Country Profile

A look at the Pharmaceutical Industry in

BELGIUM

Produced in collaboration with ISPE Belgium

ISPE
THE SOCIETY FOR LIFE SCIENCE PROFESSIONALS

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This new feature in *Pharmaceutical Engineering* is designed so that you can tear it out, three hole drill (if desired), and keep it with other Country Profiles as they are published.

Look for the Country Profile on Australia in the November/ December issue of *Pharmaceutical Engineering*.

ISPE
THE SOCIETY FOR LIFE SCIENCE PROFESSIONALS

Dear ISPE Member,

In the following pages, we have tried to give you a view of the pharmaceutical industry in Belgium, located in the center of Europe and maybe not familiar to each of you. This privileged location, where two different ancient cultures melt and where in educational programs multi-lingualism is strongly promoted as a must, evolves a highly export oriented economy. Around 75% of GNP are exported, mainly within the inner European market, but also an important part into the rest of the world.

A model social welfare system secures a high standard of living with access to all modern pharmaceutical drugs and medical techniques for the whole population.

Educational excellence, ethical management, a stable social environment and a high manpower efficiency on the workfloor guarantee a positive climate for new investments in high tech business.

Fundamental research for new pharmaceutical molecules in a close collaboration between different renowned universities or partnership with spin-offs and major pharmaceutical companies creates a well developed operation in the country, in the pharmaceutical as well as in the biological industry.

In this environment, ISPE Belgium was created in 1992 as an Affiliate of the International Society for Pharmaceutical Engineering.

The present committee is staffed with representatives from all major pharmaceutical companies that are active in the country as with members from global engineering contractors and major equipment suppliers.

Through the organization of diversified training seminars, the ISPE Belgium Affiliate grew over the years to a well recognized association with almost 500 Life Science professionals being permanent members.

In line with the strategic objectives of ISPE, the Belgium Affiliate committee continues to organize and provide training in the different disciplines of the Life Science fields in order to make sure that highly educated professionals are available to the industry.

Further information and details on this can be found visiting our Web site at www.ispe.org/Belgium.

Yours truly,

Jef De Clercq
President, ISPE Belgium

A Look at the Pharmaceutical Industry in Belgium

"A strong healthcare system, outstanding university hospitals, and a solid scientific and operational knowledge are the Belgian strengths that create a stimulating environment for the pharmaceutical industry."

Thriving Sector/ Stimulating Environment

Belgium, may be a tiny spot on the world map, but it is globally renown for many things, including its historic cities like Bruges and Ghent; its many varieties of beer and delicious chocolates; for its art nouveau, started by Victor Horta and Henri van de Velde; and for its many famous artists like the Van Eycks, Rubens, and Ensor. Belgium is a country that boasts more history, art, food, and architecture per square centimeter than most of its bigger neighbors. It also boasts a long tradition in healthcare and medical science, witnessed by the fact that there are no less than 150 pharmaceutical companies active in Belgium. And, they're not just small ones. All of the top worldwide players are present, but not merely as a lone sales organization, an R&D department, a manufacturing site, or even a logistics center. They are here with everything they've got. And they are here to stay since they are continuously investing in their Belgian branches, particularly when it comes to research.

Brussels is the lively capital of Belgium. It houses both the European Union and NATO headquarters. With its population of 980,000 added to the many contiguous communities, greater Brussels has a total population of more than one million. With its many nationalities, it is truly at the heart of Europe.

One area where Belgium has been often featured in international headlines is with its Nobel Prize winners, especially in medicine. The latter shouldn't come as a big surprise since this tiny country of some 30,000 sq km and 10.2 million inhabitants, houses no less than 13 major universities.

"Belgium is attractive on many fronts," explains Prof. Dr. Leo Neels, Managing Director of pharma.be, a non-profit society that represents the pharmaceutical industry located in Belgium. "First, there is a general and political impetus for research in Belgium. This has the effect of creating many stimulating projects. Second, academic level and standard of science is very high. Third, the pharmaceutical industry itself is very dynamic in Belgium. The industry has created a very favorable microclimate for research, working closely with university labs of very high standing qualitatively and continuously funding fundamental research."

Continuous Flow of Investments

There has been a general trend of more and more pharmaceutical companies moving their research to the US, and this has been reinforced by numerous mergers in recent years. "Remarkably, this has had very little effect in Belgium," notes Neels. Research activities in Belgium are still growing. From 1990 to 2001, expenditures in R&D have risen from 183.3 million Euro to 1.18 billion Euro. That is more than a sixfold increase. In 2001, more than 3,150 people were working in R&D. This is approximately 13% of the total workforce in the Belgian pharmaceutical industry. Major companies carrying out very successful research in Belgium include GlaxoSmithKline, Janssen Pharmaceutica, UCB Pharma, and Eli Lilly.

Herman Van Eeckhout, Director at pharma.be adds: "One of the research fields that has shown particularly strong growth in recent years is clinical research. More than 5,000 people work in clinical testing. We are even performing tests on molecules that were developed in the US. Again, this

Cat. A - Life-saving drugs: cancer drugs, insulin, etc.
100% of the reimbursement base.

Cat. B - Medicines for treatment of non life-threatening diseases
Ordinary insured parties: 75% of the reimbursement base (maximum of 9.79 Euro)
Insured party with preferential tariff: 85% of the reimbursement base (maximum of 6.57 Euro)

Cat. C, Cs - Medicines that promote well-being and Cx
Cat. C Ordinary insured parties: 50% of the reimbursable base (maximum of 16.24 Euro)
Insured parties with preferential tariff: 50% of the reimbursable base (maximum of 9.79 Euro)
Cat. Cs 40% of the reimbursable base (no maximum)
Cat. Cx 20% of the reimbursable base (no maximum)

Table A. Reimbursement policy. The Belgian social security system makes healthcare available to all.

A Look at the Pharmaceutical Industry in Belgium

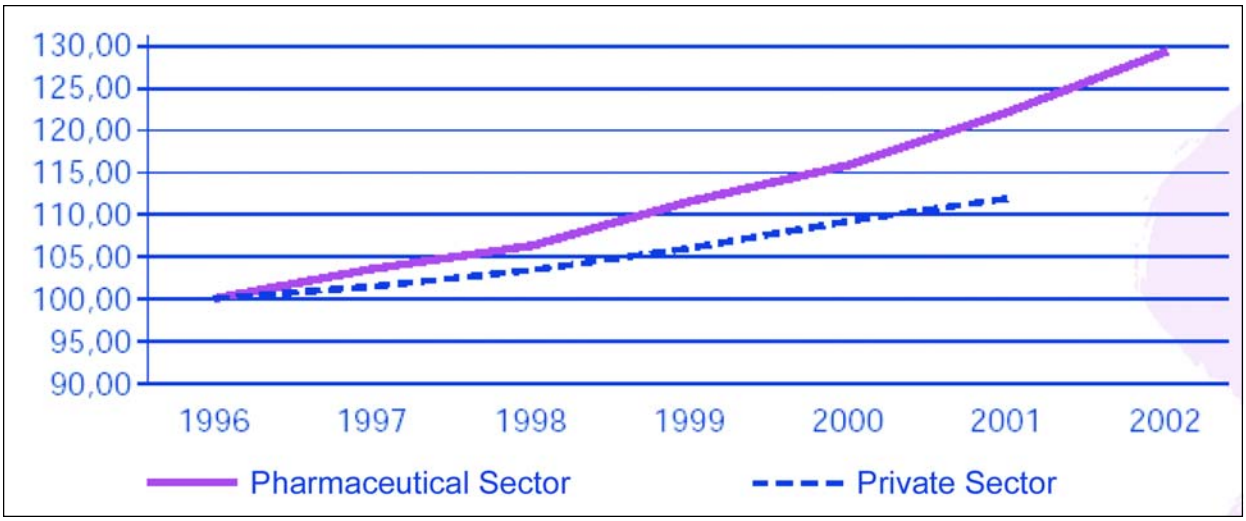


Figure 1. Evolution of the employment rate in the pharmaceutical industry compared to the private sector. The employment level of the pharmaceutical sector is growing significantly faster than the rest of the private sector.

is thanks to not only our high education level and the quality of our scientists, but also to the close interaction between research labs and medical faculties."

In recent years, there also have been considerable investments in Belgian manufacturing sites. These include, among others, Pharmacia, UCB Pharma, Schering-Plough, and Alcon. Thanks to these investments and others like them, employment has grown steadily. Many companies are growing at the rate of more than a hundred new employees per year.

Faster Access to Innovative Medicines

Like many European countries, Belgium has a reputation for bureaucracy, slow administration, and everlasting procedures. But this has improved somewhat over the last few years, asserts Neels. "Remarkable improvements have been made. But let there be no misunderstanding about it. We still have a lot of work to do in that department. We need to continuously remind the government of the importance of research stimulating projects, the need for fast regulation procedures, and a stable and attractive, economic marketplace.

"One important example of progress in this area is the procedure for pricing and reimbursement. This used to take more than 500 days, while the maximum European term is 180 days. Over the last two years, this 180-day target is generally being met. And, this while we continue to foster a consultation climate where the participation of all stakeholders is encouraged. Securing the 180-day limit is an extremely important achieve-

	Million Euros / US$			
	1999	2000	2001	2002
1. The internal market - Sales of medicines for human use via pharmacies open to the public and via hospital pharmacies, at ex-factory price, exclusive of VAT	2,576.3	2,666.7	2,849.6	3,036.6
2. External trade				
a) Exports: sales of raw materials and medicines at ex-factory price.	6,046.1	7,419.8	10,450.6	23,345.4
b) Imports: acquisition of raw materials and medicines at purchase price.	4,718.0	6,072.0	9,327.1	23,865.0
c) Trade balance: a) – b)	1,328.1	1,347.8	1,123.5	–519.6
3. Employment Number of people employed	21,851	22,732	24,201	25,408
4. Investments	295.7	318.5	380.7	453.2
5. R&D	737.9	762.2	1,178.8	1,279.5

Table B. Basic figures for the Belgian pharmaceutical sector. The pharmaceutical industry is clearly one of the driving forces behind the Belgian economy.

A Look at the Pharmaceutical Industry in Belgium

1	GLAXOSMITHKLINE	(= no 2 worldwide)	8.33%
2	ASTRAZENECA	(= no 4 worldwide)	7.05%
3	PFIZER	(= no 1 worldwide)	6.42%
4	JANSSEN-CILAG	(= no 7 worldwide)	5.44%
5	AVENTIS PHARMA		4.78%
6	AHP PHARMA		4.67%
7	NOVARTIS PHARMA		4.57%
8	SANOFI-SYNTHELABO		4.57%
9	BRISTOL-MYERS SQUIBB BELGIUM		3.72%
10	ROCHE		3.60%
11	MERCK SHARP & DOHME		3.21%
12	PHARMACIA		2.94%
13	BAXTER		2.93%
14	ABBOTT		2.15%
15	ELI LILLY BENELUX		1.96%

Table C. Top 15 pharmaceutical companies in the Belgian market; Companies/Groups in market share in % of the total pharmaceutical market in Belgium. Most top pharmaceutical companies are active in Belgium. Some of them are still controlled by Belgian capital: UCB Pharma (24), Solvay Pharma (28), and Therabel (18).

ment as innovative medicines can be put on the market much faster, often within a year! Again, this makes Belgium more competitive."

Expertise in Manufacturing and Supply Chain Management

When looking at the basic figures outlining the pharmaceutical sector in Belgium (Table B), it's striking that there is a great deal of importing and exporting for such a small country. Herman Van Eeckhout explains this trend: "Belgium has quite an extensive expertise and know-how when it comes to manufacturing and supply chain management. Indeed, we see that many companies have extensive manufacturing sites and distribution facilities in Belgium. Moreover, all major companies must comply with stringent national and international regulations. This means that we can export to virtually every country in the world. In 2002, our export figures grew to more than 23 billion Euro."

Another definite plus is the fact that the Belgian government has stimulated the distribution sector with fiscal incentives. We've become kind of a tax shelter. This has definitely worked for the benefit of the pharmaceutical sector. We see that several companies import products into Belgium from their production sites all over Europe. They then export these to the rest of the world." This has led to an exponential growth of 123.39% in exports and 155.93% in imports between 2001 and 2002.

"There's a strong political awareness of the importance of the pharmaceutical sector, and more importantly, of its research activities."

Employment Rises Faster Than Average

By mid-2002, 25,408 people were working in the pharmaceutical industry in Belgium. Belgium's top 10 pharmaceutical companies in 2001 are listed in Table G. Over the past six years, it can be clearly seen that

Holistic View on Healthcare

Currently, there is a far reaching project in Belgium to develop a long-term vision of healthcare and related costs. The Added Value Project is an initiative of the LIM, an umbrella organization of research-oriented pharmaceutical companies in Belgium. This renowned medical industry think tank has created a model methodology under the direction of Professor Jan Peers and Deloitte and Touche.

According to Neels, "the thesis is that an innovative medicine or surgery technique can have positive effects on the complete healthcare system including shorter treatments, less surgical intervention, shorter hospitalization times, less absenteeism, etc. So instead of concentrating so much on the cost of a medicine, the government also should take into account the overall healthcare and other social costs that can be saved. Figures show that in countries where the relative share of the cost of medicines in the total healthcare budget is larger, the total healthcare budget is significantly lower. Absenteeism is several times lower and the hospitalizations are less intense and shorter. The Added Value Project takes all this into account. It will help to bring new, innovative medicines, and techniques to patients faster."

Clearly, this project could be the starting point in a different and better way of looking at healthcare and related costs. Currently, all involved parties are evaluating the model. Now the government needs to be convinced that this is a sound basis for a new policy instrument.

A Look at the Pharmaceutical Industry in Belgium

Medicines registered for human or veterinarian use[1]	12,354
Medicines registered for human use[1]	11,200
Medicines registered for human use available on the market[2]	5,490
Presentation of registered medicines for human use available on the market (presentations for the public and hospitals and liquid perfusions[2])	6,502
Portion of the latter that is reimbursable[2]	3,677
Individual medicines for human use available on the market[2]	2,746
Registered active substances used in medicines for human use, available or not[1]	2,292

[1] Source: Ministry for Public Health
[2] Source: AGIM

Table D. Registered medicines in Belgium.

	Euros / US$
1. Costs to the state[2]	**1,769.4**
1.1. INAMI expenditure	1,762.5
1.1.1. Expenditure exclusive of VAT (industry share)	1,662.7
1.1.2. VAT (industry share)	99.8
1.2. Subsidies	6.9
2. State revenue[3]	**1,789.0**
2.1. Taxes on wages	765.0
2.1.1. Employers' social security contributions	320.5
2.1.2. Employees' social security contributions	128.7
2.1.3. Personal income tax deducted at source (from third parties)	315.9
2.2. Corporate taxation	245.3
2.3. Other taxes, deductions and charges	304.8
2.3.1. VAT on turnover (company price)[4]	160.0
2.3.2. Taxes on turnover and charges (INAMI)	126.4
2.3.3. Other taxes on operations[5]	5.0
2.3.4. Movable property income tax deducted at source (from third parties)	13.5
2.4. Indirect revenue from purchases from third parties and investments[6]	473.9
2.4.1. Raw materials and merchandise, miscellaneous goods and services[7]	39.1
2.4.2. Investments	39.1
3. Results (2-1)	**19.6**

[1] These costs and revenue are limited to companies marketing mainly medicines for human use. Companies involved in the marketing of human medicines and carrying out activities in the area of veterinarian medicines and/or *in vitro* diagnostics as well,were also included in this analysis.
[2] Sources: INAMI,Banque nationale de Belgique (centrale des bilans - annual company accounts); calculations by AGIM.
[3] Sources: Banque nationale de Belgique (centrale des bilans - annual company accounts); ICN: external trade and added value statistics, Ministry for Economic Affairs, INS (statistics on sales and turnover), Fedichem (investments); calculations by AGIM.
[4] VAT calculated on basis of ex-factory price (Ministry for Economic Affairs).
[5] AGIM estimates that these other taxes on operations,exclusive of Inami taxes on the turnover of pharmaceutical companies, amount to a lump sum of around 5 million Euros.
[6] State revenue from purchases and investments was estimated bearing in mind two parameters: the manufacturing industry's share of value-added in the manufacturing industry's turnover and,secondly,the share of total state revenue in the GDP.
[7] The estimate of state revenue from raw materials and merchandise does not include purchases by companies that are mainly involved in importing nor purchases by companies with solely commercial activities and that are part of a group with a production unit in Belgium.

Table E. The pharmaceutical sector in relation to the state in 2000: costs and revenue (in millions of Euros) Contrary to what many people think, the pharmaceutical industry entails a net income to the government.[2]

the employment level in the pharmaceutical sector is growing faster than the average level in the private sector: 23% versus 11.1% (Figure 1). Looking at the evolution of the employment level according to the activities of companies, it is readily apparent that general growth can be ascribed to companies that perform fundamental research in Belgium and that are active in production and export at the same time. This proves that research is still the driving force behind the sector.

Unique Healthcare System

In addition to an outstanding academic climate, Belgium also has a unique healthcare system. This has been a big factor in the motivation of students to enter medicine. In 1945, Belgium was already a pioneer in social security, strongly believing in the wisdom of mobilizing all available resources. At the moment, all employed citizens contribute part of their wages to social security. In exchange, large parts of the costs for prescribed medicines (Table A) and visits to the doctor, dentist, hospital, etc. are refunded, making affordable healthcare available to all. This has created a positive environment for the healthcare industry, and yet another reason why Belgium is an attractive country for the pharmaceutical industry.

Expensive Sector?

In Belgium, the total cost for healthcare is constantly under scrutiny. Some feel that the financial pressure on the social security system is due to the fact that the cost of medicines is refunded. Others think that the cost of those medicines is much too high. Some populists are calling on the pharmaceutical industry to make

A Look at the Pharmaceutical Industry in Belgium

"All top players have a strong presence here. To name just few: GlaxoSmithKline, Pfizer, AstraZeneca, Pharmacia, and Johnson & Johnson."

greater efforts to keep prices down. However, many of these individuals fail to take the realities of the modern pharmaceutical industry into account. It is clear that research has become extremely expensive. The average cost to develop a new drug is 895 million Euro. Only 30% of these are likely to be a commercial success. The survival of companies depends upon a sound pricing policy.

The figures clearly demonstrate that the pharmaceutical industry is not a cost for society. Of course, there are the large sums spent by the Riziv - INAMI, the Belgian institute for health and disability insurance and various other subsidies. But these are, for the most part, covered by deductions from the wages, taxes on company profits, and indirect income due to investments and purchases at third parties. If you look at this total picture objectively, it is clear that the pharmaceutical industry is a profit for the government rather than a cost - *Table E*.

Dr. Neels adds, "it is clear that we need to keep stimulating this sector to keep it investing in Belgian branches and invest in research. This will definitely be in the best interest of our country. The only rational way to accomplish this is to convince the government to initiate stimulating measures. We welcome the plans of our new government to lighten the tax load of companies with highly educated employees." This is very important, as one top scientist, for example, leads directly to 10 jobs and indirectly to another 60 within a company. "We also need to keep working on our registration procedures. The shorter they are, the faster companies can start recovering the costs of their research investments. If we add this to our natural strengths – a high academic level, strong language skills, and good flexibility - we are convinced that Belgium will remain an attractive country for the pharmaceutical industry."

Company	Number of employees in Belgium (2001)
Janssen Pharmaceutica	3,677
UCB Pharma	2,172
GSK Biologicals	1,617
Baxter	1,287
Pharmacia	1,231
GSK Bio Manufacturing	732
Alcon Belgium	644
AstraZeneca	540
Schering-Plough Laborat.	421
Innogenetics	406

Table G. Belgium's top 10 pharmaceutical companies by workforce. (Source: Trends Top 30.000, 2003)

Note: Source for all the figures in this article is www.pharma.be.

Rank	Company	Turnover in 2001 in Euros / US$
1	GSK Bio Manufacturing, GSK Biologicals and GSK Bio	1,689,469
2	Janssen Pharmaceutica	1,567,928
3	UCB and UCB Pharma	813,806
4	Baxter	747,326
5	AstraZeneca	412,829
6	Pharmacia	273,151
7	Alcon Belgium	169,610
8	Aventis Pharma	163,671
9	Bristol-Myers Squibb	134,269
10	Sanofi-Synthelabo	131,913
11	Schering-Plough Laborat. + Schering	122,843
12	AHP Pharma	109,471
13	Warner-Lambert Belgium	98,148
14	Pfizer AH	81,295
15	Beecham	48,796

Table F. Pharmaceutical companies in Belgium by turnover. (Source: Trends Top 30.000, 2003)

GSK Biologicals: Vaccines for the World

Strong Research, Responsible Marketing

The GlaxoSmithKline Biologicals Division is one of the world's largest and most important vaccine manufacturers. Headquartered in Belgium since the end of the 1960s, it has steadily grown to become one of GSK's most dynamic research centers and has been responsible for many decisive discoveries. The company's ambition is nothing less than to cover the vaccination needs of every man, woman, and child. This is particularly true for those living in the developing world, where GSK is taking part in numerous initiatives. GSK Biologicals boasts the sector's most extensive portfolio of vaccines currently in clinical testing.

"GSK Biologicals introduced the world's first genetically engineered human vaccine."

Twenty-Five Vaccines per Second

The worldwide headquarters of GSK's Biologicals Division is at Rixensart, Belgium. It has specialized in the development of vaccines since it was first built in the 1950s. The site successfully produced the first anti-polio vaccine in 1957. That breakthrough and its many other subsequent development programs have contributed greatly to Belgium's worldwide reputation as a center of expertise in the areas of virology, bacteriology, and immunology.

Today, GSK Biologicals is the world's leading vaccine manufacturer with 25% of the global vaccine market. In 2002, GSK Biologicals distributed more than 800 million doses of vaccines to 156 countries. That represents a phenomenal average of 25 doses

Figure 1. Growing sales of hepatitis vaccines and pediatric vaccine combinations drove the increase in turnover at GSK Biologicals in 2002. (Source: 2002 GSK Annual Report)

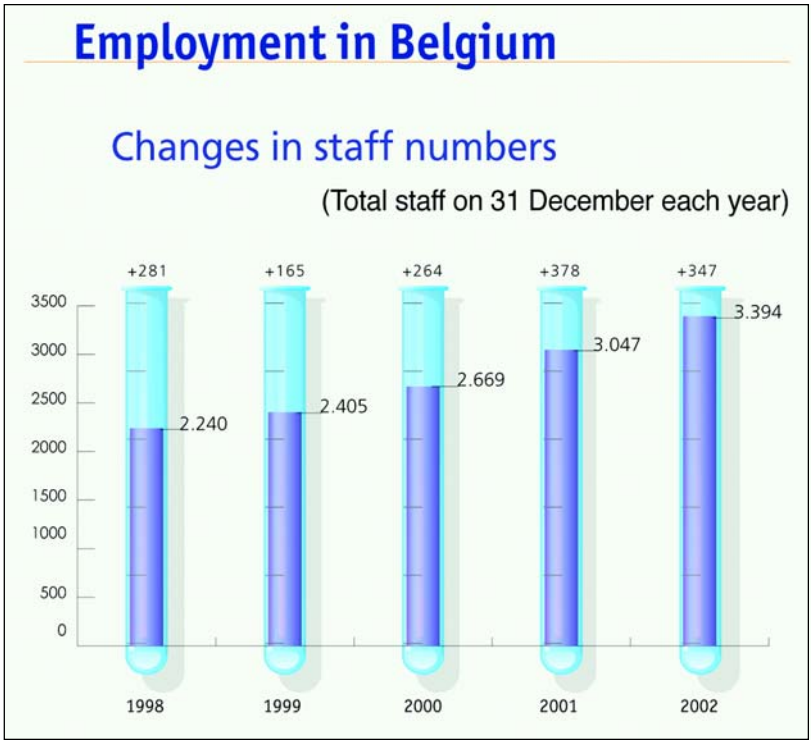


Figure 2. The number of people employed by GSK Biologicals in Belgium has grown by more than 70% over the past decade. (Source: 2002 GSK Annual Report)

GSK Biologicals: Vaccines for the World

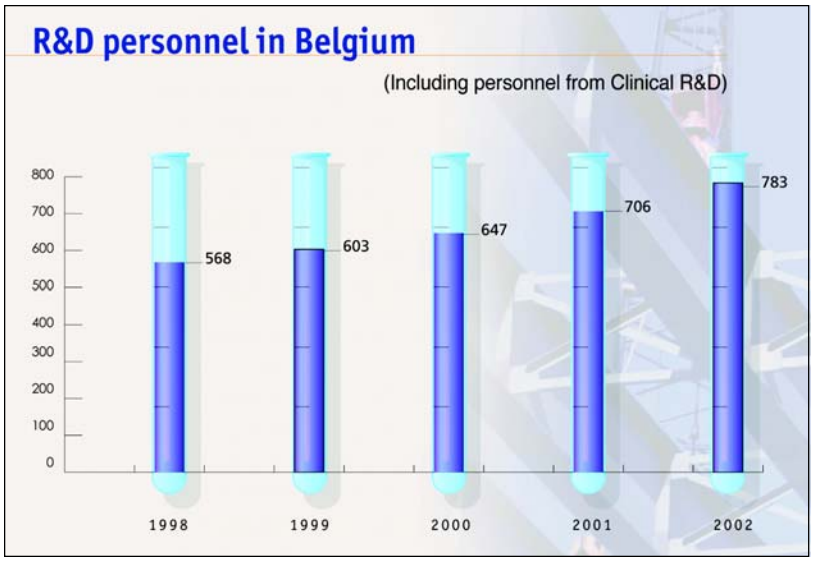


Figure 3. The number of researchers working on the development of new vaccines at GSK Biologicals in Belgium is steadily increasing. (Source: 2002 GSK Annual Report)

per second around the world. The company's best-selling products in 2002 were its Infanrix pediatric vaccine combination and its Havrix, Engerix-B, and Twinrix hepatitis vaccines - *Figure 1*. GSK Biologicals also markets vaccines against numerous other diseases, including typhoid fever, meningitis, influenza, and salmonella.

A Growing Team of Experts

The GSK Biologicals workforce has grown continuously over the past decade - *Figure 2*. The company's three Belgian sites are currently hiring one new person a day on average. Some 22% of the current 3,500 members of staff employed by GSK Biologicals in Belgium are dedicated to research and development. And, the number of researchers is increasing year by year - *Figure 3*. "Our R&D teams are involved in every step of the process, from molecular discoveries to the registration of new vaccines," says Jean Stéphenne, President and General Manager of GSK Biologicals. "If we take into account our clinical tests, quality assurance, and regulatory affairs staff, the number of people employed in R&D exceeds 1,000. Approximately 20% of our turnover is invested in R&D every year. Without question, it is the beating heart of our business."

Cross-Pollination

Research is organized into multidisciplinary project teams. Interdisciplinary communication and exchange of ideas are fostered all through the product development cycle. In the early stages, experts from various disciplines get together to stimulate cross-pollination. Specific techniques have been developed to improve brainstorming methods and knowledge management. In later stages, researchers frequently meet with business developers and staff from the clinical tests and registration departments. Together, they identify where the company stands in relation to the needs for new products and vaccines as well as what the competition is doing. Then they define priorities accordingly. This group also sees to it that the research portfolio remains well balanced. In other words, that there are always sufficient promising products at each stage in the development cycle.

"Interdisciplinary communication and exchange of ideas are fostered throughout the development cycle."

Rixensart, near Brussels, Belgium, is the center of all GSK vaccine research, development, and production.

GSK Biologicals: Vaccines for the World

Politics and Partnerships

"In recent years, the political and economic context in Belgium has been less favorable for research activities," states Jean Stéphenne, President and General Manager of GSK Biologicals. "Pharmaceutical research has not received sufficient support from the government. Likewise, universities have had to make do with restricted budgets. The result has been a notable brain drain. GSK Biologicals has therefore set up programs with the National Fund for Scientific Research to sponsor university doctorates in areas like immunology. The company also funds projects in a joint university research center which are in line with its research objectives and programs."

"Legal issues are another potential matter for concern," Stéphenne continues. "The pharmaceutical sector is closely following any new legislation by the Belgian government regarding the patenting of various aspects of the human genome or stem cells. Should the government decide on a legislation that is more restrictive than other countries, then large research projects in this promising area will almost surely move abroad."

The newly created European Agency for the Evaluation of Medicinal Products (EMEA), on the other hand, has been warmly welcomed by the Belgian pharmaceutical sector. A single registration of a new vaccine authorizes it for all 15 European Union countries. This obviously saves a huge amount of time, administration, and cost of development. Because the evaluation procedures have been standardized, assessments are more consistent and of a higher quality. For the consumer, this also means a shorter time-to-market for much needed new vaccines.

Research for the Real World

This carefully thought-out approach to R&D has produced numerous groundbreaking results. In 1986, GSK Biologicals developed and introduced Engerix-B. This was the world's first vaccine to use genetic engineering techniques against the human hepatitis-B virus. Genetic engineering methods have been a giant leap forward in the area of disease prevention. These recombinant vaccines can be produced much more quickly, on a larger scale, and in a more standardized way. This is of course critical in the event of a sudden outbreak in an area where vaccine stocks are low.

GSK Biologicals was also the first company to market combined vaccines against childhood diseases. Because they reduce the number of injections, these vaccines greatly

Product Development Pipeline December 2002

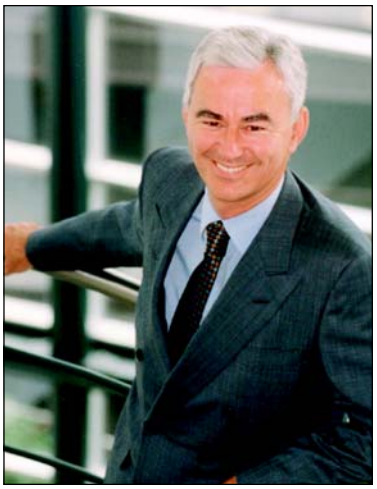
Therapeutic Area	Compound	Type	Indication	Phase	Estimated Filing Dates	
					MAA	NDA
Hepatitis Vaccines	Hepatitis E	recombinant	hepatitis E prophylaxis	II		
	Extra strength hepatitis B	recombinant	extra strength hepatitis B prophylaxis (poor/non-responders)	III	2003	TBD
	Twinrix 2 doses	recombinant	combined hepatitis A and B prophylaxis (child/adolescent)	Approved	A:Sep02	2003
Paediatric Vaccines	*Rotarix*	live attenuated – oral	rotavirus prophylaxis	II	2005	
	N. meningitidis	conjugated	meningitis prophylaxis	II	2004	
	Meningitis B (Cuba)	subunit	meningitis B prophylaxis	II		TBD
	S. pneumoniae paediatric	conjugated	S. pneumoniae disease prophylaxis for children	III	2005	
	MMR-varicella	live attenuated	measles, mumps, rubella and varicella prophylaxis	III	2005	
	Infanrix/Pediarix PeNta-HepB-IPV	recombinant	diptheria, tetanus, pertussis, hepatitis B and inactivated polio prophylaxis	Approved	A:Oct00	A:Dec02
	Infanrix HeXa-Hep B-IPV/Hib	conjugated/recombinant	diphtheria, tetanus, pertussis, hepatitis B and inactivated polio prophylaxis and Haemophilus influenzae type B prophylaxis	Approved	A:Oct00	TBD
Other Vaccines	Dengue fever	attenuated tetravalent vaccine	prophylactic use	I		
	HIV	recombinant	HIV prophylaxis	I		
	New Influenza	subunit	Influenza prophylaxis – new delivery	I		
	S. pneumoniae elderly	conjugated	S. pneumoniae disease prophylaxis	I		
	Staphylococcal antibodies**	monodonal antibody	prevention of staphylococcal infections	I		
	Epstein-Barr virus (EBV)	recombinant	EBV prophylaxis	II		
	Human papillomavirus (HPV)	recombinant	prophylaxis of HPV infections	II		
	Malaria	recombinant	malaria prophylaxis	II		
	Simplirix	recombinant	genital herpes prophylaxis	III		
	Boostrix	subunit	adolescent/adult booster for diphtheria, tetanus and pertussis	Approved	A:Oct00	2004
	Boostrix IPV	subunit	adolescent/adult booster for diphtheria, tentanus, pertussis and inactivated polio	III	2003	
Pharmaccines	GSK/PowderJect**	recombinant	hepatitis B treatment	I		
	249553	recombinant	treatment of lung cancer/melanoma	II		

Figure 4. R&D teams at GSK Biologicals are making excellent progress in the advanced clinical tests of a number of new vaccines. (Source: GSK Biologicals Web site)

GSK Biologicals: Vaccines for the World

"One of our key strategic priorities is to simplify access to life-saving vaccines in developing countries."

Jean Stéphenne
President and General Manager of GSK Biologicals



improve the comfort of newborn babies. They also reduce costs by freeing up medical equipment, personnel, and storage space. Combined vaccines are already greatly improving the efficiency of limited medical staff in both developing and developed countries.

Promising Clinical Tests

Critical advances are being made in the clinical tests phase of vaccines under development. "Our product portfolio will certainly be greatly extended in coming years," notes Stéphenne. "New vaccines, in a wide variety of areas, have now entered the clinical tests phase. These include an HIV vaccine, a recombinant vaccine against chickenpox, a meningitis-B vaccine for teenagers, and a vaccine to fight malaria. It is a matter of public record that GSK Biologicals currently has the industry's strongest product portfolio in clinical testing."

Encouraging results also have been obtained for products currently in Phase II and III clinical trials. These include a recombinant vaccine against cervical cancers due to HPV infections. Similarly, extremely positive results have been registered with a vaccine for rotavirus (infant diarrhea) that was tested in several Latin American countries. The Simplirix vaccine against genital herpes is also in its final testing stages. Diseases which affect mostly developing countries are one of GSK's priority areas and the focus of a great deal of research, especially resistant forms of tuberculosis and dengue fever and of course, HIV, and malaria - *Figure 4*. Much remains to be done however. Research continues unabated for a cure or prevention of Alzheimer disease, various types of cancer, and autoimmune affections such as allergies, asthma, and arthritis.

Vaccines for Young and Old, Rich and Poor

No one questions the importance of a balanced research portfolio. But it is equally essential to cover all market needs. GSK Biologicals' market strategy targets vaccines for the specific needs of various age groups; combined vaccines for infants, hepatitis or rubella vaccines for teenagers, hepatitis, salmonella or cholera vaccines for travelers, influenza vaccines for elderly people. This is a sound and efficient marketing strategy that aims to underline the company's contribution to a better quality of life for every citizen of the world. It is an approach that is also fully in line with the GSK corporate motto to help everyone "Do more, feel better, and live longer."

GSK Biologicals has made it a corporate strategy to provide countries in need with easier and cheaper access to essential vaccines. It has no intention of leaving the developing world to its own devices simply because they do not represent a profitable enough market. The whooping-cough component of some GSK combined infant vaccines, for instance, is produced at a lower manufacturing cost for developing countries. Community partnership projects also have been initiated whereby GSK Biologicals is distributing certain vaccines at no cost. The company's active participation in UNICEF vaccination programs is well known and widely held up as a model for corporate responsibility. GSK Biologicals also has built a number of plants in Hungary, Russia, and China to be closer to developing countries. Additional plants in India and Latin America will follow soon. Since most vaccines require refrigeration, the shorter the transportation distance and time, the easier — and cheaper — it is to maintain and stock the necessary vaccines.

An important fact emerges upon a closer look at corporate income figures. North America and Europe currently account for two-thirds of GSK Biologicals' revenue, but only one-third of their shipped volumes. Notes Stéphenne, "The greater part of the vaccines we produce are going to developing countries. Our biggest challenge remains finding a cure to the three biggest health concerns facing the world today: AIDS, tuberculosis, and malaria.

Janssen Pharmaceutica: Built Around R&D

50 Years of Research, 75 Innovative Compounds

"A good scientist is someone who succeeds in letting the different scientific disciplines work together harmoniously, just like the fingers of a hand can only function well if they cooperate fluently."

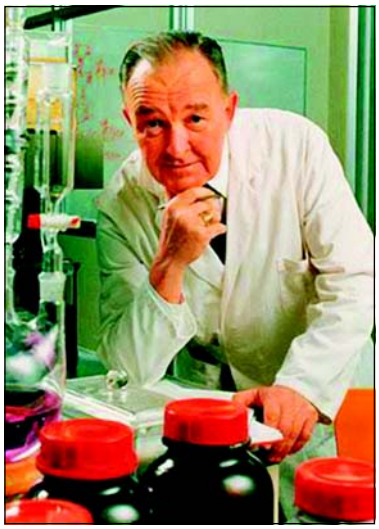
Dr. Paul Janssen
Chemist, Pharmacologist, and Physician

The story of Janssen Pharmaceutica is extraordinary. Exactly 50 years ago, it all began in a small, simple laboratory in Turnhout, Belgium. Against all the odds and in spite of a skeptical world, Dr. Paul Janssen, M.D. began pursuing his ultimate dream: creating an independent and self-supporting research laboratory. Thanks to his incredible insight – you might even say genius – and his knack for spotting talented people, he has achieved his dream. But, as it turned out, that proved to be only the beginning of the story.

Today, Janssen Pharmaceutica is part of the Johnson & Johnson Group, and one of the leading R&D sites worldwide. But it all began as a local initiative. Actually, Janssen got his inspiration from his general practitioner father, Dr. Constant Janssen. Back in the 1930s, disappointed that he could only help a fraction of his patients,

Pain Management	
Fentanyl®	Analgesic potency of several times that of morphine.
Sufenta®	An exceptionally potent analgesic (5 to 10 times more potent than Fentanyl) for use in heart surgery.
Rapifen®	Analgesic in general anesthesia for both short (bolus injections) and long (bolus, supplemented by increments or by infusion) surgical procedures.
Durogesic®	A Fentanyl transdermal patch used in chronic pain management
Psychiatry	
Risperdal®	Mental disorders
Gastrointestinal Diseases	
Imodium®	Antidiarrheal
Motilium®	Gastrointestinal regulator
Mycology	
Daktarin®	Antimycotic
Nizoral®	Antimycotic
Sporanox®	Oral antimycotic
Vermox®	Anthelmintic
Neurology	
Reminyl®	Alzheimer's Disease

Table A. Some of the main products developed by Janssen Pharmaceutica.



about one out of 200, the elder Dr. Janssen started looking for alternatives. He began importing Richter products from Hungary and sold them in his region, and later throughout Belgium, the Netherlands, and the Congo. It was mainly vitamin preparations, but it was a start.

Pioneer in Linking Chemical Structure to Pharmaceutical Activity

In the 1950s, his son, Dr. Paul Janssen, took the idea a giant step further. He had studied both medicine and chemistry and was convinced that there must be a connection between the chemical structure of a compound and its pharmaceutical effects. He wanted to reconcile the two disciplines. It would be the fundamental concept of Janssen research: synthesizing molecules with the intent of detecting the relationship between the structure and their pharmaceutical activity. After only one year, the fifth molecule that he synthesized was a hit: R5 or ambucetamide. This antispasmodic proved to be

Janssen Pharmaceutica: Built Around R&D

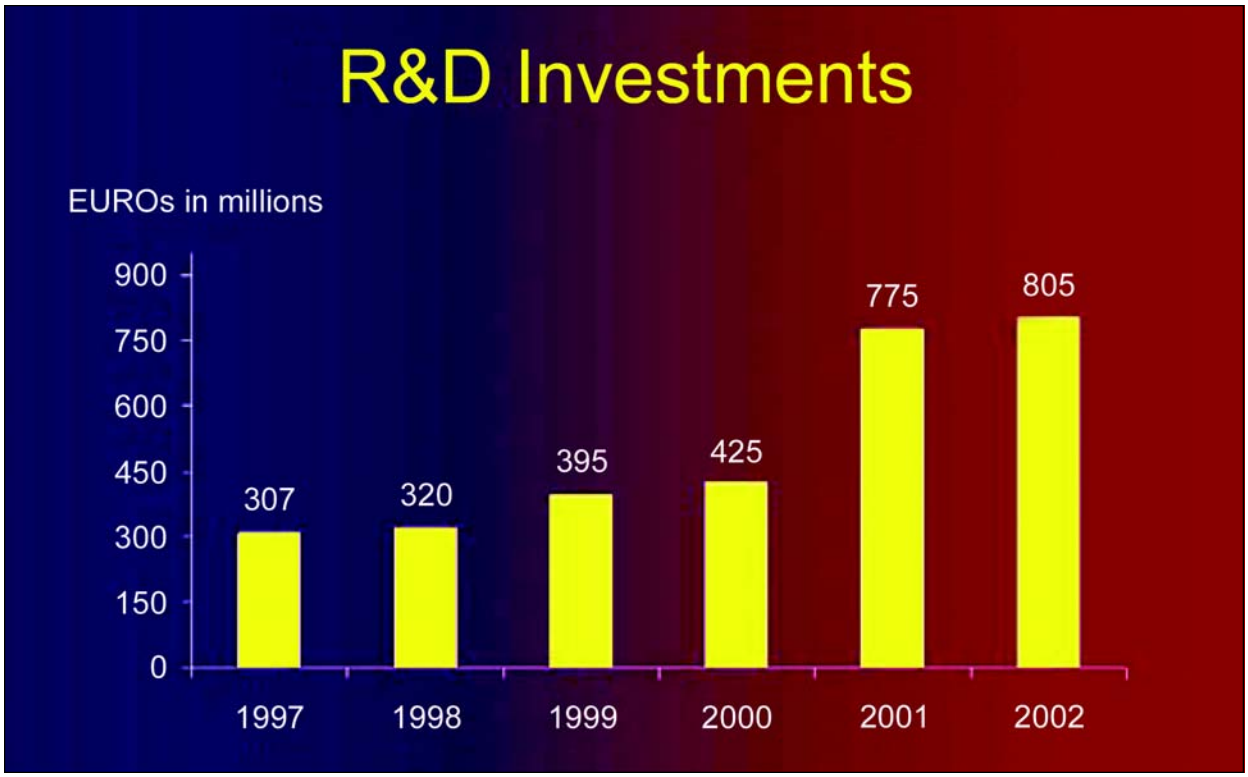


Figure 1. R&D investments at Janssen Pharmaceutica.

very effective against Premenstrual Syndrome (PMS). The product was launched in 1955 as Neomeritine® and is still available on the market today.

The second important molecule was R79, isopropamide iodide. Smith, Kline & French licensed it and then sold it as Combid and Darbid. A highly successful compound developed in the 1960s was R1132 (difenoxylate). It was licensed by Searle and launched in the US as Lomotil. Interestingly, it even traveled to the moon with the Apollo astronauts in their medical kit.

Evolutionary Products

Now, 50 years later, the record of achievements has grown to 75 synthesized compounds - *Table A*. Four Janssen medicines are currently listed among the 300 products in the WHO List of Essential Medicines. Stefan Gijssels, Vice President Public Affairs and External Communication notes that, "Annually more than 2 billion patient treatments with Janssen products are being administered around the world. Our major areas of R&D focus are pain management and anesthesia, psychiatry, gastrointestinal diseases, mycology, oncology, gynecology, and neurology. We can honestly say that

About Janssen Pharmaceutica

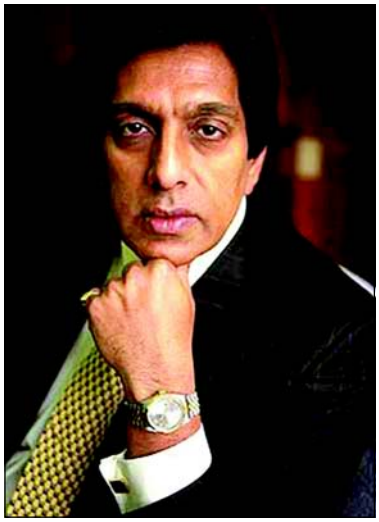
Janssen Pharmaceutica became part of the Johnson & Johnson Group in 1961. The company has expanded to an international organization with offices in 44 countries around the world, with a total workforce of 23,400. There are multiple sites in Belgium. These include Beerse, where the R&D department is seated together with pharmaceutical production and general services. In Geel, the chemical plant produces the active ingredients for more than 60% of the company's drugs. Together, they employ a staff of 4,200. This number has grown at an average of 100 employees a year over the past five years.

One of the main focuses of Janssen Pharmaceutica is quality. Dr. Ajit Shetty, CEO, states that, "We keep abreast of new regulations by maintaining a constant dialog with all of the appropriate regulatory agencies. All our sites are FDA and EMEA approved and our track record in this area is excellent."

Janssen Pharmaceutica: Built Around R&D

"During the last 10 years, we've seen a continuous increase in our production output, even against the economic tide. This is thanks to the quality and motivation of our employees."

Dr. Ajit Shetty
CEO of Janssen Pharmaceutica



many of our products have affected a revolution in healthcare. Without Fentanyl® for example, which is up to 300 times stronger than morphine, the history of open-heart surgery would have been completely different. Fourteen million patients worldwide use Risperdal® (as the successor of Haldol®) to treat schizophrenia. It has changed the lives of countless psychiatric patients. One of our recent achievements is the production of the CYPHER™ Stent, the first coronary stent coated with antibiotics, a joint project with our sister company Cordis."

Successful Vision on R&D

The R&D staff of Janssen Pharmaceutica in Belgium has more than 30 different nationalities among its 1,300 researchers. This is one third of the entire worldwide pharmaceutical R&D staff, which now operates as a fully integrated entity with the name J&J BRD. In 2002, Janssen Pharmaceutica synthesized 9000 new compounds and screened 30,000 other compounds from external sources. Its record in bringing a new medicine onto the market, starting with the synthesis of new molecules, is one out of 5000, twice as high as the sector average. In 2003, Janssen had 38 new molecules in drug evaluation. It currently has four in late development, and has filed eight others for final approval.

Janssen Pharmaceutica has one big advantage. By integrating R&D and production sites, interesting exchanges between specialists take place. CEO, Dr. Ajit Shetty: "Janssen's philosophy has always been to build research around people, rather than the other way around. We became a specialist in domains like parasitology and mycology after Paul Janssen began attracting people who had worked for many years in the former Belgian Congo. We also always see to it that there is a close interaction between scientists and patients. When scientists are actually involved with the results of their work, they know that they are making a contribution. That is highly motivating."

Figure 2. The R&D department of Janssen Pharmaceutica is situated in Beerse, together with the pharmaceutical production facilities and administration offices.

With an Open Mind

This approach has resulted in an excellent track record, one that has been recognized by senior management of the Johnson & Johnson Group. R&D investments at Janssen Pharmaceutica have shown a steep increase in the past decade. In 2002, they reached a record level of 805 million Euro - *Figure 1*. Among those investments were a new Ultra High Throughput Screening and powerful computers for bioinformatics in order to gain new insights into diseases and to identify possible links with specific molecules. Dr. Shetty notes that "With our record of 50 years of continuous top-flight research, it's not that difficult to convince J&J that their investments are in good hands. We can thank the productivity, quality, and drive of our employees for this.

"Our vision is to look beyond our own company and use - or add to - the expertise within the Group," continues Shetty. "We study and learn from other industries, we keep an open mind as to how we can best capitalize on the exper-

Janssen Pharmaceutica: Built Around R&D

Figure 3. One of the latest product innovations developed at Janssen is the Durogesic pain patch, combining the powerful analgesic Fentanyl® with the patch technology of Alza. This has been a breakthrough for the treatment of severe chronic pain.

tise of sister companies. We strive to create umbrella technology platforms. This has enabled us to get our products onto the market much quicker and to lower our costs."

Shetty concludes with his thoughts on the future: "It is crucial that R&D and production continue to go hand in hand to safeguard the future health of people around the world as well as our company."

Dr. Ajit Shetty, CEO of Janssen Pharmaceutica holds a PhD in Metallurgy from Trinity College, Cambridge University, a BA in Natural Sciences, and an MBA. He was born in India and has been living and working in Belgium for the past 20 years.

Dr. Paul Janssen, a leading Belgian researcher, pharmacologist, and general practitioner, is the founder of Janssen Pharmaceutica. Much of the growth of the company can be attributed to his passion for research and charismatic leadership.

Ajit Shetty's Thoughts on Belgium

"The business prospects for our Belgian company look good. Belgium has a central location which is especially attractive for other European researchers. The country's education level remains among the best in the world and is a good source for recruiting new researchers, engineers, and the other specialists and skills we need. Belgium has the largest per capita number of clinical trials in Europe, almost twice as many as number two on the list.

If you look at the combined levels of pharmaceutical industry capabilities, the quality of medical care, and academic and clinical research levels, then one can quite accurately state that Belgium is truly a world leader in pharmaceuticals and healthcare. The mutual reinforcement of all these factors creates a unique synergy and offers a very strong impetus for further investments and innovation."

"We believe our first responsibility is to the patients and the doctors, nurses, mothers and fathers, and others who use our products and services."

Credo of Johnson & Johnson

Biotech Start-ups: Keepers of the Flame

Belgium has a long-standing tradition in the life sciences industry. The high standard of past achievements is being upheld and even expanded by the many start-up companies that have grown out of this research. Many of these companies are ready to follow in the footsteps of giants like GSK and Janssen. The combination of high quality academic research, industrial activity, entrepreneurship, and government financing makes Belgium exceptionally fertile ground.

Many of these new players are active in biotechnology which is playing an increasingly important role in developing, producing, and marketing new healthcare products and services. This focus is no coincidence. In the 1970s, Belgian researchers were the first to record the sequence of a gene and later a complete genome. They also were among the first to identify gene defects and led the way in plant transformation. Belgian researchers such as Désiré Collen, Walter Fiers, Jeff Schell, and Marc Van Montagu are recognized as being among the best biotechnology scientists in the world.

These successes paved the way for start-up companies like Innogenetics, Tibotec, and Devgen. Today, Belgium has about 100 biotech companies. Half of them are active in the medico-pharmaceutical field. They are involved in a wide variety of activities, from the design and development of new applications and the testing and screening of new molecules and drugs to contract research.

Specialized Newcomers

In recent years, successful cooperation between universities and the pharmaceutical industry has resulted in the success of several start-up firms, as well as the commercialization of academic research. Pharmaceutical companies tend to focus on their core business of developing new therapeutic means and the marketing of registered products. "This paves the way for specialized newcomers who can carry out research assignments for or in collaboration with large pharmaceutical companies," says Jan Huybrighs of Innogenetics.

Since 1998, more than 25 new companies have been formed. Although many of them have not reached the stage where they are marketing products, there is every reason to believe that the number of biotech medicines marketed in the near future will increase rapidly.

Belgian Entrepreneurship

Belgium certainly provides fertile ground for this type of spin-off. There are currently 16 universities and specialist research centers, along with several biotech parks in Belgium. The presence of adequate financing, one of the building blocks of biotechnology, also helps. Every stage – from academic research through product commercialization – can be addressed in Belgium. A wide array of financial sources are available, from private sector firms to government grant agencies. "These facts, combined with the Belgian entrepreneurial spirit, mean that innovators are not afraid of taking risks. This ensures the future of a thriving pharmaceutical industry in Belgium."

Blazing the Trail

In Belgium, the early recognition of the importance of biotechnology has resulted in many of the start-ups establishing themselves in the pharmaceutical sector. A number of them are well beyond the pure research phase and have already commercialized their results. A few

	Number of Companies	Turnover (in Million Euros / US$)	Turnover (% of total)	Number of Jobs	Jobs (% of total)
Large companies	17	1,368	84	5,732	79
SMEs*	80	230	16	1,428	21
Total	97	1,598	100	7,160	100
*Fewer than 200 employees					
Source: BIB 2000/BBA					

Table A. Biotechnology companies in Belgium (2000).

	Number of Companies	Turnover (in Million Euros / US$)	Turnover (% of total)	Number of Jobs	Jobs (% of total)
Healthcare	48	1,250	78	5,589	78
Agriculture	17	284	18	1,026	14
Environment	9	9	1	132	2
Services	23	55	3	413	6
Total	97	1,598	100	7,160	100
Source: BIB 2000/BBA					

Table B. Breakdown by sector of Belgian biotechnology companies (2000).

Biotech Start-ups: Keepers of the Flame

companies even have a long track record of successes to their credit.

Innogenetics

Innogenetics provides high value-added diagnostics focusing on infectious diseases, neurodegeneration, and genetic testing. The therapeutics portfolio of the company is steadily expanding and consists of innovative candidates in the fields of hepatitis C, immune disorders, and wound care. Innogenetics was founded in 1985.

Tibotec

Tibotec is a research and development company seeking the discovery of innovative HIV drugs and superior anti-infectives for diseases with high, but unmet medical need. The company is at the forefront of HIV research and has two anti-HIV compounds in early clinical development and several discovery programs for compounds highly active against resistant HIV strains. Tibotec was founded in 1994 and was acquired by Johnson & Johnson in 2002.

Virco

Virco provides advanced diagnostic tools. These are based on pharmacogenomic principles for the clinical management of viral infections, HIV infection in particular. The company combines cutting edge technology in the fight against HIV with the active collaboration of doctors, patients, and researchers. Founded in 1995, Virco is a sister company of Tibotec.

Devgen

Devgen focuses on the development and the industrial production of Caenorhabditis elegans. This is the model organism that has unique benefits over traditional animal models or biochemical *in vitro* approaches for drug discovery. The company uses this model to rapidly analyze human disease states and identify and validate high-quality screening targets for further drug development. Devgen was founded in December 1997 and employs more than 90 people.

Creation	Company Name	Activities
2001	Ablynx	Therapeutics and diagnostics
1987	Analis	Electrophoresis kits, in vitro diagnostics
(*)	Baxter Healthcare	Vaccines, biosurgery therapies products, and services
1988	Beta-Cell	Cell therapy in diabetes
1996	Biosource Europe	Immunoassays, custom oligo synthesis, custom peptides and antibodies CDNA kits, Multiplex, Primers, and Tago immunologicals
1997	Biotech Tools	Vaccines correlated with allergies, gene therapy
2001	Brucells	Cell therapy, immunotherapy
1997	CAF-DCF	Human protein purification, plasma derivatives: factor VIII, Albumin, PPSB, immunoglobulins, and fibrinogens
1996	Coris-Bioconcept	Diagnostics
2001	Dyax	Development of monoclonal antibodies using phage display technology
1985	Eurogentec Bel	Customized production of oligonucleotides
1994	Euroscreen	Human receptors as drug targets
1983	Gamma	Diagnostics, monoclonal antibodies, home test, and blood bank
(*)	Genzyme Flanders	Therapeutics in Gaucher disease, serum phosphorus reduction, diagnostics for infectious diseases
(*)	GlaxoSmithKline Biologicals	Human vaccines
1985	INNOGENETICS	Diagnostics for infectious and autoimmune diseases, cardiovascular, neurological and genetic disorders, vaccine candidate for HCV (in phase II)
1999	MDS Nordion	Supplies products used in healthcare, diagnostics and therapeutics. Nuclear medicine
1950	Phibro	Veterinary vaccines and pharmaceuticals and temperature-sensitive vaccines
1998	R.E.D. Laboratories	Diagnostics tests and therapeutics for chronic fatigue syndrome, multiple sclerosis and other chronic immune diseases
2001	ReMYND	Drug testing for Alzheimer's disease and neurodegeneration
1994	Tibotec-Virco	Drug resistance testing (HIV, HCV, Tuberculosis) and two anti-HIV drug candidates (in phase II)
1999	Unibioscreen	In vitro cancer screening
1990	Zentech	RIA and EIA based diagnostics for human hormonology-thyroid and auto-immune diseases, genetically engineered proteins, prolactin,and CD4 panel
*Subsidiary in Belgium		
Source: BBA - Belgian BioIndustries Association		

Table C.

Industry Associations and Related Bodies in Belgium

AGIM-AVGI
Belgian Pharmaceutical Industry Association
Square Marie-Louise 49
1000 Brussels
Tel: +32 2 238 99 76
Fax: +32 2 231 11 64
http://www.agim-avgi.be/
E-mail: info@agim-avgi.be

National trade association representing 146 pharmaceutical companies based in Belgium.

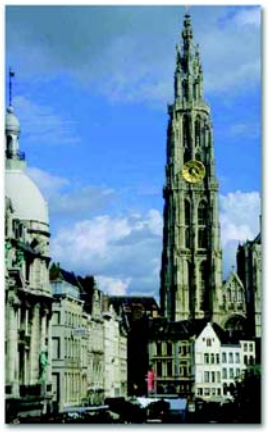
DG Public Health Protection: Medicinal Products
Bd Bischoffsheim 33
1000 Brussels
Tel: +32 2 227 55 00
Fax: +32 2 227 55 55
http://www.afigp.fgov.be/

The DG Public Health Protection: Medicinal Products has as main duty to ensure that patients have high-quality, efficient and safe medicines and related products at their disposal and that they use them safely and effectively. This holds also true for veterinary medicines.

Scientific Institute of Public Health (IPH)
Rue Juliette Wytsmans 14
1050 Brussels
Tel: +32 2 642 51 11
Fax: +32 2 642 50 01
http://www.iph.fgov.be/

The Institute tasks are: Reference activities; Monitoring; Epidemiological surveillance; Control of federal norms; Quality assessment; Risk evaluation; Evaluation of health data; National and international representation of the Belgian federal health authorities.

For information on the ISPE Belgium Affiliate visit www.ispe.org/belgium



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Pharmacia

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GlaxoSmithKline

Luc Van Hijfte
Pharmacia

Theo Van Riet
Janssen Pharmaceutica

Leo Versteynen
Janssen Pharmaceutica

This article describes the importance of maintaining bioequivalent performance for the various drug product lots produced during the development phase, and some procedural practices to manage the work and information in support of the product registration.

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Drug Product Bioequivalence During Development: Recommended Scientific and Communication Practices

by Charles F. Carney

Introduction

The Necessity for Bioequivalence at all Phases of Clinical Research

The purpose of studying clinical drug products is to show that these products will not produce unacceptable side effects and will produce a desired pharmacological effect in treating or eliminating a disease state. A primary goal of drug product development is to produce a drug product which optimizes the delivery of the drug substance to the target site. This delivery must be at least the same (bioequivalent) for each phase of clinical research (Phases 1 through 3) for each version of the drug product produced during development. The dosing regimen will be optimized over the life of these studies using the information gained at each stage to ensure the optimal performance of the drug product in each clinical trial. However, the ability of each version of the drug product that is produced during development to provide the equivalent blood level profile must be maintained in order for the clinical results from human subjects to be meaningful. This measurement is performed both with in-vitro and in-vivo analytical techniques.

In the optimization process, we must be concerned with the possibility of manufacturing a "super-bioavailable" product, one which

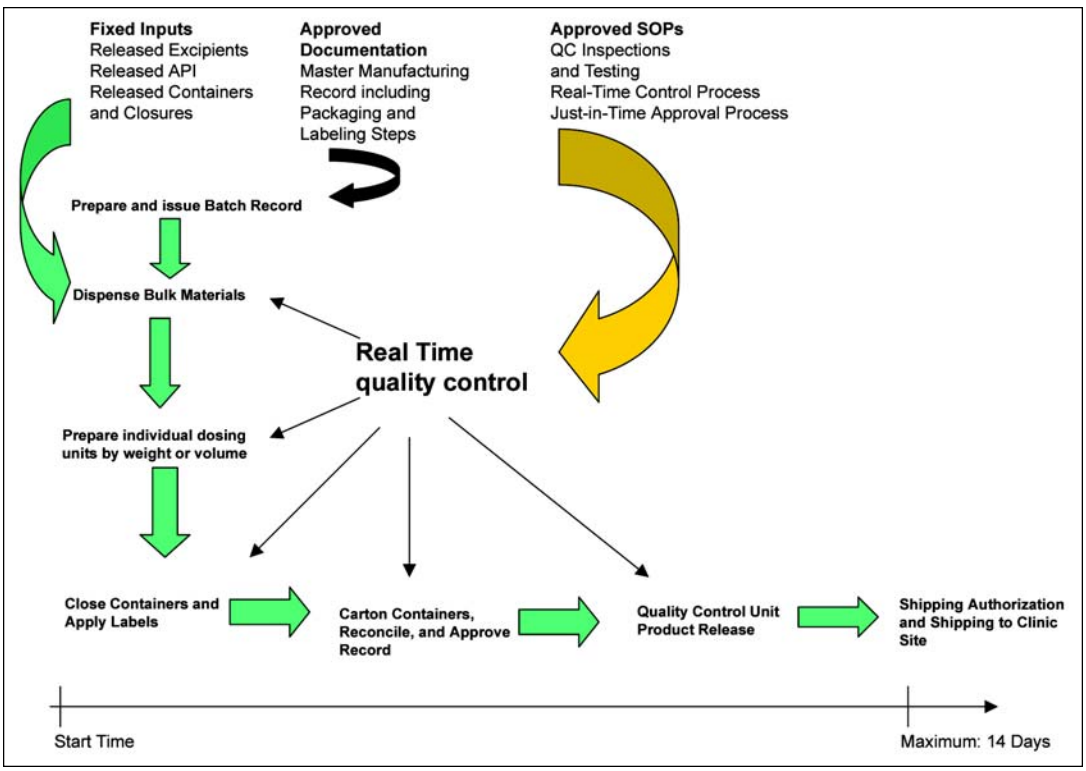

Figure 1. Fast to Phase I Trial: powder/liquid in bottle scenario.

Point of Control	Responsible Party
Definition of Prescription	Company Medical Dept. through clinical trial protocol
Evaluation of Facilities	Clinic QA Group
Compounding Formula and Process	Specified by Formulation Scientist, summarized in formal document included in clinical trial protocol
Training of Pharmacist	Performed by formulation Scientist, documented by Pharmacist according to requirements for state licensure
Container/Closure System	Specified by Formulation Scientist, implementation controlled by Pharmacist according to requirements for state licensure
Beyond Use Dating	Supportive data provided by Formulation Scientist, implementation by Pharmacist
Labeling (open label or double blind)	Specified by clinical trial protocol, controlled by Clinic QA group
Documentation and Record Keeping	Controlled by Pharmacist according to requirements for state licensure
Quality Control	Controlled by Pharmacist and Clinic QA Group and supported by sponsor QC group if necessary

Table A. Controls and organizational responsibilities for "compounding in the clinic."

provides far greater availability of the drug substance than the previous product. The clinical research data from such a drug product will be difficult to evaluate with respect to previous data, unless the degree of greater bioavailability is quantitatively known. And, we would never want to produce a "less-bioavailable" product during any phase of development once the desired bioavailability has been established in the Phase I safety trials.

While many in the industry think of "bioequivalence" mostly when comparing a generic product to the market innovation product, nevertheless "bioequivalence" between various formulation and processing versions of any drug also must be considered. Such considerations must occur during each stage of development, and during any post-marketing product changes. Such bioequivalence of versions must be ensured in order for the results of successive clinical trials using these versions of the drug product to be meaningful and interpretive. And, once the product is marketed, the producer must maintain the bioequivalence of each successive marketed batch in order to maintain compliance with the registration, NDA, or ANDA requirements.

Strategy for Developing the Drug Product with the Characteristics to Ensure Bioequivalence

Determination of bioequivalence of a drug product during development depends on knowledge of the physical chemistry of the drug substance (active pharmaceutical ingredient) alone and in combination with the inactive ingredients in the dosage form. This information must be added to the information about the bioavailability of the drug in the animal or human biological system and the distribution, metabolism, and excretion of the drug in that system which result in the pharmacological effects. Thorough and complete understanding of these factors, and the evaluation methods used to gain the information will be required to evaluate the performance of one formulation with that of another during the clinical research (Phases 1 through 3) and during the commercial life-cycle for the product (Phase 4). This information will be particularly important during Phase 4 when many ideas for cost-saving production changes and life-cycle extensions, perhaps for modified release products, will occur.

Strategy for Acquiring Comparator (Commercial) Drug Products for Positive Control Trials

Other bioequivalence trials may be required during the development process and also during the life-cycle management of the product. These trials result from the requirement to assess the comparability of the new drug product with the effects of a known, already commercialized, drug product. These positive control trials are performed oftentimes in a blinded fashion. Acquiring or producing a positive control drug product, bioequivalent to the available commercial product, in a masked (blinded) format can be a daunting challenge for the development chemist. In all cases, where there exists any manipulation of the commercial form of this drug product, which might compromise the in-vivo performance of this product either to increase or decrease bioavailability, an evaluation of bioequivalence of the manipulated form with the non-manipulated form will be required. Depending on the product, this evaluation might be performed in-vitro or it may be necessary to perform the evaluation in-vivo.

Methods for Producing Placebos to Match the Comparator

Placebo controlled clinical trials also may be required during the development of the final drug product. A debate is ongoing today whether these trials really require the administration of a placebo product or whether the same data could be derived from subjects who are not receiving any administered form. This point will not be discussed here as it has already been discussed elsewhere.[1] However, if a trial requires the administration of a placebo form, the production of appearance and other attributes-matching (organoleptic, physiological) placebos does need to be addressed. The need to report the effects of the drug substance alone in the drug product, with a complete discounting of the physiological effects resulting from the inactive materials, can only be done

by measuring these effects and subtracting them from the total effects seen after administration of the active drug product.

Maintaining the Knowledge Base for Regional Requirements for Performing Clinical Trials

Information, knowledge, and the ability to communicate and reach agreements for the collection of regional requirements during clinical research are best supported by a mature relationship between the requestor (usually the clinical trial medical monitor and the investigator) and producer (usually the development group in the sponsor's R&D sector). Establishment of expectations and agreement on deliverables and time frames will be required to optimize the process. Some aspects will be discussed below.

Considerations for Bioequivalence

Non-Clinical (Toxicology) Trials

Non-clinical trials in mammalian species must be performed prior to administering a new drug to man. These trials provide confirmation of the mechanistic hypotheses developed in the in-vitro (test tube) systems. They also provide information concerning possible negative effects of the drug in mammals which can then be interpreted to assess the risk of administering the drug to man. Contemporary bio-pharmaceutical principles should be utilized in developing the dosage form for the administration of these drugs to the animals. The heightened need for applying this thinking to these products results from the nature of the New Chemical Entities (NCEs) being discovered today. These NCEs have lower intrinsic (aqueous) solubilities, and in many cases, higher molecular weights than the NCEs developed previously. Both of these factors can decrease the absorption of the drug from a dosage form after administration.

In addition, the goal for development today is to have a registration package available within five to seven years of the decision to develop the NCE. This compares with a previously experienced average time for the industry of 12-15 years. This shorter time frame allows practically no time for an iterative process for collecting the necessary information for the dossier. In order to avoid iteration and repeat studies the best scientific principles and practices must be employed in order to optimize the collection of data, particularly with respect to safety. Thus, we have the need today to apply similar dosage form design criteria to the development of the administration form in animal studies as we have for the development of the dosage form for the final commercial form.

Absorption Models: In-Vivo/In-Vitro

The Biopharmaceutical Classification System (BCS) was developed in the last decade.[2] This concept and the succeeding studies were recently reviewed.[3] This model for thinking about the absorption of drug substances assigns compounds to four categories depending on the known physical-chemical properties of the substance: high soluble/high permeable; low soluble/high permeable; high soluble/low permeable; and low soluble/low permeable. For compounds which exhibit the properties for Class 1 (90% absorption from solution, dose completely soluble in 250 mL over pH range 1-7.5), an in-vivo/in-vitro correlation can usually be developed. The drug product performance can be measured by a dissolution test with a Q value of 85% in 30 minutes. For such compounds, the absorption will depend on gastric emptying time and thus, will strictly be under physiological control rather than dosage form control. In this case, one must be careful to develop drug products which don't interfere with normal gastric emptying time. This and other conclusions from current thinking can be found in the Dressman review article.[3] Because we now have such compelling data to indicate that particle size of the dosage form after disintegration in the stomach, gastric emptying time, pH of the various segments of the intestine, metabolism in the intestinal wall during permeation, first pass metabolism in the liver after permeation through the intestinal wall and into the blood stream, and differences for rate of excretion resulting from distribution into deep or shallow compartments in the body, we must take great care in designing all of the dosage administration forms used in the non-clinical and clinical studies.

The scientific rationale and argumentation for the BCS has been so compelling that the FDA issued a guidance for receiving a waiver to the performance of bioequivalence testing for Immediate Release (IR) products containing high soluble/high permeable compounds.[4] In order to verify bioequivalence by in-vitro techniques, a separate guidance was written describing the appropriate dissolution procedures to be used for the in-vitro evaluation and the manner of comparing the data from the two products being compared.[5] This guidance references a model independent comparison of the dissolution profiles and calculates a "difference" factor and a "similarity" factor. The % difference between dissolution values at each time point (each value is the average of the dissolution concentration for 12 individual tablets) is used to measure the relative error between the two curves, the "difference" factor. The logarithmic square root transformation of the sum of squared error, using the same data sets, gives the measure of the "similarity" factor. The difference factor should be near zero and the similarity factor should be near 100 for the two products to be declared bioequivalent, though some latitude in values is allowed in the guidance.

Phase 1

Several factors influence the choice of administration form for Phase 1 trials during the development of solid oral drug products. Availability of drug substance, availability of analytical methods and validation data, and availability of designed and manufactured solid (tablet, capsule) dosage form with adequate stability evaluation in real time all limit the choices for the administration form for these trials. The tendency today is to use a drinking solution as the administration form for these trials. This is the simplest administration form and the one for which the least efforts will be needed for the development of the form, the methods, the specifica-

tions, the manufacturing procedure, and for the evaluation of the resultant data. Often times, methods and conclusions from laboratory in-vitro studies for the drug substance alone can be utilized to support the utilization of the simple drinking solution in the clinical trial. In addition, oral administration of a solution provides the optimal way to get baseline Absorption, Distribution, Metabolism, and Excretion (ADME) data with which to compare the data derived from the non-clinical studies, and for designing the subsequent dosage form. Use of the drinking solution will allow the determination of project limiting short-term safety or ADME limitations for human administration, quickly.

The speed with which this clinical trial can be performed must not be limited by the product development group. Thus, careful consideration must be given to the methods and strategy for manufacturing the drinking solution. The issues associated with the sponsor manufacturing the drinking solutions according to its existing GMP systems versus the clinical site pharmacy compounding the drinking solution have been summarized and discussed.[6] The optimized GMP system approach includes real time quality control and quality assurance. The preparation of up to seven strengths, ready for shipment to the clinical site can be achieved in a 14 day period as visually depicted in Figure 1, which is reproduced directly from the published reference.[6] In this pictogram, the systems input requirements for meeting a two week preparation time frame are listed at the top. The major time saver in this model is the use of real-time quality control and quality assurance steps. Quality control is performed gravimetrically, and each process step and action are viewed and audited as they occur by the quality assurance function. The steps required for utilization of the clinic site pharmacy compounding approach are listed in Table A. This tabular summary of control point and associated accountability for the personnel either in the sponsor site or the clinical trial site ensures the adequate understanding of the requirements and real time management of the necessary process steps to produce the compounded product. Each system can be designed to meet the intentions for control and accountability for the preparation of administration forms specified in the good manufacturing practices. The GMP manufacturing system may be more capacity sparing for the sponsor with a fully integrated business. The pharmacy compounding approach may be more appropriate for the sponsor which is a virtual company with limited in-house capabilities.

Phases 2-3

Oral drug product administration forms for Phases 2-3 normally are solid forms (tablets, capsules) which are first approximation forms at Phase 2 and final form at Phase 3. Of course if the final form can be available for the Phase 2 trials, the process of collecting and collating the necessary registration information will be much faster. The important point is the utilization of the data collected for the drinking solution in Phase 1 as baseline data toward which to optimize the solid oral form. The combination of additional animal studies, and where allowable (when the substance class allows a clear in-vivo/in-vitro correlation), the use of the in-vitro dissolution studies, will be important in designing the optimal dosage form.[4] The physical-chemical data for the substance (solubility, permeability, stability, interactions with excipient materials), the biopharmaceutical data for the drinking solution, and the physical-chemical data for the proposed drug product (content uniformity, dissolution rate, performance after storage in controlled environments to determine the stability characteristics), must all be taken together in order to assess the probability for success in these later phase clinical trials.

A model has been proposed for collecting and documenting the information for the ongoing assurance that each subsequent formulation design will be equivalent to the previous one.[7] In this model, the information leading to the manufacture of each product lot is summarized and rationalized. It includes all previous experiences for the development of this product along with literature and experiential arguments supporting the product design concept. The model takes both the analytical data and the data for the performance of the previous dosage form in clinical trials into account in rationalizing a "bioequivalent" product for the next clinical trials. This model contains the ways to produce lots in the same way as previously (the "reproduction" model), and the ways to rationalize the changes necessary to produce a lot with improvements (the "variation" model). The improvements are usually processing improvements which result in greater amounts of product for less cost, less capacity requirements, or smaller range for the various test specifications. However, these improvements can include increased bioavailability. The model ensures that no subsequent product lot will be less bioavailable (resulting in a state of non-bioequivalence), and will allow the objective and systematic rationalization for the development and production of a lot which has improved bioavailability. This latter condition also is a state of "non-bioequivalence." However, because it is recognized beforehand and is the desired and controlled event, the model provides for this as a desired outcome, the optimal delivery characteristics through optimized bioavailability in contemporary product development.

US Special Requirements (21 CFR 320) for BE/BA Trials

Special requirements exist in the US for the study supplies used in clinical trials designed to evaluate bioavailability or bioequivalence.[8] A very clear expectation for the interpretation of this regulation was given in the preamble to this final rule.[9] This rule requires that such clinical trials be supplied with a significant excess of the amount needed for the trial. One part of the supplies will be utilized to run the trial and the other part which equals five times the amount of that drug product needed for the complete analytical testing of the drug product will be stored, segregated in a limited access area separate from the area in which the testing is done for a period of at least five years following completion of the bioavailability trial (or five years following the date of approval when this is the result for the registration request) at the site of the clinical trial, according to the conditions of the

storage statement for the supplies. The investigator must be able to choose randomly for the supplies in dispensing product for the subjects in the trial. These reserved supplies are in addition to the reserve samples required to be held by the sponsor for compliance with the cGMP.[10]

This rule has significant implications. For open-label trials, all of the product for a given strength of each test article can be contained in one bottle with one label. The investigator can open the bottle, dispense the amount needed for the subjects in the trial, and re-close the bottle for storage. As an example, if 36 tablets are needed to supply the trial, and 100 tablets are required for performing the analytical release testing one time, then the bottle should contain 536 tablets. This calculation and preparation of supplies will occur for each product, both the sponsor products and any commercial products (reference samples) used in the trial. For blinded trials, the packaging becomes more complicated. In this case, six sets of blinded supplies must be prepared from which the investigator can select randomly one set for the trial and place the other five sets into storage. Conceivably, a far greater number of tablets and numbers of bottles/labels will need to be prepared for such a trial. And, the clinical site must have the storage space for these supplies or must make arrangements with another storage site, not the sponsor, to store these supplies for the required period. Some recent GCP audits by the FDA have resulted in observations on the Form 483 because this rule was not followed correctly during the conduct of the trial, either by the sponsor or the clinical site.

The rational plan for performance of clinical trials during development needs to be developed. Considerations and a comparison of the needs during NCE development with generic product development have been summarized.[11] A proactive development and monitoring of the plan should occur to ensure that the appropriate trials have been performed with products produced to meet the requirements of bioavailability for the study.

Considerations for Drug Product Supply Chain

Requirements for the Trials - Strengths, Administration Strategy, Countries, and Label Requirements, API Supply

Just as supply chain considerations are important in the commercial sector of the pharmaceutical business, the supply chain must be considered during the clinical research phases. With shorter timelines for drug product development and shrinking budgets, the necessity for treating the clinical supply production process in a more business-like fashion is increasing. This can occur best when a systematic approach is used for collecting and utilizing the information for the planning and execution of the preparation of the trial supplies. Concepts for optimization of the supply chain for Phase 3 trials have been summarized previously[12] and the conclusions can be restated here.

A pictorial representation of supply chain optimization is shown in Figure 2, taken directly from the reference.[12] In this pictogram, the various key issues of planning by the development and medical research functions, clear decision making for the establishment of process and facilities for production, and important logistic factors for distribution are noted in each of the boxes. These all are inputs to the successful time, cost, and labor effectiveness in the design and managing of the Phase 3 clinical trials. A major part of this concept relies on the adequate and proactive approach toward information exchange between the customer/supplier partners. The greater the details that can be supplied by the medical research sector for desired dosage strengths, numbers of subjects and distribution of these in the number of centers, what countries will be involved, dosing administration strategy and duration of trials/phases, the better the planning will be for the execution of production of the supplies for distribution. Similarly, the greater the details given by the supplier (R&D) side for availability of drug substance, availability of manufacturing and testing procedures and specifications, constraints in producing any of the strengths, or constraints in achieving the desired packaging design for any trial, then the greater the ability of the medical research personnel to design and

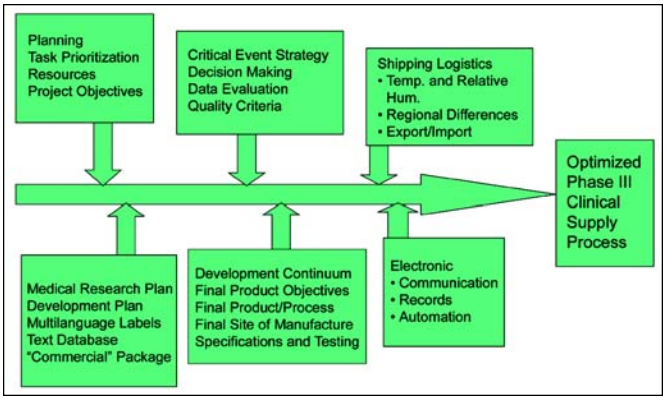

Figure 2. Supply chain optimization.

Ongoing Trials
Assess the need for resupply and/or additional supply due to expiration dating or addition of new sites and/or new countries (label text, import/export, availability of drug product(s) and labor needed for resupply or extension of trial period.
New/Planned Trials
What is the status of the IND?
Has the trial been approved and has the work been budgeted?
What are initiation/completion dates, countries?
Who are the project team members?
Is the trial a seasonal trial?
Are there any other constraints on the planning of the trial (e.g. awaiting input from a regulatory agency, or awaiting previous trial data)?
What is status of the written protocol – particularly with regard to any special requirements for timing, ancillary goods or drugs, special handling for temperature or humidity?
How many countries, how many sites in each country, how many subjects to be enrolled and what is the required number of completed subjects, what is the expected time frame for the complete trial?
Is the trial for BA or BE determination?

Table B. Checklist for data gathering for support of each clinical trial.

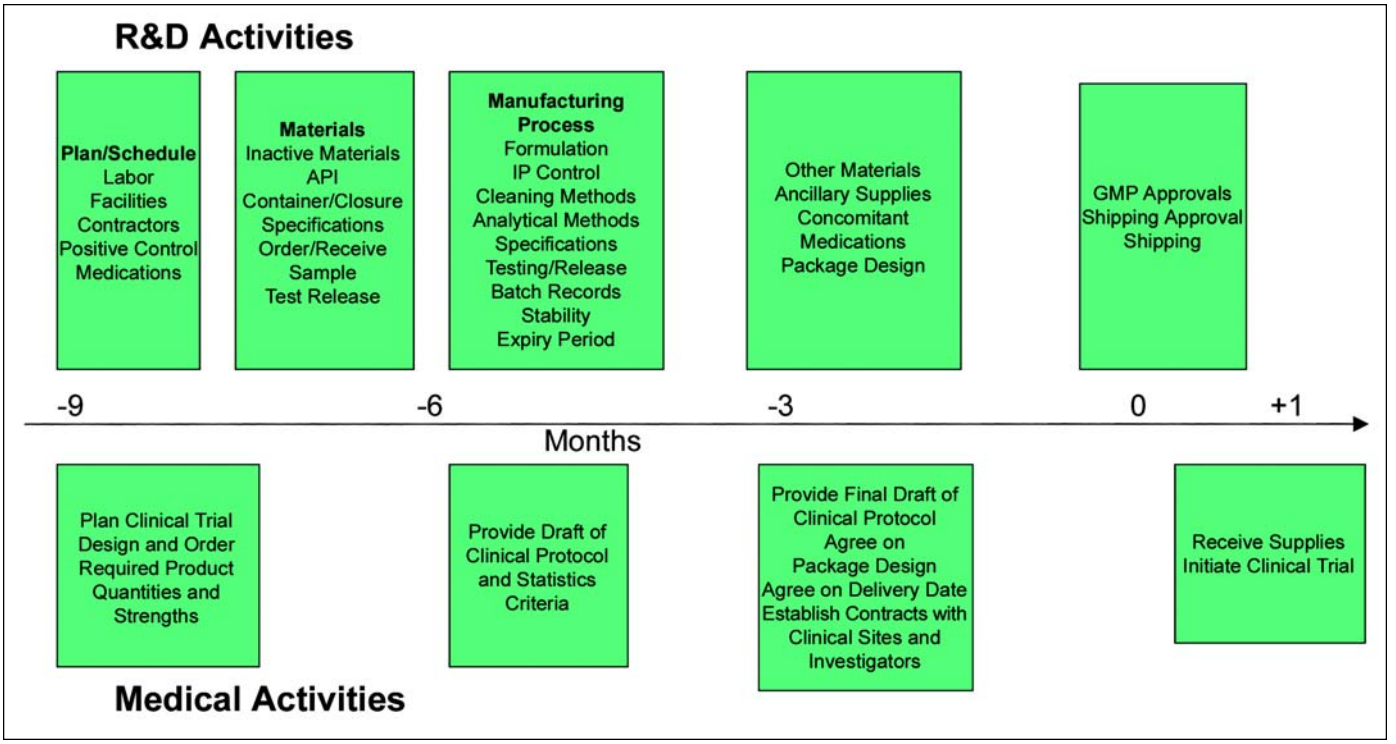

Figure 3. CTM preparation timeline - activities and months.

implement trials that can be supplied.

An important factor in this information exchange is the proactive understanding for the maintenance of the bioequivalence of the drug products in order to optimize the interpretation of the clinical trial results. The more partners there are in this relationship the more complicated will be the process. When CRO companies will be used for the execution of the trials, either for the monitoring function or for the principle investigator function, there will usually be a translation of information from the CRO through the sponsor medical personnel to the R&D personnel. This process for information exchange should be optimized. This may be achieved by having direct contact between the CRO and R&D personnel for any issues which can be handled directly. Another option may be to have only one representative from each group (R&D, Medical, CRO) always working together no matter the issue. Another option is to establish an electronic file system which contains the ongoing discussions and agreements (a kind of "chat room with conclusions"). Whatever way is used should be consistent with the cultures of each of the interacting partners.

Maintaining the Communication Link Between Medical (including CRO) and R&D

The relationship between the partners inside the sponsor firm is extremely critical. It would not be acceptable for the medical personnel to plan trials for dosage strengths that cannot be produced. And, it is unreasonable for the development group to spend time on developing a strength or delivery dosage form that is not desired. The "keep it simple" principle applies here. The work that is performed should be only that which is required to find the right product for the disease being studied and to get it to the commercial sector. While it's clear that everyone should be proactive in providing the correct and up-to-date information, it's possible that someone may have the information, but not know that this information is needed by others. In order to avoid this situation, it may be important to develop a checklist of the information which is needed on the R&D side in order to complete the work for any clinical trial. This checklist could be utilized during meetings to ensure that information is collected consistently and completely for each trial within each project. Such a list is displayed in Table B.

Maintaining the Information Database for Specific Regional and Country Requirements, Both Cultural and Legal

Information can be used as a strategic tool.[13] This information consists both of the scientific information and the logistic, pragmatic information. Some best practices examples for the interactions between the various functions in clinical supplies include the establishment and maintenance of:

- a database for importation requirements for each country in which clinical trials will be performed
- a database of the labeling requirements for clinical supply labels in each country in which clinical trials will be performed
- a database of the drug products utilized (e.g., strengths, quantities, package design, etc.) in each clinical trial in each program which is accessible by all functions from any site

- a printing system or a contract printer who can provide label text in any language, including all of the non-Roman alphabet languages

Customer Expectations/Producer Expectations

In order for each function to contribute successfully to the drug development process, it must know what information it needs to do its job and what information it needs to deliver to other functions. The R&D and Medical processes for providing clinical drug product to the clinical site can be shown pictorially as seen in Figure 3. This pictogram shows the R&D activities in the boxes on the top of the "time-horizon" line and the medical activities in the boxes on the bottom. The key activities for "time-horizon" of nine months prior to the trial initiation to one month post trial initiation are listed. Having this pictorial in mind will help ensure that the materials are available and that the associated activities occur at the correct time. If the customer is aware of these needs, he can provide the appropriate information in time so that the ordering of materials or decision on process or practice to follow in producing the goods will occur in a timely fashion. A similar pictogram could be imagined for the operations within a CRO function. Once these various pictorials have been developed and agreed by the various functions, a combined picture can be developed specifically for the particular supplier/customer paradigm within which operations are occurring. When all personnel see the overall structure, it may be easier for them to contribute their efforts more effectively. As discussed initially, the maintenance of understanding for the need for bioequivalence of products must be ensured for all participants in the process.

Producing and Supplying the Drug Products

Some general issues which apply to all dosage forms and some ideas for sharing the information that may help groups to optimize their interactions will be summarized below.

Comparator Drug Procurement and Blinding Considerations

Some of the concerns for the preparation and delivery of the NCE drug products have been discussed. Another class of drug product, which is often needed in the clinical trials, is positive control drug products, usually called comparator drug products. The acquisition of such drug products is relatively simple, though sometimes costly, for use in open label trials. Difficulties arise when a masked (blinded) drug product and appearance-matching placebo are needed for these trials. The development of these drug products, including the matching placebo, can be more challenging than the development of the NCE product. The reason for this is that the sponsor will not have any scientific information with which to proceed with the development. The formulation scientist will need to develop this information either by reverse-engineering the commercial product or by using similar techniques as he would use for his own NCE. These issues have been summarized.[14-15] A decision tree was devel-

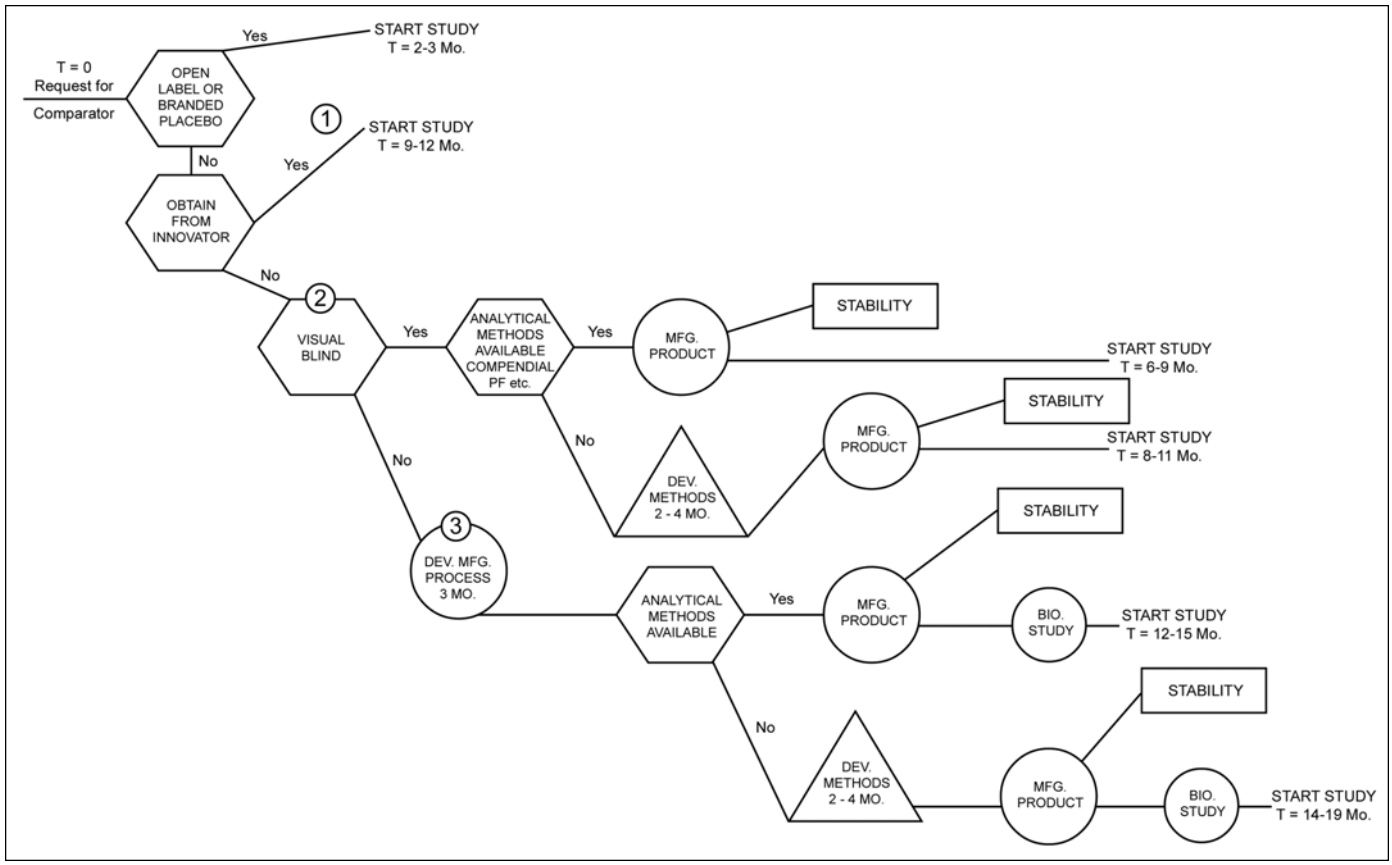

Figure 4. Clinical comparator - drug decision tree.

oped[14] which shows activities and timing for the various options in acquiring or producing the comparator drug products and this pictogram is shown in Figure 4. Three pathways can be imagined, each with its own set of difficulties:

- acquire the products and matching placebos from the innovator company
- buy commercial products and visually blind them by some over-encapsulation or over-coating process
- develop and produce a "generic" form of the product in house

The first option is best from the standpoint of having a proven bioequivalent product for the positive control drug product. However, establishment of the agreement with the competitor can take some time and allows that competitor the ability to know and affect the clinical trial that will be done with its drug.

The visual masking process must be evaluated for bioequivalence with the commercial product and for stability during its use in the clinical trial. These evaluations are more difficult when the commercial product is not listed in a compendium because of the additional time needed to develop the analytical methods and acceptance criteria.

Developing and producing a generic product will be the most difficult, again more so if the commercial product is not listed in a compendium. This development will require the establishment of a supply of the active ingredient, development of the appropriate set of physical chemical data as for one of the sponsor's NCEs, developing the manufacturing and analytical procedures, and developing the database of stability information. This can be an extremely time consuming and costly process.

Careful evaluation should occur to determine the absolute need for blinding a positive control trial, especially when the positive control drug product will be a very new drug, not yet listed in a compendium.

Establishment and Extension of Expiry Period

The expiry period for clinical drug products can be program limiting. The programs today are progressing so rapidly that stability data for the NCE drug product may be insufficient to allow a "risk free" establishment for expiry period. This is even truer for a positive control drug as discussed above. Planning for any trial must include the evaluation of timing to ensure that the products to be used in the trial will have sufficient shelf-life to allow for the completion of the trial. If this is not the case then a detailed plan and the associated customer/supplier agreements need to be made to provide for the possibilities for expiry period extension or re-supply of the clinical trial with newly prepared drug products.

Transportation Issues Especially for Temperature and/or Humidity Sensitive Products

Sensitivity to temperature and/or humidity should always be considered during the planning for a clinical program. The R&D personnel need to evaluate these factors early and communicate any concerns for the clinical drug product to the medical personnel. Collaborations should then occur to ensure that limitation for shelf-life, limitations for regions of the world in which trials can be performed, and the possible requirements for utilizing special shipment containers which control the temperature and humidity or even special transport firms for expedited delivery have been considered and put into the plan.

Export and Import Considerations

Each country has its own set of rules for importation of clinical drug products. These requirements change frequently. While many countries are trying to streamline the rules to allow and encourage the performance of the clinical trials in their country, nevertheless rules still exist and can be complicated. One way to deal with this is to establish a database of the rules for each country in which the sponsor will perform trials and update this as frequently as the rules change. Then it will be easier to assess whether there will be any problems for importing into the countries of choice for the clinical trials. In any case, it is extremely important to have customs brokers in each country, with an adequate bond limit, who know and can advise about the local requirements and who can act as a facilitation partner during the importation process.

Conclusions and Summary

Some important aspects for the preparation and execution of clinical trials with special considerations for performing trials with oral administration products to ensure bioequivalence have been presented. As important as the scientific information for the drug product is, the communication aspects between personnel and the tactical processes chosen for the execution of the clinical trial may be more important. Information exchange and rational plan development must come first. With a rational plan and good scientific principles in place, the rational collection and evaluation of the data from the laboratory or from the clinical experiments, will be optimal for rapid drug product development and commercialization.

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About the Author

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This article positions clinical materials management at the core of the evolving competitive arena in the pharmaceuticals industry and describes how CM organizations can be developed to confer strategic competitive advantage.

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Clinical Materials as Competitive Advantage

by Harry Clark

Background

Historically, the core competence profile of organizations in the pharmaceutical sector has focused on 'the science.' While not consciously at the expense of other disciplines such as manufacturing and logistics management, this focus has the potential to marginalize operating activities that in other industries, such as electronics and automotive, would be viewed as possible sources of competitive advantage.

This bias toward *discovery* and *early development* and the relative de-emphasis of *execution* activities is in some respects easy to understand in its historic context. In life sciences discovery is the touchstone of medium- to long-term commercial health. It is an expensive process, some estimates suggesting that the cost of a new drug through its development cycle is $802 million.[1] It is often a process that is born in serendipity and remains bedevilled with uncertainty. The risk and the cost are recognized in lengthy patent protection. Yet, over the patent-protected life of a drug, only three out of every 10 brought to market generate revenues that meet or exceed average Research and Development (R&D) costs.[2] This context rationalizes the hitherto accepted logic of concentration on maintaining one or two blockbuster drugs in the portfolio; however, the landscape around pharmaceutical companies is changing and the historic rules may no longer apply.

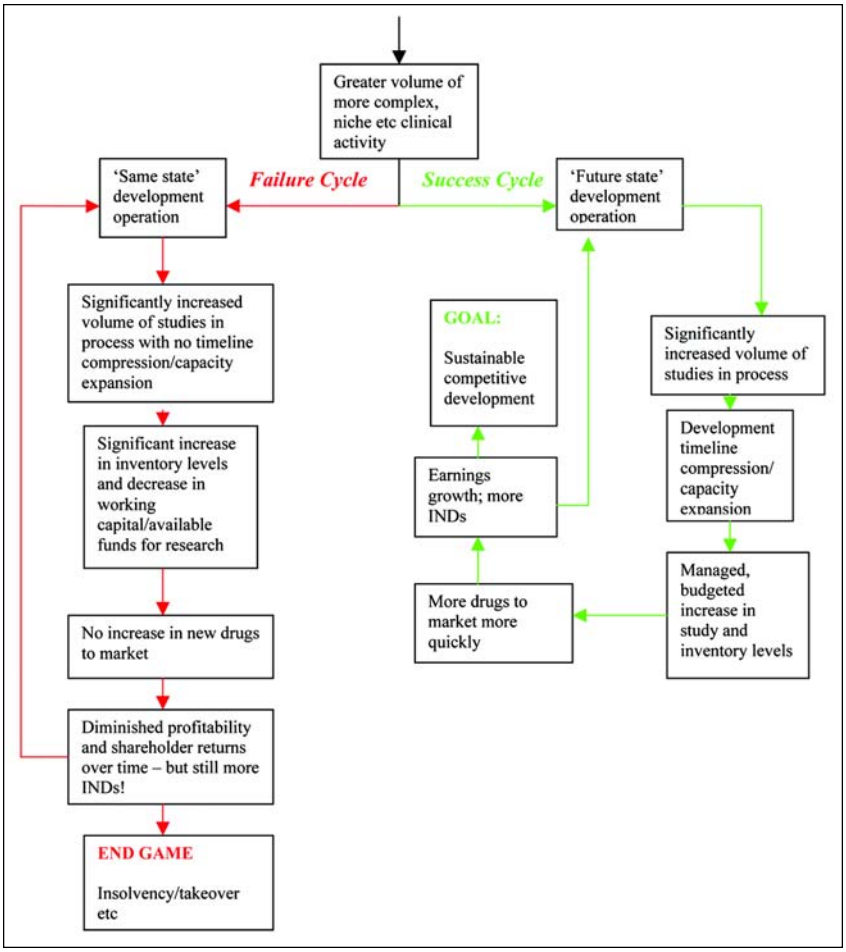

Figure 1. Influence map of development capability.

Current Context

Discovery productivity has been the rate-limiting (and hence the *performance-limiting*) factor in pharmaceuti-

cal companies bringing new products successfully to market. Therefore, it has consumed a disproportionate amount of the intellectual capital of organizations. Yet – for all of this – the number of New Chemical Entities (NCE) approved by the FDA on an annual basis continues to hover at around 25 to 35.[3] The attrition rate in drug development is formidable. According to the Pharmaceutical Research and Manufacturers of America, of 5,000 screened compounds, only 250 enter preclinical testing. Out of these, a mere five proceed to clinical trials and only one is ultimately approved by the FDA.[4] Over the last 50 years, the entire industry has concentrated its efforts on less than 500 targets. The ongoing revolution in the science driven by genomics and proteomics will transform this situation. Some commentators estimate that there will be up to around 10,000 targets identified in the course of the next decade.[5] While this will represent an incredible *scientific* challenge to those engaged in discovery and early development, it anticipates an even more fundamental transformation in the *execution* processes of manufacturing, packaging, labeling, and logistics. ***The competitiveness paradigm shift will be driven by this likelihood: that the historic performance-limiting factors will migrate from discovery to development.***

This shift will pose a fundamental challenge to the competence of pharmaceutical companies. The development process will be at the heart of sustainable competitiveness. ***The successful management of clinical materials processes is central to efficient and effective development and is therefore at the very core of the future competitiveness of pharmaceutical companies***. How will we ensure that clinical materials organizations meet this challenge?

Competitive Challenge for Clinical Materials

The competitive landscape for pharmaceutical companies will be transformed over the next 10 to 15 years. It will no longer be sufficient simply to be good at the science. Some of the characteristics associated with this change will be:

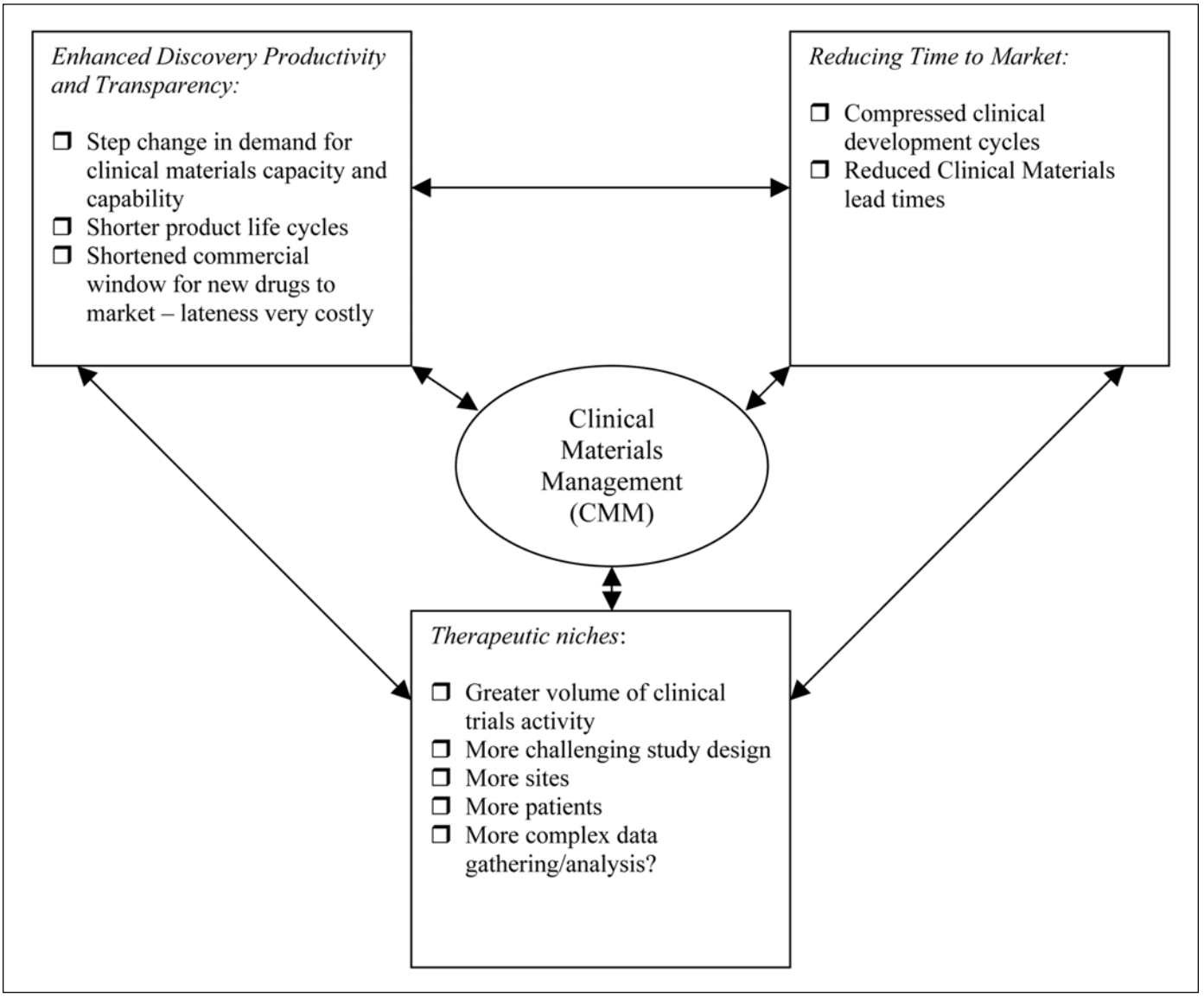

Figure 2. Competitive challenges for CMM.

- an environment that is target rich and data rich
- increased discovery productivity
- a trend toward therapeutic niches and ultimately to personalized healthcare
- a more transparent discovery environment delivering competitor products with similar therapeutic qualities faster to market
- a sector characterized by companies with a more diverse portfolio of products, striving to develop a greater number of drugs for smaller markets

All of this has profound commercial implications. This transformation will challenge pharmaceutical companies because it will require them to be simultaneously creative and exploratory on the one hand and systems-adherent and disciplined on the other. Practically, it will mean:

- shorter product life cycles
- a strategic concentration on 'time to market' as the earnings window for each drug shrinks
- a specific focus on the compression of development lead times
- a consequent expectation of improved development efficiencies – more in the pipeline and more to market *with* significantly-reduced cycle times, but *without* proportionate increases in cost

The effective management of clinical materials is central to the success of the future pharmaceutical business. Increased discovery productivity with no corresponding enhancement of the development processes will exacerbate the commercial pressures on businesses.

Conversely, improved discovery performance with greater development capacity and capability is the key to success. The former is a self-regulating closed-loop that over the lifetime of the development cycle will consign laggard companies to history – unless of course they get lucky. The influence map in Figure 1 describes the situation in abstract.

The commercial imperative of the influence map is unarguable. Irrespective of the degree of sophistication of the development operation, every organization will be compelled to engage in significantly increased levels of development activity. This will remain the case – will, even, be particularly the case – in situations where profitability and returns are in decline over time. In such situations, this 'logic' will persist until the business proposition can no longer be sustained. For some players, this will be the end game.

Therefore, unlocking development potential in the pharmaceutical industry is fundamental. In all industries that have experienced similar 'market life cycle' transformation –

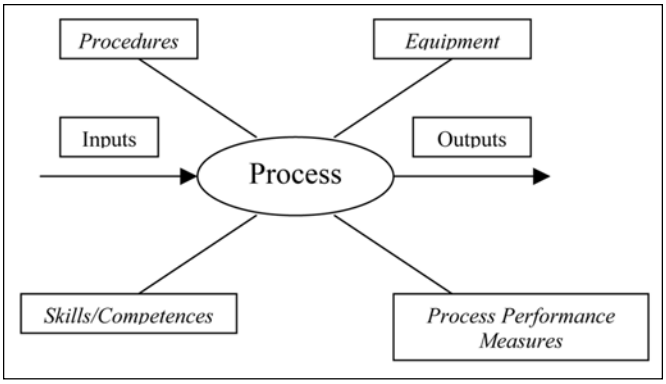

Figure 3. Basic process 'turtle.'

the automotive and electronics sectors are particularly appropriate analogies – the very language of operating undergoes change. Phrases like 'time to market,' 'development lead time,' and 'mass customization' become common currency as marketing behavior becomes niche and even personalized. Success demands that operations planning and logistics are core competencies as companies are required to become more agile and responsive within a sensible cost framework. Inventory management practices such as Just-in-Time are adopted in response. Effective planning and materials management are at the very heart of making this happen. The pharmaceutical industry will be no different and the challenge for clinical materials management operations will be significant as they grapple with an acute and growing focus on cycle times and throughput performance.

Meeting the Challenge

In the immediate future, a number of competitive issues will confront the clinical materials operation - *Figure 2*.

Each of these is a challenge in its own right. Together, they ask some fundamental questions of the capacity of pharmaceutical clinical materials management operations to transform themselves.

Clinical Materials Management (CMM) is a process in the product development operation of pharmaceutical companies. Typically, it describes the following discrete activities (or sub-processes) – the planning and coordination of clinical materials to sites for trial activity; manufacturing; packaging; labeling; and distribution. Activity is commenced with some kind of demand signal in the form of a forecast, usually originating from a marketing operation and translated through the clinical function. At its most effective, clinical materials management operates in the background and doesn't appear on the clinical development critical path. Visibility usually only means one thing – that somewhere a clinical trial is being delayed and that this delay will cause the business lost revenue. While important, focusing on the development critical path fails to describe accurately the real underlying, background performance issues surrounding many clinical materials organizations. Neither will it enable the critical question to be posed – just how much potential is there for improvement in the performance of clinical supplies functions? In the competitive situation described above, this

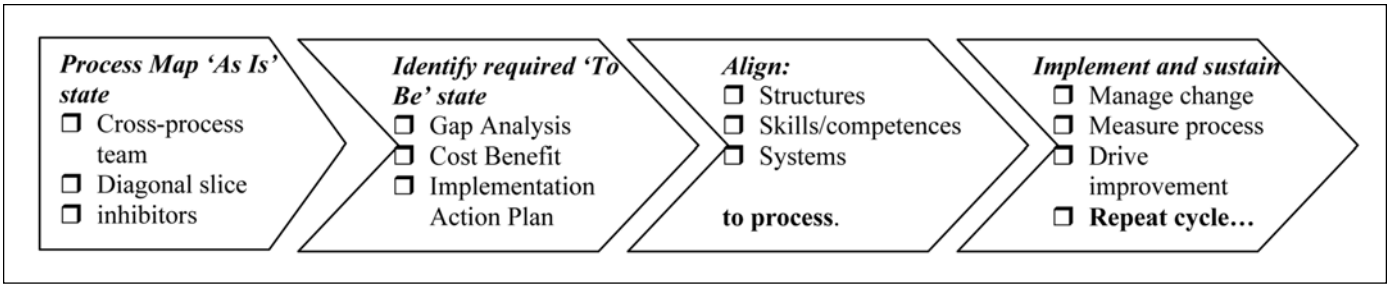

Figure 4. Process improvement change model for CMM.

question demands a response. However, each of the discrete activities referred to above is an *execution* activity and historically these have not been viewed as bestowing competitive advantage. This is misguided. In the new competitive arena, competence in these activities will be a 'must have.'

Across organizations there are common failure symptoms that inhibit CMM operations from working optimally. Some are related to organizational performance. Among these are acute and persistent material lateness; materials shipped in wrong quantities; frequent capacity clashes and resource competition; and moving bottlenecks. Others are 'softer' and more personal, but highly relevant to the underlying causes of these symptoms – working in a clinical materials function can be a lonely and misunderstood vocation. There is limited potential for the upside associated with success, but plenty of scope for the flak associated with failure. This type of situation can be stressful, prompting high levels of turnover at an operational level and consequent knowledge-flight. In this context, organizational learning can be elusive.

The above is frequently compounded by the absence of a process-based performance measurement system. So when questions on performance are asked, the responses will frequently be subjective and can be substantiated only by manipulating data synthetically from a variety of sources. The lack of objective measures of performance and supporting indicators makes managing more difficult. The ability to build, sustain, and work effectively through personal relationship networks, together with the ability to acquire and deploy knowledge on a limited 'local' basis, are frequently parts of the essential skill set in CMM. This often compensates for the relative absence of a process focus.

So, how do we equip the CMM operation for the challenges of tomorrow? Well, that's easy, isn't it? We do a quick heads-up on User Requirements, cross our fingers, and spend several million dollars on an elaborate Enterprise Resource Planning tool. Press the buttons and let it run. Now, these ***systems do have a role, and that role is clear. It is a subordinate role. It is subordinate to the process. And when did we last spend several millions of dollars understanding that?***

Let's look at the *process* in just a little more detail. Each of the operating failures described above – the materials that are late, or the Project Manager that is absent through stress – is a failure of the process. And the failure modes are remarkably common. They are a function of the pharmaceutical competence profile discussed earlier. Let's look at some of these process 'holes:'

Capacity Modeling

Operational capacities are frequently unknown. Industrial Engineering is uncommon. Accurate information on tasks or activity cycle times is absent across manufacturing, packaging, labeling and warehousing. Therefore, there is little in the way of a meaningful reference point for the planning activity that represents the core of every CMM regime.

Capacity Planning

The ability to reconcile the consolidated demand signals placed on the organization (from marketing, commercial, etc.) with available capacity and resource is frequently absent in CMM operations. In the absence of a Rough Cut Capacity Plan, commitments are made blindly.

Planning and Scheduling Tools

Planning and scheduling tools are fundamental tools enabling the planning and scheduling of inventory, manufacturing, and distribution. One survey indicated that almost 40% of CMM operations use none of these tools.[6] In their absence, there is very little to guide activity.

Manufacturing

There is significant scope for the more effective use of best practice manufacturing management techniques in development manufacturing. The deployment of manufacturing resource – for example, labor and machines – is frequently unplanned. The application of Statistical Process Control (SPC) techniques is rarely evident. Even at relatively low levels of machine utilization there are frequent capacity clashes.

Performance Measurement

CMM organizations produce masses of data. Few have developed a meaningful process-based performance measurement system that identifies and tracks key process parameters and uses this information to drive improvement.

Process Optimization

If the process optimization model is reduced to its simplest form (see Figure 3), many clinical materials operations might consider themselves delinquent.

At its simplest, a process is an activity or a series of activities designed to produce a required output. No process is self-managing and all processes tend to wander 'out of control' over time. Therefore, if processes are to continue to function as intended - that is, to continue to produce the required outputs to the required standard – they must be

managed. This management can be described along four dimensions – *equipment, procedures, skills / competences,* and *process performance measures.* Each one has meaning and relevance and each will be reviewed below.

Equipment

These are the tools necessary to do the job. In the clinical materials management environment, these are things such as information systems (inventory management, project management, planning and scheduling tools, etc.); manufacturing machinery; automated picking systems; packaging equipment. Some simple questions can be asked – *did we really optimize our processes before we implemented our systems? Do our systems enable the process to work as smoothly as possible or are we continually formulating 'workarounds'? Is our manufacturing equipment capable and in-control? Is it properly maintained? Is it available when needed or often unavailable or out of commission?*

Procedures

The pharmaceutical environment is closely regulated and adherence is simply the admission price to the game. But being compliant is not enough. We also must be competitive, and our procedures must have an operational as well as a regulatory focus. Again, some simple questions – *do our procedures really help in describing and understanding key parts of the process? How do we manage inventory, ordering, and re-ordering materials? How do we manage drug material obsolescence? How do we set up machines? How do we interpret and use statistical process control information? How do we load and locate inventory?*

Skills/Competences

The skills required to succeed in an *execution* operation are fundamentally different from these necessary in a *science*-based environment. The clinical materials environment has many similarities with a Fast Moving Consumer Goods (FMCG) situation. They share an emphasis on manufacturing, logistics, packaging and distribution. Some more questions – *is this recognized? If I look around at my colleagues, how many have non-pharmaceutical related academic backgrounds? How many have worked in other sectors – electronics, automotive, retail / distribution? Does our Continuing Professional Development in the appraisal process reflect the demands of the jobs that we do? Have we identified the skills necessary to manage our CMM processes optimally? Are our people trained, developed, and competent to deploy these skills appropriately*?

Process Performance Measures

Every process has outputs. These outputs represent the inputs to another process, or potentially someone else's sleepless night. *Do we understand what is expected of the process? Do we know what our key performance measures are? What are our performance indicators? Do our systems enable us to capture information on these? If we have this information, do we use it productively? Do these indicate that our process is improving? Getting worse?* There are relatively few key performance measures in the clinical materials operation. Three appear to be common across most companies – some form of *cycle time metric (*manufacture, package, ship to site); *delivery to plan*, and *waste* (API, etc.) as a function of inventory and planning management. An effective performance measurement system; however, does not focus exclusively on *Results Measures*. It will be derived from the optimized business process and also will identify *Enabler Measures* central to process performance. These will be process-specific. They enable us to actively manage process improvement. To give some examples - in the planning process they may be *'forecast accuracy'* and *'schedule adherence,'* in Warehousing, *'inventory accuracy'* and *'inventory efficiency / inventory turns,'* and in Manufacturing, *'machine efficiency'* and some appropriate measure of *output quality*.

Organizations equipped for the challenges of the future competitive arena will be able to answer most of the questions posed above affirmatively. Most organizations will have to develop that capability.

Building CMM for Competitive Advantage

There is no short cut to equipping the clinical materials operation for the competitive challenges ahead. There needs to be real thought on (a) how the operating process currently performs, (b) on where the blockages and inhibitors are, (c) on how the process should be configured to best meet the needs of its customers, (d) on how the organizational structure should be designed to make the process work to best effect, (e) on how to align the skills and competences of people to the needs of the process, (f) on how to properly align systems to the process – *information systems* (such as software-based advanced planning and execution tools, and management information systems to report on identified metrics), and *management systems* like performance management. The process of change is depicted in Figure 4.

This cannot be a one-off activity. At a macro level, the business environment continues to change. In the pharmaceutical industry this is a certainty, and its implications are anticipated earlier in this article. At a micro level, all processes tend to wander and over time need to be re-centered.

A number of features of this change process are worth commenting on. The 're-engineering' activity associated with the first two chevrons must not to be an exclusively top-down, functional exercise. The team that defines the future state of the process must contain some people who work at the sharp end of the operation. Representation across the processes also must be 'designed-in' to this team. Change is not sterile, and those affected by it must feel some ownership of the outcomes.

Clearly, the extent to which issues subverting process performance are identified is a function of the level of development of the operation. Typically, though, the number of identified process inhibitors (those features of the process that stop it from working as effectively as it should) can run into the low hundreds. When distilled, a range of practical issue-clusters that limit the ability of CMM operations to

perform is often highlighted. Common across organizations are issues such as: *unstable forecasts and unclear requirements; poor quality of documentation and supporting information; seriously-compromised planning regimes with underdeveloped or under-utilized planning and scheduling tools; inability to manage clients and sponsors; unnecessary replication of activities and insufficient standardization; unclear accountabilities; processes that are highly personalized; little visibility on performance and the absence of relevant metrics.*

The future-state ('To Be') of the operation addresses the things that subvert the 'As Is' process. Communication across the operation is vital, soliciting input and qualifying conclusions. Operational performance gaps are identified and the benefits associated with moving to the future-state defined (as far as possible, financially).

Clearly, in all of this, there is no 'silver bullet.' There is work to be done and understanding to be gained. ***The solutions are about simplicity and clarity, about people, and learning and understanding***. About ability and accountability. And about systems that both support people and enable the operation to deliver the necessary outcomes. The process that delivers this has to be inclusive and transparent and it must become part of the fabric of the organization. Implementation projects must pull people in to the change process. Above all, the cycle of improvement described in Figure 4 must become a regular (if abbreviated, as the level of sophistication and competence grows) routine for the operation.

So what might all of this mean for clinical materials organizations?

The Competitive Performance Benefits

The level of benefit is a function of the level of development. Experience across a number of pharmaceutical players suggests that many of the metrics associated with clinical materials management can be improved dramatically. Other equally valuable benefits include the ability to select and deselect pipeline drugs earlier in the trials process. Yes, kill early and kill often. But don't allow process under-performance to kill value or to allow promising drugs to slip out of the pipeline.

In organizations where clinical material supply appears on the critical path, *lateness can be virtually eliminated*. Where this is the case – either occasionally or persistently – the financial benefits of this improvement are huge and can be worth tens of millions of dollars.

Earlier in this article, we described the changing competitive situation facing pharmaceutical companies – the competitive imperative to expand the development pipeline and bring more new drugs successfully to market in ever-decreasing cycle times. This focus on development as the potential constraint puts clinical materials center stage and compels a focus on Order Fulfillment Cycle Time. Typically, this can be reduced by around 10-25 days achieved through time compression in planning and procurement, development manufacturing, packaging and warehousing/distribution.

Parallel capacity increases of between 25% and 40% are typically attainable with a corresponding step-change in throughput capability. Waste reduction of 10% to 20% also is commonly achieved. Recent research supports these conclusions.[7] Again, the financial implications are very significant. Ultimately, over the course of an ever-decreasing number of years it is the potential to bring additional NCEs to the market successfully.

Conclusion

The pharmaceutical sector faces a future full of opportunity and challenge. The sea change in emphasis anticipated by the step change in discovery productivity and the associated focus on development operations puts the effective management of clinical materials at the center of the future competitiveness of companies. The successful players in the sector in 15 years will be those who enabled their development operations to make an equivalent step- increase in performance. This cannot be achieved without transforming the capability of clinical materials management operations. For those who are successful, this will be the challenge they have met.

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This article explores approaches to working in a high-risk R&D environment to manage the clinical supply chain.

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Proactive Strategies for Matching Clinical Supply with Clinical Demand

by Massimo Eli, Jim Freeman, Jörgen Midander, Rob Pizzie, and Bob Shaffer

Introduction

Pharmaceutical R&D is a high-risk venture. The probability that a newly discovered molecule will become a registered pharmaceutical product is discouragingly low. Additionally, many products that do reach the market will never recover their investment costs. Despite advances in *in vitro* screening technologies and biomarkers, the industry has not yet significantly improved its success rate. Often, we learn first about human toxicities, absorption or metabolism issues, or drug-drug interactions only during the course of human trials. Because the economics of drug development demand speed, planning for large pivotal studies is usually well into the execution stage by the time many of these findings become available. Another source of change is the advice and demands arising from regulatory authority review of proposed clinical plans. It is not unusual for significant protocol design changes, or even new studies, to emerge from discussions between sponsors and regulators. Finally, technical challenges that may necessitate changes in plan can arise from many sources: ability to develop a suitable drug formulation, investigation of a novel toxicology mechanism, availability of a novel clinical biomarker technology, etc. These many causes of changes to plan often mean that new resource commitments are required, and that the value of previous work is lost. Most important is the opportunity cost associated with low success rates. Resources

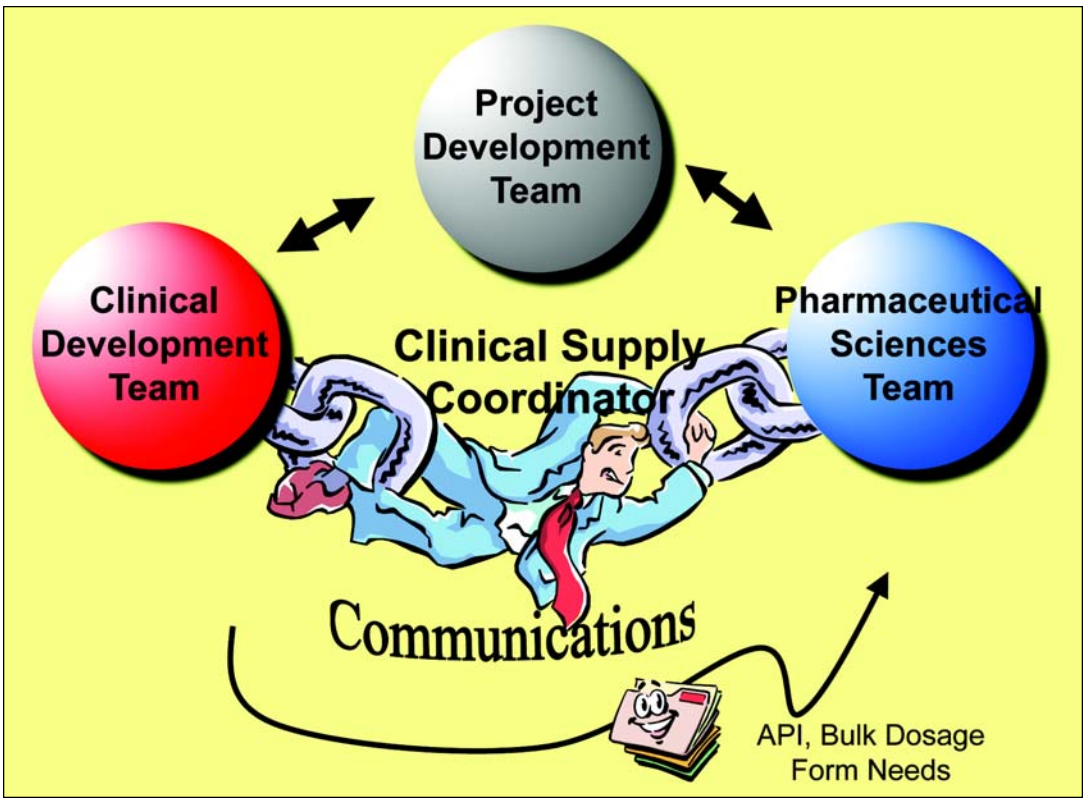

Figure 1. Coordinate strategy with internal partners.

invested in projects that fail are no longer available to invest in new opportunities.

This high-risk R&D environment poses significant challenges to managing the clinical supply chain. In this article, approaches to working in this environment to manage multiple interfaces and changing requirements will be explored. Various approaches to structured project management, proactive outsourcing, and appropriate risk taking that can help a clinical supply organization cope with these everyday challenges will be considered.

Multiple Interfaces and Changing Requirements: An Investigational Products Perspective

Proactive management of clinical trial programs requires an awareness of, and the ability to adapt to, the rapidly changing pharmaceutical research environment. New drug discovery technologies, such as high-throughput screening and combinatorial chemistry, lead to faster drug target identification and lead optimization. New development strategies based upon biomarkers are shortening timelines to proof of concept studies in humans. The net result is a larger number of drug molecules entering into clinical development and faster progress toward large-scale studies. To be successful, companies must move nimbly and react quickly to data. Drug candidates that demonstrate clinical promise must move quickly to pivotal studies. Molecules that fail to perform as expected should prompt quick decisions, either to accelerate discovery efforts toward improved candidates or to redirect resources toward entirely new opportunities. Although only a small part of the overall R&D effort, a clinical supply organization can contribute to effective execution of development programs.

Clearly, one important factor is speed. Fast execution of clinical supply activities helps to speed the progress of clinical trials. And, it helps an organization quickly respond to change. For example, the use of simple supply presentations, such as simple capsule formulations, oral solutions, or bulk Active Pharmaceutical Ingredient (API) filled into bottles, offer the opportunity to minimize supply preparation time for simple first-in-man studies (Phase I). In addition, oral solutions and API-in-bottle offer the opportunity to easily modify dosing in response to clinical results. Of course, if the advantage of speed is not to be lost, resource must be allocated in parallel to develop more sophisticated dosage forms for use in larger more complicated studies (Phase II/III).

Another strategy to achieve speed is early planning. API synthesis typically has a long lead-time, and forecasting API needs well in advance can help avoid serious delay. If clinical supply personnel are involved in the clinical planning process, they are in a position to anticipate such needs and begin to lay the groundwork for producing API and bulk dosage forms. Even prior to proof of concept there is a need for close teamwork between clinical supply groups and their medical counterparts. The extent to which clinical supply planning and clinical development planning are coordinated can have a big impact on how quickly supply preparation and study initiation will occur further down the line.

The globalization of clinical development programs has led to advantages in terms of access to patient populations and better use of global resources. However, for the clinical supply group, this offers the challenge of being prepared to supply sites anywhere in the world, often at short notice. This requires labeling capabilities in many languages. Furthermore, it means that stability studies supporting these clinical supplies must be designed to allow appropriate packages and adequate expiration dating in any climate zone. Finally, it means having the knowledge and systems in place to support rapid shipment to any global location. If not, the risk is significant that clinical supply availability becomes the critical path to timely study initiation and more importantly timely study completion. To avoid this, the clinical supply group must plan for and apply certain strategies as described in the following section.

It is important to manage the whole clinical supply process, and to participate closely with clinical activities, including design of the protocol, and operational planning for trial execution. Hand-offs within the planning process can too easily lead to miscommunication, faulty assumptions, and consequent delay. If a single person is assigned to oversee the entire supply process, the number of hand-offs, and the likelihood of these kinds of problems, is reduced. This person, the Clinical Supply Coordinator, must be intimately involved in the planning for a clinical study. For example, they should be included in meetings where the clinical plan is prepared, and where protocol design work is coordinated. This level of involvement is important because supply planning is often intimately linked to the study protocol. Early, close, and continual involvement in study design helps the clinical supply group to gather more accurate supply forecast data, it affords the opportunity for physical supply design to impact study design, and ensures that the Clinical Supply Coordinator is immediately aware of changes which could impact supply design, quantity, or schedule. Finally, close collaboration also helps to build mutual respect and trust between medical and the clinical supply groups – an invaluable commodity when unexpected events occur.

The role of the Clinical Supply Coordinator requires the combination of several skills, including communication, teamwork, creativity, problem solving, and the ability to balance broad strategy and precise details. Increasingly, the ability to work in a global environment is important for managing supplies for global trials involving multiple sites, vendors, partners, and cultures.

Within a company, close coordination among key internal partners (Clinical Development, Pharmaceutical Sciences, Regulatory Affairs, Quality Assurance, Commercial Manufacturing) is also critical. A primary forum for this interaction is the Product Development Team comprising all the appropriate corporate functions and which develops and follows the Product Development Plan.

The Clinical Development Plan, which is developed to be consistent with the Product Development Plan, is prepared with the full involvement of the Clinical Supply Coordinator

who is also typically operating within the Pharmaceutical Sciences Team, which is responsible for formulation and analytical development. Within this team, the Clinical Supply Coordinator is particularly interacting with those individuals responsible for API and bulk manufactured formulations, packaging, and the QA groups with responsibility for these functions. In summary, the Clinical Supply Coordinator coordinates all supply aspects and details both at the program and the study level - *Figure 1.*

Structured Project Management - Planning and Managing vs. Reacting and Suffering

Managing a clinical supply chain can often be a chaotic experience. In fact, it can sometimes be described as reacting to unpredicted and sometimes overwhelming events, and then coping with the consequences to timelines and morale. Is there a way out of this dilemma? Possibly – a more structured approach to managing work processes and projects holds the promise of improved predictability (less need for reaction) and transparency (less uncertainty and stress).

The need for speed, combined with the dynamic nature of research, creates an environment where a Clinical Supply Coordinator can feel like their projects are always unstable. To achieve some measure of control, it helps to think about the supply chain process in terms of a network of smaller components. If these components can be organized within a project management system that is rugged, transparent, and flexible, then it should be possible to respond more quickly to changes. This project management system should be rugged enough to withstand changes of personnel within the project without loss of critical information and should be transparent enough that all personnel involved with the project clearly understand the clinical supply plan and their role within it. A second principle is to manage risk proactively, instead of merely experiencing its consequences. In a multiple-project, fixed-resource environment, risk can be best expressed in terms of opportunity cost: every decision to commit resource to one project can have consequences for all other projects. Risk management is possible when resource-allocation decisions are taken with knowledge of assumptions, networks, and decision trees among all projects. Of course, this is a difficult situation to achieve. Clear and timely information across a portfolio of projects can only be achieved through effective, transparent communications among all stakeholders. This third principle is, of course, often the most difficult to achieve in large, diverse organizations.

A common question asked of supply-chain managers is: "How long will it take to prepare supplies for this study?" A common response is to quote a timeframe of several months – perhaps a standard time derived from previous experience, or a time long enough that the manager is 100% confident of achieving it. Both of these lines of thinking are flawed. The first probably ignores specific details of the study, and it certainly ignores other projects running concurrently. The second probably yields a timeframe much longer than the time it will actually take to complete the work. Inevitably, such a standard response will be unsatisfying to the person

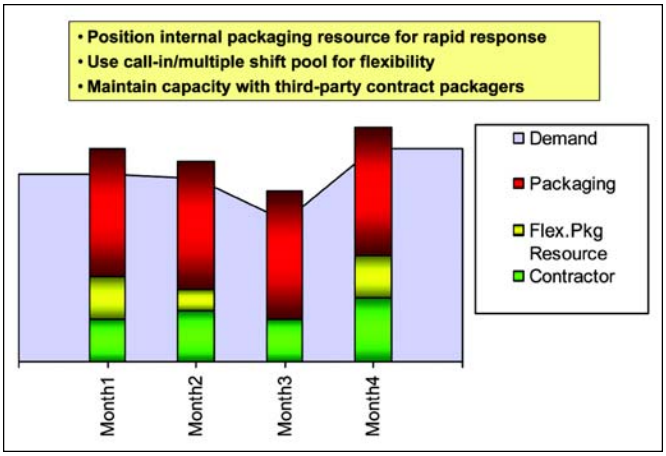

Figure 2. Capacity management.

asking the question.

A better response might be to break the process down into components, and then link those components with key decision points in the overall project network. For example, a typical supply chain progresses from production of API, through manufacture of bulk dosage forms, packaging into primary, then secondary containers, labeling supplies, and preparing for shipment. Each stage in the process requires progressively more information about the design and execution plans for the study. Each stage also provides an opportunity to take a risk-based decision. The amount of API produced will determine whether future changes (e.g., expanded trial size, new therapeutic endpoints) requiring API can or cannot be supported without delay. If some details of the clinical protocol are uncertain, it is still possible to package, and even label supplies suitable for one or multiple scenarios. For example, if the dose level is not known, but can be narrowed to two alternatives, then a possible decision could be to manufacture, package, and label supplies at both dose levels. Of course, half of the supplies would be wasted. Furthermore, it is likely that some other project will be affected by the choice of allocating twice as much resource to prepare two sets of supplies. The point is that a range of choices is possible, and conscious decisions can be based upon an assessment of the risks and benefits of the various choices.

This discussion illustrates how risk-based decisions might be taken at different points in the supply chain. But thinking in terms of component activities suggests additional possibilities. As mentioned above, when asked how long it will take to complete an activity, most people will give a response that is highly likely to be achievable. After all, one is usually expected to commit to such timeframes. But in reality, given no other competing priorities, the work can probably be completed much more quickly. It might be possible for a structured project management approach to achieve shorter timelines, if it can somehow manage the aversion to risk that causes people to quote longer "safe" timelines.

Perceptions of timeline risk are often based upon uncertainty – most activities depend upon the timely completion of other activities outside one's direct control. Uncertainty about

the completion of these previous activities feeds perceptions of risk about commitments regarding one's own responsibility. Research by Goldratt and others on the Theory of Constraints[1,2] suggests that supply chain processes can be analyzed to reveal interdependencies among component activities, and then organized in ways that stabilize the throughput-constraining activities. It is then possible to manage a process closer to "realistic," instead of "safe," timeframes, by utilizing transparent resource-management tools in combination with buffers of time to protect the overall project commitment date.

Strategic Approaches to Outsourcing: "Planned vs. Panic"

The same drivers (rapidly changing environment, dynamic development strategies, global programs, and multiple interfaces) are equally important when we consider outsourcing activities to Third Party Manufacturers or Contract Research Organizations. We have already indicated that one of the best ways to answer the demands of these drivers is to manage projects in a structured way in order to try to be able to "plan better and respond faster." We need to apply the same principles and move to a more strategic approach to accessing external capacity and expertise, rather than the more traditional tactical approach of outsourcing to cope with a short-term lack of capacity.

Traditionally, clinical supply packaging work has been outsourced in a fragmented or "piecewise" fashion based on late reaction to perceived demand. An alternative is to outsource the packaging activities for entire drug programs or at least large fractions of drug programs. It may be better to make plans for contracting out large, labor-consuming trials occurring at later stages of drug development (Phase III). In these cases, the larger capacity of external vendors, both in terms of packaging and distribution, can be exploited. Involving the contractor early in the design process also can be advantageous as by nature of their business they are exposed to many different trials and their experience can be tapped in the design of the clinical supply aspects of the new trial. By focusing the contractor on fewer larger trials rather than many smaller trials, efficiencies can be gained. For example, paperwork and the communication between the company and the contractor should be reduced, being concentrated on "replications and similarities" rather than "differences."

Consider Figure 2. Time runs along the bottom axis where the light blue background represents the demand for clinical supplies from the medical department: the multi-colored columns represent the packaging capacity with the red representing fixed internal capacity, the yellow some flexible internal capacity (call-in staff, cross-trained staff from other areas, temporaries etc), and the green represents outsourced capacity. Obviously, we never want to be in a situation where the top of the column is below the light blue line in the background because this means that there is insufficient capacity to cover the demand or to support last minute emergencies/changes in plan. Consequently, an appropriate strategy is to push fixed internal resource above the blue line by using a combination of flexible internal resource (which can be mobilized quickly but is limited in capacity) and outsourced capacity (which takes a little longer to mobilize but can accommodate bigger swings in capacity). The key to making this successful is to establish preferred provider arrangements (sometimes called "master service" agreements) with a limited number of qualified Third Party Manufactur-

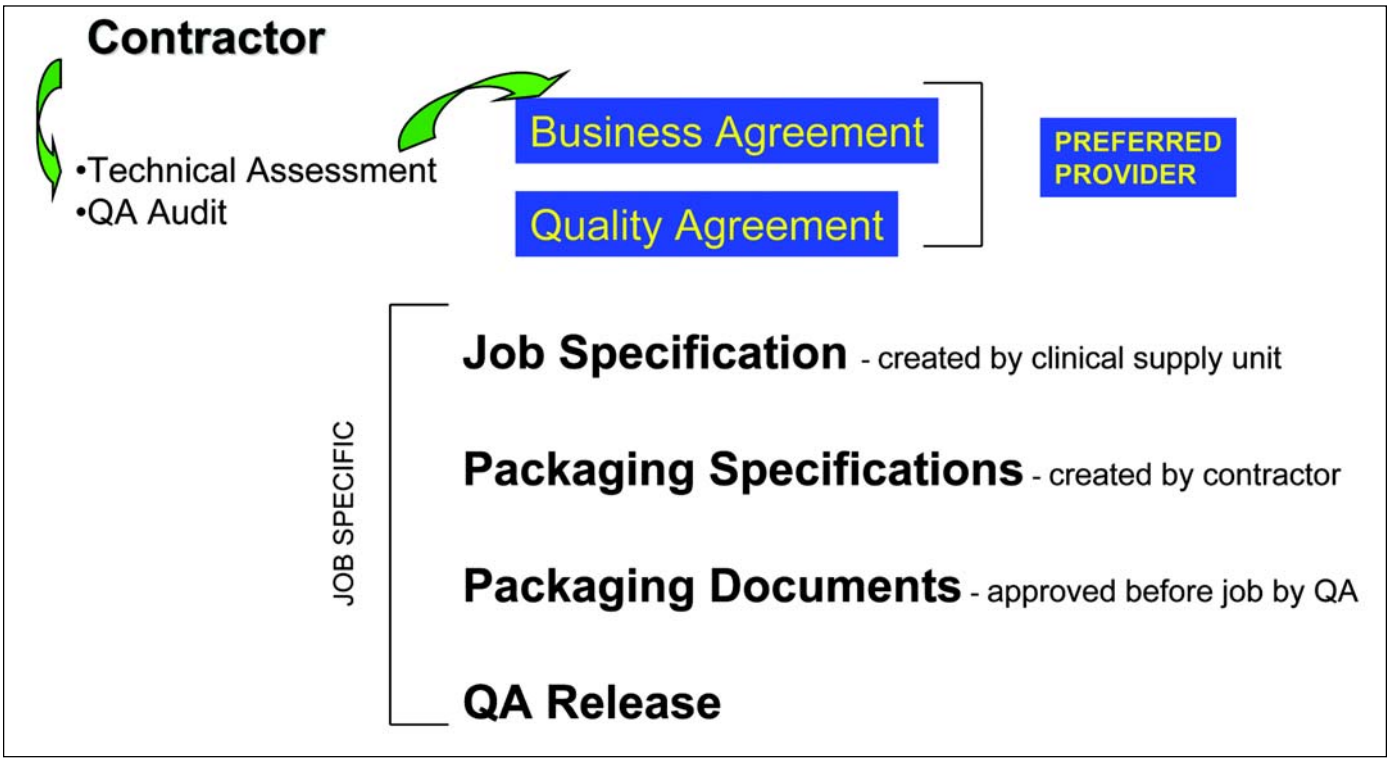

Figure 3. Clinical packaging outsourcing.

ers and routinely outsourcing a portion of total work according to well-defined forecasts of clinical supply demand. In this way, closer relationships are established and both sides are prepared to invest time and energy in the relationship to create mutual benefit over the long term. This strategy is consistent with the idea that clinical supply groups can contribute value by maximizing the speed and reliability of clinical trial execution.

Figure 3 gives an overview of one possible approach to establishing preferred provider agreements and a job specification process. An initial technical assessment of the capabilities of the contractor by the contractee clinical supply unit is followed by a GMP audit conducted by the contractee QA unit. If the contractor is deemed to be technically acceptable, a business agreement specifying legal aspects of the relationship and laying down the basis for financial terms is established. A Quality Agreement detailing non-job specific quality standards also is established. These two documents form the basis for the Preferred Provider Agreement. Subsequently, specific jobs are defined by a Job Specification that is prepared by the contractee and defines the job and a Packaging Specification or Quote from the contractor that defines how the job will be run at the contractor's facility. This kind of approach not only helps with the strategic outsourcing described earlier based on improved forecasted workload, but also helps with the last minute emergency outsourcing frequently faced in the Clinical Supply business. A contractor with whom you have an established relationship and with whom you do ongoing business is more likely to accommodate your needs even with short notice.

Key criteria for selection of a Preferred Provider are:

- Quality both in terms of GMP/GCP compliance and business reliability (on time delivery)
- Responsiveness, in terms of speed and flexibility
- Cost

It is worth noting that clinical supply costs are often small, compared with either the overall cost of running a clinical trial or the financial benefit of quickly completing the study. Therefore, there are some circumstances where it might be acceptable to trade cost for speed. Nevertheless, preferred provider agreements represent significant opportunities to achieve cost savings with vendors, and also through the streamlined work practices that can be established through close partnership.

Finally, it's important to identify specific, dedicated, skilled resources internal to the clinical supply organization to be able to deal with this strategic approach to external providers. These persons need to have knowledge of the clinical supply area plus some background on procurement/purchasing/contracting strategies and policies.

Risk Taking in a Fast Moving Environment: "How to Make the Right Decisions"

The development of investigational products and conducting clinical trials requires that an appropriate balance be struck between risks and benefits of various possible courses of action. It is important to stress that at no time as we discuss risk are we referring to risk to patient safety.

The delay in the launch of a new product can result in the loss of millions of dollars over a relatively short time period. It is therefore important to be conscious not only of the cost of the development process, but also of the time that it takes us to bring the drug to market. So, we need to balance the resources and risks of today, versus potential delays in bringing new products to market. This balance must be struck while always using good science and good business rationale to drive decisions or changes along the drug development process.

Based on the clinical study plan, the clinical supply function needs to develop clinical supply packaging options and define and assess the risks and benefits associated with each. In conjunction with the medical customer, a course of action can then be selected from the options that have been developed. For example, based on the clinical study plan, it is possible to begin to calculate how much investigational product, including comparator agents, will be needed. This calculation should include how much API will be needed to produce sufficient quantities of bulk dosage forms. There might be a risk that these forecasts are over or under what is actually needed for a particular clinical study.

Another example of risk-taking can relate to the clinical package. If, for example, the draft protocol suggests that blister packaging of an oral dosage form is needed, it might be appropriate to provide a counter proposal to use bottles for the study, if the study start timeline is critical. Typically, a bottled study supply can be provided faster than a blister packed supply. Some typical timelines for bottled product are four to six weeks while for equivalent blister packs the time might be 12-16 weeks. Set against this advantage of speed is the nature of the study and the nature of the patient population. While a bottle presentation may work well for an open label oncology study, it may not work well in a CNS study in Alzheimer patients requiring a multi-bottle escalation, maintenance, and taper dosing regimen. The configuration selected needs to be judged on the merits of the particular study.

Sometimes comparator drug products are required in a clinical trial. One could wait until the clinical trial design is well defined before calculating how much comparator to purchase. On the other hand, one might choose to take a risk and work from a draft protocol to purchase the comparator. The risk might be that too much comparator is purchased, or too little, or even the wrong comparator if the protocol study supplies are changed at a later date. This risk needs to be weighed against the critical need for getting the study started on time, versus the cost of the comparator. If the comparator is very expensive, one might wish to postpone purchasing the comparator until the need is better defined. On the other hand, if the cost of the comparator is negligible compared to the potential cost of starting a study late or the comparator is difficult to obtain, it might be well worth the risk. Such risks should be presented to the clinical study team and evaluated as early as possible in the process. Importantly, the clinical

supply group, the clinical development group, and the overall R&D/commercial organizations can share the risks inherent in these resource investment decisions.

Another risk that needs to be considered is the expiry dating of the clinical supply materials. Early in the development process for a new formulation, there is likely to be little stability data generated that would allow long product expiry dating to be assigned. This may dictate the use of smaller and more frequent clinical manufacturing and clinical packaging campaigns or alternatively an assessment of accelerated stability data alone may suggest a high probability of expiry extension and therefore larger and less frequent manufacturing and packaging is appropriate.

To reiterate a point made earlier, the cost of clinical supplies is usually rather small compared to the cost of running a trial and the potential cost of a delay in obtaining approval. Consequently, it is usually appropriate to put clinical supply resources at risk rather than compromise a clinical study timeline. An example of this is that minimizing the time between the end of Phase II and the start of Phase III is a desirable objective. Unfortunately, the dosing to be tested in Phase III is determined in Phase II, and so preparing the specific supplies required for Phase III is a difficult task. Approaches that can be used to address this dilemma are to prepare all possible doses that might be used in Phase III (recognizing that supplies will be wasted) or partially preparing supplies which can be rapidly finished prior to the start of Phase III. The options need to be developed by the clinical supply group and carefully considered by all stakeholders.

In conclusion, the clinical supply function needs to determine what opportunities exist to balance resources versus timeline opportunities, communicate them to the various development and management teams, present options, evaluate risks, and recommend which options to take. The primary objective is to get new products or existing products with new indications tested in clinical trials and approved by regulatory authorities as quickly as possible using good science and good business practices.

Overall Conclusion

In the end, we must remember that the clinical supply process is only one component of an overall R&D process aimed at effective execution of clinical trials and rapid registration of new pharmaceutical products that meet patient needs. There is little point in optimizing the clinical supply process if that optimized process does not also contribute to a company's ability to achieve these larger goals. We have outlined several concepts that can be important to improving the supply process. By maintaining a focus on the overall goals, and by building and maintaining strong partnerships among groups, a clinical supply organization can avoid becoming a bottleneck and instead contribute significant value to an R&D organization.

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This article discusses some of the more significant developments in API reactor design and use, and identifies some of the likely future trends. Future articles will focus on practical aspects of plant design, including heat transfer systems, material handling, ancillary equipment and safety.

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API Chemical Synthesis Trends in Reactor System Design

APIs: Reactor Considerations

by Stephen Hall and Andy Stoker

Introduction

This is the second in a series of articles on trends in Active Pharmaceutical Ingredient (API) reactor system design. The first article, published in the May/June 2003 issue of *Pharmaceutical Engineering*,[1] described some of the ways in which API production has changed over the last decade and the pressures and opportunities that it currently experiences. The technical issues identified included the increasing potency of recently developed New Chemical Entities (NCEs), the potential of increasingly powerful computer systems, and the gradual introduction of new chemical technology. The human genome project has led to a huge expansion in the number of usable drug targets and advanced the possibility of medicine customized for individual needs. These factors must be set alongside political, legislative, and economic issues. Above all, we noted that API production now has a truly global perspective that is driven through safety, quality, and cost, and that this brings both opportunities and pressures. Regulatory requirements are being globally harmonized. Manufacturing costs are judged on a worldwide basis and are under continuous downward pressure. The larger pharmaceutical companies operate global supply chains, where each site has a defined function to contribute to the whole network. Even the smallest independent supplier faces worldwide competition in an industry where transportation costs are a relatively small proportion of the total cost of goods.

This article discusses some of the more significant developments in API reactor design and use, and identifies some of the likely future trends. Future articles will focus on practical aspects of plant design, including heat transfer systems, material handling, ancillary equipment, and safety.

Our objectives in each article are to identify current practice, analyze it against current and future needs, and highlight some likely developments. In the first article, we encouraged readers to contact the authors with comments and ideas to share, and we are grateful to those who have responded in this way. We will acknowledge and build on these comments in future articles and will very much welcome further input.

Overview

API manufacture has developed as a large-scale version of the bench-scale wet chemistry set-up used to develop processes. Historically, there has been little reason to change this. Continuously Stirred Tank Reactors (CSTRs) delivered material reliably through a series of batch campaigns. Manufacturing efficiencies were much lower than those seen in many comparable sectors such as fine organic and specialty chemicals, but this wasn't important because the cost of goods have been relatively insignificant in the pharmaceutical industry.

Therefore, the pharmaceutical industry has focused on improving the design and operation of stirred tank reactor schemes, through advances in equipment detail, standard arrangements, and plant layouts that have enabled greater operating efficiency and batch turnarounds.

Over the last 10 years or so, there have been some remarkable developments in chemistry and chemical engineering research and in the wider process industries. Glass-lined stirred tank reactors have proved unsuitable for some of the operating conditions required and the cost of lengthy sequences of campaigns has

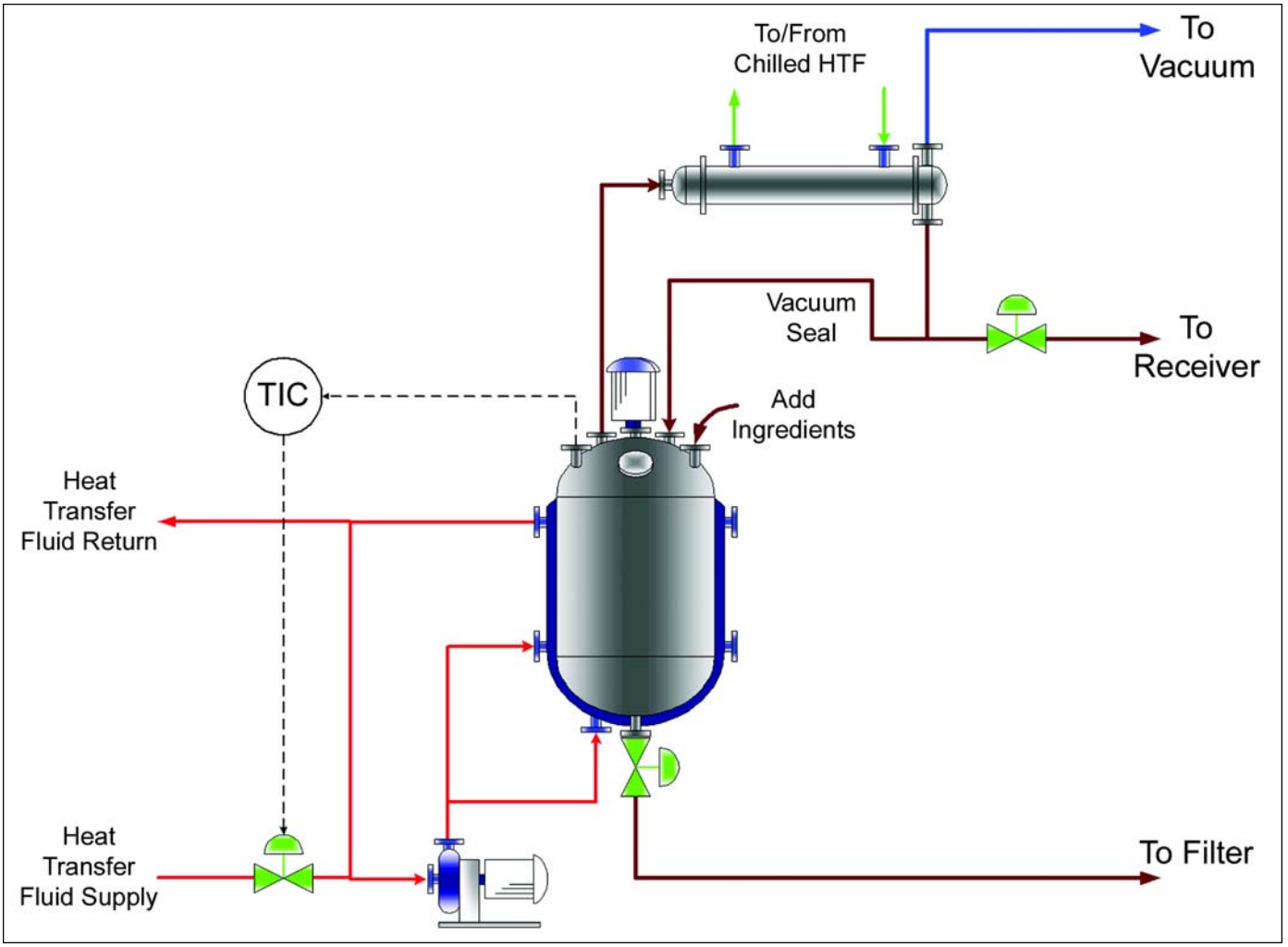

Figure 1. Simplified Flow Diagram. A typical reactor is designed as shown in this simplified diagram. Several alternative arrangements for the jacket heat transfer system will be described in the next article in this series. (Source: AMEC)

been brought into question. There also has been a drive to prepare materials where the form and structure of compounds are controlled to aid their performance and behavior, and again CSTRs have a limited capability to deliver such results.

There is growing interest in alternative reactor technologies. Three examples are described in this article, but there are many more examples being developed which we can expect to see used in API manufacture in the years to come. The use of different reactor types raises questions about the future organization of manufacturing supply chains.

In this article, we show how different reactor types can potentially deliver benefits of yield, time, and selectivity when compared to CSTRs – and we also explore how the business environment of the modern pharmaceutical industry determines the attractiveness of such technologies.

Business Drivers

A cursory review of developments in commercial API manufacture reveals much about the business drivers. From the 1970s through to the early 1990s, large API facilities were built throughout the world, but principally in North America and Western Europe. These plants almost universally included process trains comprising reactor, crystallizer, separation device, and dryer to produce bulk quantities of powder. There were variations in details such as the reactor size and materials of construction (usually glassed steel, stainless steel or a specialist steel alloy, such as Hastelloy C-276), the separation device (usually pressure filter or centrifuge), and the dryer design (either a standalone device or a combined pressure filter dryer). However, these plants tended to look very similar wherever they were built; someone walking into an API plant in the US, Western Europe, or Asia would see few major differences.

As the 1990s progressed, three locations emerged as preferred locations for the new API plants of global pharmaceutical companies. The domestic industrialization policies of Singapore, Ireland, and Puerto Rico led them to introduce favorable tax laws and offer other encouragement for inward investment. At the same time, the emergence of proven capability in Asian countries – principally India and China – and some eastern European countries was reflected in the relative growth of their API capacity for both domestic and some international companies.

There has been a marked decline in the number of new API plants built in the last few years. Fewer still have been built outside the major centers indicated above and there is usually a key technical, commercial, resource, or micro-economic driver to stay within these areas. In 2000, more than 80% of the API facilities inspected by the FDA were comprised of non-sterile batch organic chemical synthesis technology. Many new biotechnology facilities have been built, but unlike API plants, the products and processes are often more difficult to define, and therefore, they are more often near to the corporate discovery and development centers. The proportion of biotech plants is steadily growing, but this topic is not within the scope of this article.

Perhaps the most interesting feature is the technology used in synthetic API plants. Despite all the advances in chemistry and process industry technology, most plants still look remarkably like their forerunners of the 1970s (or 1950s). The major unit operations are often the same, the materials of construction are similar, and plant layout and general materials handling strategy appear unchanged. It is only in the next level of detail – such as the more sophisticated functionality of the control system, the greater levels of containment and the improved design of equipment – that advances are seen. There are some new unit operations, some are described in this article, but they are exceptions to the general picture.

Why should this be the case when there appear to be reaction technologies that would improve API performance? The answer lies in the business drivers outlined below. In various ways, these drivers encourage the adoption of a technology which might not appear technically ideal, but which is well established and which is very flexible across a range of requirements: the glassed steel stirred tank. After a brief review of developments in this equipment, some new business drivers that may lead to changes in reactor system design are examined.

Minimizing the Time to Market

Pharmaceutical companies live and die by the introduction of New Chemical Entities (NCE). In broad terms, medicinal chemists identify candidate drugs by screening very many potential molecules against selected targets. Their role is to manufacture the molecule for tests – they are much less interested in route or process. Only later do synthetic or process chemists and process engineers consider manufacturing methods. At the same time, they face demands for the rapid production of trials material. As pre-clinical and clinical trials progress, the route and then the process are frozen so as not to invalidate the trials results. This all means little time for route optimization and explains the tendency to stay with known reactor systems and technology.

Assured Supply

One major Key Performance Indicator for the pharmaceutical industry is the delivery of product – "On Time and in Full" (OTIF) – to customers in national health authorities, and distribution services. This is achieved only though a robust supply chain with, historically, considerable over-capacity. Anything that puts OTIF delivery at risk is a significant threat, and this again encourages an option that is regarded as safe – the stirred tank reactor.

API Over-Capacity

One of the main drivers for corporate pharmaceutical mergers has been the economies that are achieved through reduced headcount and better asset utilization. This has been as true in the API sector as other areas of the business. Redundant API facilities are often sold as going concerns to toll manufacturers looking to supply to the very companies who once owned the facility and who are making better use of their remaining API facilities. At the same time, the rate of NCE introduction has declined over the last few years, while products are often more potent and less material is required.

These factors mean much reduced pressure for new capacity, and instead, a drive to optimize the use of existing facilities.

Micro-economics

The financial ratios of the pharmaceutical industry would appear strange to those in many other chemical and process industry sectors. The manufacturing cost, or "Cost of Goods," is often no more than 20% to 25% of sales with significant costs absorbed by R&D and marketing. In this environment, there has historically been little incentive to reduce costs. Thus, API facilities are often utilized no more than 60% to 70% – much less than the performance of many fine chemicals plants.

Each of these drivers encourages the use of familiar and reliable technology. Chemical synthesis in the ubiquitous glass-lined reactor continues to be the industry standard and it is from this baseline that most API manufacturers are currently looking to improve – rather than introduce new technology. Therefore, the next section reviews some of the advances in glassed-lined steel reactors.

Glass-Lined Steel Mild Steel (GLMS) Batch Reactors: Flexible, Reliable, and Limited

The GLMS reactor is the workhorse of API manufacture with most facilities focused on such equipment as the main or only type of reactor. This section summarizes the primary ways in which such reactors are used, examines the rationale behind this practice, and describes some innovations that have improved the effectiveness of GLMS reactors. Finally, some of the limitations of this approach are explored.

Usage

Although there are many potential variations, synthetic API plants normally follow a sequence of Reaction – Crystallization – Separation – Dry to produce a dried solid product. In this model, the reactor and crystallizer are commonly stirred tank reactors, usually standard catalog-based items of a similar design - *Figure 1*.

Most API products are synthesized through a multi-stage sequence with solid intermediate products being isolated at each stage. The product of one stage is the starting material

for another stage, following a similar sequence of unit operations. The ISPE Bulk Pharmaceuticals Baseline® Guide describes this as "typical."[2] It is usual for such sequences to be operated on a campaign basis, where several batches of each stage are made consecutively, before the batch lots are transferred to the next stage for further conversion. The equipment used for the campaign of the stage n+1 may be very similar to that used for stage n – it may even be the same equipment with relatively minor modifications.

Design Requirements

In this light, some requirements for the reactor or crystallizer can readily be seen. The reactor must be:

- suitable for a range of operating conditions – including temperature, pressure, and pH
- able to impart or remove energy at various rates – through methods such as heat transfer and physical agitation
- able to charge and discharge or remove material in solid, liquid, gas form

The standard GLMS reactor achieves all these requirements to a limited degree. For example, a standard pressure operating range is full vacuum to 6 barg (100 psig) with a temperature range of -30°C to +260°C (-20°F to 500°F), which has proved acceptable for most API reactions. Suppliers of GLMS vessels have developed a range of standard designs, including one- and two-piece bodies, dished and conical heads, and various agitator designs, complete with systems to enable agitator changeover, such as liquid nitrogen cooling followed by ambient expansion to lock the agitator shaft into the drive mechanism.

Technical Developments

The fabricators of GLMS reactors have introduced a series of developments[3] aimed at improving their use further:

- Special glasses are available, some enabling operation up to temperatures as high as 340°C (650°F), while others provide increased resistance in acidic conditions, albeit at the expense of alkali resistance, and vice versa.
- Particularly smooth glass surfaces have been introduced to facilitate Clean-In-Place (CIP) and thus enable rapid turnaround.
- Conical bottom heads are installed to enable effective mixing and heat transfer at low fill levels, and a range of jackets, coils, and the like are available to optimize heat transfer.
- A range of agitator designs is offered, enabling a system to be selected for a specific process duty – although some 90% of all agitators supplied are of the 3-blade retreat curve impeller design.
- Reactors are now marketed for less demanding process conditions – typically with a range of full vacuum to +3 bar (50 psig) and minus10°C to +150°C (15°F to 300°F). These can normally be delivered within four to six weeks which can represent a distinct benefit in some cases.
- There is a general trend toward half-coil jackets rather than full annular jackets. This arrangement provides better heat transfer efficiency, especially when using thermal heat transfer fluids. Interestingly, 70% of the GLMS reactors in mainland Europe are of the half coil design, but less than 3% of those in the UK use this approach.
- Units are now sold complete with stainless steel cladding, primarily for use in sterile API manufacturing.
- Various techniques, such as novel sparge pipe designs, have been adopted for safe and efficient gas introduction to facilitate gas-liquid reactions.

The design of baffles in CSTRs has been extensively characterized by many workers. Vendors have built on this work by introducing specialist design features:

- The latest baffle designs provide a combination of functions, such as effective mixing, incorporating a dip-pipe, temperature or pH sensor, and sampling facility.
- It has been recently reported that some interesting work is being carried out to visualize mixing effectiveness through the body of an agitated vessel.[4]
- Glassed steel baffles which are integral with the vessel body, can offer improved agitation with virtually zero vortex and free up a nozzle on the vessel head for process use.

There is growing interest in the way in which reactors are installed, cleaned, maintained, re-configured – all factors that affect the project time to beneficial operation and operational turnaround durations. Thus, the larger vendors offer skid-mounted reactor modules, complete with heat transfer systems, sampling arrangements, transfer pumps, and so on which can be built in isolation from the building fabric. This typically enables the time to plant start-up to be reduced, compared to conventional stick build. This approach is still not widely used in the API industry, but attracts growing interest.

Two-piece vessels are used for smaller scale operations, such as kilo scale and pilot plant operations, where personnel entry is impractical. It is now common for reactor bodies to be installed on hydraulic lifting mechanisms so they can be lowered for cleaning without disturbing the reactor top works.

Limitations

The above paragraphs have demonstrated both the flexibility of GLMS reactors and recent developments that have im-

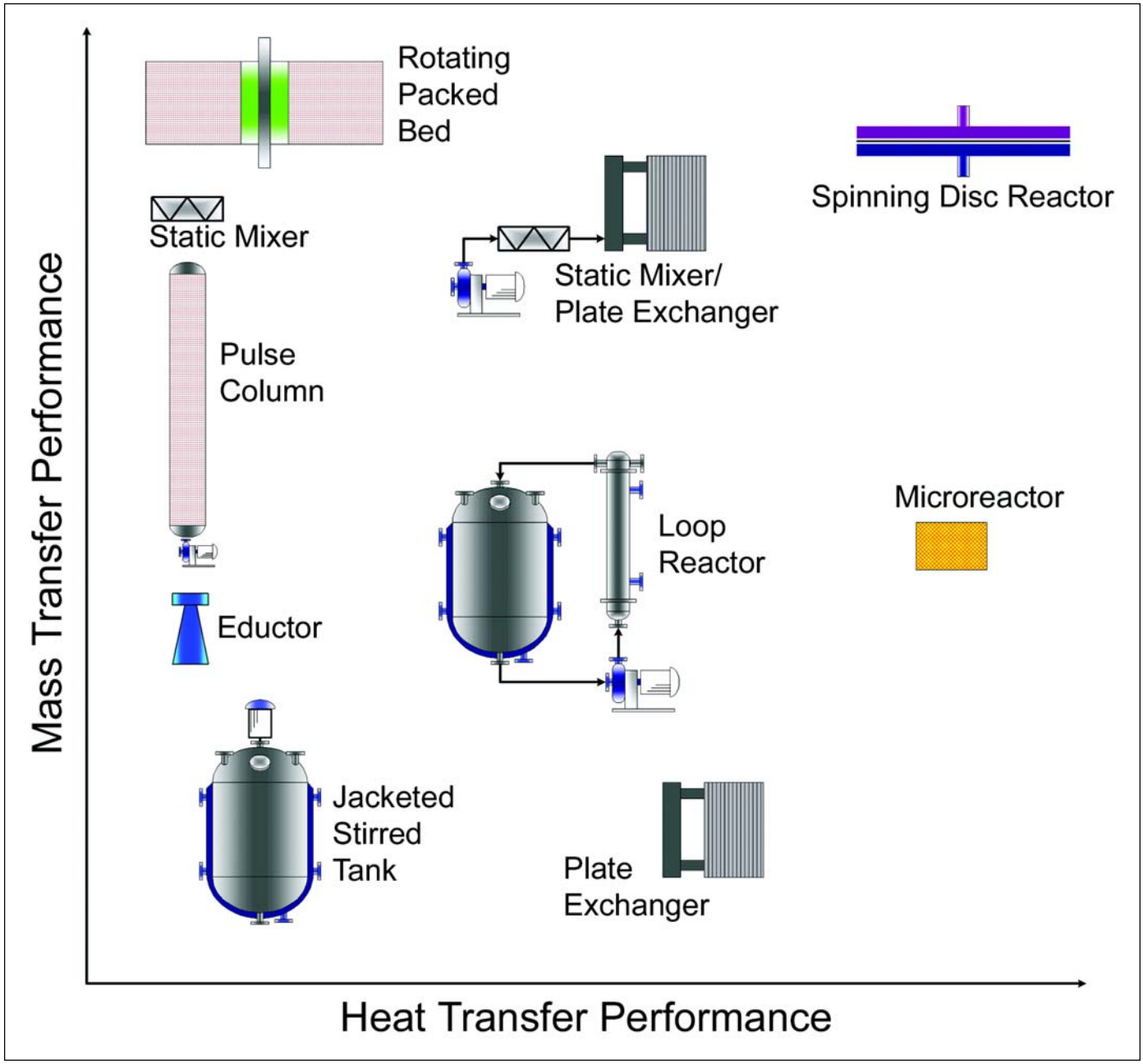

Figure 2. Reactor Technology Comparison. The conventional glass-lined steel reactor has poor performance when compared to alternatives, but it continues to enjoy a predominant role in API manufacture. (Source: Britest)

proved their performance and operability in API campaigns. However, this approach has its limitations, as can be seen from the following factors – apart from the first point, these factors apply equally to CSTRs of any material used for batch campaign manufacture, and are not specific to GLMS construction:

- GLMS offers significant resistance to chemical attack, but has a restricted temperature range that makes it unsuitable for some reactions. Glass is not a good conductor of heat, and retreat curve impellers are less effective than turbine or other metallic types so the heat transfer coefficients of GLMS reactors are less than steel reactors of a similar design.
- Stirred tank reactors offer considerable operating flexibility, but also relatively poor operating performance when compared to many other reactor designs. They deliver low heat and mass transfer results and poor control over conditions in the body of the vessel.
- Campaign operation makes good use of equipment flexibility and enables a degree of equipment customization appropriate to each stage. However, it results in a low velocity of material through the manufacturing supply chain and high volumes of work-in-progress.

These factors combine to deliver a performance that is typically low in both technical and commercial terms by the

standards of other industries. It is common for a multi-stage API synthesis to take some 200 to 250 days from raw materials to bulk product. Processing times are longer than could be achieved with different technology. The actual value-added time for each batch – for example, when process material is being reacted or converted to a required physical form — is often less than 10% and the work in progress valued at many millions of dollars/Euros. The cost of servicing this work in progress could not be tolerated in an industry like fast-moving consumer goods where margins are much lower.

At the same time, a lengthy campaign of batches means that output targets are generally set many months before product is sold. The nature of the pharmaceutical industry is such that these forecasts are generally incorrect – yet the manufacturing strategy presents few opportunities for correction.

These factors combine to demonstrate the limitations of GLMS reactors and prompt the search for better solutions. The following sections discuss what those solutions might be.

The Quest for the "Perfect" Reactor

In an ideal world, API manufacturers would be able to use reactors that delivered the following benefits:

- suitable for a wide range of operating parameters and able to handle materials in various physical forms
- able to deliver high yields of material of high purity
- flexible in operating scale, readily able to increase or decrease output
- short cycle time from raw materials to end product with minimal work-in-progress
- resistant to chemical or physical attack
- fully validatable and able to meet all regulatory requirements
- incurring acceptable capital and operating costs
- suitable for operation both near to the NCE discovery and development centers and in the tax favorable locations identified above.

The discussion above demonstrates that GLMS stirred tanks deliver only a few of these benefits, but at the same time, few API manufacturers have made significant strides to introduce alternative technologies. In the following section, we describe some advances that have been made, summarize the benefits they offer, and discuss some of their limitations and potential future developments.

Alternative Reactor Technologies

In this section, we describe three alternative approaches to GLMS stirred tank reactors. None of these examples represents a universal substitute for the stirred tank reactor; instead they are alternative strategies that offer specific benefits that may be applicable in certain circumstances. They are options from which API manufacturers may choose to meet particular objectives.

Technologies for Processing Chiral Compounds

The principle of molecular chirality has been known since the 19th century. The structure of such molecules means that there are two alternative structures at the chiral center although the stoichiometric formula is the same. The structures (enantiomers) are mirror images of each other and consequently have different physical and chemical properties. The recognition that this feature also affects the biological activity of such molecules is much more recent and has led to the systematic investigation of the properties of enantiomers in the discovery and development phases and is a critical facet of product registration. Single enantiomer products are now routinely developed to maximize the therapeutic benefits of the molecule and in some cases to extend the patent life of products originally registered as racemic mixtures.[5]

Chiral molecules can be produced in a variety of ways. For some products, a selective synthesis route is developed which leads to the formation of one enantiomer to the exclusion of the other. In other cases, a similar effect is achieved through the use of a selective catalyst or specific crystallization conditions. However, racemic mixtures are increasingly separated by large-scale chromatography, and the Simulated Moving Bed (SMB) technology is an example of this that has been introduced on a commercial scale.[6]

SMB is continuous counter-current chromatography centered on a series of packed columns to which the racemic mixture and an eluent are continuously fed. The column packing is chosen so that one enantiomer is selectively absorbed, while the other enantiomer moves through the column. Recycle streams are fed counter current to the feed and eluent streams in subsequent columns under a strategy derived from computer modeling to maximize the yield and purity of the final product.

This technique is of growing interest in the API industry. The Danish company, Lundbeck, has installed an SMB at its UK subsidiary at Seal Sands for the isolation of the required enantiomer of the drug Citalopram and the US contract manufacturer Aerojet Fine Chemicals has a unit in Sacramento. Other companies reported to be using SMB technology include Bayer (Germany), AstraZeneca (UK), Daicel (Japan), Finorga (France), GlaxoSmithKline (US), Honeywell Speciality Chemicals (Ireland), Novasep (France), and UPTI/Pharm-Eco (US).

Process Intensification

The flexibility of the stirred tank reactor has been noted, but it has many limitations. In particular, such reactors deliver relatively poor heat and mass transfer performance, and have high material hold-up times, leading to variability in the conditions experienced by each part of the reaction mix-

tures, and safety concerns when potentially hazardous materials are handled. Instead, there are a series of options loosely described as Process Intensification which offer potential improvements. The UK's not-for-profit Britest consortium[7] encourages those who develop processes to clarify the driving forces that shape their particular requirements and to select from a range of techniques that may be appropriate for their specific application. Figure 2, taken from the Britest Web site, illustrates the comparative heat and mass transfer performance of various alternative reactors. This is a qualitative assessment of the relative advantages offered by different forms of reactor. One of its main values is to prompt engineers and chemists to consider the competing merits of various reactors and to assess them in more detail against the driving forces in their particular situation.

From this, it is readily seen that the stirred tank delivers the worst mass and heat transfer performance. The heat transfer performance can be improved by using an external heat exchanger in a pumped loop, while mass transfer would be improved by installing a static mixer or similar device in this position.

A system that is attracting considerable attention is the microreactor, where reagents are brought into contact through narrow channels, thereby promoting intensive mixing and a high rate of heat transfer through the walls, and the ratio of surface area to material volume is increased over larger scale applications. This approaches plug-flow conditions and the residence time can be varied considerably. Material hold-up is small which considerably reduces the safety concerns faced in larger-scale equipment. The reactor could be run continuously, allowing a relatively low throughput to produce the modest annual tonnages currently produced through a series of batch reactions.

A German company, CPC,[8] has developed such a system which has been tested by at least one major pharmaceutical company. The initial results are reported to be promising with yield and purity at least comparable to those produced through other techniques. The major problems reported are blockage of the small channels by solid products and by-products, and stainless steel construction which inhibits the use of halogenated and other potentially corrosive materials.

If these problems are overcome and results continue to be promising, this technology offers a new approach for the future. Reactors like this could be used in early stage development to manufacture trial material. As the demand increases and the product is launched at commercial scale, then the equipment would be duplicated at relatively low cost, rather than scaled up, as would be the case for more conventional technology. This approach is explored further when we consider the future shape of API supply chains below.

Supercritical Fluids[9]

Supercritical fluids are materials held above their critical temperature and pressure, but below the pressure at which a solid is formed. In this state, some materials have properties that can deliver chemical and physical performance which far exceed that which can be obtained by fluids below the critical points. This phenomenon has been known since the 19th century, and commercial chemical syntheses – such as BASF's processes for ammonia (1913) and methanol (1923) – were carried out under supercritical conditions.

Supercritical fluids also have novel solvent properties – and this is of particular interest for API synthesis. Work by the team of Prof. Martyn Poliakoff at the University of Nottingham and by Thomas Swan Ltd in Consett, County Durham, UK has shown that the use of carbon dioxide in its supercritical state can lead to improved yields and purity[10] in reactions such as hydrogenation and Friedel-Crafts alkylation.

Thomas Swan has now built a multi-purpose, continuous supercritical fluid plant for contract manufacture in the fine chemicals and related industry. This plant has not been designed for cGMP operation, but there is no fundamental reason why such techniques should not be used for API manufacture.

A Glimpse of the Future

What might the future of API manufacture look like? What technology will be used? Who will own this technology? How will it be operated? What will be the effects?

Whatever else happens, we can expect that the initial rate of any change will be slow. Pharmaceutical companies have invested heavily in registered processes based on GLMS reactors which have historically delivered material – albeit inefficiently – and have facilities to deliver such products. In times of cost constraint and production over-capacity, there is little incentive to invest significantly in new equipment or to develop and re-register new processes at significant cost and potential risk to supply.

We may see more change in the medium term since all the major pharmaceutical companies are reviewing the new technologies and testing reactors that may offer benefits. The ideal time to introduce such equipment is when the synthetic route and processes are selected for manufacturing trial quantities and eventual scale-up to commercial production. This starts before the clinical trials phase – and thus, occurs several years before the product is launched at full-scale.

Who will own the reaction technologies? The manufacturing supply chains of large pharmaceutical companies have evolved over many years. Originally, each API production site was focused on production for the local region and needed the flexibility provided by GLMS stirred tanks to manufacture a wide range of products. More recently, we have seen the largest companies develop global networks, where each site has a specific technical and regional or global role. At the same time, outsourcing has become increasingly popular in many areas of pharmaceutical business, including manufacturing and supply. Thus, one model of the future would be that the API manufacturing organization could selectively use a range of custom manufacturers, each specializing in a particular technology to complement its own flexible stirred tank facilities.

Alternatively, pharmaceutical companies may decide to keep the reaction technology in house, which would benefit

their early activities in process development. In this scenario, API facilities will need to look different to the current style. They will need to be flexible, enable different types of equipment to be installed, and provide segregated areas of various sizes, shapes, and levels of containment. The Flexilab concept, which has proved beneficial in many discovery applications, may be a suitable model here.[11]

As the genome project and related scientific advances yield insights into the pharmacological activity of pharmaceuticals, we may see additional requirements being placed on API manufacturers. Products may be demanded with varying chemical and physical specifications to meet the specific needs of individual patients. In such an event, API manufacturers may chose to run a series of low capacity reaction systems under varying operating conditions to deliver the range of properties required.

Conclusions

The various changes, both in chemistry and to the commercial drivers faced by API manufacturers, have influenced the development of reaction technology. To some extent, the challenges can be met by conventional stirred tank reactors, and the technical advances made by the suppliers of such equipment have improved their effectiveness.

This article shows the potential benefits which alternative techniques could realize in some circumstances, including:

- Greater yields and better quality – for example, the improvements reported by the use of SCF in one hydrogenation where yield and selectivity were both raised to 100% from about 80% when using conventional technology.

- Savings in time – the use of microreactors could potentially enable final product material to be produced in hours, compared to a traditional campaign-based supply chain, taking many months to convert raw materials to final products.

- More effective products – such as single enantiomer chiral molecules and other products which can only be achieved through precisely controlled temperatures or reactant gradients.

We also have explored the wider business environment in which APIs are produced that will affect the rate at which such technologies may be adopted.

Other specific API plant design features will be discussed in future articles, emphasizing practical solutions and design procedures. We hope to hear from you, to learn your viewpoints and field your questions.

Sidebar

The authors are developing articles that have in-depth information about reactor systems, heat transfer, material transfer, ancillary systems, and safety. Readers are asked to submit their anecdotes and opinions on these topics directly to the authors, by e-mail or telephone (see biographies for contact details).

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9. Much of the material on supercritical fluids is taken from the Web sites of the UK's University of Nottingham Department of Chemistry (www.nottingham.ac.uk) and Thomas Swan Ltd. (www.thomas-swan.co.uk) and from personal communication with Dai Hayward, Director and General Manager of Thomas Swan.

10. For example, Thomas Swan report that conventional catalytic hydrogenation of 3-ethylcyclohexene gives no better that a 4:1 mixture of the desired product and a by-product with only 80% conversion. Using supercritical carbon dioxide as a solvent leads to a 100% yield and 100% selectivity.

11. The Flexilab concept was presented in the 2002 Annual Meeting of ISPE by a team representing AMEC, GlaxoSmithKline, and AstraZeneca.

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Poly(Ethylene Glycol)-Modified Gelatin Nanoparticles for Intracellular Delivery

by Goldie Kaul, Carolyn Lee-Parsons, and Mansoor Amiji

This article examines the cytotoxicity, cellular uptake and trafficking, and expression efficiency of enhanced green-fluorescent protein (GFP) plasmid encapsulated in PEGylated gelatin nanoparticles.

This article was the winning graduate poster in the Student Poster of the Year Contest held at the 2002 ISPE Annual Meeting in Orlando.

Introduction

Intracellular gene delivery involves changing the expression of genes in order to prevent, cure, or treat a disorder/disease. Therefore, this treatment method alters the expression of a gene and corrects a defective gene that may be the cause of a disease or a disorder. Current research on intracellular gene delivery is limited to somatic cells and not germ line alteration approaches.[1-3]

Non-viral vectors for gene therapy, although less efficient than the viral vectors, have inherent advantages of safety and flexibility. Serious issues of integration with the host genome to permanently alter its genetic structure, self-replication capability, recombination potential, and the possibility of complement activation (immunogenecity) of the otherwise transfection efficient viral vectors limit their use for gene delivery. Viral vectors also may be inefficient in the amount of genetic information they can carry, and in certain cases, are unable to bypass the immune defense mechanism of the host. They also are relatively expensive to manufacture. In the last decade, the focus of development has been on non-viral gene delivery systems.[4-7] Specific virus-like characteristics that must be included in non-viral vectors include small size and stability against aggregation in blood, serum or extracellular fluid, the ability to be efficiently internalized by the target cells, and the ability to disassemble and release the payload into the cell nucleus once internalized. Numerous attempts have been made to design non-viral vectors that could achieve gene expression and specificity attained by viral vectors, allow greater flexibility in the amount of the genetic information they can carry, evade the immune system, and be safe. The design of an optimal synthetic gene carrier is still the limiting factor for non-viral gene therapy. In order to be effective, non-viral vectors must display many of the characteristics as their viral counterparts; such as, particle stability, efficient cell targeting, and at the same time, find ways to elude some of the untoward effects of viral therapy like opsonization and acquired immunity against the vector components.[8] Some of the non-viral vectors employed in gene therapy include cationic lipids and polymer based systems.[9-16]

Of relevance to us is the efficient delivery of genetic constructs to solid tumors.[17] As shown in Figure 1, we propose that nanoparticles can be targeted to solid tumors either by passive or active mechanisms. Due to the porosity of the

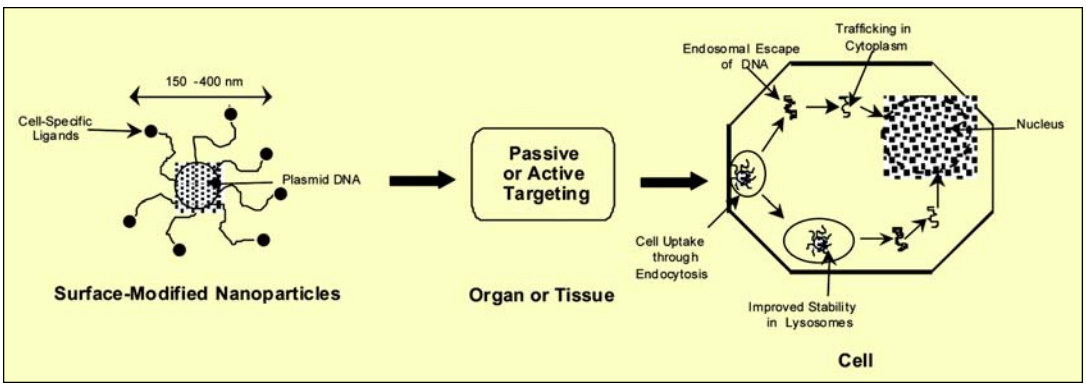

Figure 1. Schematic illustration of the proposed concept of intracellular delivery by passive or active targeting using biodegradable polymeric nanoparticles.

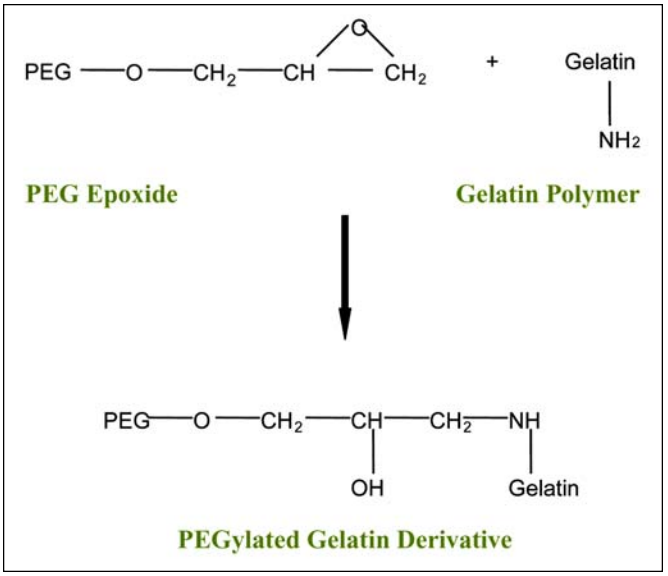

Figure 2. Chemical reaction for the synthesis of poly(ethylene glycol)-modified (PEGylated) gelatin.

tumor vasculature and the lack of lymphatic drainage, blood-borne macromolecules and colloidal particles are preferentially distributed in the tumor due to the *Enhanced Permeability and Retention* (EPR) effect. Maeda's group first described the EPR effect of tumor vasculature which has subsequently been examined and confirmed by other investigators.[18] The enhanced vascular permeability of the tumor, developed through secretion of vascular permeability factors such as bradykinin, VEGF, and nitric oxide, allows for preferential uptake of the hydrophilic macromolecules and colloidal particles into the tumor mass. The tumor permeability of macromolecules is 10 to 100 times higher than normal blood vessels.[19] Jain and co-workers[20] have found that the effective pore size of most peripheral human tumors range from 200 nm to 600 nm in diameter with a mean of about 400 nm. Therefore, nanoparticles with diameter of less than 400 nm would be retained by the blood vessels around the tumor. Additionally, colloidal particles with a positive surface charge are taken preferentially in the tumor and retained for a longer duration as compared to negatively charged or neutral particles.[21-22] Surface modification with poly(ethylene glycol) (PEG) also has been found to increase the circulation time by its property of evading the mononuclear phagocytic system.

Active targeting employs the use of targeting moieties to achieve preferential localization of the delivery system to the region of interest based on specific recognition elements. These systems may include ligand mediated gene delivery. Protein ligands can be coupled to poly(L-lysine) and then incorporated into a ligand-DNA complex by ionic interactions between the poly(L-lysine) and DNA.[23] The ligand may alternatively be coupled to intercalating agents including bis-acridine or ethidium dimers and complexed with DNA.[24] These complexes retain their ability to interact specifically with receptors on the target cell leading to more efficient internalization of the complex in the cell. Transfection studies with transferrin-poly(L-lysine)-DNA complexes have been performed in hematopoietic and pulmonary epithelium cells.[25] Gene transfer also has been done using tris-galactosyl compounds and folate-poly(L-lysine)-DNA complexes.[26] In reporter gene studies, asialoorosomucoid- poly(L-lysine)-DNA complexes have been shown to deliver genes directly to the liver *in vivo*.[27]

Encapsulation systems like polymeric nanoparticles are attractive carriers of DNA because of their versatility, ease of preparation, and protection of the encapsulated plasmid DNA. These carrier systems can efficiently encapsulate the DNA and protect it during transit in the systemic circulation. They also can be targeted to reach specific tissues and cells in the body and avoid uptake by the mononuclear phagocytic system after systemic administration through the use of cell-specific ligands and attachment of PEG chains on the nanoparticle surface. Nanoparticles usually have a high surface area to volume ratio, and thus, are able to efficiently encapsulate DNA even without a pre-condensing step. Nanoparticles also can be made to reach a target site by virtue of their size, charge, and other properties built into the polymeric system. Microspheres can be used to direct DNA to specific cells in the body such as for the delivery of DNA vaccines to professional antigen presenting cells like macrophages**.** Lastly, for industrial production, these systems are amenable to scale-up and manufacturing under the GMP guidelines. DNA-containing microspheres and nanoparticules have been prepared with natural polymers like gelatin,[29] chitosan,[30] and alginates[31] as well as synthetic polymers like poly(β-amino esters)[32] and PLGA.[33]

Experimental Methods

Preparation and Characterization of PEG-Gelatin

Synthesis and Characterization of PEG-Gelatin: Poly(ethylene glycol)-5000-monomethyl ether (PEG) (5.0 mMoles or 25 g), purchased from Fluka Chemika/Biochemika (Ronkonkoma, NY), was dissolved in 100 ml of dehydrated N,N-dimethyl formamide and 1.0% (w/v) triethanolamine mixture at 40°C. To the reaction mixture in a round bottom flask, 5 times molar excess of epichlorhydrin was added and refluxed for 12 hours. The PEG-epoxide formed was precipitated in ice cold diethyl ether and dried. To a known quantity of PEG-epoxide, dissolved Type-B (225 Bloom strength) gelatin was added and the reaction for grafting PEG-epoxide to the primary amine groups of basic amino acids proceeded for 14 hours at 40°C - *Figure 2.* The PEG-grafted gelatin derivative was precipitated in acetone to remove unreacted PEG-epoxide, dialyzed against deionized distilled water, and lyophilized. The conditions for preparation and PEG-epoxide and grafting to gelatin were optimized by systemically altering the different variables.

The percent of amine groups of gelatin that were modified with PEG were determined by reacting with 2,4,6-trinitrobenzenesulfonic acid (TNBS).[34] The procedure involves a trinitrophenylation reaction, followed by a quenching step, after which the amino content is related to the increase in absorbance at 420 nm. In our case, unmodified gelatin or PEGylated gelatin derivatives were dissolved in

pH 8.5 alkaline borate buffer to prepare 1.0 mg/ml solution. Ten-ml of the unmodified or PEGylated gelatin samples was mixed with 250 µl of 30 mM TNBS solution in methanol. After 30 minutes of reaction at room temperature, the absorbance of solution at 420 nm was measured and the percentage of amine groups of gelatin that were derivatized by PEG was calculated relative to that of unmodified gelatin. The percent of derivatized amine groups increased from 23.6% to 73.3% when the amount of PEG-epoxide was increased from 0.5 g per gram of gelatin to 2.0 g per gram of gelatin.

Preparation of Control and PEGylated Gelatin Nanoparticles

Both gelatin and PEGylated gelatin (30% PEGylation) nanoparticles were prepared by the solvent displacement method that involved controlled precipitation of either rhodamine-labeled dextran (Rho-Dex, Mol. wt. 70 kDa) or plasmid DNA containing gelatin or PEGylated gelatin solutions (pH 7.00) at 37°C. In the final mixture of 100 ml, the water to ethanol volume ratio was maintained at 35:65.The resulting nanoparticles were then crosslinked with 1 ml of 40% (w/v) glyoxal and centrifuged at 14,000 rpm for 90 minutes. The formed nanoparticles were washed twice with distilled water and freeze-dried.

Characterization of Nanoparticles

Particle Size Analysis: for each batch of the nanoparticle suspension, particle size analysis was performed to ensure reproducibility from batch to batch. The colloidal system of gelatin or PEGylated gelatin nanoparticles was analyzed for mean particle size and size distribution by a Coulter counter. A sample of the diluted (1:4) nanoparticle suspension in deionized distilled water was used for particle size analysis at a scattering angle of 90° and a temperature of 25°C using Beckman/Coulter N4® plus (Fullerton, CA) instrument.

Scanning Electron Microscopy (SEM): the freeze-dried gelatin or PEGylated gelatin nanoparticle sample was mounted on an aluminum sample mount and sputter coated with gold-palladium to minimize surface charging. The samples were then observed for surface morphology with an AMR-1000 (Amray Instruments, Bedford, MA) scanning electron microscope at an accelerating voltage of 10 kV.

Loading Studies: one-hundred milligrams of Rho-Dex or plasmid DNA containing gelatin or PEGylated gelatin nanoparticles were weighed into Eppendorf tubes and 1.5 ml of PBS or PBS containing protease (0.2 mg/ml) was added. At varying time intervals, the fluorescence intensity of Rho-Dex in the release medium was determined by Perkin-Elmer LS-50B (Norwalk, CT) fluorescence spectrophotometer. The cumulative amount and the percentage of Rho-Dex released over time were calculated from appropriate calibration curves. The amount of enhanced green fluorescent protein (EGFP-N1) plasmid DNA loaded was determined by the PicoGreen® (Molecular Probes, Eugene, OR) assay method by fluorescence detection at excitation wavelength of 480 nm and emission wavelength of 520 nm according to the manufacturer's instruction.

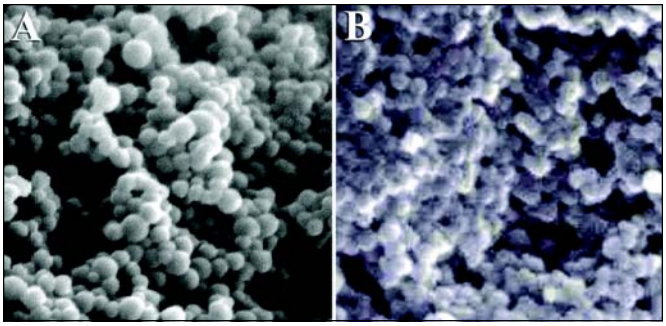

Figure 3. Scanning electron micrograph of gelatin (A) and poly (ethylene glycol)-modified gelatin. nanoparticles (B) prepared by the solvent displacement method. Original magnification was 13,000X.

Cellular Uptake, Trafficking, and Transfection Studies

BT-20 (Human breast tumor) and NIH-3T3 (mouse embryo fibroblast) cells were grown to 50-70% confluence in supplemented Eagle's MEM and Dulbecco's modified Eagle medium (DMEM) respectively in 6-well tissue culture plates on Corning's circular glass cover-slips at 37°C and 5% CO_2 atmosphere. A suspension of Rho-Dex or plasmid DNA containing gelatin or PEGylated nanoparticles was prepared at a concentration of 0.5 mg/ml Rho-Dex or 20 microgram plasmid DNA per well in the culture medium. After filtration, the nanoparticle suspension was incubated with the cells at 37°C for a period of 12 h. The media was then removed and the plates were washed thrice with sterile PBS. After the final wash, the cells were fixed with 4% (v/v) paraformaldehyde in PBS for 1.0 h at room temperature and were washed four times with PBS. Individual cover-slips were then mounted cell side up on clean glass slides with fluorescence-free glycerol based mounting medium (Fluoromount-G®, Southern Biotech Associates, Birmingham, AL). Both differential interference contrast (DIC) and fluorescence images were acquired with a Zeiss Axioplan-2® confocal microscope (Thornwood, NY). The images were digitized and processed with Adobe Photoshop® software.

Results and Discussion

Characterization of Nanoparticles

Particle Size Analysis: for both control and PEGylated gelatin

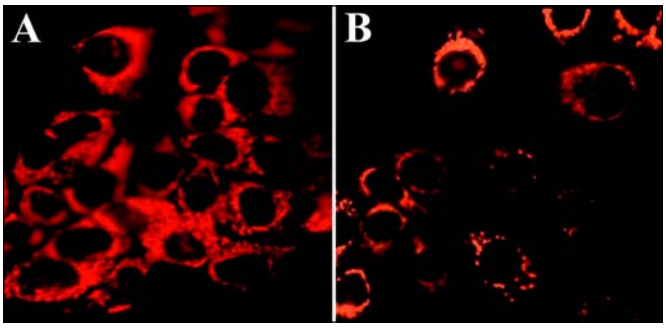

Figure 4. Fluorescence confocal images of rhodamine-dextran (Rho-Dex) (10 kDa)-containing gelatin (A) and poly(ethylene glycol)-modified gelatin (B) nanoparticles incubated with BT-20 human breast cancer cells. The nanoparticles were incubated with the cells in culture for 12 hours.

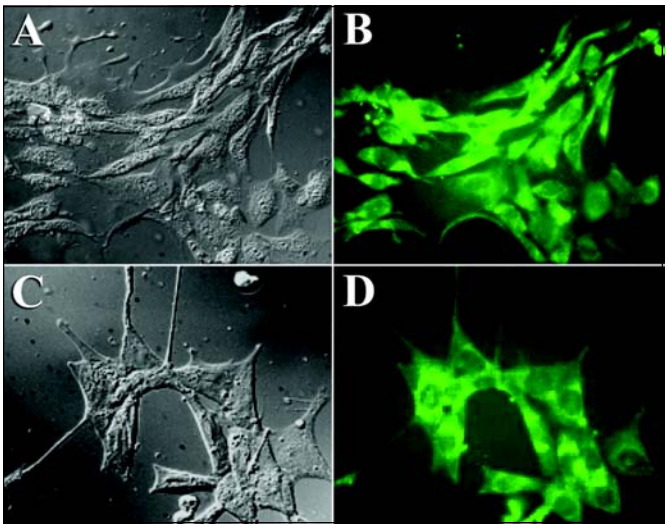

Figure 5. Differential interference contrast and fluorescence confocal images of green fluorescent protein expression in NIH-3T3 mouse fibroblast cells transfected with plasmid DNA complexed with Lipofectin® (A, B) or encapsulated in poly(ethylene glycol)-modified gelatin nanoparticles (C, D). The fluorescence confocal images were obtained at 40X magnification after 24 hours post-transfection.

nanoparticles, the mean particle size was around 300 nm and a range of 200-500 nm and with a narrow size distribution.

SEM Analysis: the SEM micrographs of the lyophilized control and PEGylated gelatin nanoparticle samples, shown in Figure 3, verified that the nanoparticles were smooth and with spherical shape. The SEM micrographs also indicated that high-speed centrifugation and freeze-drying did not affect the nanoparticle morphology. Based on the studies by Jain and co-workers[31], most peripheral human tumor vessels have a permeability cut-off of less than 600 nm. The gelatin and PEGylated gelatin nanoparticles, therefore, should provide an effective means of DNA delivery to solid tumors after intravenous or intratumoral administration of the formulation in future for *in vivo* studies.

Cellular Uptake and Trafficking Studies

The nanoparticles containing Rho-Dex were found to be localized mainly in the perinuclear region of the BT-20 cells after 12 hours of incubation. Also interesting to note here is that the cells remained viable during the course of this study, and as such, these nanoparticles do not confer any overt cytotoxicity. At initial time points, we observed the nanoparticles to be present mainly on the cells' surface with subsequent uptake though the vesicular transport system. Once the nanoparticles were endocytosed, they were able to escape the endosome and found primarily in the cytoplasm around the nuclear membrane. In the case of gelatin nanoparticles, the fluorescence confocal image (Figure 4A) shows that some of the fluorophore was released and stained the nucleus. PEGylated gelatin nanoparticles, on the other hand, remained intact as the fluorescence image (Figure 4B) shows discrete particles around the nucleus. When Rho-Dex was added to the cells in solution and incubated for 12 hours, the fluorescence was completely diffused throughout the cell. Kinetic analysis of GFP expression showed that the protein was expressed after 24 hours post-administration of the DNA-containing control and PEGylated gelatin nanoparticles (Figure 5). GFP expression also remained stable for up to 96 hours.

Conclusions

In the present study, we have prepared PEG-modified gelatin nanoparticles as long-circulating intracellular delivery system. The control gelatin and PEGylated gelatin nanoparticles, prepared by the solvent displacement technique, had a mean particle size of 300 nm and could efficiently encapsulate hydrophilic macromolecules including plasmid DNA. Cellular uptake and trafficking studies showed that the nanoparticles were internalized by tumor cells and were found near the nucleus after 12 hours. The PEGylated gelatin nanoparticles were also very efficient in expressing GFP. The results proved that this system could be used for intracellular delivery of hydrophilic macromolecules such as DNA.

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