AN AUDIENCE WITH…

Paul Brown

In August the US Food and Drug Administration (FDA) simultaneously approved Roche and Plexikkon's BRAF inhibitor vemurafenib for metastatic melanoma and a companion diagnostic, the Cobas 4800 BRAF V600 mutation test. Shortly after, the agency gave the green light to Pfizer's ALK inhibitor crizotinib and a companion diagnostic for non-small cell lung cancer. These decisions, which marked the first co-development successes since the approval of trastuzumab for HER2-positive breast cancer in 1998, suggest that the era of companion diagnostics has arrived, at least in oncology. Yet Paul Brown, CEO of Roche Molecular Diagnostics, argues that the field still faces considerable uncertainties. Speaking with **Asher Mullard**, he discusses the regulatory and reimbursement concerns that remain key hurdles to success.

What was your regulatory experience like with the FDA while working on this co-development programme?

Even though the FDA have issued some draft guidance, there is no formal mechanism for the approval of companion diagnostics at the moment. So it was a learning experience not just for industry but also for the regulators. We need to acknowledge that. And there were good things about the experience. But there are also significant opportunities and areas for improvement.

Let me start with the good things. The FDA made it clear very early on that the BRAF mutation test was very important for them and they were certainly intent on trying to ensure that we ran a coordinated companion diagnostics programme. They worked hard to bring together the two parts of the agency — the Center for Drug Evaluation and Research (CDER) and the Center for Devices and Radiological Health (CDRH) — that had to work closely together towards approval. We had several meetings in which both of these parties plus our pharmaceutical and diagnostics teams sat around the table. And this worked well. We certainly learned from it, and I'm sure the agency would say they did as well.

As for the troublesome parts, we found the discussions around agreeing on what information we were allowed to put on the labelling of the test to be particularly challenging. The FDA did not allow us to include some of the data that we believe are very important. And if you compare and contrast the label we got in the United States versus the recent CE-marked label that we have had approved in the European Union, you'll see that there is quite a bit of difference in terms of how much supporting data we've been able to include. I think that the labelling is very important for people who are deciding whether to use this test or not.

And if they don't use your test?

The vemurafenib drug label says that patients need to be selected using an FDA-approved test. And at the moment the only FDA-approved test is our BRAF test. But there are a lot of laboratory-developed tests that are being used despite this requirement.

The big frustration, that I think many people share, is that we have a very unlevel playing field when it comes to competing with laboratory-developed tests. The FDA hold manufacturers like ourselves to very high standards in terms of what is required for the approval of a test. But there are different requirements for laboratory-developed tests, which don't have to go through an FDA process. And at the moment the agency doesn't have a way to really regulate or manage laboratory-developed tests.

Do you see change on the horizon?

The FDA have issued statements saying that they want to look at how laboratory-developed tests are managed. And no one wants to restrict their use completely. But in instances in which an FDA-approved test is available, I think something needs to be done. My hope is that there will be regulations going forward to address this issue.

In the meantime, how do you and others in the companion diagnostics space compete?

Well, we have to operate in the market environment that is out there. We will continue to try to convince laboratories that are going to be doing BRAF testing of the value of our approach, and try to reinforce the requirements on the vemurafenib label. We can lobby multiple stakeholders to make sure that doctors and laboratory heads follow the label, but ultimately it will require the FDA to have control and police centers.

Another issue, though, is reimbursement. I think we've got a fairly antiquated system in the United States that doesn't reflect the true value of medically advanced tests like the one we have just had approved for BRAF. The way the system currently works is to reimburse for the number of steps that a laboratory takes per test: the more steps it takes, the more money it gets. A high medical value test that may involve fewer steps, therefore, gets penalized. As a result, I fundamentally believe that the reimbursement of our diagnostic tests really undervalues their medical value: they allow us to select the right patient, for the right therapy, at the right time.

In light of the regulatory and reimbursement issues you've mentioned, what do you foresee for the future of companion diagnostics?

I still think that companion diagnostics have truly arrived and that we will see more examples of them as we move forward. The majority of these in the near future will be around oncology, but we will also start to see them for other therapeutic areas including inflammation, virology and central nervous system indications.

What does your own pipeline look like?

Roche Molecular Diagnostics and Roche Pharmaceuticals currently have somewhere in the realm of 160 collaborations looking at biomarkers, with the intent of establishing and validating biomarkers early on in the drug development cycle. Out of these 160 biomarker research collaborations, I'd say that about 25 are for companion diagnostics that are in the Phase II/III stage.