New Manufacturing Technologies – From Drug Discovery to Final Product

By Benjamin Bryant, Global Communications, at Honeywell Industry Solutions for Chemicals, Life Sciences and Consumer Goods

Benjamin Bryant co-ordinates global communications for Honeywell's Chemicals, Life Sciences, and Consumer Goods business, his employer since 2000, when he represented the POMS business exclusively. Prior appointments include service as well-known radio and news presenter in Austin, Texas, and work for the United States Army & Exchange Service in merchandising and promotions. Benjamin is a member of the Association of the United States Army and the Public Relations Society of America, where he serves on the 12-member executive board of the society's international section. He has attended the University of Texas and the business programme at the University of Phoenix.

Anyone working within the life sciences industries knows that it takes significant investments of time, human and monetary resources to bring a new drug from discovery to the finished goods state. During the last decade, average times for this process peaked at 15 years from inception to launch. During that time, all pharmaceutical firms worked aggressively to reduce the time to develop and market, and the late 1990s saw dramatic reductions (some as much as 40 per cent, but on average, reductions took the process from 15 years to around nine to 10 years).

The industry was once quite unique in its record of business success. With high growth rates, barriers to entry and profits, the pharmaceutical industry was recognised as one of the most successful business spaces in the world marketplace. Recent years, however, have seen the industry running up against a number of unforeseen changes in the manufacturing life cycle. These changes have inhibited the development, marketing and eventual sales of new drugs, and have increased potential risks and the costs associated with them. Similar changes have taken place across the breadth of life sciences manufacturing, extending beyond pharmaceuticals to nutraceuticals/dietary supplements, to clinical and biotech manufacturing, resulting in heightened risk, threats to agility, challenges in enterprise-wide collaboration, and impaired time to market.

Considering the old (but accurate) industry maxim that each day in the pre-market life of a blockbuster drug can cost a company up to US$1 million, the reductions of the 1990s have been worth billions to the industry, with the potential of further improvements that may save billions more. However, uncertainty has arisen regarding the determination of where future reductions should come from. Intensified competition has made the pursuit of increased agility, decreased risk, and expedited time to market about more than shareholder dividends. The challenges hit large global manufacturers, particularly with regards to enterprise-wide activity, and affect the smaller manufacturers even more deeply. The very survival of many firms as independent entities depends upon the continuous improvement of their development and commercialisation process, cleanly containing risk and improving overall time to market.

As the total time to develop and launch new drugs has been greatly compressed, pharmaceutical companies are increasingly noting missed handoffs and 'constraint surprises' causing missed launch deadlines in 25 – even as high as 60 per cent – of products. Many of these delays are coming from the chemical and manufacturing control (CMC) requirements for filing rather than the 'usual suspect' – the clinical side. This is partly because the latter has been the greatest beneficiary of re-engineering and harmonised regulations. And these challenges are proliferating just as pharmas are gearing up to double the number of products they develop and launch per year.

Areas showing promise as the agility and cost reduction engines of the next decade are electronic specification and unified (or collaborative) manufacturing innovations. The pressing need for electronic product life cycle management has grown from these and related industry challenges. Such a system would be required to manage the development and deployment of the complete specification required to plan, source, make and deliver a product. It would also have to incorporate all specifications of raw materials, intermediate and finished products, resources/assets, and processes/recipes. As an essential baseline, any

innovations will have to be mindful of the current process and needs in practice today.

The development of a drug encompasses nearly 1,000 discrete steps stretched across continents, years and thousands of professionals. As a drug is first approved to enter man, there is already a wealth of knowledge accumulated about the molecule; its tendency to be absorbed by animal models; to be broken down and excreted. Soon, data on its side effects, toxicological patterns of the molecule and its metabolites become known. Also, the typical impurity levels of the raw drug, as well as its tendency to break down on storage with heat, moisture and so on, are measured. And this is years before the ultimate dose form that will be registered is defined.

"Packaging creates one of the greatest volumes of data on a pharmaceutical product as every component's content and appearance must be controlled and pre-approved. Some countries require transparent blister packs, some child-proof packaging. All require an unambiguous label that cites the product name, firm logo, address, brand, ingredients, and so much other data that a 10- or 12-page insert must accompany the product."

If the dose form is a tablet, there will be data on those degradents, including their FDA allowable limits. Ninety per cent of the tablet will likely be made of inactive binders, fillers, coatings and colorants. Each of these in turn will have set proportions defined to the active – as well as defined-degradation 'children' (not to mention the results of component interactions!).

By the time Phase III trials are beginning, the final dose form would not only have been chosen and made to be tested in those trials, but its shape, imprint, hardness and so on, are defined by data and set in bounds called specifications. All possible packages will have been roughly defined and the products would have already been put up on tests to see if the package protects or interacts with the materials it holds under different conditions. All of these final summary statistics are evaluated, reported on and submitted to regulatory authorities. But it does not end there.

Data on the cost and process of making the active molecule as well as the tablet are captured and controlled according to set processes and specifications. Economic estimates and then accurate costs of materials are linked to the actives as well as the inactive materials and packaging components.

Packaging creates one of the greatest volumes of data on a pharmaceutical product as every component's content and appearance must be controlled and pre-approved. Some countries require transparent blister packs, some child-proof packaging. All require an unambiguous label that cites the product name, firm logo, address, brand, ingredients, and so much other data that a 10- or 12-page insert must accompany the product (the information cannot even fit on a large bottle). And each country may have unique, specific language and registration formats or codes on the label and/or insert.

While it is reasonable on a generic basis to describe all of these data as being 'specifications', they are not treated as such in a uniform basis through the entire 10- to 15-year process. Information is passed on in stages and in some firms it is kept in an evolving 'product definition file'. This begins as a description of what the ideal product character is hoped to be, and it is actually compared with that ideal as data comes in.

Ultimately, the medical data is garnered from clinical trials, and that data is distilled into a strong framework required for the regulatory filing. The non-clinical data is also distilled into the complementary CMC section, as 'ownership' of that data passes on from clinical and development groups to regulatory (a department within that company). Other groups that 'own' data include the analytical group, the toxicology group, finance, marketing and sales. Packaging is a subset within manufacturing that files considerable amounts of unique data, as well as the manufacturing operations themselves, including the quality control group. One of the groups that would be most interested in a product life cycle management system is the 'tech-transfer' function. These groups take the bench- or pilot-scale manufacturing process and help scale it up in the ultimate site of manufacture. There, it must continually meet the target specifications for as long as the product is made.

'Collaborative' activity also has to mean more than the process enabled by innovative market solutions. The very development and marketing of such solutions, already underway by major providers to the pharmaceutical industry will require close collaboration itself with the industry itself. As the developers of existing innovations in this space have already found,

collaboration with customers – the industry itself – facilitates not only the creation of a solution that addresses customer needs most accurately, but in the potential of resulting co-development activity, can also cut development costs. This activity has been an outgrowth of the increasingly valued culture of 'customer intimacy' embraced by major industry solutions providers.

New and comprehensive manufacturing technologies in these areas are springing up in the marketplace, both addressing existing industry needs and in anticipation of future ones, such as those discussed at the beginning of this article. Collaborative processes between manufacturers and major solutions providers have yielded comprehensive manufacturing technologies for the resolution of these challenges. These customer partners have found that manufacturing operations are becoming more diverse and complex, with a clear need for a complete specification management system to define their products. The extensive experience of a major solutions provider combined with the complimentary domain expertise of major health care firms, is now being used to develop unified and electronic specification systems that respond to the ultimate identified needs of the pharmaceutical industry.

Simply, what these emerging technologies deliver are practical solutions for the regulated and non-regulated process manufacturing industries, allowing them to operate with more flexibility and more innovation, reducing risk and hand-off delays. Such innovations are proving ideal for companies that use flexible manufacturing facilities to develop many new products (or variations of the same product) in many different forms, such as varied dosages in the pharmaceutical industry.

Going back to square one, it is an increasingly universal truth in the competitive climate of today's manufacturing that a product development department in any industry needs a highly flexible development sandbox where a number of alternatives can be evaluated. After the development process is completed, a global standardisation department creates a specification that can be applied constantly throughout the enterprise. The manufacturing site may need to make an adaptation for local legislation, language and unit measure. The manufacturing plants require a level of detail that is sufficient to support manual, computerised and automated execution of the procedure. Accurate, real-time, electronic communication amongst business functions, sites, partners, vendors and customers is not only valuable but necessary. Unified manufacturing enables this communication and in doing so, simplifies and speeds all collaborative steps, providing near immediate benefits in risk management and expedited time to market, and with regards to electronic specification technologies, can specifically provide the capability to define dedicated environments for these development stages tailored to specific requirements.

"Going back to square one, it is an increasingly universal truth in the competitive climate of today's manufacturing that a product development department in any industry needs a highly flexible development sandbox where a number of alternatives can be evaluated. After the development process is completed, a global standardisation department creates a specification that can be applied constantly throughout the enterprise."

As the technology is developed and introduced to the marketplace, the industry will have to be both wary and discerning in the purchase, selection and implementation of such next generation innovations. Any application considered must support the entire extended supply chain by enabling co-operative development and exchange of specifications with customers and internal or external suppliers through the Internet. It should be an object-oriented, web-based application, conforming to industry standards and designed to adapt to changing business requirements, fully incorporating S88 manufacturing standards. Compromises that deliver less may prove costly in upgrade and services/support costs over time.

The value of these newer manufacturing technologies, is truly found in the ability to apply innovative, flexible and open-ended solutions to the resolution of specification and other issues tied to the real capability to reduce overall development to market time, addressing every step along the way. This can lead to savings of up to millions – potentially billions, depending upon the industry – of dollars in a wide scope of manufacturing industries, all the time increasing enterprise agility and product consistency. ◆

Acknowledgement

This article contains information contributions from John Delhez of Honeywell Industry Solutions

The author can be contacted at Benjamin.Bryant@honeywell.com