Introduction

I am going to speak on the present status of manufacturing in the Republic, briefly describing how we got here, and what threats and opportunities are emerging. Before starting I should explain why I take an interest in this subject.

I spent the seventies and eighties working on the design and project management of pharma-chemical plants, in the UK and Ireland. This included inputs to site selection, obtaining planning permits, and access to utilities. I ultimately ended up leading Intel's Corporate Services organisation in PHX, which included a major input to selection of all new locations for plants, laboratories and offices across the globe.

As part of a transition to retirement, I am an exec director of two Irish engineering services companies. These companies undertake work in operating process manufacturing sites, which typically spend 2% plus per annum of their invested capital on upgrade works. Hence my interest in changes in manufacturing investment. In essence the demand for engineering services is a bell weather for the manufacturing sectors' health.

Manufacturing in the Recession Years

The recession post the 2008 market collapse coincided roughly with a wave of patent expiries for extensively used small molecule drugs. Many of these were manufactured in the Republic. The expiries opened the way for generic manufacturers to produce lower cost copies, most often in Eastern Europe. Demand for engineering services was subdued, indicating that investment was curtailed.

But there was a growing network of bio-pharma plants in Ireland, including fill-finish facilities, as well as plants for the manufacture of vaccines[1]. Overall worldwide demand for existing and new block-buster drugs continued to grow strongly, particularly in Asia.[2]

With the collapse of construction spending, the level of demand for offsite supply chain manufacturers dropped significantly. It did prompt a search for new markets by this industry, principally in the UK, where a number of the companies have built, or continued to grow market positions. This often involved broadening their offering to include design and other services in addition to supply only. Kingspan would be a prime example.

During this period, Intel started the upgrade of Fab24 for manufacturing at the 14nm node. This was complex conversion work, which provided employment for 2000 plus construction

[1] Baxter Castlebar & Swinford.
[2] CAGR 2015 to 2018 is **2.1%** for advanced economies and **6.1%** for emerging economies

craftsmen, for three years, at a time of low opportunity in that industry. The start-up of production copper-fastened 4000 plus manufacturing jobs.

Indigenous manufacturing companies, outside those engaged in the construction industry, had a mixed recession. World demand for agriculture products was buoyant, following the contaminated milk powder scandal in China. This prompted the drive to expand milk production after the ending of milk quotas, which required significant investment in milk powder production.

But manufacturers of specialist agricultural equipment experienced continued growth, mostly in global markets.[3]

The pending FDA approval of a range of bio-pharma products, which had been in clinical trials for years, prompted a prediction at a conference of the International Society of Pharmaceutical Engineers[4] in 2014 of a shortage of seventeen major bio-pharma plants worldwide in the remaining years of the decade. What is of note is that a stream of relatively new companies are building bio-processing facilities, rather than selling their FDA approved products to established MNC's or using contract manufacturers.

Many of the redundant API factories, closed after the expiry of patents, have either been taken over by generic manufacturers, or by bio-pharma companies, who converted the manufacturing processes to biological drug production, taking advantage of experienced workforces, in a then tightening market for skills.[5]

All through the recession the medical devices industry has grown.

As well as the presence of 18 of the top 25 MNC's, the industry has over the past decades produced a very significant number of indigenous companies, who now constitute 50% of the total, and who continue to innovate and trade successfully. The regulatory process is shorter than that for pharmaceuticals, and hence the cost of developing new products is significantly lower. Time to revenue is typically in the order of magnitude half that for drugs substances, making it a more fundable proposition for start-ups.

Characteristics of Bio Pharma:

The predominant increased in value of output from manufacturing in Ireland will come from biopharma products. So what are the characteristics of these products? They are complex molecules, containing up to 25,000 atoms[6], which have high efficacy and fewer side effects

[3] Dairy Masters, Keenan Systems, McHales, Dromone.
[4] ISPE:
[5] Most recent example is rumours of the possible purchase of Organon facility by Biomarin.
[6] 2,000 to 25,000 atoms

than small molecule drugs. Their development has been aided by the increased accessibility of medical records and genetic data from clinical trials, and to general medical histories. The plants to manufacture these large molecules cost in the region of $200m to $500m, compared with a range of $30m to $100m for those manufacturing small molecules drugs.

The bio-pharma plants are expensive to run, have manufacturing processes that require longer durations, produce low titre, and require expensive raw materials, such as genetically modified living cells that, like the final product, require temperature controlled environments for shipping. But bio-pharma drugs are experiencing a growth of 8% per annum, double that for small molecule drugs.

There are reputedly 1500 bio-pharma drugs in clinical trials, with a greatly increased success rate of 13% going to product launch. This compared with the previous rule of thumb of one or two in a thousand for small molecule drugs. The contract manufacturing organisation (CMO) network for bio-pharma drugs is still immature, although the South Korean conglomerates[7] have included the development of a large CMO capability in their strategic plans to become significant players in the bio-pharma business in the coming decade.

The bio-pharma drugs are typically highly priced, justified by their reputed effectiveness, as they potentially avoid more intensive treatment for chronic ailments. There is obviously push back from cash-strapped health services, and a pre-launch price negotiation process has been introduced by central treatment purchasing agencies, like the UK's NICE.

[Slide Six]

Governments in the developed and developing countries are well aware of the potential advantages of biopharma products in improving their citizen's health. They are aggressively supporting alternative ways to procure more cost effective versions of these drugs, including supporting the development of what are called bio-similars. These are close copies of a successful large molecule drug, which have enough molecular differences to be deemed not to infringe patents. As such they minimise the development cost risk, and require only the relatively less challenging demonstration of similar performance to the parent drug for FDA approval. The effect will be to increase price competition for the parent drug owners, forcing them, inter alia, to closely manage their costs, and embark on a constant regime of continuous improvement.

[7] Samsung Biologics, LG Life Sciences, Green Cross (vaccines) Celltrion (CMO & BioSimilar version of Remicade)

Response of MNC's

The large bio-pharma companies[8] are not taking the threat from bio-similars lying down, searching for and patenting bio-similar copies of their own drugs, and deploying large legal teams. They also seek to acquire companies with competing bio-similars in the later stages of development[9].

But the first bio-similar drug, *Zarxio,* developed by Sandoz (the generic side of Novartis) has been approved by the FDA, competing with Amgen's *Neupogen*. A consortium of Merck and Samsung Bioepis are developing a range of bio-similars for popular drugs like Humira[10] Eventually bio-similars are predicted to take 50% of the market, so their impact on pricing will be significant.

What's Happened in the Past Two Years?

ICT:

Tool install in the retro-fitted and expanded Fab24 commenced and is now largely completed. The factory is on a steep ramp to full capacity on the 14nm node, as is Intel's normal practice.

While Intel is the predominant manufacturer in the sector, other ICT firms have significant manufacturing operations in data storage, and the manufacture & assembly/test of analog & FPGA chips in the Republic[11], using legacy tools and interposers to stay aligned with the trajectory of Moore's Law. However most chip designers in Ireland use foundries for their chip manufacture, or licence their technology.

Food:

Irish dairy companies have a track record of supplying milk powder to multi-national baby food manufacturers[12]. At least three new major milk drying plants have been commissioned in recent years by the domestic agri-food giants[13] to absorb the targeted increase in milk supply post the ending of milk quotas. Each new plant has incorporated the results of a thorough hazard analysis & critical control point's assessment. The most recently completed plant in Ferrybank has incorporated the latest in bio-security techniques, mirroring the separation and compartmentation that is required in bio pharma plants. This attention to detail is essential for sustaining a reputation for food safety, as any New Zealand milk product company will attest.

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8 Sanofi Aventis, Roche, Abbvie, Pfizer, BMS, Merck, Novartis. Eli Lilly.

9 Pfizer's acquisition of Hospira.

10 Remicade, Humira, Herceptin. "*Samsung Bioepis has been building the capabilities needed to develop high-quality biosimilars* "

11 **Analog & Xilinx** (FPGA & CPGA; first fabless semi manufacturer)

12 Lakeland supplies Pfizer, Abbot.

13 Lakeland, Dairygold, Glanbia.

These new milk plants are best in class, capable of competing with market leaders on quality, as can Guinness with their new state of the art brewery in St James' Gate.

Presented by: John Mc Gowan
President, Irish Academy of Engineering

Other Indigenous Manufacturing Plants.

The general recovery and new investment in food, biologics and other high value manufacturing has opened opportunities for growth for those companies providing piece parts to these industries. The primary opportunities in the bio-pharma sector appear to be in fill-finish plants[14].

The growth of the number and sophistication of stainless steel vessel fabricators in Ireland, supporting the food and pharma industry, is an example of successful localisation of a market that was dominated by overseas firms twenty five years ago[15]. One SS fabricator, ABEC, who recently purchased Kells Stainless, and is prefabricating modular bio-process plant skids for the new Regeneron plant in Limerick.

Manufacturing companies serving the construction industry are seeing an uptick in demand as residential and office space development continues to expand. The construction industry is in the process of adopting so-called Level 2 building information modelling (BIM). This is based on the creation of a multi-discipline, common digital model of the planned building, as a replacement for drawings. Aside from helping to eliminate clashes, BIM models will improve dimensional accuracy, and ultimately facilitate much more prefabrication, capturing the improved quality possible in a factory environment.

Pharma Manufacturing.

In the past two years, six[16] major new investments have been commenced by bio-pharma companies. Many are relatively new companies, investing in Ireland for the first time. Their investments are sizable, in the range of €100m to €500m. Many have located on vacant industrial sites, leveraging the existing utility infrastructure and the ease with which planning permits can generally be obtained for such sites.

Separately five[17] established multinationals have announced major expansions, again in the bio pharma space. The two most telling are the BMS investment in Cruiserath and Pfizer's' major expansion of their existing facility in Grangecastle.
The key point is that pharma manufacturing in Ireland is being catapulted to the leading edge of biological manufacturing technology, and these plants <u>will</u> deliver high value outputs for the coming decades.

[14] *Avenue Mould Solutions* in Sligo is an outstanding example
[15] In addition to the SS vessels *(Radleys, ABEC. Sapphire, Spectac*) and Carten Valves already manufactured in Ireland?
[16] Alexion, Jazz Pharma, Regeneron, Amgen, Eli Lilly, Biomarin, Allergan.
[17] BMS, Pfizer, Shire, Amneal, Merck (Carlow)

Medical Devices:

Since the beginning of this year over €300m has reputedly been invested in the medical devices industry, a significant percentage of which is being spent on R&D and innovation. The number of vertically integrated companies in the sector is noteworthy. The sector now boasts a strong services sector, and a contract research and manufacturing base, all three of which comprise the core part of the 50% of companies that are in the business to business space. The sector continues to thrive, with annual exports of €8bn.

Why Ireland? [Slide Nine]

Why Ireland for all this investment? Ireland has a track record in delivering the construction and start-up of capital intensive manufacturing plants, invariably meeting market entry dates. This is the portal to a start of revenue streams to defray the accrued R&D costs of product development and trials.

Ireland also has been able to supply the skills required to successfully and predictably operate complex plants. Ireland has developed a disciplined working ethos that is pretty deeply engrained, largely the result of the investment by MNC's in management, leadership and motivation capabilities. The bottom line is that employees can be trusted to manage complex processes, and stick to operational rules, while using their initiative when appropriate. This is not so in many emerging locations.

In the context of the pharma and medical devices industries, Ireland has a peerless record for compliance with FDA Good Manufacturing Practice, with only very rare excursions noted in FDA inspections.

Despite the frequent complaints by fellow citizens about infrastructure, the present networks for water, sewage, electricity, gas, broadband, roads and air transport connectivity are apparently sufficient not to be deemed "*a show stopper*" by companies contemplating FDI. Local inadequacies can usually be dealt with during the plant construction stage.

The current infrastructure, supplemented by already planned upgrades, will probably not be a constraint on investment in manufacturing for the rest of the decade. However there is a very long lead-time of up to ten years on significant networks' strengthening, so it is important, as other speakers will note, to increase the pace of planning for investment in all utilities networks, to support investment in productive capacity in the coming decades.

As the ability to differentiate ourselves with tax regimes is being curtailed, we should strive to instead differentiate ourselves with the efficiency of our industrial & services infrastructure, if this is affordable, and likely to be cost effective.

The opportunity to minimise corporation tax has obviously been a major factor in attracting FDI. This seems to be particularly so for the newer bio-pharma companies. Many have burnt through significant investments in developing new drugs, testing and clinical trials. Obviously with an FDA approval they have a potential blockbuster. Events in recent years have shown that without availing of tax minimisation, a company with a limited product range leaves itself vulnerable to a leveraged buy-out, with the debt theoretically defrayed by the additional tax saving of an inversion.[18] This seems to have been a major incentive to locate in the Republic in the past two years.

Patent Law, and the independence of the legal system, are undoubtedly advantages, as is the growing capabilities of the third level colleges to provide process development services and tailored training to the manufacturing plants.

Looking Forward: [Slide Ten]

So what are the threats and opportunities that we face going forward?

Skills Shortages

The sheer number of new bio-pharma plants, and the success of the IDA in finding generic manufacturers to take over redundant small molecule plants, is creating a skills shortage. Salaries in the industry have already started to rise significantly, and the training facilities, such as NIBRT in UCD, are pretty full. Inevitably the industry will have to look to a wider market to recruit. One target will be those with industry experience who emigrated to Europe and US.

But the recruitment companies have grown significantly, fuelled by a continuing demand by MNC's for flexible contract professionals, and the need of the ICT service sector for specialist skills.[19] They now have networks within the larger EU countries and can both source and supply professionals to and from Ireland. While this makes planning future third level graduate numbers more complicated, it does provide a measure of contingency on staffing.

The other complicating factor is the apparently poor image of manufacturing as a career.

Erosion of Competitiveness

Obviously salary inflation originating from skills shortages is going to impact competitiveness across the whole economy, possibly undermining the viability of some manufacturing plants.

[18] Examples: Irish HQ'd Activis's acquisition of Forest Labs (generic drug maker)*.." new entity will reap $100m tax saving"*
Irish HQ'd Mallinckrodt acquired Questor, then Cadence Pharma.
Valeant Pharmaceuticals failed take over the Allergan.
Jazz Pharma acquisition of Irish owned Azur Pharma (21% owners of merged entity)

[19] Only 55% of the technical professionals employed by the ICT services sector are graduates of Irish TLI's. 45% are recruited overseas.

The level of personal taxation may militate against the return of significant numbers of emigrants. The competitive environment that will eventually pertain from price pressure on the sale of biologic drugs, may eventually force their manufacturers to direct investment to lower cost locations. But it is hard to believe that relatively new plants would not be reused by other more cost conscious manufacturers.

OECD anti-BEPS Measures.

The OECD directions on anti BEPS measures are intended to increase the level of taxes MNC's pay in the larger markets. This was scaled at $250bn per annum in last weekend's FT. If this set of measures do not deliver, further measures will, no doubt, be instituted. The import for the Republic and, separately, Northern Ireland, will probably not be apparent for some years.

The Patent Box concept has worked effectively for Belgium, as is apparent from the scale of pharma FDI in the Flemish part of that country. But if the "substance" test is linked to where substantial R&D is undertaken, this is unlikely to move from the pharma R&D hubs in the US and EU[20]. Thus our knowledge development box may be of more advantage to MNC service companies, and to food and smaller indigenous manufacturers.

The bottom line is that we will likely need to improve our offering in all input categories to a decision on location. For instance, the Amcham program on promoting new concepts in education, such as certified experiential learning, leading to stackable credentials, has this as its end goal.

Availability of affordable housing, and its linkage to an efficient transport system, may be another such differentiator.

World Market for Food Commodities

Obviously the ability to make a reasonable return on milk powder depends on the world market. But it is inevitable that continuous improvement on the costs of production will be necessary to protect against future fluctuations in commodity prices.

This may also apply to sections of the medical devices sector. China and Japan have both identified medical devices as a growth sectors for exports.

Opportunity for BioPharma Titre Increase. [Slide Eleven]

The present bio-processes have a low titre. These were as low as one gram of product from each 100 litres of fermented liquid. Higher yields, such as 7g /100litres, are being

[20] Oxbridge M25 / BENELUX / Switzerland

progressively developed, thereby reducing the size and cost of manufacturing plants. A transition to continuous manufacturing is being investigated in Switzerland.

Such programs of process optimisation are an opportunity for Irish engineers to demonstrate and hone their manufacturing engineering expertise.

Growth of Bio Similars

The present bio-pharma global market is worth $200bn per annum.

Bio-similar are predicted in time to take half of this market. There may be an opportunity for a sizable CMO plant in the Republic, configured for quick changes between product lines, possibly using disposables manufacturing equipment.

Potentially troubling is the decision by Korean conglomerates to target the bio-similars and CMO markets. This could disrupt the established bio-pharma players, whose operations dominate the pharma-chem manufacturing sector in Ireland.

Industrie 4.0

The advent of what Germany has designated as Industrie 4.0 will give a quantum increment to product design and quality. It essentially means measuring all aspects of manufacturing, and the subsequent product's operation, storing the data in the cloud and statistically mining it for potential improvements.

The key issue is that sub-contractors supplying components or sub-assemblies to firms who have transitioned to Industrie 4.0 will require their suppliers to do so too. Ireland's strength in automation, cloud computing, data centres and internet services should make the move to Industrie 4.0 relatively straightforward. But German manufacturers, especially the *mittelstand* ones, are wary of IP loss when using MNC supplied cloud services.

Another Manufacturing Investment by Intel?

Intel has now been in Ireland for twenty five years. In that time they have repeatedly upgraded their campus, generally every second two year generation. Intel are one of six firms that can afford the cost of a new 10nm or 7nm wafer-fab.[21] Although I have no inside knowledge, it would not be a major surprise if the cycle of reinvestment was repeated in coming years, although the duration for inter-generational transitions is lengthening.

[21] Intel, Samsung, Micron, TSMC, Global Foundries, Hynix

Digitisation of Construction.

And finally the potential for increased demand in the construction industry, coupled with the availability of BIM virtual construction models, should encourage the development of more prefabricated sub-assemblies and sophisticated high performance building components. These will require capital intensive plants, needing large markets and early mover status to be viable.

A strategy for prefabrication of components would probably need to be based on a combined Republic and UK market.

Last Slide [Slide 11]

In summary, growth in manufacturing output and value add will be strong for the rest of the decade. Thereafter, it is too early to call

After that, the impact of the anti-BEPS measures, by then incorporated in tax law across all OECD countries, may make FDI more difficult to capture, but the Republic's reputation for manufacturing excellence will be sustained, and all the new factories build in this Millennium will very likely continue to operate through the next Decade.

Thank You.