NEWS IN BRIEF

FDA gears up for meta-analysis guidance

Regulators rallied stakeholders to discuss best practices for the conduct and assessment of meta-analyses.

The lowdown: Meta-analyses offer a unique opportunity to combine and analyse data from multiple studies and draw inferences from populations of interest. But despite their widespread use, the US Food and Drug Administration (FDA) says that there is a lack of consensus on the best statistical practices and design of these studies, which undermines their utility. The FDA therefore held a workshop in November to establish a robust and transparent approach to meta-analyses. A resulting guidance document "will provide a consistent framework for how meta-analyses should be designed, analyzed, reported, and interpreted in the context of product safety regulation," said the agency.

Key topics covered at the workshop included bias and multiplicity in meta-analyses, the hierarchy of evidence, the need for prospective planning, the quality of constituent studies and the statistical persuasiveness of generated evidence. The agency also presented its perspective in a white paper published before the workshop. Participants at the workshop discussed the possibility of a "refuse-to-file" action for submitted meta-analyses that do not meet adequate FDA standards.

On the same day as the workshop, the FDA retracted some of the restrictions on GlaxoSmithKline's antidiabetic drug rosiglitazone. A meta-analysis published in 2007 suggested that the peroxisome proliferator-activated receptor-γ modulator increases the risk of cardiovascular events, triggering a high-profile investigation into rosiglitazone. The agency subsequently restricted access to the drug, but has revised its position in light of a re-review of data from a clinical trial known as RECORD.

Returns on R&D investments continue to fall

The expected return on investment for late-stage drug candidates has fallen by more than 50% since 2010 for many of the biggest pharmaceutical companies.

The lowdown: Analysts at Deloitte and Thomson Reuters started tracking the expected return on investment (ROI) on late-stage pipeline candidates from a cohort of 12 large pharmaceutical companies 4 years ago, and the 2013 analysis makes for grim reading. Although the companies have advanced 167 products with a risk-adjusted value of US$819 billion into Phase III trials since 2010, the anticipated average ROI on late-stage candidates is now only 4.8%. The comparable ROI for late-stage candidates was 7.2% in 2012, 7.7% in 2011 and 10.5% in 2010.

The total size of the late-stage pipeline has remained steady since 2011, at around 200 compounds, but the cumulative projected value shrank from $1,369 billion to $913 billion during this time, a 33% drop. Peak sales estimates for each asset also fell by 43% from $816 million in 2010 to $466 million in 2013, the report shows, potentially due to austerity measures and difficulties in securing reimbursement from payers. Late-stage failures accounted for $243 billion of the lost value of the pipeline.

There were, however, wide variations in the ROI predictions for the different cohort members. The top performer looks forward to an ROI of 10.7% on its late-stage candidates, while the worst dreads an ROI of −5.7%. The cohort is made up of Amgen, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Merck, Novartis, Pfizer, Roche, Sanofi and Takeda, but the ROIs for specific companies were not disclosed.

"Life science R&D returns remain challenging, but there are signs that the leaders in the cohort are weathering the storm," the authors conclude.

Tracking drug levels in blood in real time

An oligonucleotide-based biosensor offers the tantalizing potential of continuous, real-time monitoring of drug dosages in patients.

The lowdown: Personalized medicine promises the right drug, at the right dose, for the right patient, at the right time. Progress is being made on all four fronts, but in terms of dosage most available biosensors can currently only measure drug concentrations at a single time point. Continuous, real-time monitoring offers the possibility of more effectively tailoring dosages to each patient, maximizing efficacy and minimizing toxicity. Brian Scott Ferguson, of the University of California in Santa Barbara, USA, and his colleagues therefore set out to develop a biosensor that can "continuously measure *in vivo* concentrations of a wide range of circulating biomolecules". They describe the resulting microfluidic electrochemical detector for *in vivo* continuous monitoring (MEDIC) in *Science Translational Medicine*.

The MEDIC device is built around drug-specific aptamer probes tethered to gold electrodes. As blood is drawn through the device, the probes reversibly bind to their target drug and the resulting electrochemical signal provides a drug dosing readout. As a proof of concept, they used probes specific for the anticancer drug doxorubicin and the antibiotic kanamycin to measure drug concentrations in blood drawn continuously from live rats. "The modular architecture of MEDIC means that it can be adapted to a wide range of target molecules simply by exchanging the aptamer probes," the authors report.

The authors note that by integrating multiple probes into one device, they will be able to simultaneously measure concentrations of the drug and the biomarkers that are indicative of response, facilitating optimal dosing in real time. "Such adaptive dosing technology could also enable the expanded use of drugs with narrow therapeutic indices," they write.