

Life cycle stages: DP, DS, and R&D

One of the most common risks for an industry newcomer is planning to do too much at once, hurting their chances of success with any of their chosen plans.

Vaccine manufacturing and development falls into the following life cycle stages:

- **Drug substance (DS):** Producing antigen, the key substance that triggers an immune response.
- **Drug product (DP):** Using drug substance to formulate and fill vaccines into a form ready to administer (e.g. a glass vial, glass syringe or plastic tube).
- **Research and development (R&D):** Discovering new and refining existing DS and DP production processes.

If you're not working with a multinational budget in the billions of dollars, you should think carefully about your organization's specialization before you begin. For each life cycle stage, you will need different facilities, staff, training, timelines, partners, and face different levels of risk/reward. You not only need to consider your target life cycle stage, but what products you plan to make and how to have a good chance of success.

In this article we'll take a look at the main stages of the life cycle and their pros and cons, along with our recommendations for where to start and where to wait until you have more experience.

Drug substance (DS)

Producing antigen, or "drug substance", is the foundational step of vaccine production. This is achieved by using biological systems (except for mRNA), such as cells or whole organisms, that act as "factories" to produce the necessary components. In most cases, this process is defined by biology. As such, in the same way that you can't get a baby in one month from nine pregnant women, you can't usually speed up antigen generation, which can often take weeks or months..

Drug substance facilities are defined by the antigen they produce, as well as the biological system and reactor (known as a platform) used to produce the antigen and make it safe enough to be injected into a human. Vaccines can be made using chicken egg cells, Mammalian cells (e.g. human, canine, hamster, monkey, etc) and various types of plant, bacteria, fungi or yeast cells. These cells can be housed in reactors varying from plastic bags, stainless steel tanks, small glass bottles and even in whole chicken eggs.

All of this not only affects how to keep the cells happy, alive, and producing the right antigen (upstream), but also how you process and purify the antigen (downstream), with the ultimate objective of it giving an immune response without causing the disease. Needless to say, there are so many combinations of processes that each DS facility is more or less specific to a specific product. For example, the five antigens used in the pentavalent vaccine are produced on three different platforms, and even though tetanus and diphtheria are produced

in similar ways, tetanus requires a segregated production suite or often a totally different facility due to cross-contamination concerns.

Due to the complexity of the processes and difficulty of finding a tech transfer partner, most newcomers don't jump straight to producing drug substance. Additionally, most experienced manufacturers who want to expand to drug substance production initially focus on a single product and platform to build experience. There are opportunities for all platforms, and choosing one to specialize in will increase your chances of success now and in the future.

Drug product (DP)

Drug product involves taking drug substance from another manufacturer and performing the essential steps which turn it into a vaccine ready to be stored, shipped and ultimately administered to a patient. Steps such as formulation (i.e. adding stabilizers, preservatives and adjuvants which boost immune response), filling, packaging, final testing and sometimes lyophilization (i.e. freeze drying to increase heat stability), take place in a DP facility.

I've previously discussed some of the complexities of drug product manufacture, how different vaccine types often cannot be made in the same facility, and how production processes vary between products and between tech transfer partners. While specializing in just one product is less important here than for drug substance, focusing on doing less well than more badly is still the winning formula.

R&D

R&D is somewhat of a separate sphere from DS or DP production with inherently different objectives. For DP/DS, your objective is to strictly follow an existing process each time without letting it diverge from a set of hundreds or even thousands of parameters. On the R&D side, however, your objective is to discover new processes through hypothesizing, innovating, and experimenting and ultimately fix the boundaries of those parameters.

This requires different staff – typically a higher ratio of advanced degree holders to technicians. Production scales are very different as well, small R&D batches to prove concepts instead of larger batches to benefit from economies of scale, which require completely different facilities.

Even on their own, timelines and costs for R&D and commercial scale DP/DS can be large. However, trying to do both together also adds the risk of letting your production facility lie fallow waiting for your R&D to be ready, or vice versa. This is why you see many firms start out doing one or the other, rarely both, and even more rarely managing to do both well. It is so common for an R&D firm to outsource commercial production to contract manufacturers or commercialization partners, or for a production-focused firm to buy a small innovative research company to fill its product portfolio.

However, researching new antigens and processes is not the only area where you can develop R&D skills. Refining tech transfer processes and researching ways to produce more efficiently and safely is an accessible way for a DP or DS company to branch into a new area.

Pathways to success

With this information in mind, how can you give yourself the best chance of starting successfully as a newcomer to the industry? Few start by trying to produce drug substance. Even if you wanted to do this, you'd be very unlikely to find a tech transfer partner without a proven track record.

Depending on your starting parameters, your risk appetite, and type of staff you have available, both R&D and DP production can be places to start. R&D can often start as a spinout from a university or publicly funded entity which can raise funding and seek partnerships as the research looks more promising.

A successful DP tech transfer under your belt can be a stepping stone towards receiving a tech transfer to start producing the DS yourself. Alternatively, you can create a budding R&D division to refine your DP process and make it more efficient and profitable. And for any option you choose, remember that less is more.

*Want to assess your starting capabilities? Identify paths forward and potential partners?
Contact me for help*

For over 20 years, I've helped clients such as Merck, Sharp and Dohme (MSD), InterAmerican Development Bank, the World Health Organization (WHO), Africa Centers for Disease Control and others to evaluate, develop and implement plans to sustainably manufacture life-saving vaccines in Low and Middle-Income Countries (LMICs).

I work with governments, funders, and manufacturers to bring the clarity needed to confidently navigate the decisions and challenges faced while establishing or expanding sustainable local vaccine manufacturing in LMICs. I specialize in supporting:

- Manufacturers looking to establish or expand vaccine production*
- Countries or regions looking to improve health security*
- Investors or donors providing the funding to achieve these.*

