Bob Ruffolo discusses the rhythm of drug development

Interview by Katharine E. Barnes

Bob Ruffolo, President, Research & Development, Wyeth Pharmaceuticals

Since 2002, Robert Ruffolo has been President, Research & Development, Wyeth Pharmaceuticals, and Senior Vice President of Wyeth (http://www.wyeth.com). Following his postdoctoral fellowship at the National Heart, Lung and Blood Institute, he has worked in the pharmaceutical industry, initially spending 6 years at Lilly and then 16 years at SmithKline Beecham. He joined Wyeth in 2000 as Executive Vice President, Pharmaceutical R&D. Also an Adjunct Professor in the College of Pharmacy at Ohio State University, Bob has published nearly 500 full-length papers and has received many awards more commonly presented to academics, such as the John Jacob Abel award from the American Society of Pharmacology and Experimental Therapeutics (ASPET) in 1998.

Is there a project that you have been most proud of and why?

The highlight of my scientific career was the work I did on carvedilol (Coreg, Kredex) while I was at SmithKline Beecham (SKB). We started working on it in 1985 and found it had a lot of activities: as a beta-blocker, an alpha-blocker and anti-oxidant. When we identified the anti-oxidant activity, we realized that this was effecting intracellular redox reactions and turning off a number of transcription factors and also gene expression, in particular genes responsible for cardiac remodelling and apoptosis. We proposed that the drug be used for congestive heart failure, which was heresy at the time because the drug was a beta-blocker, and these were contraindicated. After many years and a lot of effort we worked out many of the effects of the drug, from the animal down to the cellular and gene level. We were able to make a strong case that this drug, even though it belonged to a class that was contraindicated, could be a drug that might have effects in heart failure.

In the 1990s we began the heart failure studies. There was a lot of trepidation about this and some people seriously doubted the potential of the drug. We initiated Phase I and II studies and it looked like patient's heart failure was not progressing so badly. So we launched the largest Phase III heart failure trial ever to be conducted, which was quite brave for SKB to do given that this class of drug was contraindicated for heart failure.

I'll never forget one day during the Phase III trial. My boss, George Poste, who was President of R&D at SKB, called me and said, 'Bob, the Data Safety Monitoring Board (DSMB) have stopped the study'. I said out loud 'the drug killed people, and it's my fault'. But it turned out that the trial was terminated early because of a dramatic, 65% reduction in death, and it was unethical in the view of the DSMB to retain the placebo arm. In February 1995 it went to the FDA and the drug wasn't approved because they couldn't believe the results: they thought the results were 'too good to be true', in the words of an FDA official. Fortunately, we had other studies in Australia and New Zealand and the results confirmed what we had found in the US trials, so the drug was eventually approved. Now it's done well commercially but, more importantly, for patients it is considered the standard of care.

In any of your drug discovery posts, if there is one thing you would have done differently, what would it have been?

I have made some significant mistakes in my career. The objective is to learn from those mistakes and not to make them again. When I was working at Lilly in the late 1970s, we discovered a drug that was a novel anti-hypertensive. As project team leader developing this drug I, like many scientists, got married to this drug and I lost my objectivity. The drug ran into a big problem early on related to mutagencity, which really is a death sentence for most drugs, especially if it occurs *in vivo*, as was the case. But I kept pushing and pushing, one of my strengths, but also one of my weaknesses. It should have been stopped and there were people who wanted to stop it. Because of my lack of objectivity, I ended up wasting nearly 2 million dollars – and that is in 1980s dollars.

But I learnt a couple of things. One, I – like many scientists – can get so involved with research that I lose my objectivity and I swore I would never ever let that happen again. Nor would I allow scientists that work for me to ignore their objectivity and not be able to see the data for what it is. Two, I was devastated when that drug failed because it was my life at that time. I thought about that drug almost 24 hours a day. All the work I did was on that drug and when that drug died I was absolutely devastated. I swore that no scientist who worked for me would ever work on just one project because in our business almost everything we do fails. I thought that it would be much better for a scientist to work on three, four or five different research projects, so that when one dies, you've still got the others, and it's only one piece of your life that ends. It's easier to mourn a smaller piece than mourn everything you are doing.

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If you hadn't discovered the attraction of pharmacy and pharmacology, what other career path might you have chosen?

When I became a Vice President at SmithKline Beecham, they set me up with an executive coach. I still have an executive coach, 15 years later, because nobody has all the answers and no matter what stage in your career you get to, you have a lot to learn. The executive coach did a psychological profile on me, to see whether I was matched to the right job. My profile indicated that I would be suitable for an executive position in a large

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industrial company; the job I had. But it also showed other things for somebody with my background and my particular traits, and one job was an officer in the military, and I could see that.

But what I would really like to do, and this is going to sound funny but it is true, is be a rock star. I love rock music and have the taste in music of a fourteen-year-old boy, so about 7 years ago I decided I'd really like to play the guitar. I play in a band and in September we plan to play in public for the first time. I'm not telling anyone where though!

In the past you have suggested setting objectives for each stage of drug development. How well are these objectives being met and have any unexpected challenges arisen?

Three and a half years ago when I got to Wyeth, we decided to have a major overhaul of R&D and we set objectives and metrics for improving R&D productivity. Typically, scientists don't like this; they don't like to be held accountable, or to be managed. We set objectives for drugs to be discovered, INDs to be filed and Phase III studies to be started. When we set the objectives, we had to tear apart R&D. We started with discovery, tearing it apart, and putting it back together with governing systems, standards, processes and measurements. Then we moved to the preclinical development functions, then Phase I and finally, last year, we tore apart all of clinical research and put it back together.

We actually did pretty well. We have had a 400% increase in the number of drugs coming out of discovery and entering development compared to the previous 10 year average. The standards also went up, because our success rates getting to INDs went up. Our output from the preclinical development functions went up 600%. Our throughput through Phase I went up over 1000%. The number of drugs in Phase II and III trials went up threefold.

Things are working more efficiently now. All the changes we make we call Breakthrough Projects because we are not looking for minor improvements or incremental changes, but quantum leaps. And we've run about 40 of these Breakthrough Projects now. Part of the change we made was to link our scientists bonus level to performance against a pre-specified and pre-agreed set of objectives and metrics, linking a portion of their compensation to the performance of R&D. Our scientists know what they need to do, and have risen to the occasion and dramatically enhanced their performance. As a result, their bonus level was increased the first year we put this plan in place. I'm so proud of the group.

So, the initial outlay of cost to make the changes was definitely worthwhile?

Yes, although we didn't get extra money to make the changes, we had to find it. The first thing many scientists like to do with any problem, and I put myself in the same category here, is to say 'give us more money and we can fix it'. But there wasn't more money so we had to use the money we had much more efficiently.

We did work with a number of consultants. Accenture clearly had the greatest impact on us, and they have been with us from the beginning. Accenture didn't fix our problems, we fixed them, but they were there to facilitate that whole process, to hold our toes to the fire. They made us do what we said we would do, and were very good at this. We still work closely with Accenture, in fact, we have set up a new way to manage clinical data by outsourcing it to Accenture. We call it ACE (Alliance for Clinical Excellence). Other industries outsource data management and we simply copied what they did, and our cycle times and clinical data management costs have come down as a result. Our quality, which was already pretty good at Wyeth, has even gone higher. The numbers that Accenture has generated are, we believe, industry leading in terms of quality. We took a big risk but it is working out very well. I want Wyeth to be the first company in the industry to do new things. So we look around at other industries to see what they do better than the pharmaceutical industry and are not embarrassed to take their ideas and be first to do it in our industry.

Do you think that the current enthusiasm for new technologies (e.g. combinatorial chemistry and HTS) is leading to the loss of valuable features of the 'old fashioned' structure–function approach?

The new platform technologies, such as genomics, combinatorial chemistry, HTS, bioinformatics, functional genomics, and so on, are crucial technologies. We need them now that we have access to the whole genome to look for new drug targets. So it is an important feature of what we do in the early stages of discovery. The later stages of discovery, which is where systems biology and the more standard *in vitro* and *in vivo* kinds of tests occur, get a little bit less attention now but they are still every bit as important as they used to be. Maybe even more important as we are discovering more novel molecular targets than we could even think about years ago. Any drug that comes from the new exciting technologies still can't make it to the clinic or to the market without the more traditional disciplines; biochemistry, pharmacology, physiology and so on.

It can be tough to find people who have backgrounds in those areas because perhaps NIH funding isn't there at universities to support them as it used to be. But the traditional disciplines are every bit as important. New technologies have changed how we've done things, but have also created new bottlenecks. Before these new platform technologies, people like me used to lie awake at night worrying where the next new molecular target would come from. Now we lay awake at night thinking 'my goodness, we've got an avalanche of new molecular targets, how are we going to pick out which ones we work on and which ones we don't?' It's been a change in how we operate, but I'm not one of those people who refers to these new technologies as a 'technology wasteland'. Some people believe that there has been an over investment and over-hype, and I do agree it has been hyped too much, but the fact is I can see they are important technologies. I think people are disappointed because they expected them to lead to new drugs instantly. But they couldn't have; certainly not in the unrealistic timeframe that people had expected.

I was fortunate that when I was at SKB the company made the first leap into genomics, and I was involved in that because the head of R&D at that point, George Poste, was a real visionary. It created a lot of stir in the industry.

You have been quite sceptical about personalized medicine in the past. So do you think pharmaceutical companies will be able to recoup their investment?

At Wyeth we define personalized medicine as translational medicine, experimental medicine, pharmacogenetics, or genomic profiling. These technologies may enable us to predict who should take our drugs,

who shouldn't take our drugs, who is going to respond to our drugs, who should be in our clinical trials and who shouldn't be in our clinical trials. I view this area as an experiment that still has to be done. I don't think we are going to have it in 5 years, not on a large scale. Maybe in 20 years we will. It's the timeframe that I've been sceptical about in the past more than the actual technology and whether or not it will occur.

I've also been sceptical about how we as an industry, and regulators, are going to deal with it. If we make drugs for smaller and smaller populations how do we do the clinical trials? If the FDA still wants a certain number of patients for safety reasons, it could actually paralyze us. There are a lot of things that need to be sorted out and at Wyeth we are heavily involved in this area. We are working with the FDA to deal with some of these issues because if it is going to become the norm, I want Wyeth to be there first. We're making an appropriate investment, not a huge investment, but one that is appropriate for the degree of risk and the time frame we are talking about.

What I have been really sceptical about is gene therapy. I remember somebody telling me in 1989 that I shouldn't bother developing drugs for restinosis after an angioplasty because 'gene therapy was right around the corner'. Now, 15 years later, gene therapy is nowhere near round the corner. In fact, many gene therapy programmes have been stopped or halted because of safety concerns. I am not optimistic that we will see gene therapy in a reasonable time frame. We might see it in 20 or 30 years, but I still don't think we will see it on a large scale.

You have said in the past that 'there's no fun in merging', so do you think the mergers have been worth it?

Companies don't merge for fun. They merge in my opinion because one or both companies are in trouble. Maybe not right at that present time but they see it coming. They can't sustain the high levels of growth in earnings that are needed to keep shareholders interested in our very risky business. I think there have been very good mergers. One of the ones that I lived through, between SmithKline and Beecham, I thought was a wonderful merger. Some others haven't gone as well.

One analysis of the pharmaceutical industry showed that 75% of the mergers that occurred over the last 20 years have not delivered the savings and synergies that were expected at the outset. I don't think this means they didn't work, I think the synergies that people expected to find were probably unrealistic. Mergers are hard and they are disruptive. Typically you see a 3-year paralysis in R&D following a merger, especially if its not done right, and I suspect they disrupt other parts of the company as well. You can't bring two large companies together and make an even bigger company and not have some disruption. Often people don't understand how risky this business is, but if you look back at all the mergers that have occurred you understand that you don't do them for fun, you do them because you need to. You can see the kind of pressure that pharmaceutical companies have been under to deliver returns to the shareholders.

Do you think there are good alternatives to mergers?

Companies merge because they can't sustain growth, usually because R&D couldn't deliver the products to sustain the required growth. The best way to avoid having to merge would be to have a more productive R&D group that would provide enough new molecules to the market of sufficient scale to keep earnings at an acceptable level. I believe mergers occur because R&D groups fail and this is one of the reasons we are focusing obsessively on productivity in R&D.

All of the productivity increases I've mentioned derive from our objective to deliver two new drugs per year, every year, to the market. Based on this bottom-line objective, you can establish everything that needs to be done to reach it. Our model, based on accepted industry success rates, predict that we will reach our objective of launching two drugs per year in a timeframe of 2–3 years.

Do you have any strategy at Wyeth for developing drugs for neglected disease?

We have quite a few products on the market that are 'orphan drugs'. I even worry sometimes that we may have too many because you can't survive just by developing drugs for orphan diseases. But it is one of the obligations that we have in the pharmaceutical industry, so we at Wyeth, and most other large companies as well, do develop orphan drugs when we have the ability to do so. For example, we have a cancer drug called Mylotarg, which was the first antibody targeted cytotoxic agent to reach the market. This drug is for relapsed acute myelogenous leukemia. We made an antibody to CD33, which is an antigen found on white blood cells in these patients, and we linked that to a very powerful cytotoxic agent called calicheamicin. The chemistry linking the antibody and cytotoxic agent was extremely complicated, and last year Wyeth won the PhRMA Discoverers Award for this achievement. Mylotarg is not a big income producer, but people with acute myelogenous leukaemia are lucky to have it.

Right now we are developing one of our drugs, moxidectin, with the WHO. We are developing this drug for Africa, to prevent river blindness. We do have products in some parts of the world that really are not profitable at all, but we keep them available because people need them.

I don't think our industry gets enough credit for the work that we do for orphan indications. It typically goes unnoticed, but if you look at the number of drugs on the market that are for orphan indications from large pharmaceutical companies, including Wyeth, you would be impressed. I believe that we are actually a highly socially responsible industry, and that is the story we probably should talk about more.

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How do you think that drug development and clinical trials can be best achieved in developing countries?

Clinical trials are extremely expensive, lengthy and difficult to do, and patient enrolment is critical. Doing them in developing countries poses some potential benefits, but also some obstacles. The benefits would include better recruitment for clinical trials with a source of patients that are not available elsewhere, or increasingly difficult to identify. The downside is that you need a very sophisticated health care infrastructure to do clinical trials, which may not exist in developing countries.

Another question is: Do you recruit patients in a country that will never be able

to afford the drug? I don't have the answer but the question is high on our agenda as we start to look at other parts of the world where we want to do clinical trials.

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Do you think that more global clinical trials will be the way of the future?
It's already starting to be the case now at Wyeth, and I think it's the case in most large pharmaceutical companies. One of my pet issues is the negative impact that regulatory agencies are having on global clinical trials, and the lack of harmonization between these regulatory agencies. This causes us to do different clinical trials in the USA, Europe and Japan, and this is inefficient and wasteful of our limited resources. Lack of harmonization among regulatory agencies is in large part responsible for the increase in time and money it takes to get a new product to the market, and is one of the reasons why R&D productivity has gone down in the industry.

What makes this issue so frustrating for us in the pharmaceutical industry is the fact that this lack of harmonization between the USA, EU and Japanese regulatory agencies has occurred despite all of these agencies having agreed to harmonize by signing on to the ICH (International Conference for Harmonization). In my opinion, the ICH has largely been a failure. Regulatory agencies are describing it as a success but people like me, who are responsible for large R&D groups, we don't see it that way. For example, the USA insists on placebo-controlled clinical trials, and they don't want a comparative trial. In contrast, Europe wants a comparative trial, and they won't accept a placebo-controlled trial, so that means we've got to do both. And then Japan insists that we repeat our trials in Japanese patients, because they often don't allow us to use western data in our registration dossiers. In an era of modern medicine, it is incomprehensible that we don't yet have one standard. This lack of harmonization is incredibly inefficient and wasteful and, unfortunately, the pharmaceutical industry has to pay the price.

Wherever possible, we try to do global studies that include the USA and Europe, and increasingly Japan. Going forward, the regulatory agencies could help us a great deal by getting their act together and doing what they said they were going to do when they signed on to the ICH. That is to develop one single set of standards through the world, rather than have separate standards in the USA, Europe and Japan.

You have said that the pharma industry needs people with broad training. Do you think the current educational system is best set up to provide suitable people?
I am not seeing as many people as I would like with the broad training. To work in the pharmaceutical industry, it is important to have a broad background and to be adaptable. The last thing we want to do as an industry if we exit a particular area is to let people go. It's expensive to do and it's also traumatic and bad for morale. We don't always have the luxury of doing the same thing forever, so good scientists, with broad training and a broad background, are important.

How do you think the pharma industry can best improve its image to the general public?
I think our image is probably at an all time low and I don't believe it's fully deserved. I think there has been a one-sided presentation of our image. We as an industry are proud of what we have done – we have better drugs on the market and treat diseases we couldn't even think about treating in the past. Those in developed nations live almost twice as long now compared to people who were born in 1900, in part because of sanitation and hygiene, and in part because of the medicines that we make.

We are concerned about our image, and we're working to turn it around, but it's not easy. There are differences in pricing in the USA and Europe, because prices are highly regulated in Europe, so the only free market left is the USA. Europe is simply not paying its fair share for biomedical innovation, and is living off innovation that's occurring increasingly in the USA. Pharmaceutical research is decreasing in Europe and increasing in the USA. Sales are increasingly coming from the USA, more than any other part of the world, and prices are also higher there because they are often held artificially low elsewhere. It's not fair, and Americans are angry about it.

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We understand that healthcare costs are spiralling out of control all over the world, but we think drugs have been disproportionately singled out as the cause. Actually we are still a relatively small part of healthcare. We are one of the most visible parts of health care in terms of what patients in the USA see because they often pay for their prescriptions, but they don't pay their hospital bill because insurance takes care of that. So there are many issues behind our poor public image right now that are not totally fair, and it will be difficult to undo that. We are working hard on it, but it's an uphill battle.

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We were really encouraged with the FDA Commissioner, Dr Mark McClellan, because he told the story for us, that Europe was not paying its fair share for medicines. Hopefully this message, and the other initiatives that Dr McClellan had planned will still move forward despite the fact that that he has moved on to a different part of the government. But people like me, who love and have spent their entire career in the pharmaceutical industry, are really pained by the image of what I consider a noble industry. We do good things for people, but we're not perceived that way right now.

Where do you see yourself being in 5 years?
I hope on a beach! With a drink in each hand!

Playing guitar?
Yes, playing guitar. I have been head of R&D now for approximately 4 years. It is a great job, but I didn't know how hard it

was going to be, and I have an awful lot of respect for every former head of R&D I have worked for because it is a consuming job. It can consume your life. Some of the best heads of R&D that I know held that job for 5 to 7 years. That's all you get, then you've done everything you knew how to do, so it's probably time for someone else to come in, with new ideas. So I'm not sure that it would be good for me to run R&D for another 5 years. Hopefully I am retired.

I love this industry, so hopefully I'll be doing something related to the industry while I am retired, maybe consulting,

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sitting on a board, even representing the industry in dealing with some of the issues we have spoken about, some of the political, regulatory and image issues. I can't ever imagine myself, even in retirement, not wanting to do something with this industry and for this industry. I absolutely love the pharmaceutical industry. I always did, and I always will.

Do you think you might get more involved in academia?

I could see myself, maybe not teaching at a university, but teaching science at an inner city school or at a small community college. I won't be looking for a large income, but rather for a way for me to give back. I live a fairly privileged life now, and I would like to give something back.

Bob Ruffolo
President
Research & Development
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A quiet revolution in lead optimisation services?

The article by Clark and Newton [1] in a recent issue of *Drug Discovery Today* on the outsourcing of lead optimisation is aptly sub-titled 'the quiet revolution'; lead optimisation is the cylinder block (i.e. the silent component) of the drug discovery engine. The lead optimisation stage of the drug discovery process is precisely where novel drug compositions are invented and new primary intellectual property is generated. Unlike many other areas of the pharmaceutical research and development pipeline that can be considered for outsourcing, the lead optimisation phase does not fit squarely into a compartmentalised, component model.

Several important issues are raised by the change of heart of the large pharmaceutical companies with respect to the outsourcing of lead optimisation. Currently, increasing numbers of quality medicinal chemists are employed by a growing number of service companies. Several such companies are located in India and China, where the economic laws of supply and demand create a comfortable environment for the client. There is no doubt that the issues of offshoring present a set of complex and real challenges for the lead optimisation service company.

In the mid 1990s, the intense demand for the new technology that was inherent in a collaboration with a combinatorial chemistry company led to these partnerships being structured with the supplier in mind, and the majority of deals incorporated a set of structured milestone payments, and perhaps royalties. Currently, contractual relationships are the order of the day. Indeed, cost restraint that is imposed by competition from relatively cheap offshore industries is driving down profitability for many European and US companies that offer lead optimisation services.

There is a danger that the economic parameters that govern today's market inadequately recognise quality among the various lead optimisation service providers – this is a cry that could become increasingly vocal from those companies that provide services at a relatively high cost. The generation of quality lead development candidates is difficult to benchmark because the output cannot be measured in simple terms. Therefore, although lead optimisation might not represent a hot new technology in the same way that combinatorial chemistry did ten years ago, it should not be considered a ready-made component of

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