Outlining the success of its efforts to overhaul R&D, as evidenced by the late-stage assets presented during GlaxoSmithKline PLC’s Dec. 3 R&D day, the company noted the time has come to revamp manufacturing and commercial processes to keep up with the productivity of the pipeline.

The company is creating small-scale commercial teams akin to the Discovery Performance Units on the R&D side.

GSK has been at the forefront of industry’s attempts to improve R&D processes, experimenting with smaller scale operations and other ways to foster scientific creativity. “A lot of credit is really deserved by my predecessor, JP Garnier, who was really one of the first in the industry to stand up at the peak of the industry and identify that R&D needed to change the way it operated and the way it thought and the way it delivered to ensure long-term sustainability of the industry,” CEO Andrew Witty told the Dec. 3 crowd.

But Witty also deserves a lot of credit. Upon his arrival at GSK in 2008, Witty made an overall review a priority and doubled down on the attempts to recreate and reinvigorate R&D— including the introduction of the small-sized Discovery Performance Units (“Pipeline Dreams: GSK’s Witty Outlines Plans To Lower Phase III Attrition” — “The Pink Sheet,” Jul. 28, 2008).

“Over the last five years [GSK has] had a very clear and focused strategy: grow a diversified global business to drive our sales growth, to really rebuild our capacity, to have a sales growth after the genericizations of our older portfolio and the loss of Avandia, deliver more products of value, and to simplify our operating model,” Witty summarized.

As the pipeline has been replenished by the transformational efforts in R&D, the need has grown for equivalent transformation of manufacturing and commercial operations. “We’ve moved into a phase of restructuring our manufacturing organization and of course our commercial organization to be ready for that pipeline coming to market,” Witty explained.

It’s been more than a decade since GSK launched major new molecular entities, and more like 20 years since it’s launched multiple new products at the same time, Witty noted. “That era is about to arrive again at GSK, and we need to have a very different and appropriate set of skills for how we commercialize in 2013, 2014, 2015 compared to what was happening at the end of the 1990s or even at the end of the 1980s.”

Meeting The Needs Of A Changing Commercial Environment

The commercial environment has changed significantly in the past few years, with evolving dynamics in the U.S., Europe, Japan, China and emerging markets.

“We’ve gone from an environment of easy access, relatively simple pricing dynamics … into a much more challenging, fragmented marketplace. In all geographies, Europe in particular, [the market is not] pro-innovation as it once was, hurdles [are] much more significant, [with] far greater delays to access, and of course, in many cases, pricing pressure continuing to make it more and more difficult to find the space for new products to really contribute from Europe,” Witty said. More and more emerging markets will become launch markets. The U.S. has remained more pro-innovation and remains key, he noted, but it has its own pricing dynamics and “the need for more evidence, for evidence both to justify the pricing of the medicines, to really justify the entry patient populations, is getting greater and greater.”

As reimbursement gets tighter globally, there is more demand for real-world evidence that payers can use to understand how a drug fits into the armamentarium (“Maintaining a Sustainable Environment for Innovation: Ending the Evidence Arms Race for Regulatory and Reimbursement Decision-Making” — The RPM Report, March 2012). Companies are readjusting to collect more data throughout
a product’s lifecycle and to collect more outcomes and patient-reported data (“A Call For Action: Pharma Strategies For Development Of Payor Evidence Programs” – IN VIVO, February 2012).

With the pipeline more productive, R&D head Moncef Slaoui has been charged with creating an aligned commercial organization that is more connected to the drug development side. The resulting “global franchise model” is primarily “a change in the way of working, in the way we go about positioning our medicine, the way we go about defining the label of this medicine, and the way we go about pricing these medicines, and the way we go about seeking access and reimbursement and to achieve that in a way that really builds on the key learning that we have gathered from R&D,” Slaoui explained.

Similar to the R&D remodel, GSK is creating small teams with a strong commercial leader with product directors from a small number of countries that have been identified as core to a particular medicine; aligned with that will be a manufacturing leader to ensure there is an integrated and optimized supply chain for the drug.

“That team’s mission is to fully understand the technical potential of the medicine, and to translate it into evidence generated to define what I call a sweet spot between what the medicine can do technically, what the medical need is, what the standard of care is geographically defined, and ... where the standard of care allows for the optimal extraction or delivery of value for that particular medicine,” Slaoui said. Europe and the U.S. will no longer be the de facto targets as the company takes a more global approach. And the team will also focus on what it will cost to deliver that evidence, how likely it will be able to deliver the evidence, and what the return will be.

These so-called Meds and Commercialization teams are being put in a particular therapeutic area into franchises led by an executive commercial leader, with a board of general managers of the countries targeted for a particular drug. “The franchises will allocate capital between the various medicines they have in their portfolio in an accountable way,” Slaoui noted.

To maximize discipline around decision-making, there will be a new investment board for commercial accountability, akin to the investment boards in place for discovery and the pipeline.

The Commercial Accountability Board “will allocate capital for evidence generation to each franchise, and will hold accountable the franchise [that] is the central, global strategic commercialization organization and the commercial operations into the countries” – reminding them that they are together accountable to deliver on the P&L, that they share that P&L, and they’re incentivized around it, Slaoui said.

“We believe that through this model we will be able to drive higher performance, better commercialization, better positioning, and we will be also able to generate more appointed evidence to support the best commercialization in the right geographic footprint, for each one of our new medicines.”

The global franchise model was developed based on the lessons learned from the R&D improvements, including creating a culture of leadership and accountability, clarity of decision-making and disciplined capital allocation. Slaoui also detailed the workings of the R&D side, and explained how it successful delivered a promising slate of drug candidates.

**An R&D Revolution**

What GSK tried to do was take things to a smaller scale and instill a culture of ownership of the projects. It divided discovery and development into small teams focused on a particular scientific subject or a particular project in development, which were highly enabled with a strong leader with decision-making authority and accountability; a governance board (one for discovery and one for the late-stage pipeline) ensures that investments are being allocated and looked after properly (“Incentives And Less Fear Of Failure: How GSK Is Driving Early-Stage Research In Its DPUs” – “The Pink Sheet,” Apr. 9, 2012).

With these Discovery Performance Units or Medicine Development Teams, the firm was able to refine its experiments and focus on collecting data on one critical question, rather than a raft of questions that were “nice to have” but not as directly relevant. That freed up enormous capacity, Slaoui said, and enabled a focus on return on investment and improved productivity – allowing more reallocation of capital. To that end, the investment boards were used to prioritize projects. The process also decreased attrition, the holy grail of R&D.

One aspect Witty is particularly proud of is how this has been achieved within strict financial limits. It’s difficult enough to fill a pipeline, he said, so it must be impossible to do that without increasing your overall R&D budget - but that’s what they did, and he thinks they’ve improved the quality of the assets at the same time. The numbers are secondary to the quality gains, he said. The firm has a mid-term goal of increasing its internal rate of return for R&D to 14%, and it was at 12% at the last assessment.

“If there is one key lesson learned in the last five or six years, it’s that true commitment to improving the quality of decision-making, to focusing on high-quality assets, and making sure that we are asking high-quality questions in our trials are all delivering much of the benefit we're seeing in terms of lower attrition rates, less project failure late in development, and a rise in net present value of the pipeline for GSK, all within a broadly fixed R&D budget, all therefore giving us a return on investment.”

This has been accomplished by taking away fixed infrastructure, moving more cost towards late-stage rather than early-stage development, increasing productivity at every level of the organization through accountability and incentive plans, and creating capacity wherever possible.

“Combined with the growing attractiveness of many of the profiles of the assets that have progressed through the late
stage, [the changes have] really started to help build our projected rate of return. Combine that with a reduction in late-stage attrition, and you start to see the ingredients for a winning recipe in what long-term R&D success can look like,” Witty asserted.

The First Wave

It has been a banner year for GSK. Out of at least the past 20 years, 2012 “has been by far the most productive year in terms of output,” Slaoui said, citing the approval of two vaccines and the filing of a third, plus the approval of significant indications for Promacta for treatment of hepatitis C and Votrient for sarcoma.

The results can also be seen in the flow of the pipeline. In February 2011 the firm said it would have 15 trial read-outs by the end of 2012. It has had 12, with two still to read-out and one delayed. Of the already-reported 12, 10 were positive and two failed. From the 15, two have already been approved, three are filed and three more should be filed by the end of the year.

Looking out further, there are around 50 lined up for 2015-2020; though that number will change, it will stay sustainable, Witty said. “So whereas in the past we've often seen a very productive period of one or two years in R&D followed by a decade of drought, we really are starting to see the possibilities of multi-years of delivery,” Witty said.

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Still, he pointed out, GSK has had more approvals for new molecular entities/new chemical entities than any other company over the past few years, a sign of its regulatory prowess. “GSK’s been a very prolific company around product approvals and product launches,” the CEO said. Some have been niche products, some have been specialty products, some have been more general market products. But, he said, “none of them have been enormous contributors individually to the overall business. About 7% of our turnover is made up of products launched in the last five years,” which he described as a decent but not spectacular figure.

The advances of 2012 should change that. The targets of those medications bring the company back into major markets, moving away from niche markets and toward “quite substantial medicines in terms of addressing very high medical needs such as asthma, COPD or diabetes,” Slaoui said. Mepolizumab targets severe asthma, albiglutide will give the company another contender for type 2 diabetes and UMEC/VI is the first of several drugs for COPD. Coming soon are a shingles vaccine, the Crohn's treatment vencirnom and darapladib for atherosclerosis. Plus these are “areas where we have a track record, where we have expertise, where we have an organization prepared to launch them,” such as respiratory or oncology (“Glaxo Confident In Output From Its Revamped R&D Engine” – “The Pink Sheet” DAILY, Dec. 3, 2012). That means they can have strong launches without significant increases in investment, Witty noted.

Witty indicated that while rare diseases have been a source of innovation in the past few years, it won’t be a continued focus for the company as its reformed R&D delivers what it feels are sound opportunities in major markets. GSK has a couple of orphan drugs coming up in the next year – migalastat in Fabry’s and drisapersen in Duchenne muscular dystrophy – but Witty explained that in both those cases, the firm had a larger purpose in mind.

Both were opportunities for molecules targeting rare diseases (with the lower risk proposition for gaining regulatory approval), but also places where working on those orphan programs would “at the same time validate technology or approaches to drug development,” Witty said. Data isn't in yet and the programs aren't proven, but he commented that in “both cases we've learned a lot as an organization on those technology approaches.”

What Happens Next

For some of the assets, GSK is going to have to adapt and Witty said it is ready to take alternate routes. With albiglutide, there are some parts of the world where GSK is well-equipped and ready to go because sales resources were kept in place after the Avandia drop-off, “but there are other parts of the world where that's not so true.” So GSK will be looking “in a very open-minded way at how we can maximize return for GSK shareholders, minimize upfront risk for GSK shareholders and ensure that the medicine gets properly shared out-for-licensing or partnering with a company more heavily deployed.”

The goal, Witty said, is to be more flexible on how GSK brings these assets to financial return: “Inevitably from time to time, we are going to find an asset which surfaces and doesn't fit one of our key portfolios,” for example, retosiban for pre-term labor, which he noted was moving nicely through the development pipeline. “But we are not a business with the strength in obstetrics or gynecology,” so that’s an asset where it is highly likely that the company will pursue out-licensing or partnering with a company more heavily deployed in that space.

“So whereas for the last 10 or 12 years, we've been known as a company to in-license assets, much more likely over the next several years we will become a company which looks to
partner and to possibly out-license assets ... [when they fall] slightly outside of our core expertise zone."

There is one area where in-licensing can be expected – biologics. Sanford Bernstein analyst Tim Anderson noted that Glaxo was sixth of nine in a survey of how much of the pipeline is in biologics, which is out of synch with the firm’s earlier talk of wanting to get away from “white pills in Western markets.” Witty admitted, “hands up, the company was late to really get into the biopharm field.”

But even there, Slaoui was there to tout Glaxo’s progress. About five years ago the firm set out with an aggressive plan to build up its biologics portfolio. Along with in-licensing – which brought in Benlysta, mepolizumab, albigrutide, sirukumab and a PD-1 agent – it created and accelerated a biopharmaceuticals discovery engine with the acquisition of Domantis Ltd. So there is a whole pipeline of candidates not yet in the clinic and not visible, he said. GSK’s objective was to have 20% of the overall pipeline in biopharm by 2015, and the firm is on track to meet that ahead of schedule.