Biopharmaceuticals

In-Line Analytics

Weighing Systems

Process Analytical Technology

Process Development

Scale Up

Commercial Manufacturing

Optimizing Scale Up & Manufacturing

Analytics & Weighing to Improve Efficiency

METTLER TOLEDO

Effective Scale Up & Manufacturing
Upstream & Downstream Processing

The development and manufacture of large pharmaceutical molecules offers society new ways to tackle some of the most complex health problems. To solve these problems, the pharmaceutical industry must constantly innovate in order to ensure the effectiveness of a treatment while preserving the safety of the patient and increase productivity while reducing the possible time to market of a new molecule.

Shortening Time to Market

To produce a biological molecule effectively and efficiently with a scale manufacturing perspective, pharmaceutical companies must implement analytical tools that embed QbD principles. Such analytical alignment when including early stage discovery and process development will accelerate product knowledge and process understanding, and could help to achieve successful technology transfer, while shortening the time to market.

Process development understanding and knowledge is critical for effective transfer to manufacturing operations. PAT is now foundational to process scale up and ensures quality, yield and safety of the finished biological drug product.

Challenges at Commercial Scale

Meeting the challenges of biopharmaceutical manufacturing at commercial scale requires the ability to see, understand and make quick decisions on critical process parameters. Inefficiencies that have small impact on a small scale can have a devastating impact under a larger production scale. Therefore having the right tools to monitor and understand your biological process from process development to full manufacturing is critical.

Measurement Expertise

With expertise to design and commercialize process analytical solutions, bioprocessing sensors and weighing sensors, METTLER TOLEDO offers a complete and unique portfolio for characterization, optimization and manufacturing of large molecules.

Contents

In-Line Process Analytics

Continuous, real-time monitoring of critical analytical parameters in cell culture, fermentation and downstream processes to increase productivity, maximize yield and defined quality attributes.

pH/ORP Sensors
Dissolved Oxygen Sensors
Dissolved CO_2 Sensors
Conductivity Sensors
Single Use pH/Oxygen Sensors

Automated Reactors and In-situ Analysis

By collecting highly repeatable analytical data at regular intervals throughout each experiment, scientists and engineers get the best understanding and complete investigations in less time. Obtaining accurate and frequent samples from bioprocesses reveals fundamental insights and leads to quick, well informed decisions.

Automated Workstations: EasyMax and OptiMax with biophysical sensor and mass control integration
In-situ Spectrometers: ReactIR and ReactRaman
Particle Size Analyzers: EasyViewer and ParticleTrack

Industrial Weighing

Comprehensive portfolio of weighing platforms, smart sensors, and transmitters able to endure rigorous cleaning protocols and reliably deliver the weighing precision required to help you produce every batch correctly.

Floor scales, bench scales, weigh modules, terminals and transmitters for connectivity, SQC and Formulation management systems, and comprehensive service to maintain ongoing calibration.

Media & Buffer Preparation

METTLER TOLEDO has a long history designing bioprocessing sensor technologies for large molecule environmental process conditions, including media & buffer preparation, cleaning, and utilities, meeting analytical requirements for pH/ORP, Conductivity, Turbidity, TOC, Ozone and bioburden.

Managing media mixing and inventory is easy with the right equipment. With a full portfolio of bench scales, floor scales and weigh modules, you'll find the right tools to measure ingredients precisely from small to large scale.

For upstream and downstream operations – effective processes begin with a qualified, reproducible media and buffer preparation. Robust processes developed with in-line PAT ensure complete powder dissolution and achieve a verified target component concentration while reducing batch failures.

Process Development, Characterization and Scale-up Studies

Scientists build process understanding over the course of a development project to reach a threshold of understanding and deliver material at scale. As molecules become more complex, more information is needed at a quicker rate than before, and with the same resources. METTLER TOLEDO process analytical technology (PAT) helps scientists maximize information from every process to obtain answers faster than has ever been previously possible.

From the bench to the manufacturing floor including related scalability studies, toxicology, tech transfer and upstream analytical harmonization, including in-line analytics used with single-use bioreactors, the METTLER TOLEDO process analytical portfolio has the highest industry validation rate in clinical and commercial phase over the past 30 years.

Commercial Fermentation & Cell Culture Operations

Achieving the right analytical performances at various scale under various process conditions has defined the METTLER TOLEDO analytics portfolio as the upstream analytical standard for a vast majority of cell culture and fermentation commercial operations. Dissolved oxygen, pH, ORP and dCO_2 sensors are available in reusable or single-use formats.

For each size reactor, METTLER TOLEDO delivers the right industrial weighing device. High-precision bench scales, floor scales, and integrated weigh modules (smart or analog) give you the accurate measurements needed to effectively control amount and rate of buffer or media dosing to improve consistency batch-to-batch, independent of reactor type.

Separation, Harvest & Clarification

This is the first step to separate product from bulk debris while optimizing product yield and quality. In-situ, real-time, probe-based particle size analyzers measure particle accumulation and size distribution of cell broth feeding into or escaping filters and can provide capacity correlation or feedback control to minimize process disruptions.

Probe-based microscopy with real-time image analysis extracts particle accumulation, size distribution and morphology information from in-line images of the process. Placed above or below filters, microscopy can provide capacity correlation or feedback control, but is most valuable when applied for root cause analysis, characterization and morphology studies.

Purification & Bioconjugation

Automated reactors provide precise CPP control, and when integrated with PAT and biophysical sensors, enable data-rich experimentation for viral inactivation, buffer exchange and bioconjugation studies. In-situ, probe- or flow cell-based ATR-FTIR spectroscopy provide detailed mechanistic information in real time and is advantageous for supporting purification methods, TFF and polishing chromatography.

Weighing equipment enables appropriate control and automated workflows while avoiding contamination. Platforms designed using hygienic principles, including floor scales with lifting decks, enable you to achieve less downtime and reduced risk of contamination. Ultra-flat floor scale models are easily integrated into modular single-use manufacturing concepts.

Formulation, Fill & Finish

Characterize drug substance and drug product stability, final concentration, adjuvant synthesis, polymerization, encapsulation, adsorption and other events with automated reactors and PAT including in-situ spectroscopy and particle size analyzers and microscopy.

High-performing scales, renowned in the pharmaceutical industry, enable precise formulation of ingredients. Final filling of vials and syringes demand the speed, resolution and repeatability offered by automated precision weigh modules.

Align Discovery & Manufacturing
Reduce Time to Market

Since the early 20th century, the development of industrial microbiology has made it possible to meet the growing worldwide market demand for antibodies, vaccines and many other molecules for therapeutic applications. Whether for the production of a blockbuster, facing a pandemic situation or the treatment of a rare pathology, the dynamism of the pharmaceutical industry during the 21st century will make it essential to reduce operating costs and time to market of an API.

Harmonizing R&D with Manufacturing

Whether operating in a clean laboratory environment or manufacturing of an API under specific bioprocessing conditions, pharmaceutical manufacturers must think beyond the performance requirements for equipment used in a given process. The demands of an evolving industry requires bioprocess scientists to assess how their equipment enables integration of process development and scale-up characterization information into a production operation that will work semi-continuously or continuously.

The dynamics of the industry also require pharmaceutical manufacturers to look for ways to ensure faster, successful tech transfer and reduce their time-to-market of new drugs. To meet these challenges, the way that you assess and harmonize your equipment can have a monumental impact. In-line analytical harmonization is one of the driver to succeed and reduce upstream processing (USP) and downstream processing (DSP) operating costs.

Measurement should be compatible with, and help you to manage, all stages of your production process. The METTLER TOLEDO portfolio of analyzers, automated chemistry tools and weighing equipment is widely recognized as a market reference that is used from R&D through scale-up under a cGMP commercial manufacturing environment.

Equipment to Ensure Accurate Scale-Up

From the qualification of raw materials and their preparation for production, to the commercial manufacturing of a finished product as a liquid, an aerosol or solid form, a METTLER TOLEDO's in-line and offline equipment support pharmaceutical companies to enable continuous manufacturing, optimize commercial manufacturing processes, and ultimately maximize yield while maintaining quality attributes.

How METTLER TOLEDO Tools Enable Faster Scale-Up

Process Analytics

From early stage discovery to manufacturing, METTLER TOLEDO helps pharmaceutical manufacturers to meet analytical demands for connectivity and control, including development of soft sensing models and PAT initiatives. pH, ORP, conductivity, dCO_2, turbidity and dissolved or gas-phase oxygen sensors are designed to fit into specifics manufacturing step, whether reusable or single-use measurement, USP or DSP.

Automated Chemistry

Evaluation of all CPPs for a downstream bioprocess or formulation can be tedious and laborious. Automated bioprocess development platforms such as EasyMax™ not only streamline historically manual development but ensure your fundamental variables are well controlled and understood. Integration of spectroscopy or particle PAT highlights key process events and accelerates knowledge for effective scale up.

Industrial Weighing

Weighing accurately is critical at multiple stages of upstream and downstream manufacturing, as important materials are added to batches and cell growth is carefully monitored in different bioreactors and tanks. Where weighing is present, METTLER TOLEDO provides the right industrial weighing sensors, with the connectivity options you need and the expertise to be confident your equipment is fit-for-purpose.

Multi-scale Media Preparation
With Enabling Process Analytical Technology

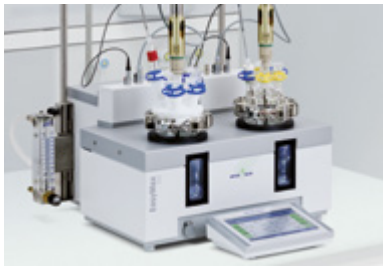
A new set of automation and analytical tools provides real-time insight into critical unit operations to speed development, increase quality, eliminate media and batch failures and provide comprehensive information about every process. This toolkit enables the utilization of QBD approaches across many unit operations throughout upstream and downstream bioprocessing, including viral inactivation, buffer exchange and bioconjugation, replacing slow and labor-intensive offline analyses to obtain critical process information.

In-situ spectroscopy

ReactIR™ and ReactRaman™ quantify concentration of critical components during media preparation and fermentation. Glucose and key metabolites can be monitored as dissolution occurs, verifying that weighed masses actually result in calculated concentrations under varying process conditions such as pH and temperature. Measure and identify deviations in raw materials and non-defined media sources. Perform deviation and root-cause analysis[1] for stabilizers, excipients and impurities in real time without delays or costs associated with offline analysis.

Particle Systems Characterization

In-line particle analysis monitors the rate and degree of change to particle count and size of dry-powder[2] media dissolutions which is an important process parameter in maintaining cell culture consistency and performance. This information can be used to optimize parameters such as concentration, particle size, powder compactness, pH, temperature and mixing. ParticleTrack™ and EasyViewer™ enable rapid kinetic, morphology and mechanism understanding and are used to accelerate process development, troubleshoot dissolution issues and measure consistency of production scale media.



Automated synthesis and process development

Media preparation is perceived as a simple operation, yet parameters such as temperature and mixing can have drastic effects on pH and media component solubility. EasyMax™ is a simple and robust process development platform used to precisely control and document critical process parameters such as pH, dosing, conductivity, oxidation reduction potential (ORP), dissolved O_2 and more around the clock.

Read the Full Articles

1. Brunner et al. Towards robust cell culture processes–Unraveling the impact of media preparation by spectroscopic online monitoring, Eng Life Sci. 2019. https://doi.org/10.1002/elsc.201900050
2. Salazar et al. Compaction of chemically defined cell culture media increases its dissolution rate through an increase of solvent accessible surface area. Powder Technology. 2016. http://dx.doi.org/10.1016/j.powtec.2016.05.065

Streamlined biophysical transmitters from lab-to-plant

Leverage multi-function transmitters for any biophysical sensor measurements with Intelligent Sensor Management (ISM®) and streamlined controls, documentation and diagnostics. Connect across scales during media development and scale-down studies to bring the same measurement and controls from your pilot and manufacturing suites into smaller scale while ensuring confidence that methods and leanings will transfer and scale up seamlessly.

Gold standard pH and DO

Leverage decades of Good Electrochemistry Practice and experience developing world leading sensors for biopharmaceutical and biotechnology applications. Ensure consistent and drift-free measurements for both pH and optical DO, even over extensive, continuous conditions such as long perfusion runs beyond 250 days with single-use and sterilizable probes. With media preparations, ensure confident and reproducible measurements without concern for selective ion behaviors with problematic excipients.

Hygienic and efficient floor scales and load cells

Large-scale media prep not only contends with CMC considerations but also with practical considerations such as handling and manipulation of large masses and volumes. Hygienic floor scales and load cells systems conform to the suite needs and make dosing of powders and liquid-handling seem like second nature. Fulfill needs for protocol and process event capture through connectivity, integration and overlay of orthogonal measurements such as pH, mixing, conductivity and advanced PAT such as spectroscopy and particle distribution.

Cell Culture and Fermentation
mAbs, Recombinant Proteins and Vaccines

To manufacture large quantities of antibodies, proteins, vaccines and any other large molecule with a therapeutic interest, fermentation and cell culture are the two methods mainly used by the pharmaceutical industry. Both of these methods require precise monitoring and control to optimize their operation and to ensure that productivity remains consistent from process development to full manufacturing scale.

Quality & Accuracy

Ensuring consistent productivity and quality attributes of the molecule of interest means balancing a range of analytical parameters in the cell culture or fermentation to keep the media within your critical specifications. Deviation from these specifications create stress conditions for the cell population, which lead to negative impacts on both productivity and quality attributes of the desired molecule.

pH & ORP Control

pH is one of the most common and critical control parameters for a bioreactor. Careful control over pH is required to maintain the desired growth environment of mAbs and recombinant proteins. There is a trend towards the measurement of Oxidation Reduction Potential (ORP) in addition to pH in cell culture and fermenters.

This provides additional information how to manage the oxygen feeding strategy in order to minimize changes in productivity during scale up of production batch sizes.

Oxygen Feeding Strategy

As mentioned above regarding ORP, the oxygen feeding strategy is important. In-situ oxygen sensors need to provide stable, continuous measurement to ensure that the oxygen levels remain appropriate to respond to respiration demand and maximize cellular output.

Often resulting from inlet gassing process conditions with vertically or side-installed sensors, bubbles from sparging create erratic measurement often qualified as process related noises. Such process conditions have a measureable negative impact on the performance of oxygen control, inducing unwanted process conditions as hypoxia and hyper-oxygenation that will directly affect cell metabolism.

In-Line dCO_2 Monitoring

Dissolved Carbon Dioxide (dCO_2) monitoring can provide a beneficial effect on productivity and quality attributes when the cell culture process or fermentation is going to be amplified on a larger scale. In-line monitoring of dCO_2 directly in the bioreactor allows you to understand trends in the respiratory output of the cells so that you can prevent accumulation of dCO_2 that would have a negative impact on cellular productivity. dCO_2 will affect process performances and technical transfer across different bioreactor design and scale.

Optical Density Measurement

Optical density plays a critical role in understanding the particle concentrations in cell culture and fermentation. The right optical density measurement equipment can monitor well in low, medium and high cell densities of suspended solids. Continuous in-line OD measurements avoid the lag time of offline manual sampling.

Each of these measurements plays a critical role in the bioreactor, and they are all intertwined in the role they play in managing both productivity and quality of the resulting mAbs, proteins or vaccines being produced.

InPro 3253i pH & ORP Sensor

The InPro® 3253i is the optimal pH and ORP electrode for cell culture with extended fed-batch and perfusion. The ISM diagnostics provide a clear indication of whether fouling is occurring in these longer processes, and they guide the user on when sensor maintenance will be required.

InPro 6860i oDO Sensor

InPro 6860i optical oxygen sensor is designed to run under long perfusion batches without having to be extracted from the bioreactor thanks to ISM technology, which provides diagnostics before, during and after a batch on whether the sensor has the remaining life to withstand the duration of next batch.

InPro 5000i dCO_2 Sensor

The InPro 5000i dCO_2 sensor measures dCO_2 in-line during fermentation long perfusion runs with same precision as an offline Blood Gas Analyzer. It continuously detects changes in dCO_2 content in media, giving the possibility to implement a stripping control strategy.

Semi-Continuous Manufacturing
Using the Perfusion Model

Perfusion cell culture is recognized by pharmaceutical industry experts as one of the technologies that will transform the industry during the 21st century, whether perfusion is applied with a benchtop bioreactor, at larger volume when the bioreactor is sterilizable-in-place or applied using a single use bioreactor.

Increasing Productivity with Perfusion

Although perfusion became a medical term at the beginning of the 20th century, it was not until the 1990s that perfusion was applied for biological manufacturing at commercial scale to produce large quantities of monoclonal antibodies (mAbs).

Perfusion, an upstream process where cells are retained inside the bioreactor while continuously removing spent media and adding fresh media at the same rate, offers both challenges and benefits when compared to a traditional fed-batch. Perfusion mode is an open-system that is more complex to maintain technically for several weeks or even months, and preventing cross-contamination of the batch in progress is critical.

pH, DO & dCO_2 are Critical

As it is required during fed-batch mode, when running a batch under perfusion, it is essential to monitor and control the following analytical parameters beyond agitation and temperature: pH, dissolved oxygen available for living cell population, and dissolved CO_2 to prevent excess levels from accumulation, which may become cytotoxic to the living cell population.

In perfusion mode, due to the significant variation of media, exchange rate per day from one process model to another, it is essential to monitor and control the pH variations at the earliest point as they may indicate an early stage contamination.

Continuous Monitoring of Changing Conditions

At high to very high cell density, the availability and excess of oxygen can induce faster generation of oxidative stress and is critical to regulate according to the oxygen demand of the cell population.

Even if media is exchanged daily, spikes and accumulation of dCO_2 can generate considerable additional stress on the culture, reduce growth rate while becoming cytotoxic when dCO_2 is critical at low and high concentration.

It is therefore important when applying a continuous model, in particular for perfusion to monitor and control these four critical process parameters: pH, dissolved oxygen, dissolved CO_2 and culture media ORP.

ORP Helps Understand Oxygen Use

Beyond the characterization and monitoring of oxidative stress, the ORP signal could help understanding bioreactor poor oxygen homogeneity, effects of rich cell culture media, high productivity rate and daily waste accumulation. Several cell culture media components such as vitamins, amino acids, glucose, and even antioxidants can generate ROS in the presence of oxygen. For all these reasons, it is important to consider the variations of the ORP signal as critical as pH or CO_2 because both signals are critical, process-scale and cell line dependent.

Digital Sensors for Bioreactors

METTLER TOLEDO offers a range of analytical sensors designed for all bioreactors. These sensors are fully sterilizable and autoclavable, and provide reliable accurate measurement. Intelligent Sensor Management (ISM) technology provides real-time adaptive diagnostics of sensor health and performance to ensure that the sensor is measuring properly to protect batch integrity.

Fast and Effective Process Development
For Late-Stage Bioconjugation

Bioconjugates are a class or generation of molecules designed for increased therapeutic efficacy, enabled by the combined function of two or more different types of molecules. The complexity of bioconjugate chemistry is ever-increasing while its optimization is further confounded by variable parameter controls. More often, the requirement for robust processes wins over optimization.

The tools historically adopted for bioconjugate applications, including microcentrifuge tubes, beakers, hot plates, magnetic stir bars and transfer pipettes are no longer able to meet reproducibility demands around pH, temperature, dosing, mixing, and other parameters. With requirements for shorter process development times, increasing regulatory diligence, statistical redundancy and complementary data streams, scientists have a clear need for new technology to multiply productivity and safely speed development.

Today, bioconjugate scientists can adopt automated parallel reactor workstations such as EasyMax™ or OptiMax™. This technology provides integration of historically disconnected operations into a cohesive architecture where data from process parameters including, conductivity, temperature, pH, mass flows and other parameters are accurately captured and precisely controlled. At pilot and manufacturing scale, load cells and mass-flow controls are incorporated. Automation enhances data integration, process event correlation and experimental integrity during Design of Experiment (DoE) and scale up studies.

Whether implementing a turn-key bioconjugation platform or integrating and connecting existing systems, efficient processes and modern processes developed, validated and manufac-

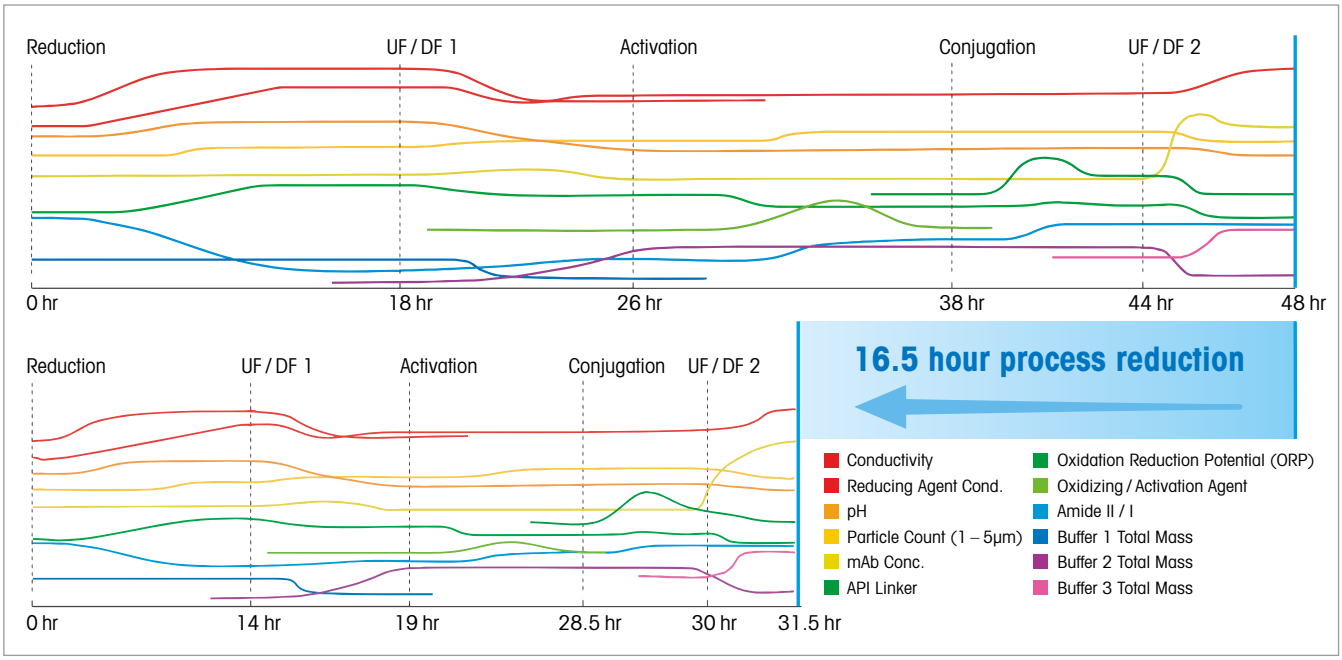


Figure 1. Time savings resulting from real-time overlay of multiple parameters during a conjugation process. In-line measurement of all parameters with minimal intervention required.

tured in parallel rely on solutions for PAT measurement and CPP controls from a unified provider source. Ensure pH titration and conductivity controls communicate seamlessly with reactor control modules, floor scales, load cells, as well as your particle and spectroscopy PAT.

	Before (Phase 1)	After (Optimized)	Advantage
Reduction	30 min	Omitted	Time ↓
Linker: Target	1.4 : 1	0.95 : 1	COGs (55 %) ↓
Activation Buffer	MES pH 7.0 (30 min RT @ 4.0 mg mL^{-1})	Lactate pH 4.0 (60 min RT @ 6.0 mg mL^{-1})	COGs / Hold Time ↓/↓
Target: API	4.7 : 1	3.0 : 1	COGs (36 %) ↓
Conjugation Buffer	MES pH 7.0 (Crude: ~ 60 % + 2 Product)	His, Sucrose pH 6.5 (Crude: ~ 74 % + 2 Product)	Product Distribution ↑
Conjugation Time	48 h (~ 5C)	24 h (20C)	Time ↓
Yield	~ 250 g (input: 400 g mAb)	~270 mg (input: 400 mg mAb)	Similar •
Total Process Time	~ 5 days	~ 3 days	Time ↓

Figure 2. Before and after results of bioconjugation DoE studies performed in EasyMax with pH and conductivity sensors as well as mass controls which demonstrate economic, process and quality attribute improvements[2].

Increased Productivity & Financial Savings

Automation allows re-task and allocation of Full-Time Equivalent (FTEs). Scientists realize an 80 % reduction in hands-on experimental time coupled with up to 75 % reduced need to repeat experiments through high levels of confidence supported by data correlation.

Shorter Project Timelines

With automation, scientists capture the same quantity and quality of information in two weeks versus an estimated previous three months using legacy approaches.

Increased User Safety

By reducing 80 % of the human intervention required for sampling and dosing operations, potential exposure to highly toxic Active Pharmaceutical Ingredients (APIs) is significantly reduced.

Data-rich Experimentation for Improved Product Quality

The ability to rapidly overlay and correlate multiple process parameters from a series of reactions enables a high degree of confidence in defining the next operation. Both process time and quality attribute improvements result. This enables greater process control and understanding, shortening time required to achieve quality through a well-designed and defined process space.

Read the Full Articles

1. Hu et al. Development of commercial-ready processes for antibody drug conjugates. Organic Process Research & Development. 2017. https://doi.org/10.1021/acs.oprd.7b00023
2. Dirksen et al. Process development of a FGF21 protein–antibody conjugate. Peptide Science. 2018. https://doi.org/10.1002/bip.23042

Buffer Preparation
Separation & Purification

Buffers play an important role in all downstream processing steps including harvest, capture chromatography, viral inactivation, multiple buffer exchanges, polishing chromatography, formulations, and even crystallizations. They protect proteins from variations of pH that can be damaging to the final product. Proper buffer preparation ensures a quality and effective final product.

Batch-Mode Buffer Preparation

The traditional method of preparing buffers is in a batch-mode, where individual components of the buffer are manually weighed and added together to make the buffer. This batch-mode of buffer manufacturing requires a variety of scales with diverse capacity ranges and resolutions to ensure that each ingredient is properly measured prior to addition.

A weight-driven buffer preparation process, combined with in-line analytical measurements, can help make buffer preparation, and related downstream separation and purification activities efficient and consistent.

Large & Small Component Addition

One of the major challenges in buffer preparation is the requirement of different capacity measurement equipment. An effective way of doing large-capacity measurement is to fit the tank on weigh modules. Weigh modules allow measurement directly in the vessel without a separate scale, these weigh modules can work on both low and high capacity systems. For smaller vessels and mobile mixing tanks, a floor scale may be the suitable solution. These systems with large capacities, paired with smaller, high precision scales offer the package needed to manage the buffer preparation process.

Analytical Control over Purification

Typically, buffer quality and other attributes are measured as an endpoint rather than in real time. In-line, in-situ ATR-FTIR spectroscopy directly observes aqueous dissolution and quantitative in-situ concentration of multiple components simultaneously, without need for grab-samples or offline endpoint methods.

In-situ particle system characterization follows dissolution kinetics of media components and informs method development, especially for challenging hydrophobic components such as Tryptophan or various surfactants. Particle and spectroscopy PAT combine with weigh module mass-flow and biophysical sensors to indicate process attributes such as preparation time or cycle times, especially for point-of use preparation.

Product recovery, purity and throughput can be adversely affected by pH, conductivity, particle dissolution or precipitation and in-situ concentration and composition, especially if deviating from an expected preparation

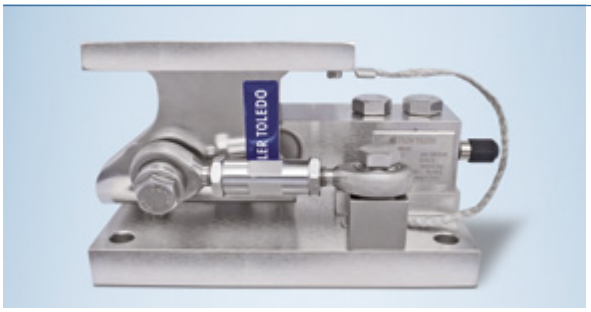
In-situ component concentrations such as surfactants and poor solubility excipients can be verified spectroscopically and in real-time, well before any endpoint analysis.

Purification is only reproducible under optimum pH conditions. Therefore, pH, conductivity and in-situ concentration of critical components should be continuously monitored to verify homogeneity of buffer preparation and salt concentration for all downstream buffers. Wrong pH or composition could lead to product failing to bind to a chromatography column varying elution consistency, deviation in viral inactivation and clearance, incorrect reliance on diavolume-based kinetics and concentration assessments, or improper formulation of bulk drug substances.

Digital Integration & Industry 4.0

Separation and purification processes, which include capture and polishing chromatography, matrix processing during viral clearance and buffer exchange processes all require fast feedback of changing conditions, which is why they are primed to benefit from digital integration and industry 4.0 (or

Industrial Weighing



PowerMount weigh modules have on-board microprocessors that provide load cell diagnostics to ensure accurate weighing of critical components in buffers. Weigh modules come in high capacities (up to 300 t), with some designed according to stringent hygienic design principles. METTLER TOLEDO offers a wide range of weigh modules and floor scales for buffer production include the MultiMount weigh module series for low capacity weighing (5 – 4400 kg) and portable floor scales.

Component Concentration Control

In-situ component concentrations such as surfactants and poorly soluble excipients can be verified spectroscopically rather than assumed by mass alone or by other indirect methods such as visual inspection for complete particle dissolution. Accelerate root-cause analysis with rapid identification of precipitation or other adverse stability conditions.

Transmitters for Integration

ACT weighing transmitters connect weighing components – including analog, POWERCELL or high-precision sensors – to the PLC, using standard communication protocols. Access to security-relevant data such as adjustment of values and weights-and-measures settings are restricted by security switch, password or user PLC. Easy connectivity speeds up installation and enables faster scale up.

Analytical Sensors

Conductivity and pH and ORP sensors designed for in-line measurement provide continuous, real-time monitoring during buffer preparation and can streamline preparation, reducing offline sampling for buffer release.

Industrial Internet of Things) concept for process control. The current biopharma industry demands intelligent process equipment based on smart sensors. The automation interface used in the smart sensors produced by METTLER TOLEDO include built-in security features such as synchronization, equipment status and heartbeat, which notify disruptions in real time.

Formulation, Fill and Finish
Ensuring Quality and Profitability

Biopharmaceutical molecules, such as peptides, proteins, and DNA- or RNA-derived products, require the utmost in process management to ensure end products are safe, compliant and effective. Risk-based equipment selection and end-to-end process control can help to improve product quality and overall profitability for biologics and biopharmaceutical manufacturers.

True process control

Containment manufacturing of high-potency products usually requires accurate weighing of small ingredient or excipient quantities. This type of weighing benefits from the use of hygienic, high-precision balances. Higher-quantity weighing is performed with bench and floor platform scales, while very large volumes may require systems in which tanks, hoppers or vessels are turned into accurate scales through the addition of high-capacity weigh modules.

In each case, when potentially active molecules are involved, it is important that these weighing installations comply with clean room, hazardous-area and cGMP requirements. In these sensitive areas, condition monitoring becomes critical to detect malfunctions that could falsify weighing results, which in turn could risk expensive material loss, safety incidents, or even consumer health. Smart load cell technology helps to ensure the kind of accurate condition monitoring that prevents unexpected downtime or poor batch performance. When such installations pair fit-for-purpose weighing devices with active condition monitoring, process control, regulatory compliance and product quality attributes can be achieved.

Leading-edge accuracy

As newer, more potent therapies emerge, many of them are produced in smaller lot sizes that require extremely accurate weighing. For example, the filling and finishing of small-volume biologics-based parenteral products is performed with high-precision weigh modules embedded in instruments, machines and isolators. This type of weighing, whether it enables manual or automatic filling, often requires the kind of accuracy found on the very edges of current metrology practice.

Additionally, regardless of installation or application type, high-potency filling or dosing requires safe and compliant cleaning procedures. Selected equipment must be able to withstand these procedures.

Traceable materials and data

In the midst of highly specialized formulation and filling operations, traceability presents another challenge. The improvement of data transfer for material tracking, recipe management and production staging is critical.

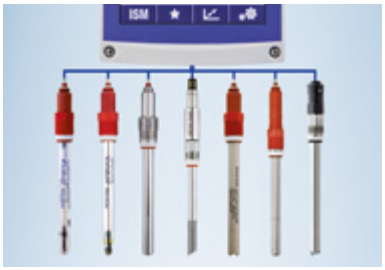
Formulation software helps to ensure consistency and automated batch evidence reporting. Software that enables statistical quality control enhances cost-effectiveness and safety by controlling over/under filling and ensuring compliance to FDA 21 CFR Part 11 and other pharmacopeia guidelines applied. The addition of necessary peripherals, such as printers or barcode readers, further prevents data-entry errors and supports traceable processes.

In short, end-to-end process control enabled by smart condition monitoring, repeatable hygiene practices, and data integrity is especially critical for accurate, safe formulation and filling of biologics.

How Easy Connectivity Enhances Your Process
An easy ability to connect static and mobile scales, weigh modules, checkweighers, metal detectors and other devices to process logic controllers or higher software systems helps to ensure tracking, tracing and materials management for sensitive biologics processing. Learn the benefits offered by easy-to-connect scales, sensors and more:

Industrial Weighing
Connected terminals and transmitters enable automated filling and formulation control as well as easy communication with ERP systems. METTLER TOLEDO solutions fulfill Industry 4.0/ IIoT requirements for data integrity, connectivity and automation.

Transmitter Integration
We offer a range of analytical transmitters that bring ease, performance and outstanding process control to your pharmaceutical formulation and filling processes.



Analytical Sensors
METTLER TOLEDO offers a full portfolio of weighing, analytical and inspection solutions across the pharmaceutical value chain. See how integrating smart sensor technologies can help you enhance productivity, ensure accuracy, and control costs.

Managing Water Quality
To Ensure Compliance and Control

Water is the most widely used excipient in biopharmaceutical manufacturing processes. It is used as an ingredient, reagent, solute, delivery device and cleaning material. In pharmaceutical production, the accurate measurement and control of water quality is critical to the water purification process.

There are two critical components to water monitoring: Compliance and Control.

Compliance

Global pharmacopeia requirements mandate a range of testing and process requirements for the testing of pharmaceutical grade waters. Ensuring that you have equipment that meet those pharmacopeia requirements helps to make sure your water system stays compliant.

Control

In addition to compliance, the right analytics on your water system help you to demonstrate control, implement root-cause analyses and take immediate steps if you trend out-of-specification.

METTLER TOLEDO offers the analytical tools to help meet both your compliance and control needs so that you have safe, compliant waters for each part of your production process.

Total Organic Carbon

Meet USP <643> and EP 2.2.44 requirements for TOC monitoring while ensuring unprecedented control. The 6000TOCi offers real-time monitoring, with built-in reporting on peak TOC levels and trending over time.

Bioburden

Online Water Bioburden Analysis (OWBA) offers a recognized method to quickly detect microbial contamination in your water system. The 7000RMS™ shows immediate increases in bioburden so quick actions can be taken.

Conductivity

USP <644> and <645> provide specific guidance for conductivity monitoring. The digital UniCond® sensor ensures you meet the accuracy requirement of ±2 % and requirement that the electronics can to be calibrated separate of the sensor.

Efficient and Compliant Offline Testing
In the Quality Control Laboratory

Every product needs to adhere to a defined set of quality criteria. Within the highly regulated environment of the biopharmaceutical industry, the objective of a quality control lab is to achieve reliable results in the most efficient way possible, never jeopardizing traceability, data integrity or compliance overall.

Quality control laboratories play a critical role in pharmaceutical manufacturing, from the evaluation of raw materials through to the release of the final packaged product. They are pivotal in ensuring the safety and efficacy of products administered to patients. As the complexity and testing requirements of pharmaceutical manufacturing increase, laboratories face growing pressure to improve operational efficiency, better manage and allocate resources, and ensure they deliver real business value. All of this must be done within a highly regulated operating environment in which there are ongoing concerns about data integrity.

The variety of equipment in a pharmaceutical quality control lab often presents challenges of integration and compliance recording. METTLER TOLEDO offers a wide range of instruments and balances that, in combination with the LabX™ software, ensure that compliance with FDA 21 CFR part 11 is achieved.

In addition, all data from these Excellence line instruments and balances, including metadata, is automatically stored in a centralized database at the time of creation. LabX reduces the time necessary for manual data recording and eliminates the risk of transcription errors. It helps labs and production sites meet FDA ALCOA+ requirements for data integrity. In addition, the data can be accessed 24/7, from anywhere, and customized reports are easily generated – tailored to any need.

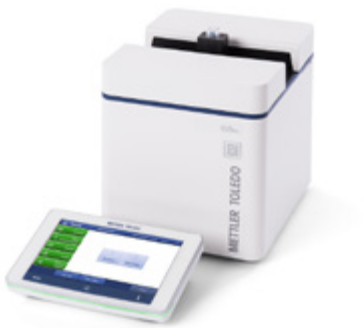
Reliable Weighing Results

Proper sample preparation and careful data handling are crucial. When there is no room for compromise, Excellence Weighing and Dosing Solutions deliver accurate results the first time and every time.

Compliant Pipettes

To accommodate GLP/GMP compliance, the E4 pipette makes it possible to password-protect pipette settings, protocols and service alarms. Service records, cycles and status data are completely tamper proof. Your data is everything. Trust the E4 XLS+ pipette to deliver!

UV/Vis Workflow Control



The LabX PC software expands your UV/Vis spectrophotometer with a sophisticated graphical editor for spectra evaluation. Data management is simplified in one FDA 21 CFR part 11 compliant software package. To optimize and secure your workflow even better, let the task scheduler organize your measurements.

Modular, Multi-Channel pH Meters

SevenExcellence™ is the perfect choice for applications where maximum accuracy and GMP compliance are required. The multi-channel instrument allows measurements of up to three parameters simultaneously. You can choose from pH, ORP, ion concentration, conductivity or dissolved oxygen.

METTLER TOLEDO Solutions
for Biopharmaceutical Manufacturing

Process Analytics

METTLER TOLEDO Process Analytics provides equipment for in-process analytical measurement in upstream and downstream processes. In-line analyzer and sensor solutions help biopharmaceutical manufacturing make better, faster and more accurate decisions to optimize biomanufacturing from the bench to the cubic scale. METTLER TOLEDO Thornton water analyzers and sensors help ensure purity and compliance of pharmaceutical grade waters.

Learn more or request information/pricing on these process and water analyzers:

▸ **www.mt.com/PRO**

AutoChem

Learn how scientists and engineers apply automated workstations, in-situ spectrometers and particle size analyzers in downstream bioprocess development to improve tech transfer to manufacturing and speed time to market.

Understanding how process conditions impact protein concentration and yield helps identify factors that contribute to bottlenecks and impurity formation. Overcome challenges associated with offline analytical techniques, including inaccuracy and time delays, and improve unit operations such as purification, chromatography, viral inactivation, buffer exchange, up-concentration, bioconjugation, vaccine adjuvant synthesis and formulation.

▸ **www.mt.com/Bio-PAT**

Industrial Weighing

METTLER TOLEDO Industrial Weighing equips biopharmaceutical manufacturers with the reliable high-precision weighing solutions to meet exacting production standards, connect with production management systems, and ultimately enable maximized yields.

▸ **www.mt.com/industrial**

www.mt.com

For more information

METTLER TOLEDO Group
Process Analytics
Local contact: www.mt.com/pro-MOs