IN brief

Transatlantic PML

The European Medicine Agency and US Food and Drug Administration (FDA) published in September the proceedings of a joint workshop held to address questions related to progressive multifocal leukoencephalopathy (PML), a rare and sometimes fatal brain disease that can occur as an adverse drug reaction to some therapeutics that affect immunological functions. The meeting attended by 170 regulators, academic scientists, funding bodies and clinical researchers, called for work on animal models, predictive biomarkers and long-term studies. "No one company is going to answer all the questions; they're going to be answered by research consortia," says co-convener and European Medicines Agency (EMA) pharmacovigilance head Peter Arlett. Five companies—Cambridge, Massachusetts–based Biogen Idec, New York–based Bristol-Myers Squibb, Elan of Dublin, Pfizer of New York and Roche of Basel—already fund basic research into drug-related PML through a nonprofit consortium. Concerns over drug-related PML were prompted by patients receiving Biogen's multiple sclerosis therapy Tysabri (natalizumab) and other biologics such as Roche-Genentech's antibody Rituxan (rituximab) (*Nat. Biotechnol.* **28**, 105–106, 2010). By weakening patients' immune system, these treatments allow the reactivation of John Cunningham (JC) virus, which is normally latent, to infect the central nervous system and cause the disease. According to risk calculations that took into account duration of treatment, published by the FDA in April 2011, in an average sample of 3,333 people taking Tysabri, up to 5 could develop PML and of those one would die. In June 2011, the EMA released a more complete risk stratification algorithm, which also accounts for the presence of anti-JC virus antibodies and prior exposure to immunosuppresants. However, there is no treatment for JC virus or PML and even diagnosis is difficult. In addition to the consortium-funded research, Biogen is at work on two potential JC virus therapies that might help protect its large investment in Tysabri: one is a small molecule targeting the large T antigen on the JC virus and one is a neutralizing antibody against the JC virus. But the biggest result in the last year, says Biogen Idec senior vice president and global head of drug safety and risk management Carmen Bozic, is the improved quantification of risk factors for PML now available in the EMA label. As *Nature Biotechnology* went to press, Biogen was awaiting a decision from the FDA for a new label for Tysabri that would include anti-JC virus antibody status to help clinicians stratify the risk of PML. *Lucas Laursen*

IN their words

"It's a double whammy—we don't allow farmers to import these GM [genetically modified] crops because they haven't been approved here, and you can't cultivate them either. We're putting ourselves into a corner."

EuropaBio Secretary General Nathalie Moll reported to EU policymakers that that their approval process takes 15–20 months longer than that of the US, Brazil or Canada. (*Reuters*, 11 October 2011)

Box 1 FDA circulates guidelines on companion diagnostics

On July 14, the FDA issued the first of several planned guidelines on companion and co-developed diagnostics. The guidance has drawn a wide range of reactions. Elizabeth Mansfield, director of personalized medicine in the FDA's Center for Devices and Radiological Health, points to several key features. First, the guidance defines *in vitro* companion diagnostics (IVDs) as devices that provide essential information for the safe and effective use of corresponding therapeutic products, largely by identifying individuals most likely to benefit or suffer adverse reactions from treatment. Second, it states that FDA will review targeted drugs for approval only in the context of their corresponding IVDs. And third, it aims to clarify drug labeling, by referring specifically to what sorts of FDA-approved IVDs are appropriate for use in selecting patients and monitoring them during treatment.

FDA spokesperson Erica Jefferson says the guidance was drafted to limit the chance that personalized drugs are prescribed for patients who won't respond to them. "It highlights our goal to review drugs and diagnostics simultaneously," she says. "And we suggest early interactions between drug companies and the FDA to avoid any surprises during development." Jefferson emphasizes that under the new guidance, targeted therapies can be approved in the absence of an IVD, but only if they address urgent, unmet needs in treatment while the manufacturers continue to validate appropriate diagnostics for safety and efficacy in clinical work. "We don't want to delay access to a needed drug while we wait for the diagnostic," she says. Risa Stack, a partner and life sciences specialist with Kleiner Perkins Caufield & Byers, a venture capital firm, says there's an ongoing need for regulatory clarity in personalized medicine. "And this guidance signals a recognition by the FDA that diagnostics are increasingly important in clinical decision making," she says.

Sheila Walcoff, a founding principal with Goldbug Strategies, in Rockville, Maryland, says the guidance skirts around a key issue—namely the potential for regulatory changes concerning laboratory-developed tests (LDTs), or 'home brews', that FDA currently regulates under a loose policy of "enforced discretion." As it stands now, the US Center for Medicare and Medicaid Services regulates the laboratories that develop these tests are under the Clinical Laboratory Improvement Amendments policy. "The challenge now is to understand how the FDA views companion diagnostics with respect to LDTs," she says.

Plexxikon's medical director, Mai H. Le, has submitted a ten-page letter to the FDA that sharply criticizes the guidance, suggesting that it doesn't sufficiently consider logistical and economic barriers to the drug industry and deters drug companies from pursuing treatments for rare diseases, among other problems. "As it stands now, the guidance leaves everyone in a void," says Plexxikon's CEO, Peter Hirth. **CS**

Glaub should know. Roche's Zelboraf (vemurafenib)—an oral drug that is active in melanoma patients with the BRAF V600E mutation in their tumors—originated with Plexxikon. The biotech partnered with Roche Molecular Systems (RMS), headquartered in Pleasanton, California, to develop the 'cobas 4800 BRAF V600 Mutation Test,' a PCR-based diagnostic. Plexxikon is the only biotech company of many queried by *Nature Biotechnology* that agreed to comment on companion diagnostics.

Thus far, either diagnostics specialists, such as Deerfield, Illinois–based Vysis (now part of Abbott), DAKO or Salt Lake City, Utah–based Myriad Genetics, or diagnostic subsidiaries of pharma companies, such as RMS and Abbott Molecular Oncology, have dominated the companion diagnostic space.

One exception is Clovis Oncology, a Boulder, Colorado–based company. The biotech recently teamed up with Roche and Ventana Medical Systems, in Tucson, Arizona, to develop companion diagnostics for Clovis' preclinical drug CO-1686. The small molecule targets T790M mutant forms of the epidermal growth factor receptor (EGFR) tyrosine kinase. Roche will be using the PCR-based diagnostic platform 'cobas 4800' to identify patients with the EGFR T790M mutation. Clovis is currently in S-1 filing with the US Securities and Exchange Commission and could not comment for this story.

In terms of other small companies eyeing companion diagnostic options, "You're more likely to see startup biotechs approach startup diagnostics companies, but that's happening slowly," says Terry McGuire, a partner with Polaris Venture Partners, in Waltham, Massachusetts. For Martin Murphy, partner at MVM Life Science Partners, a venture capital firm in London, the promise of companion diagnostics in oncology is clear but he has reservations about biotech involvement. "Can smaller companies develop therapies and diagnostics hand in hand? It's a very capital-intensive process that I think is in range for these companies, but it's going to be challenging," he says.