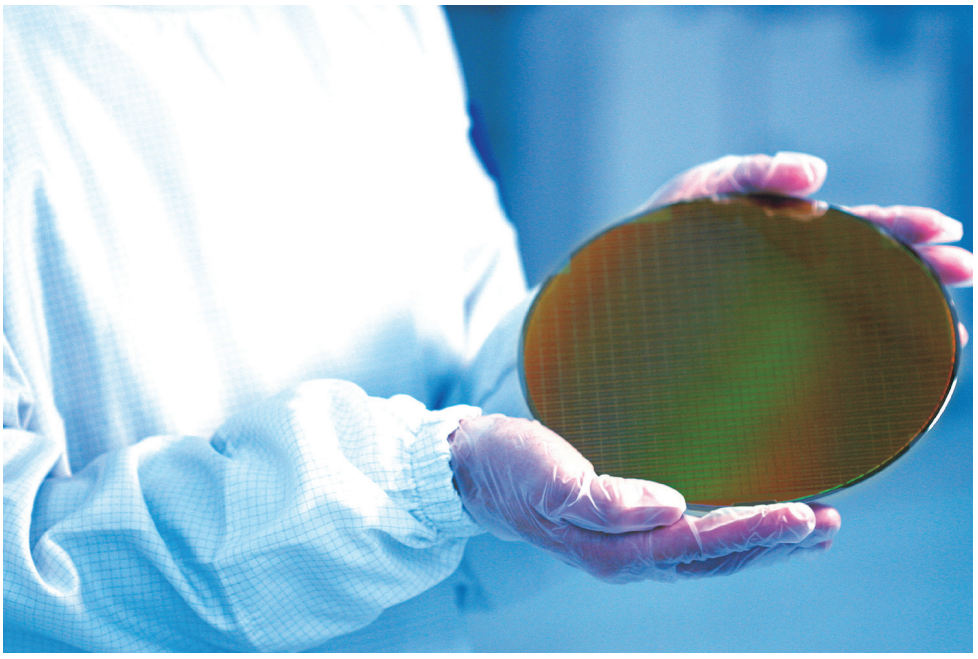
BioPharm INTERNATIONAL



Applying Lessons Learned from the Semiconductor Industry

Raw materials' characterization and supply-chain control allow more rigorous control of the manufacturing process.

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Two of the world's most complex manufacturing industries—semiconductor fabrication and biopharmaceutical production—share a common fundamental objective: to maximize process yields through rigorous control of production equipment and process variables.

One process variable that the semiconductor industry has long focused on is raw material quality. Thorough analysis and full characterization of each raw material used will determine the precise composition, down to the parts-per-trillion level, providing information on how this composition might impact the production process. Recently, biopharmaceutical manufacturers have also begun to focus on understanding and controlling the characteristics of the materials they use. In upstream and downstream processes, biopharma manufacturers seek to correlate raw material data with variations in their bioreactor and process chromatography yields, with a goal of achieving greater predictability and control of process results. In formulation, a lot of emphasis goes into correlating how variables in excipients affect drug product stability (and therefore bioavailability) throughout the shelf life of the product.

There is significant value in assessing and potentially applying the semiconductor industry's highly developed advanced materials analysis, characterization, and supply-chain control practices to materials' management and process control issues in biopharmaceutical operations.

MAXIMIZING SEMICONDUCTOR YIELDS

Semiconductor manufacturing is expensive. The cost of building a semiconductor foundry can exceed $10 billion when all the tooling, automation and management systems, environmental controls, and quality control costs are considered (1). And once in place, the additional cost of the raw materials and associated processing to make a sin-

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gle wafer adds to this expense, which is why semiconductor manufacturing operations must focus on maximizing process yields.

At the beginning of the process, a raw wafer, composed of a highly refined form of silicon, can cost approximately $500 (1). There can be 25 to 50 wafers in a batch, and a large fabrication plant can process 50,000 wafers per month, with each wafer going through more than 1000 process steps. A wafer containing finished memory chips can be valued in excess of $1600, and a finished high-end processor wafer can reach $5000 (1). Every process step has an impact on yield and, ultimately, profitability.

It is crucial for a manufacturer to control process variables and eliminate unknown factors that could interfere with or contaminate each step of the process. In complex integrated circuits such as processors in smart phones, a single chip can contain several billion transistors, each only a few nanometers wide. If any foreign material is present in those transistors, the chip may not function according to its design. The risks associated with these challenges has led the semiconductor industry and the companies that supply its materials to make investments in ultra-precise materials characterization procedures in order to maximize predictability of manufacturing outcomes.

Each process step is controlled by a process of record that defines every detail. For example, the exact chemical makeup and level of impurities in a chemistry used to remove post-etch residue must be characterized down to the parts-per-trillion level. While it may not be practical to manufacture a chemical to meet 100% purity, the chemical should be as pure as the best technology can deliver. Any trace materials in the post-etch strippers used in the process need to be identified and quantified so they may be incorporated into a process of record and monitored. Once set, the foundry operator has the statistical data to assume that, with the properly characterized material, that post-etch residue step will yield the defined result, and the wafer can move on to the next process step. Any variation in trace elements—even just a few parts per billion—can result in less-than-desired post-etch cleaning that may interrupt production and lead to significant costs in time, labor, testing, materials, and other areas to investigate the cause of variation.

IMPROVING BIOPHARMA STABILITY AND YIELD

Materials characterization has also been of interest in the biopharmaceutical industry; however, rather than yield, manufacturers were initially interested in using it to determine stability. Highly accurate and detailed materials characterization has been performed for the excipients used in fill/finish processing. During this process, the biological drug substance is combined with a variety of excipients to enable delivery and stability and is formulated into a final drug product. Because the excipients would be used within the body during the administration of the final drug, such characterization is necessary, and requirements have increased over time to satisfy strict regulatory and safety requirements. Also critical is the stability of the drug product; reducing drug product degradation during storage has become a significant focus for raw material characterization.

From this initial focus on meeting regulatory requirements and drug product stability, biopharma producers seeking to improve their process yields have more recently begun to assess the impact of stricter and more comprehensive materials characterization in upstream and downstream process steps.

Unlike fabrication of precisely engineered semiconductors, however, biologics production has an inherent variability. Even under similar process conditions, a molecule can react slightly but measurably differently, often depending on genetic sequencing for that particular molecule. All these molecules react differently to a variety of trace metals. When large-scale production of biologic drugs originally began, the focus was on characterizing excipients, but not nearly as much attention was paid to the buffers, salts, cell culture media, and other materials used upstream, until further study and analysis tied to improved process control was undertaken.

A further challenge to understanding and applying rigorous materials characterization practices to biologics production is that the presence of trace minerals can actually be beneficial to upstream and downstream processes. The addition of metals, including iron, manganese, and zinc, can enhance glycosylation yields upstream in certain molecules. It has also been shown that understanding and controlling the ratio of trace metals, as well as their levels, can impact upstream yields positively or negatively—all dependent on the molecule.

As biopharmaceutical manufacturers have begun turning their attention to improving trace material characterization, they have determined the critical importance of lot-to-lot consistency of the trace elements in critical materials used upstream and downstream. Variation to that consistency, including minimal changes at the parts-per-billion levels, can impact glycosylation patterns in the reactor, reduce overall target cell growth upstream, and impact recovery downstream. This knowledge has been gained by the biopharma industry while responding to problems or unexpected shortfalls in upstream yields. As a result of lessons learned, the biopharma industry is turning to a more formal and comprehensive process of trace materials characterization as a tool to boost yields.

APPLYING BEST PRACTICES

The biopharma industry has already made great strides in improving its trace materials characterization efforts and applying that data to improving upstream and downstream yields. To advance this further, three rigorous processes used in the semiconductor industry can be applied to the biopharma industry: statistical control,

analytical capabilities, and in-depth management and control of global supply-chain resources.

Statistical control

It is well established in the semiconductor industry that every process step, including a change to a step, goes through a comprehensive qualification process that ensures every material used in a process is qualified at specific ranges down to parts-per-trillion levels. Once qualified, suppliers commit to and document that every lot has the same level of trace materials. Some suppliers are able to commit to characterizing, within two sigma, each of the components of a certificate of analysis (CoA). In fact, the trend is moving in the direction of even stricter, three sigma levels of control of impurities in raw materials.

Although biopharma processes can deliver projected yields with a parts-per-billion characterization, there are advantages to adopting the comprehensive model used by the semiconductor industry. By establishing the principle that all materials used in upstream and downstream processes will be fully characterized and controlled, it should become easier to predict process yields, identify whether materials are contributing to a shortfall, and leverage the ability to modify the levels and ratios of trace metals in bioreactors to potentially improve yields.

Analytical capabilities

For biopharma manufacturers to effectively implement statistical control along the same lines as the semiconductor industry, they will need to increase investments in analytical capabilities and tools and begin to implement a data-driven production environment. Compared to other process industries, the biopharmaceutical industry lags in the aggressive use of data and predictive analytics to uncover ways to improve productivity, yields, and costs. The industry is, however, making significant investments to improve its use of data.

The objective is to use production data to optimize the process, then manage the critical parameters within it so it can be reliably repeated. These efforts are being conducted for both upstream and downstream production, but often in isolation. There is an opportunity to expand the application of data analytics beyond a specific process component to more completely characterize the entire process, including the raw materials used in both upstream and downstream production. Ultimately, this can be integrated into the overall optimization efforts for the entire production process.

Supply-chain control

One of the most important benefits of greater statistical control and analytical capabilities will be the ability of biopharma manufacturers to have more complete control of the quality of the materials they receive from their global supply chains. This is a key capability that has been established by the semiconductor industry to prevent variations in trace materials from impacting their operations.

For example, there are multiple processes in semiconductor fabrication that use organic solvents. Many of the precursors for these solvents are manufactured by petrochemical producers, who normally don't need to exercise ultra-stringent control of impurities. As a result, suppliers of solvents to the semiconductor industry have invested in the tools and processes to manufacture their products with tight purity levels and fully characterized CoAs. In addition, they work with their suppliers to document any changes made to source materials or production processes, well ahead of time. This lead time lets the supplier build stock and evaluate that change as it comes through the process to see if it introduces change to their end product.

This same attention to detail and supply-chain control is also crucial for biopharma materials for essentially the same reason; minor changes in processes or raw materials used upstream can significantly affect the downstream product.

In addition to variation caused by trace minerals, biopharma processes may use organic or plant-based materials. For example, sucrose and galactose are sugars derived from sugar beets. Plant-based materials will inevitably have some variation in their properties. There are significant advantages to working with suppliers who have implemented technologies and purification to further purify and narrow variability in elemental impurities that would affect biopharmaceutical production.

By building networks of suppliers who are fully committed to following global current good manufacturing practices for manufacturing processes and documenting all source materials completely, it is possible for the biopharma industry to achieve a similar level of materials management and control over the variability and quality of critical sourced components.

CROSS-COLLABORATION

Although the two industries have vast differences, both semiconductor manufacturers and biopharmaceutical manufacturers have some core common ground. Both begin with raw materials and process those materials in a highly controlled, multi-step fashion to produce products of high value. And both industries are driven to invest time and resources into continuously improving those processes to achieve better yields and return on investment.

By applying some of the hard-earned principles and approaches the semiconductor industry has developed, the biopharmaceutical industry has the potential to significantly advance its ability to analyze, characterize, and control the trace elemental properties of the materials used in biologics production and ultimately achieve new milestones in process efficiency and yields.

REFERENCE

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