

BIOGENERICS

Surrogate endpoints present mAb options

Using surrogate endpoints where available, such as tumour-response rates over specified time intervals, will be a key strategy for developing biosimilar monoclonal antibodies (mAbs) for European Union (EU) markets, according to PharmaNet experts Jeffrey Freitag and William Egan. The clinical research organisation believes using such endpoints could “limit the size of clinical trials to feasible levels”.

Commenting on the flexibilities presented in the EU’s recently-released draft guideline on ‘similar biological products containing monoclonal antibodies’ (*Generics bulletin*, 3 December 2010, page 1), PharmaNet’s chief medical officer Jeffrey Freitag – who is also senior vice-president of PharmaNet Consulting – observes that the guideline offers “manoeuvrability on the design of trials”, with the European Medicines Agency (EMA) appearing to be willing to contemplate novel trial designs. “The aim is to demonstrate comparability, not reinvent the wheel,” points out Freitag.

“The goal of biosimilar development is to front-load the development programme with as much pre-clinical information as possible,” Freitag asserts. This is not only more economical in terms of the cost of programme development, but also more ethical, as it can reduce the extent of the clinical comparability programme. The goal should be to demonstrate similarity at every step and explain any differences to the reference drug that arise, he says.

However, Freitag highlights, response rates for certain mAbs, such as cancer treatments, are often as low as 15-20%. “Adequately-powered equivalence trials – comparing the biosimilar candidate to the reference mAb – in situations where the response rate is low will require large numbers of trial participants, perhaps more than were enrolled in the original approval trials,” he indicates.

And even reducing the number of trial participants for efficacy studies through novel trial design could be a “double-edged sword”, Freitag notes. Relatively small numbers of participants may not be enough to generate sufficient safety and immunogenicity data, he says.

Adverse immunogenicity events linked with mAbs tend to be relatively small in number, Freitag observes. “Just because events do not show up in a trial of a few hundred patients does not mean that they do not exist,” he stresses, adding that much depends on the mode of administration, frequency of dose and the patient’s immune status. Therefore, he adds, post-marketing pharmacovigilance programmes will generally be required.

PharmaNet Consulting vice-president William Egan believes the guideline is correct in recognising that relevant animal models may not be available, and in stating that ‘the conduct of large comparative toxicological studies in non-human primates is not recommended’, as well as that ‘immunogenicity assessment in animals is generally not predictive for immunogenicity in humans’. “It is not possible to get good comparability information from such studies,” he asserts.

“In many cases, *in vitro* assays can demonstrate comparability more accurately than *in vivo* clinical trials,” Egan maintains. Indeed, he notes, the guideline recognises that “there is often a lack of specific pharmacodynamic endpoints for clinical studies”, so the emphasis will often be on *in vitro* biological and biochemical evaluations.

Over time, Egan expects, the draft guideline will evolve into an overarching mAb document, complemented by mAb guidelines on specific indication areas, such as oncology or anti-inflammatory uses.

Freitag notes that while the draft guideline makes extrapolating mAb indications possible, this would be difficult without clinical trials. “The mechanisms of mAbs are often not well understood,” he says. **G**

ALLERGY DRUGS

Australian firms win fexofenadine ruling

Mylan’s Alphapharm, Watson’s Arrow and Aspen’s Sigma have convinced a federal judge in Melbourne that most claims of Albany Molecular Research’s (AMR’s) Australian fexofenadine patent 699,799 should be revoked for lack of novelty.

Judge Christopher Jessup also dismissed AMR’s infringement proceedings against the fexofenadine products that the generics firms market under brand names such as Xergic and said there was “a question whether the patent as a whole should be revoked for false suggestion”.

Noting that prior-art Australian patent 531,146 had already disclosed compounds including fexofenadine, Jessup observed that AMR’s ‘799 patent claimed ‘substantially pure’ piperidine derivatives.

Referring to 2009 rulings on the novelty of escitalopram and clopidogrel patents (*Generics bulletin*, 16 October 2009, page 13), Jessup concluded that “the disclosure of a compound by exact naming in the prior art is sufficient, of itself, to constitute anticipation”. **G**

ALZHEIMER’S DISEASE DRUGS

Japan upholds Aricept patent

A patent covering the use of Eisai’s Aricept (donepezil hydrochloride) for severe Alzheimer’s dementia was properly extended until 22 June 2013, Japan’s intellectual property high court has ruled. Several generics firms had challenged a decision by the Japanese patent office in November 2009 to grant a patent-term extension.

Eisai – which had filed for the extension on the basis of approval for severe dementia granted by Japan’s ministry of health, labour and welfare (MHLW) in August 2007 – recorded domestic Aricept sales ahead by 11% to ¥80.4 billion (US\$976 million) in the nine months ended 31 December 2010. Over the same period, Eisai’s US donepezil sales rose by 12% to US\$1.66 billion. This included US\$137 million from the authorised generic that Greenstone launched during Ranbaxy’s 180-day exclusivity period (*Generics bulletin*, 14 January 2011, page 24). Eisai said Greenstone’s version had accounted for around two-thirds of US prescriptions for generic donepezil. **G**

ORAL CONTRACEPTIVES

Lupin and Watson are denied

New Jersey district Judge Stanley Chesler has denied summary-judgement motions of invalidity for double-patenting brought by Lupin and Watson against US patent 6,214,815, which protects Ortho McNeil’s Ortho Tri-Cylen Lo (norgestimate/ethinylestradiol) oral contraceptive until 9 December 2019.

Chesler said there was sufficient doubt over the double-patenting defence to require a full trial. “The ultimate factual determination of whether the prior art taught away from the ‘815 regimen, and of whether the ‘815 regimen produced unexpected results, will likely rest on a battle of the scientific experts at trial,” he stated.

But Chesler granted Ortho-McNeil summary judgement against Watson’s defences of lack of utility and enablement, stressing that it was enough for the ‘815 patent’s specification to have shown utility in reducing the incidence of irregular bleeding. “Nothing in the law requires that contraceptive efficacy be shown,” he insisted. **G**