Biopharmaceutical Process Development: Good Manufacturing Practices or Breaking Bad?

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Good afternoon, I'm Andrew Warr. As Chris said, I graduated in 2010. I can't quite believe it's been that long already, although Leicester has found a king under a car park in that time so maybe it's longer than I thought. I work for Actavis Biologics, a Bio-Pharmaceutical Company based in Liverpool.

When I was writing the talk I was wondering how I can briefly summarise exactly what it is that I do. It reminded me of a similar dilemma back in Primary School when we had to share with the rest of the class what our parents did as jobs. My dad actually worked in the same industry. Back then I didn't really know what he did, so he just said to say that he makes medicines. Twenty years later I'm saying the same thing basically. Sometimes when my friends ask me "Andy what do you actually do?" I try and shock them and say that I manufacture drugs, so they instantly imagine something like *Breaking Bad*. But before I get lawyers after me, that's obviously not what the Biopharm industry is about.

So, what is it about? I'll give a bit of an overview of the industry, and introduce process development, which us the area that I work in, which is a big focus of Actavis Biologics. So I'll say a bit about what PD is and what I do as a PD Scientist. Then I'll move on to the company itself, what they do and who they are. Then finally, I hope to offer some advice, a bit about my move from Leicester to Liverpool, essentially the last five years and then answer any questions you might have.

Firstly, what is a biopharmaceutical? A famous online encyclopaedia captures the definition quite well. A biopharmaceutical, also known as a biologic medical product or more simply as a biologic, is a medicinal product manufactured in or extracted from biological sources. Most often when people say Biologics they meaning a product made in cell culture, and generally they mean in cell culture using recombinant DNA technology – which is something you'll know a bit about from your course here.

Actavis is currently focusing on a few main biologics, including monoclonal antibodies – MabS -and we also have a hormone product. The first approved biologic for commercial manufacture was back in 1982, just over 30 years ago, so I guess that makes the industry quite young. The future of the biopharmacy sector is in so-called biosimilars. These are essentially second generation biologics, a version of a drug that is already on the market that is about to come off patent. The original product will have been patent protected, but in the next five to ten years a lot of the big, blockbuster drugs are coming off patent. So companies like Actavis Biologics, can work on biosimilars, trying to make their own version, and to do so more cheaply. Importantly, they still have to prove to regulators that their version is efficacious, that it does the same thing as the original, and that it's safe.

In making biologics, we have to adhere to good manufacturing practice, GMP. These are a set of guidelines from regulator authorities to ensure that the manufacture of the drugs can be reproducible and consistently controlled, so that exactly the same drug is produced batch after. It has to meet identity, strength and purity and quality attributes. The main regulators are the FDA in America and the European Medicines Agency over here.

some of the GMP guidelines seem quite obvious. Personnel need to be appropriately qualified and trained. The materials that you are producing and the raw materials that you're using in the process have to meet special quality controlled guidelines, so that's quite a big deal if you are on the side of manufacturing and quality controlled side. Everything is done standard operating procedures – SOPs – so that each time you

get a new employee in your company the manufactured product is going to be the same as if I did it, or if you guys did it. And of course the records to demonstrate that you've met these GMP compliance have to be properly maintained because you can get inspections from regulatory agencies. When you come to actually submit for commercial approval, all the documents need to be in order. So it really is quite an important side of the process.

I asked some of my colleagues, some of the bosses, what they think makes a successful biological product. There four points are that it meets the patients' requirements, in a manner than can be supported by the local healthcare provider, with a supply chain that can reliably support demand. In other words the processes you have in place must match the demand for these drugs. And fourthly, you need to make money from these drugs. That might sound a bit shallow, but the reality is that they're not free to develop - a lot of money is spent and has to be made.

If you Google-image "Biopharma company logos" you'll see a number of companies, some of which are household names. You've probably heard of GSK and AstraZeneca which are big UK companies. Then there are other powerhouses of the industry Pfizer and Roche. These are some of the top firms in terms of revenue.

If I was to ask you for the combined revenue of the top ten global Biopharma companies in 2014, what do you think it would be? Ten billion? It's actually 442 billion dollar! That's just from the top ten companies, in one year. So that gives an idea of the amount of money that is being turned over. At the top is Johnson & Johnson at just over 71 billion dollars. I can't even imagine how much money that is.

I've mentioned the manufacturing side of it, but I work in the process development department. As you'd imagine from the name, PD are basically the guys that are designing, producing and refining the process before it gets to commercial approval. Throughout process development it is also important to keep two things in mind. Firstly, **product quality**; you need to ensure throughout the process you are actually producing drug of the right quality. Secondly, the **manufacturability**. It is all well and good being able to do your experiments in your lab with a benchtop scale bioreactor of 1 or 2 litres, but can it be scaled up to commercial manufacturing? Back in the day bioreactors were 20,000 litres. These days with improvements in titre they are smaller but still in the thousands of litres, maybe one to two thousand litres are common. You have to be able to keep in mind the need to scale up.

So what does a process development scientist actually do? As I've just said they, are responsible for devising new processes, or refining existing ones; even when a product is on the market it can be refined and post market approval changes can occur. So if you work with a company who has multiple products on the market your job would be developing new ones in the pipeline as well as refining existing ones. Obviously the idea is to improve the efficiency and profitability of the manufacturing process, for example by reducing the costs of goods. Implementing new technology is increasingly important these days. As I'll discuss a bit later, advancement in new technology can significantly improve your product yields and drive down costs. As I said earlier, it is important that the process is controlled; it has to be reproducible and it has to be able to be scale up. Last, the most boring aspect but arguably the most important is the actual reporting, recording all of the information and data because if the regulators come knocking then you have to show them.

Process development can probably be split into three broad categories. Where I work is an upstream group, then there's cell line development, CLD. They are at the start, so they are essentially making the cells produce what you want them to make. In upstream we are developing the bioreactor process, ensuring the cells are growing in optimum conditions and they are able to make as much product as possible. Then in

downstream they're essentially purifying the product. I am going to ignore downstream for now as that's a different job to me, but I'll set the scene by thinking about CLD.

I mentioned that biologics are often manufactured in mammalian cells. There are products made in microbial cells as well, but 8 out of the top 10 selling biologics are in mammalian cells. Most important are Chinese hamster ovary or CHO cells, they are the industry standard as 7 out of those top 8 compounds are produced in CHO. They account for 57 billion dollars of the biologic sales, which is a lot of money. So why are CHOs so good? Because they are the industry standard and have been round for a long time, there's been a lot of refinement work done on them to increase their titres. They are quite easy to work with, they're quite hardy you can give them quite tough conditions if that's needed to maximise productivity, and they allow human-like post translational modifications which are important.

This is a typical upstream process development stage, illustrated from the company Sartorius who provide lots of the kit. Once a cell line development group has optimised the cell line, they've selected the best clone, then they would store it in liquid nitrogen. It would then come to my group. Our starting point is that 1ml Cryophile. 1ml of cells would contain maybe ten million cells, depending on your conditions. Then it basically goes through a process of scaling up. In each of the stages you are essentially increasing the volume of the culture, until you get to the final production scale. Here they're advertising their one thousand litre vessel. You would revive your cells, take them out of the liquid nitrogen and thaw them out, then they're grown in liquid medium in shake flasks. They will typically be up to 1 litre, maybe not quite that big, and you might well use some like this in your final year project. You scale up of the bioreactor because you wouldn't have enough cells in the thawed vial to go straight into 1000 litres, you have to build up the culture.

As I said the bioreactor is your main piece of kit. A stir tank bioreactor is a bit like a big bucket where you can just pump in gas and some other liquid nutrients. Stirring makes sure the cells are kept in suspension, then gases can be bubbled through: air, oxygen, CO_2 to regulate the pH, other things too. You start with your liquid medium, full of nutrients, but as time goes on the cells are using the nutrients which can gradually get depleted. So that's part of process development, we would be developing a good feeding regime, when to add extra feeds, when to add alkali or CO_2 to help to maintain pH. Then you have a whole group of probes to measure the environment within the vessel, to ensure it is controlled and optimal to grow as many cells as possible and to make your desired product. Temperature, pH and DO – that's the dissolved oxygen content. Our labs are focussed on development, so we are typically working at 2 litre or 10 litre scale which is pretty small really, pretty easy to work with. Back in the day people would eventually have headed towards 20,000 litre stainless steel vessels, but now we know how to achieve much higher cell titres, and the normal vessel has been brought down to a 2000 litre, single use, unit. The modern bioreactor has metal outer casing but inside, where the liquid is held, is essentially just a plastic bag. It is for a single use, so after each use you would just discard that bag. I remember when I first started at the company I thought that's such a waste, what about the environmental impact? But actually once you factor in the amount of energy, the steam and the water that went into cleaning a traditional stainless steel bioreactor and then the validation processes to confirm that it is really was clean again, that was a bigger environmental impact than replacing single-use plastic bags.

One of the main modes of operation for a bioreactor would be **fed-batch**. These are quite simple to develop. You would start with your liquid medium and then on certain days, typically towards the end of the run, you would supplement the medium with additional nutrients, for example a concentrated feed of more sugar, amino acids, things like that. The viable cells densities in a typical fed batch process would be 10-20 million, although maybe 20 million is a bit optimistic for a fed batch process. What that means is you have 10-20 million cells in every millimetre of liquid in the bioreactor, and you've 2000 litres, so the

numbers are unbelievable. They are all producing tiny amounts of your desired product, so in a fully optimised fed batch system you might get 5 grams per litre of product. You'd run the reactor for 10 to 12 days, 14 maximum, then once a certain percentage of the cells had died you would then harvest the bioreactor. You don't want the percentage of live cells to dip too low because as the cells die they lyse and can release proteases that could end up degrading the product, so you'd be kicking yourself if you left it too long and ruined your yield.

In my lab we have a room full of 2 litres bioreactors. It looks crazy and complicated with tubes all over the place. Each reactor has a red heated jacket keeping it warm, multiple tubes for liquid additions and then gas lines for supplying the gases. One downside of the fed batch process is that the cells are getting fed with these nutrients, they're using them but as they do so there is a build-up of waste product. That can cause the downfall of a culture. If we could keep conditions optimum inside the bioreactor and get rid of the waste then that sounds like the perfect process. So this is where we come onto the **fusion** processes.

Fusion isn't a new thing, I think it has been around for a while but it went out of fashion because it can be harder to develop and control, But fusion processes are making a bit of resurgence at the moment and this is actually what the group I'm working with is currently doing, developing fusion processes. This approach gives you much longer run duration than fed batch. The productivity is about a gram per litre per day. That doesn't sound very good compared with fed batch which, as I said, gives about 5 grams per litre. But bear in mind that fusion is 1 gram per litre per day, so you are getting a constant harvest stream of product.

There's basically two ways of running the fusion process. I'm not sure that there's any commercially-approved process using the first one yet, which is an extended or concentrated fed batch. In this system, the product is retained within the bioreactor and purified as a single harvest, the same as it would be for fed batch. The key here is that the cells are also retained, the medium is constantly replenished, but spent medium is also removed at the same constant rate as addition, so the conditions inside the bioreactor remain optimal at all times. A concentrated fed batch is essentially like a fed batch but with ultra-high cell density, over one hundred million cells per ml.

In classical fusion there would be continued harvest, a gram per litre per day, for example, for up to 60 days. This is easy for the upstream team because you can set it up, you have everything controlled and you can just let it run for 60 days. It's harder work for the downstream guys because they have to do multiple harvests per one upstream batch.

So how are the cells retained in the bioreactor whilst the product or the spent medium is removed? Essentially you need a filter that keeps the cells inside whilst allowing liquid waste products to be removed. The filter is a hollow fibre module; there's a diaphragm pump at the bottom constantly pumping up and down so that the culture is circulating between the bioreactor and filter. You can retain the product in the bioreactor or you can harvest the product constantly via an access point.

In terms of the optimum conditions within the bioreactor, you are trying to find the perfect design space for your cells; the limits of pH, the limits of temperature, the limits of everything to ensure they are in the best conditions and to assess the range of variation that wouldn't impact on your process. Nowadays there's quite complex software to help design your experiment, to evaluate interactions between every variable in the bioreactor, or you can define how many variables you wanted to look at and that can then spit out a number of experiments it is telling you to try. We do a lot of our work in the 2 litre bioreactors or in shake flasks. They are ok for an initial screen of some parameters but of course they are not as controlled as they are in a bioreactor. In the early stages of development the quicker you can get the conditions as close to the final production parameters as possible the better.

We're recently got a fairly new bit of equipment developed by Amber systems. All of the top ten biopharma companies have these, at least that's what the salesman said when they were trying to sell us one. They are mini, mini 15 ml bioreactors. Allegedly it's no coincidence that they look like a tic-tac box as that was actually the look they were after. You can run 24 or 48 of these to test all of the various conditions you might want to employ. You can pilot multiple sets of conditions at one time without the faff of setting up larger scale vessels. So it looks like these Amber systems might be the future, but they are pretty expensive at the moment.

So you can look at the constituents of the medium and feed components, the culture duration. The longer the cells are in the culture and remaining healthy the more product you are going to get at the end. It seems quite straightforward, but there are so many variables that can affect this; pH, temperature, dissolved oxygen tension. The idea is that you want to maximise the growth productivity and product quality. Alternatively, you can try to increase specific productivity from each cell, but that's a cell line development job.

I've said all along that we are trying to increase the numbers of cells and the amount of product the cells are making, but it also needs to be of the right quality. This is a big thing, drug quality can have a big impact on the patient. Remember, we are talking here about biological materials. Take monoclonal antibodies as an example. They are glycosylated when they are produced. If there's a slight variation in the glycosylation profile from the original then, firstly, they won't get approval as a biosimilar and, secondly, it's possible that they just won't work.

Impurities are another potential issue. Your product is secreted into the supernatant within the bioreactor. When you harvest it, you need to get rid of the cells but also you've got hundreds of other proteins in there, normal host cell proteins that the cells are producing naturally. You need to get rid of them. Some of that will be done in downstream development, with multiple chromatography stages.

Also contaminants. They're the bad guys of the industry, viruses for example. Or if you get a bacterial contamination in the bioreactor it quickly goes a horrible yellow colour and stinks the whole room out. If you find it like that when you arrive in the morning then you know you've got a contamination and it's a waste and you have to throw that away.

I've given you an outline of what process development involves, now to tell you a bit more about the company I'm working for. It's called Actavis Biologics, and we're based up in Liverpool. It was founded as a company called Eden Biodesign, and they were originally a CMO. That's a Contract Manufacturing Organisation. So they weren't originally making their own product. Instead some of the big boys of the industry would say 'we've developed this process but we need you to manufacture it for us' and they would give you a whole load of money, transfer the whole process to you and you would just do the manufacturing.

CMOs are still a huge part of the industry in general, but Actavis is no longer a CMO. It was acquired by a company called Watson Pharmaceuticals just before I started there and then Watson went on to merge with Actavis, I think in 2012, but they kept the name Actavis. When it started there was just five or six people who set up the company. They're all still working there, they're the bosses. It's grown to around 180 employees now, so it's got fairly big after only about 15 years. Actavis is a center of excellence for biologics. The whole Actavis company has around 25,000 employees worldwide, with turnover around 9 billion, so not quite in the top ten. We do a lot of process development in Liverpool, but it is important that we also have a GMP manufacturing facility. Not every site would have that, which is they would contract out to a CMO. Our site the process development labs, then we have the GMP warehouse which is the

manufacturing facility. We've also recently bought adjacent land, so the plan is to build a much larger manufacturing facility there.

Chris asked me to say a bit about my career journey and to offer some general advice. I wouldn't really say I've had a "journey" yet, because this is my first job. But I have got some things that it would be useful to say.

Firstly, everybody says you need **experience**. I remember when someone said that to me thinking "Yeah, but how am I going to get experience if I can't get a job in the first place without it?" If you can get an industrial placement year I would definitely recommend one. Although I didn't do one, I know a good handful of people that I worked with who did and they say it was really valuable for setting them up for getting their first proper job. What I did was to get a summer placement. So after my first year here I basically wrote to GSK and said "Can I come and work for you over the summer?" I did a 2-3 month paid placement at GSK. Even now the things I learned there, basic lab techniques in *industry* rather than academia, really set me up for my job. Several times I thought "Wow, I've done this before", I already had a baseline knowledge. If you don't get any luck with paid work try volunteering. There was a guy I used to work with, he basically started as a volunteer just for work experience and ended up getting offered a job there. If you don't ask, you don't get.

Interview. So you've got your experience and you've been offered an interview, what can you do to prepare? You need to do a bit of research about the company. Try not to just recite what's on their website because they know what their website says. Ask some questions. For my interview at Actavis they asked me to prepare a presentation. I presented it to just two people but I was instantly a lot more instantly relaxed because I didn't feel like I was being interrogated. It turned into more of a conservation, so I spoke about my final year project here and my GSK experience. So there are different types of interviews if you like. Try and relax. Obviously everyone gets nervous at interviews and getting questioned, but the interviewers have been interviewees as well, so they know what it's like.

Try and keep an open mind when you're job hunting. You may already know what you want to do, perfect, but I remember in my final year I didn't know exactly what I wanted to do. I thought I wanted to work in a lab, but there's a million different types of labs. Events like these are extremely beneficial to you guys you've got speakers from different industries.

Relocation. I always put that in when I speak to people because I relocated, and you might well have to as well. I wasn't that keen on the idea, but it's unlikely you will get the dream job available at the end of your road. If you wanted to work in the biopharma industry in the UK, where could you do that? There's a bit of a hub in the Liverpool and Manchester area, and then around Oxford and Cambridge, especially Oxford, that's kind of the heart of the biotech industry in England. But it's definitely an international industry; you could go and work in Australia, India, America, anywhere. The experience you are getting is transferable to any sites.

So why do I like my job? It might sound a bit corny but it is really rewarding and relevant, because the companies are making drugs to improve patient lives. That's what drug companies do. Sometimes I take a step back if I'm having a bad week and think "I wanna just go home and watch football". But then I remind myself that this is an important job. It puts things in perspective to think that what you're working on now could be on the market in 5 to 10 years and a doctor might be prescribing it to me. So that's quite cool. Biotech is at the forefront of healthcare, especially moving forward. Without development of manufacturing processes a lot of drugs won't get onto the market.

Travel. I think every industry probably tries to say they offer travel opportunities, but biotech really is an international industry. There's training courses, conferences all over the place. Just in the last year I've been to Germany, all expenses paid, and Barcelona, all expenses paid, so you get to go around a bit.

I'm happy to answer some questions.

Q: On career progression, what kind of scope is there so at the moment, what is the potential for earning and what can you work your way up to?
A: That's a good question. A lot of it is company dependent; the bigger the company the more potential for internal progression. Whether with each change of job you're going up or I guess sideways it is still a promotion. So at the moment, my friends and I sometimes joke about the fact that as basic level scientists we're at the bottom of the food chain in the company. We then have senior scientists, so kind of five year plus experience; I'd be looking for a promotion to senior. Above that you then have team leaders but at that stage it kind of splits out a bit; you then get technical specialists in certain areas. That's the prospects within Actavis itself. Other companies are different. I know someone who works at GSK. When I try and compare the structure in their department to our department I just can't because they have team after team after team, so there's hundreds of opportunities.

Q: One of the reasons why I'm hesitant about going into this kind of job is because in a big pharmaceutical company it seems the profits are priority not ethics. Is it all political or is that a misrepresentation?
A: I see what you're saying, but I haven't experienced that. It's true that at the very top of companies the bosses are probably not scientists, they're managers looking after the business side of it. But on the science side of it I'd say the scientists involved are want to be making drugs to improve patient's lives. I wouldn't let that put you off at all, definitely not.

Q: With reference to work experience, would doing a Masters in Biopharmacy or something like be an advantage or did you find work experience more beneficial?
A: If you can get onto a relevant one then a Masters would definitely be beneficial. A couple of people I work with did MScs in Biotechnology or something like that and 6 months of their course was an industrial placement. That gives you the best of both worlds really, the theory side of it and a placement. So a Masters would be good.