NEWS IN BRIEF

Busy panels recommend Pfizer's tofacitinib, Arena's lorcaserin and more

The FDA held seven advisory panel meetings last month, yielding at least four recommendations for drug approvals.

The lowdown: The arthritis panel voted 8–2 in favour of Pfizer's tofacitinib for rheumatoid arthritis, paving the way for the first approval of a Janus kinase (JAK) inhibitor in the anti-inflammatory space (*Nature Rev. Drug Discov.* **10**, 717–718; 2011). Although panellists were unanimously convinced that the drug was effective, concerns over long-term safety and the risk of infection and malignancy split the final vote. Advisors also voted that data did not show that the drug substantially reduces joint destruction, as measured by radiographic assessment. The US Food and Drug Administration (FDA) is due to make its decision in August. Other JAK inhibitors in development for autoimmune indications include Lilly/Incyte's LY3009104, Vertex's VX-509 and Galapagos/Abbott's GLPG0634, all of which are in Phase II trials.

The endocrinologic and metabolic panel meanwhile voted 18–4 in favour of Arena's anti-obesity drug lorcaserin. In September 2010, panelists voted against the drug owing in part to concerns that it might be carcinogenic. This time around, Arena presented a re-adjudication of animal carcinogenicity data and clinical data to assuage these fears. The positive vote came despite residual worries that the drug's 3% placebo-adjusted weight loss might be insufficient to offset its risks, which may include cardiotoxicity. A final decision is due by the end of this month. A decision for Vivus's obesity drug Qnexa (phentermine plus topiramate) is also due this summer, following a panel endorsement in February.

The antiviral panel recommended Gilead's Truvada (tenofovir plus emtricitabine) as pre-exposure prophylaxis for HIV, setting the stage for the first prophylactic HIV drug. It also recommended Gilead's Quad (elvitegravir plus cobicistat plus emtricitabine plus tenofovir) for HIV.

Finally, the arthritis panel gave the thumbs down to Regeneron's interleukin-1 blocker rilonacept, the latest of several developments in the gout space (see page 425). As *Nature Reviews Drug Discovery* went to press, panels were preparing to discuss Johnson & Johnson's rivaroxaban for acute coronary syndrome and Pfizer's tafamidis for transthyretin familial amyloid polyneuropathy.

Roche's dalcetrapib dies, but CETP field carries on

Roche has discontinued development of its CETP inhibitor dalcetrapib, renewing fears for the cardiovascular drug class.

The lowdown: Cholesteryl ester transfer protein (CETP) inhibitors, an anti-atherogenic class of drugs that raise high-density lipoprotein (HDL) and lower low-density lipoprotein (LDL) levels, have been in and out of the spotlight for years because of their potential blockbuster value and their turbulent history (*Nature Rev. Drug Discov.* **10**, 163–164 ; 2011). The class hit its first major setback in 2006 when Pfizer was forced to halt development of torcetrapib, the leading CETP inhibitor at the time, owing to an increased risk of death and heart problems. Further studies eventually suggested that torcetrapib failed because of a compound, not a class, effect, but Roche has now become the second company to suffer a late-stage CETP disappointment: it has discontinued Phase III trials of dalcetrapib, which had inherited the position of the leading CETP inhibitor, owing to a lack of efficacy.

For those few companies still in the CETP space, Roche's decision may come as mixed news. Merck & Co.'s anacetrapib now picks up the mantle of potential first-in-class drug, but the discontinuation further challenges the hypothesis that high HDL levels may be beneficial. Barclays analysts argue, however, that because anacetrapib has a greater effect on HDL and LDL levels (modulating them by 138% and –40%, respectively) versus dalcetrapib (31% and –2%), the setback should not be "interpreted as a negative omen". Merck's Phase III trial is testing the drug in 30,000 patients, and results are expected in 2016. CETP inhibitors in Phase II development include Lilly's evacetrapib (previously LY2484595) and Dr Reddy's DRL 17822.

The HDL hypothesis was also questioned this month by an article showing that although individuals with a loss-of-function mutation in their endothelial lipase (*LIPG*) gene have higher HDL levels, they do not have a reduced risk of myocardial infarction, a possible complication of atherosclerosis (*Lancet*; 17 May 2012). "Interventions … that raise plasma HDL cholesterol cannot be assumed ipso facto to lead to a corresponding benefit with respect to risk of myocardial infarction," the authors conclude.

Fuel for the debate on clinical trial shortcomings

An analysis of trials registered in the ClinicalTrials.gov database suggests that most trials are too small, and highlights heterogeneity in the design and execution of studies by different therapeutic specialties.

The lowdown: In an effort to assess the basic characteristics of clinical trials, Robert Califf of the Duke Translational Medicine Institute in North Carolina, USA, and his colleagues analysed a data set of the 40,970 interventional studies that had been registered with ClinicalTrials.gov between October 2007 and September 2010. Reporting in *JAMA*, they found that these were "dominated by small trials and contain significant heterogeneity in methodological approaches, including reported use of randomization, blinding, and [data monitoring committees]" (*JAMA* **307** 1838–1847; 2012). Around 60% of the trials registered between 2007 and 2010 enrolled 100 or fewer participants. Preliminary analyses showed that many of these small trials had been designed to enrol more patients, "raising questions about their ultimate power".

An analysis of trials in three therapeutic areas — oncology, cardiovascular disease and mental health — highlighted discrepancies between the design and enrolment criteria of the different specialties, including the fact that the use of data monitoring committees was less frequent in mental health trials, and randomization and blinding are less frequent in oncology trials. The analysis also showed that 44% of trials were funded by industry, 9% were funded by the US National Institutes of Health and 2% were funded by other US federal agencies. "We anticipate that the 'sunshine' on the national clinical trials portfolio brought about by ClinicalTrials.gov … will engender much-needed debate about clinical trial methodologies and funding allocation," the authors write.

The analysis also points out deficiencies in the completeness of the registration of trials, leading the authors of a linked editorial to call for better engagement from investigators, clinicians, editors, trial sponsors, regulators and patients to improve the value of clinical trial registries (*JAMA*, **307** 1861–1864; 2012).