costs. In the pharmaceutical industry, lean six sigma tools are implemented. The tools from the two integrated processes are combined in lean six sigma [8].

Lean tools are:

1. 5s- this is a tool used took keep the working space in order
2. Kaizen- It's a process expedited by subordinates focused on making small improvements in the organization
3. Gemba - This is real time observations of the process aimed at pinpointing the process defects.
4. Value stream mapping (VSM) -Tool used to identify process waste and the cause of waste
5. Automation- this stops production in case a defect occurs
6. Kanban -A system which manages inventory levels and brings into attention excessive or low inventory [9].

Application

The Mark A. Watson Centre for Operations Excellence was launched at Akron Children's Hospital in 2008, and since then, it has educated hundreds of employees, saved $13.4 million, and decreased NVA work time by more than 41,000 hours. In addition to financial savings, these measures have resulted in shorter patient wait times. A number of projects at the hospital have been successful, according to the facility.

The sterile processing section was reconfigured to prevent a $3.5 million expansion while also enhancing the working environment and lowering surgical instrument turnaround time. A 90% reduction in MRI wait times in the radiology department resulted in a rise in MRI volume, which improved income and made the service more accessible to the community. The use of LSS to gain faster insurance authorization, more efficient scheduling, and coordination between physicians who do the studies and those who give sedation for the operation resulted in these benefits. Improved weight estimation accuracy for paediatric burn patients in order to decrease medication and fluid delivery mistakes.

These are a few instances of how LSS has revolutionised hospital care, with advantages in both increasing patient care quality and lowering costs.

In the future, clinical applications will become increasingly

common. Medication mistakes have long been an issue in paediatric inpatient settings. Kaushal *et al*. investigated medication mistakes in a paediatric inpatient population in a 2001 article. A medication mistake rate of 5.7 percent was discovered in the research, with majority of the errors happening at the point of care while the physician was ordering the drugs. Despite the fact that computerised order entry systems were supposed to decrease mistakes, additional causes of error have emerged as a result of their implementation [10].

ARTIFICIAL INTELLIGENCE

Artificial intelligence and machine learning are undoubtedly the next big thing for the pharmaceutical industry. Artificial intelligence is already being used in the healthcare industry for conducting repetitive tasks such as data entry, lab test analyses, data management, analysis of healthcare systems to identify errors or inefficiencies, medical consultations by artificial intelligence-based apps, medication management that monitored by an artificial intelligence-based system, etc. Machine learning is also being used in disease identification and diagnosis, radiology and radiotherapy planning, clinical trial research, personalized medicine, rare disease identification, and new drug invention, etc.

Artificial intelligence, according to healthcare specialists, will be widely integrated into pharmaceutical corporations. Artificial intelligence will almost certainly play a significant role in accelerating the development of novel treatments and medications. It refers to artificial intelligence systems' ability to test and simulate thousands of biomedical conditions at once in order to identify which chemical and substance combination achieves the desired effect. This cuts down on the time it would take active human teams to manually go through each set of combinations to uncover formulations that could provide effective therapy with minimum adverse effects. Artificial intelligence will be heavily integrated into the enhancement of pharmaceuticals, in addition to developing them from the ground up. Artificial Intelligence has proven to be extremely beneficial in tracking and predicting epidemic outbreaks using all available data, ranging from satellite images to social data. Using artificial intelligence-based software can considerably assist specialists in preventing the risk of an epidemic disease, whether it is malaria or Ebola. This could aid pharmaceutical companies in developing potential treatments ahead of any epidemic or pandemic [11].

ARTIFICIAL INTELLIGENCE IN THE PHARMACEUTICAL INDUSTRY

Improving the manufacturing process

Artificial intelligence offers several chances to optimise processes in development and manufacturing. It can help with quality control, design time reduction, material waste reduction, production reuse, and predictive maintenance, among other things. Artificial intelligence can be utilised in a variety of ways to increase manufacturing efficiency and reduce waste. A procedure that traditionally requires human intervention to input or handle process data, for example, can be done using computer numerical controls.

Drug discovery and design

Artificial intelligence is used in drug target identification and validation, target-based, phenotypic, and multi-target medication discovery, drug repurposing, and biomarker identification, among other things. The potential for artificial intelligence to decrease the time it takes for a drug to receive approval and reach the market is a major benefit for pharmaceutical companies, especially when used during drug trials. This could result in significant cost reductions for patients, as well as a wider range of therapy options. Pharmaceutical researchers, for example, can use data like longitudinal data to find and validate novel cancer medication targets. To develop representative models of individual patients, data such as longitudinal electronic medical records, next generation sequencing, and other 'comic data are used.

Processing biological and clinical data

Until far, the most advanced use of artificial intelligence has been in algorithms that read, group, and interpret vast amounts of textual data. This can save time for researchers in the life sciences business by allowing them to review vast amounts of data from an increasing number of research publications in order to validate or reject theories. The advantages of employing artificial intelligence in this manner include faster data research and cross-referencing, as well as combining and extracting data into usable formats for analysis.

Rare diseases and targeted therapies

Artificial intelligence is being used to diagnose diseases like cancer and even anticipate health difficulties people may encounter based on their genetics by combining data from body scans, patient biology, and analytics.

Identifying clinical trial candidates

In addition to assisting in the interpretation of clinical trial data, artificial intelligence is also used in the pharmaceutical business to find patients to enrol in trials. It can analyse genetic data to identify the right patient population for a trial and calculate the right sample size using advanced predictive analytics.

Predictive biomarkers

Biomarker development is a critical work not only in medical diagnostics, but also in the drug research and development process. Predictive biomarkers, for example, are used to detect likely responders to molecular targeted therapy before it is tested in humans. Artificial intelligence employs biomarker models that have been "trained" using massive datasets in this process [11].

NANOROBOTICS

Nanotechnology offers a wide range of new methods for improving pharmaceutical product medication delivery. Patients suffering from chronic diseases such as cancer, multiple sclerosis, cardiovascular disease, and others have new hope because to nanotechnology. Nanotechnology is an applied science whose goal is to manipulate matter at the atomic and molecular level. Nanomedicine is a branch of nanotechnology that focuses on the repair, creation, and control of human biological systems with nanotechnology-based devices. The full promise of nanomedicine is unlikely to be realised until after complicated, high-sophisticated, Nanomachines and nanorobots that can be programmed medically are being developed. These nanorobots would be delivered into the body and used in nanomedicine to repair or detect damages and infections. Nanotechnology is a branch of applied science concerned with the design, production, characterisation, and usage of nanoscale materials and technologies. Through the design, characterisation, production, and use of nano-sized, intelligent materials, nanotechnology has the potential to significantly change the cure, alleviation, and prevention of disease, and eventually strengthen the restoration and preservation of health.

The nanorobots or nanoparticles because of its molecular peculiarities, a mixture of a polymer and a protein called transferrin has the ability to detect cancerous cells. Once within the cells, the chemical sensor instructs them to dissolve; once dissolved, the nanoparticles release chemicals that act on the RNA of each cell, inhibiting the cancer-causing gene. The nanoparticles specifically deactivate ribonucleic reductase, a protein linked to cancer growth that is manufactured by the defective gene. With today's medical technologies and therapy methods, cancer can be successfully treated. However, how early a cancer was found is a crucial component in determining a patient's chances of survival; this means that, if feasible, a cancer should be detected at least before the metastasis has begun. Another crucial factor in achieving a successful treatment for patients is the development of effective targeted drug delivery systems to reduce chemotherapy side effects Nanorobots with chemical biosensors embedded in them can be utilised to detect tumour cells in their early stages of development inside a patient's body. In order to determine the strength of E-cadherin signals, integrated nanosensors can be used. As a result, for the application of nanorobots for cancer therapy, a hardware architecture based on nanobioelectronics is described. Real-time 3D simulation is used to produce analyses and conclusions for the given model [12].

Medicines with Nanorobotics

Sugar level monitoring bots

By injecting specific sensor nanobots into the blood, an electrical

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impulse signal is emitted by microchips covered with human molecules, the sugar level in the blood may be measured. The drug carriers have thin walls of 510 atoms and an interior drug-filled cell that is typically 50100 nm wide. Thin wires in their walls generate an electrical pulse when they detect signs of sickness, causing the walls to melt and the drug to be released. One of the most significant advantages of employing nanobots for drug delivery is the ability to modulate the electrical pulse, which allows for precise control of the amount and timing of drug release to a specific spot. Furthermore, the walls simply melt and dissolve, making them completely harmless to the human body.

Enzyme-proprelled nanorobot

In a urea-containing liquid, urea-coated nanotubes act as a propulsion system because the enzyme breaks down the urea into gaseous components. Because the tubes constantly contain tiny asymmetries, the reaction products generate a current in the liquid. When compared to traditional approaches, this active motor-based drug delivery approach promises to be more effective and efficient. These nanobots have outstanding acid-driven, self-propulsive properties and can pack a lot of cargo.

Cancer detection and treatment

Scientists from Arizona State University and China's National Centre for Nanoscience and Technology have successfully programmed nanorobots to detect and reduce cancer tumours in the brain. With a resolution of 25 million nanometers per inch, these microscopic robots may be able to assist oncologists in reducing cancer by improving their ability to detect, diagnose, and treat cancer cells. Cancer medicine distribution is challenging to control today. Chemotherapy wreaks havoc on both healthy and cancerous tissue. Chemotherapy's side effects on other regions of our bodies are unavoidable. Nanobots, on the other hand, do not do this. Nanobots could be utilised to deliver medications specifically to tumour cells, preventing the drug's supplementary effect. Nanobots are initially sent to the targeted tissue or tumour to excite it, which is a part of the machine gun technique, however a large number of bots will be wasted. However, only the tumour is triggered; no other tissues in the body are impacted. A second wave of bots is now despatched to the targeted area, this time containing the chemotherapeutic medication. Only after sensing the stimulated tissue does it release its cargo, i.e. the medication. As a result, we have a highly concentrated targeted activity with no side effects [13].

Applications

Diabetes: Nanorobots are being hailed as a new way for the medical industry to improve instrumentation, diagnostics, and therapeutic treatments. To keep glucose levels under control, diabetic patients must take tiny blood samples several times a day. Such procedures are both unpleasant and inconvenient. To avoid problems like this, the level of sugar in the body can be monitored continuously using medical nanorobotics. This automated data can assist doctors, experts, and formulation professionals in providing real-time health care and refining a patient's pharmaceutical regimen. The use of a large number of independent nanorobots can provide a variety of benefits. Embedded and integrated devices, which can contain the following components, should be included in the construction of medical nano robots:

1. Sensing
2. Actuation, Data Transmission
3. Uploading of Remote Control
4. Connecting power supply subsystems for biomedical instrumentation essentials.

The integrated platform, which includes nanorobots for diabetes monitoring, provides diabetics with painless and helpful information. It provides a practical technique to improve a person's awareness of daily protein and calorie consumption, hence minimising the amount of time a patient spends suffering from hyperglycemia.

Cancer Nanorobots: The primary hurdles in cancer therapy are targeting and localised delivery. To circumvent the limitations of conventional approaches, we must target cancer cells specifically while sparing non-malignant tissue from severe drug toxicity. The proposed nanorobot should theoretically be able to do the following:

1. Nano-sensors to detect the presence of cancer cells in the body.
2. Nano carriers for delivering the Nano Sensor-Nano Drug Encapsulate combination to malignant tissues.
3. Nano drug delivery particles to encapsulate medications for regulated drug delivery at specific malignant tissue locations.
4. A Nano-Computer/Brain to integrate the preceding activities in a complicated In-Vivo scenario [14]

BLOCKCHAIN TECHNOLOGY

Blockchain technology is an open ledger of data that is distributed and validated across a peer-to-peer network rather than through a single central server. To put it another way, it's a digital public ledger that can be used to save nearly anything to a spreadsheet or database. Each transaction or block is broadcast to all network members and must be validated by each node by solving a difficult mathematical challenge. Once a block has been confirmed, it cannot be changed without affecting the entire network. Because there are several shared copies of the same database instead of a single database, distributed ledgers are intrinsically more difficult to attack. Blockchain is a growing set of records (blocks) linked together by a cryptographic mechanism known as hashing. Each record carries a cryptographic hash of the previous record, which links the records together and prevents them from being altered [15].

A blockchain of pharmacological dosage units is a concept of cryptopharmaceuticals. Each new record contains particular information on the product that has been made (disclosed as a hash by the manufacturer during CHECK-IN and revealed by the patient during CHECK OUT) accompanied with a cryptographic hash from the previous record, which will link the records together and prevent them from being changed. The cryptocurrency bitcoin is the most well-known application of the technology. In the pharmaceutical industry, blockchain offers exciting possibilities, such as the ability to examine a patient's whole prescription history. In this paper, we provide a proof-of-concept application for integrating a pharmaceutical product into an Internet-of-Things-based healthcare system. This app provides a technical foundation for combining machine learning-based diagnosis with patient data which includes healthcare records and information from point-of-care sensors, eventually leading to a secure manufacturing chain of completely serialized individualized items. Data security is a critical component of a healthcare facility, as it protects sensitive information. Patient information is included in healthcare data, which should not be provided to any untrustworthy third party due to security concerns and information misuse. This sort of data consists of a list of patient information stored in medical repositories from the start of the patient's illness to their recovery. A series of time-bound information recorded by hospitals are also included in such data. Healthcare data and clinical information, on the other hand, are dispersed among several medical repositories [16].

Implementation of block chain

To integrate blockchain technology into the pharmaceutical supply chain system, we must first comprehend how the blockchain ledger works. A built-in identity method, a cryptographically secure key pair, is integrated into the blockchain (as mentioned in the above section). These keys are used to assign each network participant to a specified activity. A device, a human, or an entity can all be participants. The original identities of participants are secret, and these keys are the only way to find out who they are. A key pair contains no information about the participant, but it can be linked to extra information (such as a name, contact information, or professional qualifications). However, keeping this additional data off-chain and merging it with on-chain data (key pair) using their IDs is the optimal way. Participants in pharmaceutical supply chain management include the producer, packager, distributor, and doctor, among others. On the network, each of these participants will be identifiable by their unique key pair. Drugs will be treated like assets, with each one having its own unique key (or hash). In the form of a QR code, the ID will be connected to the medicine. The choice of a

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specific blockchain network for storing transactions is also critical, but first we must understand the many types of blockchain. Public blockchain and permissioned (or private) blockchain are the two basic types of blockchain, with more information available here. Not everyone can write to the blockchain in a permissioned blockchain. In a permissioned blockchain, not all can write to the blockchain; only those who've been granted access can write or access data on the blockchain. In the context of the pharmaceutical supply chain, a permissioned blockchain is the superior solution. The next step is to save the transaction record on a certain blockchain network, however this is entirely up to the developer. Several forms of blockchain networks are currently available on the market, including the pioneering Bitcoin Blockchain, Ethereum, Hyperledger, and even BigchainDB. However, the permissioned Ethereum blockchain is the one we recommend [17].

Benefits of Blockchain

Improved Security of data and privacy- The immutability aspect of blockchain considerably improves the security of health data placed on it, as it cannot be corrupted, altered, or retrieved once it is uploaded to the blockchain. On the blockchain, all health data is encrypted, time-stamped, and appended in chronological sequence. Furthermore, health data is stored on blockchain utilising cryptographic keys, which enable to safeguard patients' identities and privacy.

Ownership of health data-Patients must be the owners of their data and have control over how it is utilised. Patients require assurance that their health data will not be misused by third parties, as well as the ability to detect such misuse. Strong cryptographic protocols and well-defined smart contracts enable blockchain achieve these needs.

Decentralisation-The nature of healthcare, with its numerous stakeholders, necessitates a decentralised management system. Blockchain could serve as the decentralised backbone for health data management, allowing all parties to have regulated access to the same health records without a single person acting as a centralised authority over global health data.

Availability and stability-The availability of health data saved on blockchain is ensured since the records on blockchain are duplicated in numerous nodes, and the system is strong and resilient against data losses, data corruption, and various security attacks on data availability.

Transparency and trustworthiness-Blockchain fosters trust in distributed healthcare apps by virtue of its open and transparent character. This makes it easier for healthcare stakeholders to accept such applications [18].

PROCESS ANALYTICAL TECHNOLOGY

Understanding the analysis needs (e.g., Purpose, specificity, sensitivity, cycle time, on-line/off-line, qualitative/quantitative, accuracy, precision) and selecting the technique (which is at the receiving lab) that will meet these criteria are the first steps in developing an Analytical Quality-by-Design (AQbD) method. In-situ analytics, chemo metrics, and modelling (i.e., Process Analytical Technology (PAT) tools) are some of the analytical methods used during the development and scale-up of pharmacological compounds and dosage forms. The performance criteria, techniques, and drivers for employing PAT in development can differ dramatically from those for commercial manufacturing, despite the comparable tools. When compared to standard off-line analyses, in-situ analytics has the potential to deliver a better (and faster) understanding of the process. During the creation of a process, qualitative or semi-quantitative evaluations are frequently sufficient, and the speed with which data is analysed is frequently the most important factor [19].

Tools

To better control processes and hence increase their robustness, on-line monitoring of some essential parameters is required. Spectroscopy (near infrared, infrared, Raman) is a common instrument, although other optical sensors like turbidity probes or FBRM are also utilised (Focused Beam Reflectance Measurements). Several applications of these approaches are detailed in this paper. To examine huge multidimensional spectrum data generated by PAT techniques, multivariate data acquisition and data processing tools are also required. Chemometrics is a chemical discipline that uses both statistical and mathematical methodologies to extract and evaluate useful data from PAT spectrum instruments. Furthermore, knowledge management or continuous improvement software is frequently used to better define process flaws and perform process improvement projects [20].

What exactly is PAT

PAT is a system for analysing and controlling manufacturing processes based on timely measurements of essential quality characteristics and performance attributes of raw materials and in-process materials, according to the FDA.

It is a procedure for ensuring acceptable end-product quality when the processing is completed. PAT, according to the FDA, entails:

1. The best way to use process analytical chemistry (PAC) tools
2. Feedback process control techniques
3. For the manufacture of pharmaceuticals, information management tools and/or product–process optimization methodologies are used [21].

PH probe, vibration spectroscopy (mid-infrared, near-infrared, Raman, ultraviolet), mass spectrometry, chromatography, focused beam reflectance measurement, and nuclear magnetic resonance are all examples of PAT. There is no single in situ analytical tool that will work for all applications, just as there is no single off-line analytical tool that will suit all process development knowledge or control strategy needs for a product. Indeed, in situ tool use is difficult at best for some types of chemistry, and sample and off-line testing may be preferred. As a result, PAT tools are simply one set of analytical techniques to think about when deciding which analytics are best for understanding, monitoring, and controlling processes and products. Chemistry, stage of development, technique availability (in development and at the manufacturing site), process equipment accessibility and configuration, personnel skill sets in the technique, and regulatory acceptability are used to determine the appropriate analytical techniques for the process or product [22].

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