

# Technology - Changing the way we do things

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**T**oday the pharmaceutical industry is under tremendous pressure to reduce the time required to get new products to reach the market place. In addition, they are looking to find better ways to reduce their cost for research, development and manufacturing. With the rapid loss of market share due to generic introductions, Pharmaceutical Companies are under the gun to get products out faster and maximize patent life.

Today's manufacturing utilizes large inefficient batch operations which are more capital and labor intensive. In principle, the large pharmaceutical companies are using high technology for R&D and low technology for its manufacturing. As technology continues to move forward, we find a shift in the way we do things. The large pharmaceutical companies are recognizing that they need to be better and faster if they plan to reduce costs.

For the pharmaceutical industry, implementing changes and new technologies is not always preferred. In fact, for the large pharmaceutical companies, any thing that involves risk is not looked upon favorably. For large pharmaceutical companies "New Technology" is often been around for years. Some of the original patents for Simulated Moving Bed (SMB) Chromatography date back to the late 1950's. However some of the first industrial applications for the pharma industry did not occur until well into the 1990's. It has taken years for some of this to develop to the point that the large companies are prepared to use these methods to produce their products. In fact in many cases the pharmaceutical industry is content to wait until other markets develop and commercialize technology before they will use it in their plants.

For the Contract Manufacturing Organizations, they will most likely mimic the big pharmaceutical companies. If requested

by the innovator or if they can bring true economical value or some type of differentiation, they will look at new technologies. Some are starting to look more at technology however and investing heavily in this area. F.I.S. announced the formation of a technology group to start looking at what technologies can be used in the future. Saltigo routinely looks at micro-reactors and SMB technology as part of its development process. Ampac (AFC) scales-up chemical routes using continuous technologies such as SMB, liquid-liquid extraction or energetic chemistry on a routine basis.

**W**hat we are starting to see is new technologies being implemented at a faster rate. Therefore, there is a shift in the way we do things. It is not only the technology that is changing; the way we do things is changing and our overall attitude is also changing. One can see this starting in the universities. Also, medicinal chemists are being asked to work like business leaders and are finding themselves staying with projects longer than in the past. The process development chemists have adopted tools that have been in the past limited to medical chemistry. Scale-up processes are incorporating more technologies such as simulated moving bed, micro reactors and new asymmetric processes. Innovation is much more accepted and the balance between risk and reward considered more often. Cost drivers are being placed on the entire development process and anything that can reduce costs, increase speed and minimize risk is being given serious consideration. Waste cost, green chemistry and solvent use reductions have become even more important in the process.

This transition could have more far reaching affects. Several companies have already discussed increasing the role of the medical chemist to be more concerned about the process as well as both safety and

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environmental aspects. This means that there is a better connection between research and development and should lead to a better understanding of the tools that they both are using as well as the needs of both groups. An important point may be the connection between the research portion and the development portion has becoming more connected. In the past, often the medical chemist simply through the product over the fence and that was the end of their involvement. Today things are changing and the process to develop new products is no longer two isolated pieces but a combination of the Research and the Development functions.

Technology comes in many forms. There has been a considerable amount of technology developed to describe the chemical processes and how we can reach various targets. From both the academic side as well as from the industry side, there has been a number of far reaching chemical methods developed and commercialized. These advances in chemical synthesis continue to allow us to develop innovative ways to produce molecules today. This research is coming as much from the academic arena as it is coming from industry itself. One of the most powerful tools for the formation of the C-N bond is the Buchwald-Hartwig amination reaction. This reaction allows us to consider a more convergent approach to producing C-N bonds and avoids more conventional reactions such as Nitro group reductions. This work has lead to an ever-increasing list of Phosphine based ligands. MIT has licensed this technology to Saltigo and Rhodia and this has been scaled-up (1).

Several groups have been working on developing broader applications of Suzuki-Miyaura reactions. Their objective was to use protected haloboronic building blocks. SUGINOME and coworkers demonstrated that they could address the problems associated with the production of by-products. BURKE and GILLIS reported that the blocking groups could be easily removed using very mild conditions. These types of improvements can lead to more practical applications and greater acceptance in the production units (2).

Dr. WILL WATSON wrote in an article in the September, 2009 issue of *sp2* a summary of several of the innovations in chemical synthesis discussed at the Modern Synthetic Methods conference. This included the work by Dr. BARRY TROST in the use of dinuclear zinc catalysts while Dr. RICHARD LAROCK of Iowa State University discussed synthetic methods to make a wide range of heterocycles. Dr. ANDRE DE VRIES of DSM and Dr. CARL BUSACCA of Boehringer Ingelheim discussed asymmetric hydrogenations. At the same conference, Dr. HUANG of Schering Plough spoke on the synthesis of the natural product Psymberin

and Dr. SCHROCK of MIT covered some innovation in Metathesis chemistry.

Advances in chemical synthesis continue to move ahead and processes that we might never have considered are now being run on industrial scale. Reagents such as diazomethane and other hazardous reagents are now handled safely at industrial scale. AFC has been conducting semi-continuous diazomethane reactions at 750 gal scale (ca. 3 m<sup>3</sup>) for many years. This allows the development chemists to have more tools at their disposal going forward.

The ability to perform chiral reactions has increased over the years. The number of chiral ligands available has multiplied and allowed us to do more chemistry. Companies like Solvias, Chiral Quest and a number of other ligand producers continue to develop new and better ligands. The University of Claude Bernard Lyon reported a new series of BINAP derivatives that can be used in water, ionic liquids as well as super-critical CO<sub>2</sub>. We also find that as the patents for these older products come off, chemists are more likely to try them in their processes.

Professor BOEZIO of the University of Montreal reported work on the asymmetric synthesis of alpha-chiral amines using a combination of metal ions with BozPHOS. The original work based on a di-organozinc complex gave good results but used a high level of catalyst. Dr. BOEZIO was able to reach higher chemical and higher ee's in general and reduce the Zn. This method uses less catalyst with an overall higher yield and purity thus also reducing the potential waste issues (3).

The direct amination of allylic carbons has been a problem for years. Professor WHITE at the University Illinois has developed the first method to catalytically convert an allylic C-H to the C-N. According to Dr. WHITE, this could be a good way to produce 1, 2-amino alcohols. This gives us a more direct route to unnatural amino acids and amino sugars. Professor HOFFMAN of Philipps University in Germany commented that this allows adding functionality late in the synthesis (4).

Oxidation while a powerful tool in the lab has not always found great success on the larger scale. As a result of environmental, heavy metal and safety concerns, Oxidation Chemistry has been limited. Dr. CAREY reviewed this area and reported that less than 4% of the reactions performed by development groups were in fact oxidation reactions. Drs. WILKES and WILSON reported work done on heterogeneous metal oxidation catalysts. Solid supported reagents and catalysts offer a potential for cleaner and more efficient chemical reactions. PhosphonicS has developed a wide range of solid supported

oxidizing agents that can be used safely in a manufacturing setting. Solid supported catalyst can often reduce the metal leaching issues and contamination of both the product and the waste stream with environmentally unfriendly metal by-products. In addition, these products can often be used with environmentally more friendly solvents and lower temperatures. The company Selox has licensed from Shell oxidation technology that is environmentally friendlier as well as having a safer operating profile. These technologies have all been run at industrial scale. The net result of advances like this is greater applications and a smoother transition from the lab to production. Consider the cost of waste treatment and the drive for greener chemistry; these products fit well in the corporations desiring to operate in this area. It is important that we have commercially available reagents that can be used in the lab and taken into the scale-up process using standard equipment (5).

There has always been competing technologies. Classical resolutions and biotransformations are often cheaper and more readily available. As the patents expire on more of the classical ligands such as BINAP and there are significant improvements in our ability to synthesize chiral ligands, we should see more chiral transformation in production. DSM and Rhodia have both scaled-up asymmetric processes (6).

The use of enzymes to perform various transformations has been used in many chemical processes. In the past, these transformations have had serious drawbacks including low reactant concentrations, low productivity, high catalyst cost as well as downstream processing issues. Most commercial applications have been directed to kinetic resolutions using lipases and esterases. Their ability to catalyze the enantioselective hydrolysis or synthesis of esters makes these enzymes powerful tools in the resolution of Carboxylic Acids and Alcohols. Many solid phase and solution phase peptide synthesis could be performed using some type of Proteinase. This could avoid the need for side chain protecting groups (7).

Recently, Pfizer working with Codexis developed practical methods for producing R-2-Methylpentanol as well as a biocatalytic reduction of Tetrahydrothiophene. Codexis plans to publish their work on developing a three-enzyme process for one of the key intermediates used in the manufacturing of Atorvastatin. And have worked on an alternate process for the development of Montelukast replacing the use of the DIP-Cl mediated asymmetric reduction.

In general, immobilization technologies have improved our overall ability to use enzymes. We find that enzymes can offer greater selectivity and specificity. In addition,

since most of these reactions can be run at milder conditions, energy cost can be reduced. Today, there are only a few immobilized enzymes in the market place being used as catalysts in industrial processes. Immobilized Penicillin G acylase has been used for the production of antibiotics for decades. Glucose isomerase is being used for the continuous production of fructose. Potential suppliers of enzymes such as BASF, Degussa, DSM and DowPharma have all formed their own biocatalysis groups. These improvements should help the overall biocatalysis market to continue to grow. As with all technologies, the use of enzymes has become almost trivial and part of normal screening for many companies. The number of companies offering commercial enzymes continues to grow as well (8).

In addition, companies are re-engineering products to make them more user-friendly. Dissymetrix reported that they have developed a more stable form of the Corey's catalyst. This product is less moisture sensitive and can be supplied as a dry powder. This could be important since the normal product is supplied as a solution in THF or Toluene. Where high ee's could be a function of solvent effects, improvements like this make these products more readily available and more likely to be used by the development chemist. With a more stable and ready to use product, the medicinal chemists can add this to their tool box. In addition, improvements in recycling the product can also help to reduce costs. We are beginning to see the re-engineering of older reagents to make them more practical and a more far reaching usage as well.

In general, we have seen an increasing number of ligands developed for asymmetric reactions. Since the early work of Drs. KNOWLES and NORIYORI, hundreds of chiral transformations have been developed. Few however have reached a commercial scale. This development has been hindered by several issues. There is a time to market pressure that does not lend itself well to the development and optimization of an asymmetric route. Cephalon decided to go with an SMB route in order to get its product on the market followed by an asymmetric transformation. In the past, another hurdle to overcome centered on the licenses for the technology. As these products come off patents, one expects to see companies more comfortable using these products.

Chiral Quest has scaled the manufacture of mono-methyl amino alcohol (MMAA) intermediate for Duloxetine in its Suzhou facilities, up to multi-hundred kilogram scale and should reach metric tons by the end of the year, further demonstrating that asymmetric hydrogenation using privileged P-chiral

ligands is commercially viable and scalable. Chiral Quest is cooperating with Lonza in this area.

The general outcome of this work could be two-fold. For one, we have more tools to develop more complex molecules. Potentially many of these methods will help us develop more convergent synthesis. This could reduce operating time and in principle chemical steps required. Also, we are starting to see the development of more processes that require a mixture of several technologies and more are being considered. This could include combinations of asymmetric reductions with SMB purification followed by some type of enzyme isomerization to recover the unwanted isomer and recycle it.

**H**igh throughput screening (HTS) has become a valuable tool for the medicinal chemist. Large scaffolds can be built with relative ease. Several companies have also looked at using this method to scan for various reaction parameters including solvent selection and optimization as well as catalyst selection. This allows for the accumulation of many data points in a relatively short period of time. An important advancement in this methodology has been our ability to not only generate data but to be able to review and analyze the data from both an analytical point of view as well as from a statistical review. I would not be surprised that in the future, we find a greater emphasis on data management and acquisition.

HTS has had a big impact on the development of catalytic asymmetric hydrogenation processes. In general, HTS allows us to obtain more data points with fewer samples. One can reduce the amount of material that one needs to screen as well as to reduce the time required. With more data points, one can gain a greater understanding of the process and what is going on. This will require a greater understanding of the operating parameters and help in developing the information one needs for a regulatory filing. These methods are not without faults. One must recognize that a 96-well plate does not give the same mixing and mass transfer effects that one sees in an autoclave (9).

We have also seen the development of other new HTS tools that can assist the development chemist as well. Several companies have launched small devices to help screen for solvent systems as well as selection and optimization of various route parameters. This includes the use of catalysts and other reagents. I would not be surprised to see the next group of students coming from the universities better equipped to handle the influx of data. These methods reduce the need for large quantities of API for the development process and allow the development chemist

to have better data points for the optimization of the process.

**T**he miniaturization of chemistry has also led to an increased usage of micro-reactors. These small units can be used by the medicinal chemist to generate additional material for clinical trials. The pilot chemist can rapidly increase capacity by adding additional plates. This helps the development chemist to have additional time to develop and optimize the commercial process. In addition, for some of the higher potency compounds and low volume drugs, these methods can easily be used through scale-up and commercialization. Considering the attrition rate, it is important to minimize the cost of developing processes until there is greater certainty of the drug moving ahead. The medicinal chemist can transfer the process directly to a process chemist and maintain the clinical time lines. As a result of these types of activities, the line between the medicinal chemist and the development chemist is getting more blurred.

In general Process Intensification has grown in interest over the last few years. While the idea has been around since the 70's and used by many industries, for Pharma, it is just coming into its own. Recently, we have seen an increase in the number of suppliers as well as the designs. Microchannel reactors which is most likely the simplest and best know design has been joined by a range of reactors from spinning tubes to spinning disks. Several companies in Europe have commercialized smaller units for the manufacturing of APIs and advanced intermediates. AET in France have commercialized the "Raptor" Design (continuous stirred tank reactors design) and are producing products on a commercial scale. They have installed units at LaMesta which are producing several hundreds of kilos per day of product. AFC decided to go with the cascading reactor design which employs several smaller reactors to produce large quantities of compounds. Nitech has developed a series of continuous oscillating baffled reactors which are good for handling solids. Several other companies including Corning and Syrris offer small reactors which can be used to produce grams to kilos. DSM published their work on the formation of a nitrated analog of Naproxen.

The advantages of these reactors are well documented. The ability to handle extreme temperatures and pressures as well as exothermic reactions has been demonstrated. For the medicinal chemist however, smaller units are available for development and production of small quantities of compounds. The technology can be readily transferred to the pilot plant and into full commercialization. The advantage to all of this is the ability to

scale-up rapidly and to develop useful information at the bench scale and translate this into pilot and commercial results. At a recent meeting Dr. DE PANTHOU of AETDEV, commented that they were able to take a process from the lab to pilot in only a few weeks. In addition, with the ability to handle more difficult types of chemical reactions, it increases the tools that early development has to work with to produce material and can be carried over to larger quantities.

In the past, process optimization could have been considered a three part process. First you fixed the process then you fixed the polymorphs and finally the particle size. With our ability to see what is going on and the tools that we can use, it is more likely that we will see all three processes being fixed at the same time. We have already seen more team approaches in the development process. The potential for development using micro reactors will allow us to do more experiments and to determine the process in a more direct way. The medicinal chemist will no longer be responsible for the development of targets and scaffolds. His function will be more dimensional and part of a larger chemical team. As stated earlier, I expect to see more statistical people on the team. All of this should eventually lead to shorter development times and reduce costs in general.

**A**s the chemistry improves, our ability to understand what is going on in real time has been greatly improved. With the *in situ* FTIR, and related in-process controls, we gain a deeper understanding of what is going on in real time. Process Analytical Technology has been recognized as a tool for manufacturing for some time and can lead to more improved systems and allows us to get there quicker. The FDA is pushing more for implementation of PAT's. Control of the process starts with the development and now can go back to the medicinal chemist and the data generated. For the FDA, this will fit well into their goal of both continuous improvements as well as defined controls of the reactions.

This could be one of the major advances that will change how we develop products in the future. Being able to determine what is going on during the actual reaction is a valuable tool for the development chemist. With this type of equipment, we can determine what is actually going on and to see the formation of compounds either they be desired or impurities. To be able to view the overall rate of the reaction also helps develop manufacturing processes.

In addition, this work is not limited to just chemical transformations. Mettler has launched in process controls for crystallization and polymorphs formation. With the increase concern by the FDA for

polymorphs and the patentable claims being made, this can help the development chemist as he moves the process from research to full commercialization. These probes are becoming smaller and more sensitive allowing for broader use and could fit well in a commercial setting, micro-reactors or potentially more important with the medicinal chemist.

Couple this with our ability to develop these processes and this information at a micro-scale, Design Space and Quality by Design can be distilled down to define the process and the product. What could be more important as we slowly make the transition from batch reactions to continuous reactions, these methods help us design the process, monitor the process and control the process. This is one tool that has rapidly gained acceptance from all fronts and the data generated from the beginning is easily transferred through the development process (10).

Crystallization has always been a concern and rapid optimization of the process can lead to significant economic improvements. In process controls help to gain a better understanding of the dynamics of the crystallization process. However, to be able to generate the correct particle size without milling can increasing yields and potentially controlling particle size can reduce the waste. Companies are already using Super-Critical Fluids (SCF) to control particle size and polymorphs. In Europe, Plantes is already reported to be using SCF's to develop the correct crystal form and particle size. In the US, Thar has looked at this for many years and can offer equipment and services to control these issues. This could be a real advantage for products that require very small particle sizes and have high toxicity. SCF technology is not limited to crystallization. Several companies have already begun looking at more far reaching usages including various chemical reactions and chiral separations. Thar Technologies founded in 1990 and sold to Waters in 2009 reported more companies are looking at using this technology to produce various processes including aminations, Fischer-Tropsch reactions and Diels Alder. The potential to link chemistry directly to particle size and polymorphs formation could be a significantly better way of making highly toxic drugs. With the acquisition of Thar by Waters in 2009, it gives additional credibility to the technology for both analytical and industrial applications.

**C**hromatography has also moved more into the frontline as a way of producing intermediates and API's. Based on a study at Penn State in 2002, two thirds of the drugs on the market are chiral drugs. The use of simulated moving bed (SMB) technology including the subset of

supercritical chromatography (SFC) has become more of a tool not just for the medicinal chemist but for the production of API's. Over the last few years, there have been major advances in chromatography and the use in process development and manufacturing. In 2000, UCB announced that they were manufacturing a multi-ton API using Simulated Moving bed Chromatography. Lundbeck announced it too would be using similar technology to produce products. By 2004, several products were being commercially manufactured and several plants already had FDA inspections. AFC reported in 2009 that their latest FDA inspection was for three APIs which included two products using a SMB step in the manufacturing process. Today, there are at least five manufacturing groups using this technology and many more companies with small units developing new products (11).

Cephalon announced that it would develop R-Modafinil using SMB technology and planned to launch the product with this technology. On a parallel track, they would continue to develop an asymmetric route and supplement their NDA after launch. From the beginning, the plan was to shorten the time line to launch. This was about speed to market. Armodafinal has been approved and the launched products are produced with SMB (12).

Sertraline (Zoloft) by Pfizer has been produced using SMB technology. The SMB route eliminates several classical chemistry problems and reduced the time to market, solvents and reagent needs. This resulted in a greener process with less waste (13).

For GSK, the development of Radafaxine could follow several potential routes. The desired drug is an S,S-enantiomer and the R,R configuration has undesired side effects. One process developed uses multi-column chromatography. The MCC process was able to reduce significantly the amount of solvent used in this process as well as other reagents. GSK estimated that the MCC route at full production meets its economical requirements while reducing waste by an estimate of 5,000 metric tons per year (14).

Several companies have installed large production units. Companies like AFC, Novasep and Sigma Aldrich (formally the Honeywell site) have large process units producing commercial quantities. In addition, several companies have invested in development units and routinely look at using SMB as an alternate to more traditional chemistry. Saltigo has looked at using this technology in a number of products. They have added this to one of their many tools and allows them greater flexibility in chemical development. In addition, companies like AFC, SK, Carbogen and others to name a few have lab

prototype units available for development.

Novasep, a long time supplier of SMB products and services, expanded its technology base with several acquisitions over the last few years. With the addition of chemical capacity in Europe, they have the opportunity to offer classical solutions as well as Chromatography solutions. Ampac Fine Chemicals (AFC) currently has several SMB units operating at its site in California. During the early development of a new chemical entity, Dr. DAPREMONT commented that both isomers can be produced and used for testing. In addition, the scale-up is linear and the solvent usage can be decreased.

There have been several hurdles to using SMB technology. The cost of the equipment is one for sure. However, with improvements in stationary phase, the cost can be significantly reduced. Separations using SMB are normally measured as a function of the amount of kilos produced per kilo of stationary phase per day. Originally, these coefficients were below 1. Today, the average is above 2 and climbing. Chiral Technologies, Inc. is looking at the next generation of stationary phases and have improved the stability as well as the separation coefficients. More stable stationary phases not only reduce the cost but avoids costly shutdowns. Increased reliability makes this an excellent tool in the eyes of the process chemist. Since the equipment output is dependent on the stationary phase, any increase in the performance will significantly decrease the operating costs. With a low labor contribution to start, this becomes an effective tool for the production of both API's and chiral intermediates. AFC has been using the same stationary phase for a commercial scale separation for many years resulting in a very low cost contribution of the CSP to the product final price.

In addition, one can rapidly screen for the stationary phase and the scale-up is truly linear. The same tool that the medicinal chemist is using can be used by not only the development groups but in principle, the commercial people see the same thing. This allows the innovator to maintain his clinical development line and shorten the time to production. Short development time coupled with rapid scale-up makes this a viable technology for production.

With the FDA pushing for more data on the various enantiomers, the need for rapid synthesis of both isomers is important. SMB technologies allow us to develop rapidly processes to produce pure compounds. In addition, this technology can be translated into processes that can be scaled-up. For the medicinal chemist, it is relatively simple to set up a separation. The information generated can be used by the development chemist to produce larger batches and maintain clinical time lines. With the

development of more products and shorter time lines, these processes are becoming more common and there is less resistance to using them in production.

In today's world, the reduction of the use of hydrocarbon solvents is important. SMB technology has been shown to be able to reduce significantly the quantities of solvents used in a process. This reduces both the cost of solvents as well as the disposal fees associated with the removal of these products. The purification and recycling of the solvents will also help reduce costs even further. Cost containment has become an issue not just for the development chemist but with closer ties to the medicinal chemist, even they are thinking more forward and looking at these issues. Novasep has been looking to improve the solvent use and reduce the total solvents in the process. AFC won the green chemistry award in 2007 for the implementation of the 99%+ solvent recycling on a commercial scale SMB process, showing significant reduction in waste resulting in better process economics.

SFC technology has also improved and could help us focus more on "green chemistry." Carbon Dioxide has a low viscosity and greater diffusion and potentially more important is easy to remove and recycle at the end of the process. If there has been a limitation, it is most likely based on the availability of equipment and its cost. However, this is changing. For the lab, the medicinal chemist has some good choices. For the pilot and production people, the costs are decreasing while the use of SFC is increasing. Dr. CHORDIA of Thar Research is focused on developing SFC technology and has already been involved in plant size equipment able to produce ton quantities of material. Imagine a chemical process that allows you to develop a pure isomer and potentially can give you the particle size and polymorph you require (15).

While the capital cost could still be considered a hurdle needed to overcome, we see more lab and small units appearing in China and India. Chiral Technologies, Inc. has technical support team located in China. Novasep has a development lab in China to assist customers there. They also have a group located in India.

More important, pharmaceutical companies like UCB, Pfizer, Merck, Glaxo, Lundbeck and Astra Zeneca are all reported to have large development groups focusing only on chromatography solutions. These functions no longer seem to be independent groups competing but intellectual centers focused on developing rapidly the best process. With both the CMO's and the pharmaceutical companies adopting these technologies, we can expect to see more products produced using mixed technologies to reach the targets of

time, cost and environmentally friendly processes.

The advantage of MCC technology has been speed to market and its ability to supply early on pure forms of either isomer for testing as well product for clinical trials. Improvements in the technology has also allowed for processes in which the solvent use has decreased significantly making the processes less expensive and environmentally more favored. What started out as an analytical tool has grown to a well accepted process technology opening new avenues of technology to help the development chemist.

Catalytic transformations continue to grow. A key development in the use of metal-based catalyst has been the development of economic methods for the removal of traces metal impurities from the final product. With the increase in development of metal based asymmetric reactions, coupling reactions and deblocking, the ability to remove traces of Palladium, Rhodium or Ruthenium is becoming more important. As these steps are performed further down stream there is less opportunities for purification and removal (16).

This follows Dr. HOFFMAN's comment about being able to add functionality later in the synthesis. Often, we would look to perform the catalytic step early on and allow the multiple chemical steps to improve on the quality. In addition, our process design can allow for increased functionalization of the reactants which can increase flexibility in our synthetic design and allows us to consider more convergent synthesis. As a result of the efficiency for these types of products, we can reduce the costs associated with re-crystallization and waste disposal. Consider that the estimates for the cost of goods for the pharmaceutical industry is placed around \$ 90 billion, a small percentage of saving can translate into a large economic gain. Add the saving associated with the environmental costs and the reduction of waste throughout the process, these products can bring significant savings (17).

Various types of chromatography have been long used by the manufacturers of biological molecules. It is not uncommon to find process requiring the use of more than one chromatography steps. One often sees some type of rough product purification followed by a polishing type step to remove small amounts of impurities. The ability to separate small amounts of very similar molecules is strong plus for chromatography.

Today, several companies have developed products to easily remove these traces of metals. Coupling reactions and reductions can be done at the very end of the synthesis. This is critical to process

development as we find the limits set for metals continue to decrease. BASF, Phosphonics and Silicycle have developed products that have very high thermal stability and are very stable. BASF and Phosphonics have also worked on recovering the metal from the scavenging agents and recapture some additional economic value. In principle, these products are not dependent on the oxidation state and can be used in a wide range of solvents (18).

Consider that in 2006, the global demand for Platinum, Palladium and Rhodium was estimated to be in the range of 22,000 kg. Considering the cost of metal today, even a small loss of metal could add a significant cost to the manufacturing. In addition, if the metal makes it way into the waste stream, the environmental cost can also be significant. Also, one must realize that with changing regulations and the reduction of the metal limits in the API, the reduction of the metal in the final product can add cost, increase waste and reduce overall yields (19).

The presence of genotoxic impurities has become more of an issue. It has been defined that some chemicals can cause genetic mutation and compounds like aromatic amines can covalently bond to DNA and cause mutation. This has resulted in several products being developed being placed on clinical hold by the FDA. The recalls of Nelfinavir due to unexpected high levels of ethyl mesylate, a well known genotoxic substance, increase our overall awareness of the problem. PhosphonicS reported that they are looking into the removal of targets such as sulfonated esters and their precursors, alkyl halides and haloalkyl heteroaromatics, alpha-chloroketones and haloalkyl amines.

In general the removal of impurities that are similar in molecular structures can be a costly and time consuming operation. A series of organic scavenging agents can be used to remove these impurities. This can be a useful technology for the development of large peptide chains using solid phase technology as well as purifications of natural products. This could reduce the need for some crystallizations and remove the more difficult impurities. This can help develop more environmentally friendly processes. SMB can certainly be used for this kind of application as well. SMB is a binary separation technique and by combining the high throughput and high recovery yield, SMB can successfully remove specific impurities such as genotoxic impurities to below detection limit at a fraction of the cost of multiple crystallizations.

Other methods of purifications have been coming forward for some time. Ionic liquids have been developed and now used on commercial processes as solvents. Ionic liquids can be less toxic and with no vapor

pressure can be considered safer to handle and easier to use. Eli Lilly reported that at the pilot scale they have used Ionic Liquids as a solvent for ether cleavage. Degussa has used Ionic Liquids at the pilot scale to perform hydrosilylations. They have been used in wide range of chemical markets.

BASF has commercial operations for acid scavenging in which the Ionic Liquids can be used as an auxiliary and in the pilot have performed extractive distillations. In many cases the formation of azeotropes does not allow the separation of two or more compounds by a simple distillation. Very well known azeotropes with an industrial relevance are for example water/ethanol or water/THF. Sometimes the azeotrope can be broken by addition of another compound. These compounds are called entrainers. Ionic liquids do also act as entrainers for a great variety of azeotropic systems. Especially if water is one component of the azeotrope, very high separation factors can be achieved. Ionic liquids usually are quite hygroscopic materials, which show their strong affinity to water. Obviously the interactions between ionic liquid and water are much stronger than between water and the other component of the azeotropes. The ionic liquids literally graps the water and releases the second compound which can be distilled off as pure material. In other words the ionic liquid is acting as an extractant for water.

Ionic Liquids have no vapor pressure to speak of and can be considered safer to handle. They also work well in exothermic reactions and act like a heat sink. In addition, they operate under a wide range of temperatures and could give greater flexibility in process design. They can also be recycled at very high yield reducing the overall costs of solvents and reducing disposal costs. With increased concerns for halogenated solvents and disposal cost increasing, Ionic liquids could become a useful tool for the pharmaceutical industry.

Technology is not limited to just the manufacturing process but the handling of chemicals in a safer way. Our ability to produce highly toxic products has improved over the years. Companies have been developed better isolators, control valves and general containment equipment. Since often while the product is moving through the development time line, the scale-up is moving faster than the toxicity data. These advances in containment and product transfer systems have helped to alleviate this problem while maintaining time lines and development. ILC Dover has developed several products that can be used to weight, contain and transfer. In addition, these products can be used to take samples. PSL has worked for years on transferring products. These systems will allow us to develop products faster and safer.

## CONCLUSION

Overall, the development process is evolving as is the industry. At the end of the day, what much of this may have done is get the development process beginning with the medicinal chemist and ending with the commercial production to be one continuum. As our universities continue to generate more graduates, we also seem to see that even the academic groups are more business oriented.

I have tried to cover some of the many examples of technologies that are affecting the way we do things. Any new technology has to take time to develop and mature. As we chemists become more comfortable with these technologies at all levels, we will be more comfortable in adapting these more efficient routes to our process development.

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