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RAW MATERIALS

Gradation in Pharmaceutical Manufacturing

A look at industry trends and how suppliers help

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Drug development is a lengthy process, sometimes taking up to 15 years to get to the final commercial manufacturing phase. Whether biologics or small molecules, all medicines have to meet strict regulatory and quality standards to ensure patient safety and product integrity. Within these standards there are different ranges of quality for the raw materials used in biopharmaceutical manufacturing depending on where manufacturers are at in the development process. Often times, the quality of raw materials used in discovery and pre-clinical phases can be very different than those in the clinical trial phases and through to review and commercial manufacturing.

Involving quality raw material suppliers from the beginning of drug development can reduce many risk factors.

As drug manufacturers are increasingly looking to minimize costs in the research and development phases of a product, they may choose a lower-quality version of the regulated raw material, not wishing to pay for full traceability or GMP-standard manufacture when it is not necessary. When looking at the right level of quality to use through the different phases of manufacturing, it is important to take all factors into consideration. In this article, we take a look at raw materials, why grade matters, the responsibilities of a supplier, and the importance of a clear remediation policy.

QUALITY ALONG THE WAY

While the regulatory demands are clear for commercialized drug products, they tend to be much less specific during development phases. It is true that many potential medicines will go through the scale-up process only to fail in Phase III trials. In other cases, they may successfully make it through clinical trials, only to have regulatory authorities reject them when a market authorization application has been made. Yet a biopharmaceutical manufacturer

should be looking to the final manufacturing process even at this early, uncertain stage of the development process.

As the product moves through the pipeline, from the medicinal chemist's lab bench to the commercial product, the approach should change. Ideally, the raw materials being used are subject to a grading system to determine whether they comply with industry regulations at each point.

To save costs during scale-up, a company may be willing to accept non-critical raw materials that do not meet all the stringent requirements for items of GMP or other high quality standards. However, pursuing supply chain transparency and demanding extensive documentation earlier should minimize risks and help to avoid problems further down the line.

WHY GRADE MATTERS

Undocumented materials introduce the risk that undefined or unquantified contaminants might be introduced into the process, which could impact the final product. Those may also affect the manufacturing process itself, altering the yield or even the product of a chemical reaction, or the composition of a peptide for a biologic.

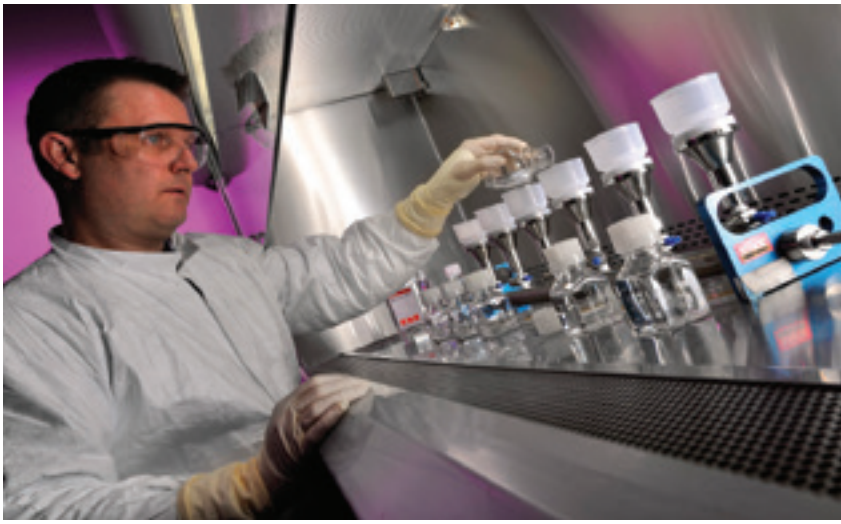
As the quality level of a raw material increases, the risks it poses decrease. The most difficult decision for a manufacturer is frequently balancing cost and risk in the early stage of development in terms of raw material choices. While those higher-quality products do increase costs, there are other advantages on top of the reduced risk – should the product advance into clinical trials, the necessary supply chain transparency documentation will already be in place-with certificates of origin for those raw materials.

Consequently, biopharmaceutical manufacturers have become increasingly reliant on their suppliers to assist with product compliance. They are looking to meet all the necessary standards without engendering excessive cost and will consult on what grades are appropriate. Raw materials must meet the regulators' quality requirements for each stage of the process – so here, the real consultation is looking into the end product itself, learning actual details and staying in line with the precise requirements (which can also vary from one region to another).

IDENTIFYING OPTIONS WITH A SUPPLIER

The simplest – and safest – solution is to work with a supplier who is capable of providing raw materials of different grades. This will make the transition between the different phases of manufacturing development more straightforward, and it will also shorten the timelines, as new suppliers will not have to be qualified every time the project advances through the pipeline. The supplier should have a clear understanding of what, in quality terms, is acceptable at each stage of the development process and whether the raw materials are non-regulated, non-GMP quality or highly regulated materials manufactured to the exact criteria laid down in GMP regulations.

Perhaps the most important thing a supplier can provide is insight into precisely what regulatory requirements are demanded by the agencies in each region where the biopharmaceutical manufacturer may want to sell their products. These regulations are complex and subject to updating, and a good supplier will remain on top of the regulations at all times, helping ensure their customers will, too. Impartial advice relating to the quality standards required for raw materials for any particular application should also be available.



Ensuring the quality of raw materials at every stage of manufacturing development helps to shorten timelines.

This will constitute a strong supply chain – one that is validated with full documentation and transparency of all the ingredients they supply, and one possessing an understanding of the necessary product quality for each step of the development process. Any changes in their supply chain should be passed on to the customer in a timely fashion.

A secured supply chain is equally important. However good that supplier may be at manufacturing and documenting the raw materials they provide, if disaster strikes this can cause enormous problems for the manufacturers who rely on them. This is where the importance of redundancy comes to the fore. If a manufacturing facility has a major fire or is hit by a natural disaster, it may be out of commission for some time. While such occurrences are rare, they do happen. If that supplier manufactures its raw materials in more than one location, it will be able to mitigate the problems in the stricken facility and ensure continuity of supply.

They should also be competent at dealing with any quality issues that do arise – in the real world, problems do happen and speedy, effective resolution is essential if the manufacturer's business is not to be adversely impacted in the long term.

Process control is also a key factor; a qualified supplier will have up-to-date facilities and control technology. Not only will this assist in providing clear documentation and full disclosure to the customer, perhaps more importantly it helps them manufacture contaminant-free products that meet all quality standards.

WHEN THINGS GO WRONG

Even when supply chains are carefully planned, developed and monitored, the occasional quality control error can still occur. As it is impossible to remove all risks from the supply chain, it is essential that there is a remediation plan in place. Routine regulatory inspections should reveal deficiencies and enable problems to be isolated and addressed. Complete transparency in the supply chain is a crucial factor, as it makes it easier to take up technical or regulatory issues at the outset, and it facilitates the creation and revision of guidance documents.

At its heart, remediation recognizes problems, fixes them and then closes any gaps to ensure regulations are met in the future. Regulators are not so much looking for perfection as they are looking to ensure that the manufacturer is well versed in its own processes and their optimal operation; it is imperative to understand how data is stored, managed and analyzed. Proactive involvement can help predict issues that might occur before they cause recalls and warning letters. Often, the best person to do this is a remediation expert who has experience and expertise in managing such situations.

BALANCING COST VS. RISK

It is no secret that biopharmaceutical manufacturers have a great amount of choices to make when investing time and money into the development of a new product. When looking at what raw materials to source, and in what grade, it can be hard to know what the right answer is. In many cases, involving quality raw materials from the start addresses and removes the risk factor that a manufacturer may have. However, there is no such thing as a perfect situation. Each case brings its own individual implications, so it is important to work with a knowledgeable supplier who can offer piece of mind with a back-up plan to keep things on track. ■