Understanding Good Manufacturing Practice and how Biological Industries can support cell therapy development

When selecting raw materials or ancillary materials for the production of a cell-based therapy product, you have many options from various classifications: research use and further manufacturing, cell culture grade, medicines, medical grade, medical devices, IVD, USP grade, EP grade and all kind of brands private grades. It can be very confusing and unfortunately sometimes misleading.

When choosing materials for your product, it is important to check the following basics with the manufacturer:

1. Does the manufacturer comply with GMP?
2. Does the manufacturer have a QMS Certificate, ISO 13485 or ISO 9001 certification?
3. Is the specific product registered as IVD, MDD, medicinal?
4. Does the specific product have a Drug Master File (DMF) filed?

In the following article we will try to shed light on these important topics.

## Good Manufacturing Practice (GMP)

Current good manufacturing practice (cGMP), also known as Good Manufacturing Practice (GMP), is a set of guidelines, standards and regulations published by health authorities to ensure consistent and closely controlled products that are safer for patients. GMP (and corresponding standards – GDP, GCP etc.) covers every step of the manufacturing and production process, from product development and selection of the raw materials, to manufacturing and testing the product, to shipping and storing the product prior to use.

It is important to consider GMP throughout the development of a potential therapy to enable it to advance more easily from clinical trial to clinic. Authorities around the world publish GMP guidelines, such as the US Food and Drug Administration (FDA), European Medicines Agency (EMA) and the UK Medicines & Healthcare Regulatory Agency (MHRA).

For certain products, like therapeutic products and medical devices1, cGMP is a regulatory requirement mandated by law. When, for example, manufacturing a medical device for U.S. distribution you must be in compliance with these regulations and the product must be manufactured under a quality assurance program, be suitable for the intended use, be adequately packaged and properly labelled, and must have an establishment registration and device listing on file with the FDA.

Various products are exempted from cGMP regulations (borderline products), and authorities do not approve the product or the manufacture to cGMP standards.  In these cases it is the manufacturers' choice whether to follow cGMP standards or not.

### GMP and ISO

Both GMP and ISO are quality systems in their own right. As the revised GMP became final in June 1997 and the issue of ISO 13485 in 2003, the two systems grew to be similar in regards to the guidelines a company should follow to achieve quality.

There is, however, a real difference between GMP compliance and ISO certification.

The GMPs are a regulatory requirement mandated by law. ISO, on the other hand, is a voluntary certification obtained by a company when they determine that the certification is beneficial to their operations and/or marketing strategies. In addition to GMP and ISO 13485 quality management systems, an organization may adopt additional standards and guidelines in order to minimize the risk of its products and processes and to fit to its customer's demands and applications.

## In vitro Diagnostics (IVD) and ancillary products

A company can classify its products as suitable for use in In Vitro Diagnostics (IVD). IVD products can be considered as medical devices and can be used in the collection, preparation or examination of human samples. In addition, products for cell therapy are considered ancillary materials. Ancillary products are materials that come into contact with cells that will ultimately become a medical product or are part of a medical product. According to their designation, ancillary products and certain IVD products are suitable to be utilized in clinical trials. Ancillary products are part of the cell therapy development process but do not form part of the final product, although they are still an important part of the procedure.

### Drug Master File (DMF)

A Drug Master File contains detailed information about the ingredients, manufacturing facility and procedures involved in the production of a specific product. The process of registering a new cell therapy product with the FDA is significantly shortened when utilizing a product with an approved Drug Master File. It also demonstrates to the consumer that a company that manufactures such a product conducts its manufacturing operations in a transparent and correct manner and complies with quality and safety requirements.

### Biological Industries- Your partner in cell therapy development

Implementing GMP in your manufacturing process can be complex and costly especially when dealing with sterile products. Whether conducting basic research, pre-clinical or clinical trials, at each stage you can trust BI's expertise to accompany and support you. Their extensive knowledge and experience in regulatory affairs has led to many successful collaborations and clinical trial approvals for their customers.

BI’s manufacturing capabilities are ideally placed to support researchers in the early stages of developing the next cell therapy. Their state-of-the-art ISO 9001:2015 and ISO 13485:2003 certified facilities contain the highest quality equipment and clean rooms (graded from ISO 8/Grade D up to ISO 5 /Grade A (classified from class 100,000 to 100)) controlled environment.

In order to maximise  the quality and safety of BI's products to the use as ancillaries in the manufacturing of advanced therapies and cell therapies, BI chooses to adapt many of the sterile pharmaceutical cGMP standards and guidelines, and following the implementation BI has filed a Drug Master File (DMF) for several products. BI products that hold a Drug Master File are the human pluripotent stem cell culture media - [NutriStem® hPSC](http://www.bioind.com/nutristem-hesc-xf-medium/" \t "_blank) and the complete human mesenchymal stem cell media - [MSC NutriStem®](http://www.bioind.com/nutristem-msc-medium/). You can find out more about both these media here.

For products seeking approval from regulatory agencies other than the FDA, BI has complete technical dossiers which contain most of the information in a Drug Master File.

## Scale-up

Scaling-up your process in a reliable way is a key part in commercializing a therapy and taking it through clinical trial approval. BI’s know-how and experience can support your scale-up process, from development of a small scale research project to large commercial volumes and quantities. BI’s expert formulations scientists are also on hand to support you as you optimize your process, helping you identify the best available starting medium.

### Complying with the latest guidelines

It can often be difficult to keep up to date with changing regulations around the world. BI’s regulatory department utilizes international consultants and attends conferences and seminars around the world to ensure they are aware of any updates or upcoming changes to GMP requirements.

Although the FDA does not inspect facilities manufacturing ancillary products, to ensure complete compliance with regulations, particularly in the pharmaceutical sector, BI’s customers often perform quality audits on the manufacturing facilities. They also devise quality agreements which are reflective of current GMP standards. BI’s facilities routinely pass these audits without special remarks and apply any lessons learnt to further improve maintenance of their manufacturing and consultation.

As a contract manufacturer for several customers BI has passed successfully many Notified Bodies audits.

### Further reading

* Biological Industries’ [Quality System and Regulatory Affairs](http://www.bioind.com/israel/about/quality/)
* [cGMP: What every Life Science Researcher should know about current Good Manufacturing Practice](http://blog.bioind.com/cgmp-what-every-life-science-researcher-should-know-about-current-good-manufacturing-practice/)

### Notes

1. "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

* recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
* intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
* intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."

Source: [FDA: Is The Product A Medical Device?](https://www.fda.gov/medicaldevices/deviceregulationandguidance/overview/classifyyourdevice/ucm051512.htm)