AN AUDIENCE WITH…

# Robert Dworkin

In the hopes of curbing high attrition rates for pain drugs, the FDA launched the Analgesic Clinical Trial Innovations, Opportunities and Networks (ACTION) initiative last year. This public–private partnership — which has been granted access to the FDA's treasure trove of clinical trial data — has been tasked with revamping trial design. Under the leadership of Robert Dworkin, Director of ACTION and Professor at the University of Rochester Medical Center in New York, USA, industry leaders, academics and regulators held their inaugural meeting in June. **Asher Mullard** spoke with Dworkin after the meeting to hear how the group hopes to bring relief to the field.

***Why was ACTION created?***
The mainstays of our therapeutic armamentarium for pain are non-steroidal anti-inflammatory drugs, acetaminophen and opioids. These have been around for a long time, but there are issues with efficacy: not everyone responds, and for those who do pain typically decreases by not more than half. There are also safety issues, including hepatotoxicity, gastrointestinal toxicity, cardiovascular toxicity and more.

Both the US Food and Drug Administration (FDA) and the medical community are concerned with the pace of development of novel improved analgesics. It's been very slow. My sense is that the reason for this is not because of a lack of targets, but because of the striking attrition rates of Phase II and Phase III trials. This was the impetus for the FDA's Bob Rappaport, who came up with the idea for ACTION, to spearhead a programme that could answer important questions about trial design and methodology.

***Why do you think the problem is primarily with clinical trial design, rather than with preclinical models or target choice?***
Clinical trials of pain drugs that have already been approved have occasionally failed to meet their primary end points in subsequent pain studies. We believe these results show that we can get false negatives with agents that are known to be efficacious, and so we think that by extrapolation some of the negative results we are getting with experimental agents are false negatives as well.

***What about the alternative conclusion that even approved agents may not be effective?***
I don't know where that would leave us. If all of the drugs that have been approved by the European Medicines Agency and FDA for pain — including opioids, which we've thought are good painkillers for thousands of years — don't really work, that leaves us with a kind of therapeutic nihilism that is hard to reconcile with clinical experience.

But even if we did throw the problem back to the preclinical researchers, I would still argue that we need better research designs for Phase II and Phase III trials. To me, it appears that there is a lot of evidence that we can do a better job in the design and conduct of trials.

***What is your plan?***
A primary focus will be to assess clinical trial methods; not only research designs but also approaches to data analysis, the effect of patient training and various other things. We hope that this work will provide the foundation for an evidence-based approach to designing analgesic trials.

To this end, we are developing a standardized database format for analgesic clinical trials, which will make pooled analyses much more efficient. We've already contracted this out to the Clinical Data Interchange Standards Consortium, and expect the work will be done by March 2012. It can then be applied to both prospective data and the FDA's legacy data. This FDA database was created to review the efficacy and safety of individual drugs that had been submitted for approval, but we think it will be a rich source of untapped information, on patient subgroups and natural history of disease, for example.

We will also analyse published and otherwise available clinical trials for neuropathic pain and osteoarthritis to assess their methodological features. And we have subcontracted John Farrar, at the University of Pennsylvania, USA, to analyse clinical trials of neuropathic pain in the hopes of identifying predictors of placebo-group responses. We don't know whether age, sex, baseline pain or other attributes predict placebo-group response. If we find some factors that are associated with greater placebo responses — which could reduce the assay sensitivity of clinical trials — then we can ask how excluding those patients might affect study outcomes.

***Could the placebo-group analyses have implications beyond pain indications?***
Certainly with respect to psychiatry indications, in which high placebo rates have proved to be problematic, the answer is yes. I would also imagine that some of our findings could be extrapolated to Parkinson's disease trials, in which placebo responses have also sparked interest and concern.

***What are ACTION's other priorities?***
We need to spearhead the creation of fellowships and research grants for junior investigators. There is a lot of concern that we don't have enough young researchers involved in clinical pain research.

Another priority for us is to look at whether there are subgroups of patients that may respond differently to treatment. This work includes patient phenotyping and genotyping, as well as biomarker and diagnostics development, so that we can identify those patients who are either going to have a more robust response of pain relief or who are less likely to experience side effects.

We are also going to pay attention to preclinical and Phase I studies. At our inaugural meeting in June, a colleague asked what is known about: the assay sensitivity of preclinical methods; and whether one preclinical model is better than another for identifying which drugs will work in patients; and whether we could start to assemble databases of preclinical trials and analyse them for methodological features and values that are predictive of efficacy in humans? And I was just speechless: resource permitting, we could study all of those questions.