

## **Biosimilarz Podcast Notes (September 10, 2015)**

- Been way too long since I did one of these.
- Last one was in Feb 2015, and a lot has happened since then.
- Will try and summarise some of the key events and what they could mean.
- Unlikely to be exhaustive and I might miss out what you think is important.
- If I do, please get in touch via Twitter or my blog and we can discuss.

My five key events of the last six months

### **1. The biosimilar mAbs story in Europe**

- a. Launch of infliximab in EU5 in February 2015
  - i. Early signs are that uptake has been slow
  - ii. Deep discounting (45%) in France allows Hospira to win a key tender with Inflectra
- b. Biosimilar infliximab in the Nordic region
  - i. Biosimilar infliximab reached 51% market share in April in Norway
  - ii. Biosimilar infliximab now has a 70% market share in Norway, and a 90% market share in Denmark
  - iii. Payers have driven usage, have given physicians no choice

### **2. The biosimilar filgrastim saga in the US**

- a. AdCom
  - i. Sandoz nailed it, 14-0 recommendation, great job!
  - ii. High level of focus on analytical data, unlike the EMA
  - iii. Interestingly, no interchangeability approval despite the pivotal PIONEER study being a switch study
- b. Approval
  - i. Almost a foregone conclusion
  - ii. Indications awarded by extrapolation
- c. Legal strategies
  - i. As I've mentioned many times before, originator companies will not go gently into the night and allow biosimilar companies to steal their market
  - ii. AMGN's number one strategy has been focused on litigation
  - iii. Not a surprise, but some of the outcomes of the legal battles have been
  - iv. In July 2015, the Federal Circuit ruled on two issues related to the development and commercialisation of Zarxio:
    1. Whether the BPCIA's patent exchange provisions are mandatory (Amgen's view) or optional (Sandoz's view), and what the consequences of non-compliance or "opting out"

of these exchange provisions should be – **panel of judges ruled in Sandoz's favour (2-1)**

2. Whether the 180-day pre-launch notice may be given immediately upon FDA's acceptance of the biosimilar application (Sandoz's view) or only upon FDA's approval of the biosimilar product for licensure (Amgen's view) – **panel of judges ruled in Amgen's favour (2-1)**

d. Launch

- i. This month a judge for the US Court of Appeals for the Federal Circuit declined an Amgen motion for a temporary injunction that would have prevented Zarxio from launching
- ii. Zarxio was launched almost immediately at a 15% list price discount to Neupogen.

e. Questions remain?

- i. **Is the discount big enough?** Sandoz are likely to provide higher discounts through rebating to drive usage, but what if Amgen decides to increase its rebating for Neupogen? A win for payers and patients, but not the biosimilars industry.
- ii. **Can Sandoz get in front of enough physicians and payers?** No interchangeability designation means that the company will need to market and detail Zarxio. Does Sandoz have enough firepower in the US? Remember, this is their first proper biosimilar in the US.
- iii. **Will reimbursement issues get in the way?** Specifically, will proposed changes to Medicare Part B reimbursement – and the use of the same J code for all biosimilars – slow adoption? Need to remember that in the US today, less than half of Neupogen claims are billed through a pharmacy benefit (Medicare Part D). Claims billed through the medical benefit are subject to less clinical management such as less prior authorisation [PA], quantity limits, or step therapies. Rates paid for drugs under the medical benefit are generally higher than those paid under the pharmacy benefit. To take advantage of the lower pricing of Zarxio payers need to strongly consider shifting all coverage to the pharmacy benefit.
- iv. **Will physicians use the product?** We've run a few physician polls over at FirstWord and the feedback looks positive. Oncologists seem pretty happy with the data, naming and labelling of Zarxio.
- v. **What will be Amgen's tactical response?** Will they play the price card? Will the focus be on driving patients to Neulasta's new on-body delivery system?

### 3. The pipeline keeps marching on

- a. New clinical trials
  - i. Boehringer Ingelheim; Phase III studies for biosimilar rituximab in low tumour burden FL (likely to be a marketing study, rather than a registrational study), along with Phase III studies for biosimilar bevacizumab (NSCLC)
  - ii. CHRS; Phase I studies on biosimilar pegfilgrastim, Phase III studies on adalimumab biosimilar (including switch arm), long-term safety study for etanercept biosimilar
  - iii. BAX/MNTA; Phase I studies on adalimumab completed
  - iv. PFNX; Phase I studies on interferon-beta-1b initiated
  - v. ONCOBIOLOGICS; Phase I bevacizumab studies completed
  - vi. SNY; Phase III studies on biosimilar insulin lispro (type 1 and 2 diabetes)
  - vii. MYL; Phase I studies on biosimilar bevacizumab, Phase III studies on biosimilar adalimumab (psoriasis) and pegfilgrastim (breast cancer). Phase III studies on biosimilar trastuzumab (in mBC) completed → unsure what the regulatory strategy is? mBC not seen as the best indication for trastuzumab, so could limit filings to emerging markets
  - viii. NVS; new Phase III switching study for biosimilar rituximab. Study objective is to identify potential safety risks of the transition from US-licensed Rituxan or EU-approved MabThera to GP2013 (proposed biosimilar product) as compared to continuous treatment with the originator product in terms of general safety and immunogenicity
  - ix. PFE; Phase III studies for biosimilar bevacizumab (NSCLC)
- b. New clinical data
  - i. Supportive data for infliximab in gastro indications
  - ii. Truckloads of data for biosimilar programmes presented at EULAR, ASCO, ADA, ASH, DDW, ECCO
  - iii. Samsung Bioepsis reports positive Phase III data for SB2 (infliximab; numerically higher ADAs in the SB2 arm), SB4 (etanercept; SS lower immunogenicity compared to etanercept) and SB5 (adalimumab)
- c. New regulatory submissions
  - i. Samsung Bioepsis/MSD; SB2 (infliximab) in Europe
  - ii. Samsung Bioepsis/MSD; SB4 (etanercept) in Korea
- d. New approvals and launches
  - i. Celltrion receives approval for Remsima in Brazil, Russia and Venezuela, and confirms that the product has been launched in Canada

- ii. Eli Lilly and Boehringer Ingelheim; launch biosimilar insulin glargine in CEE and the UK
- iii. Hetero Drugs launches Maball (rituximab copy) in India
- iv. Intas launches Intacept (etanercept copy) and Razumab (ranibizumab) in India
  - 1. Razumab has since been removed from the supply chain in India. A source tells me that Razumab isn't available in India anymore, and physicians don't know when it will be re-supplied
- v. Samsung Bioepsis/MSD; Brenzys (etanercept) in Korea, took 6 months to approve

#### 4. Regulatory changes and refinements

- a. Finalised guidelines by the FDA
  - i. Still no interchangeability guideline?
  - ii. Do companies actually need the guideline?
  - iii. My argument is no; switch studies being done, so FDA obviously has an idea in its mind about the best study design
- b. Biosimilar naming has been a significant area of debate
  - i. Sandoz and Hospira came out against the WHO's BQ proposal, arguing that "patients receive the full benefit of greater access and lower costs that these medicines can bring."
- c. Draft naming guidelines (use notes to highlight concerns)
  - i. **Is it me, or is the guideline's introduction a little long?** The first 7 pages are background and justification. The actual naming bit is only 3 pages long. Seems a little odd to me.
  - ii. **Have naming guidelines come too soon?** What about labelling and interchangeability guidelines? Seems odd to publish a guideline on naming – which refers to interchangeability – when there's no interchangeability guideline.
  - iii. **Why are shared names are not appropriate?** What about the European experience? There have been no prescribing errors or safety issues with biosimilars in Europe, so having the same INN seems to be OK.
  - iv. **Is the definition of interchangeability missing something?** Shouldn't it have the caveat of "where state laws allow it" added to the end?
  - v. **Does having the same really indicate a relationship?** For example, filgrastim-sndz and filgrastim (Neupogen) are related as they were studied head to head. But what about tbo-filgrastim (Granix)? This wasn't studied head to head vs. Neupogen so could it be wrongly assumed that there is a relationship between the two products.

- vi. **Will different proper names be needed for biologics that have the same API but different indications, strengths and formulations?** For example, with denosumab need to be called denosumab-abcd when we talk about Prolia (for osteoporosis) and denosumab-wxyz when we talk about Xgeva (for oncology). Same goes for aflibercept (Zaltrap/Eylea) and insulin glargine (Lantus/Toujeo).
- vii. **Is it wise to allow companies to choose their own four letter suffix?** Surely it would make more sense for the FDA to assign these randomly. As long as they don't give out suffixes like CRAP, SEXY and SAFE, all should be good.
- d. NICE recommends biosimilar infliximab ahead of Remicade in RA patients
  - i. Follow similar guidance for ulcerative colitis
- e. EMA opens up consultation for new filgrastim guideline
  - i. Is this is the first step to not requiring Phase III studies?

**5. A change of heart in terms of biosimilar safety, switching and substitution?**

- a. New position papers from various medical associations (e.g. Finland, Netherlands) arguing that biosimilars can now be considered as clinically equivalent to their reference products
- b. Australia's PBAC 'a' flagging infliximab, meaning that Remicade can be automatically substituted for biosimilar infliximab
  - i. Caused huge uproar
  - ii. Patient safety issues pushed front and center
  - iii. Guess it's inevitable that this will happen
  - iv. Australia has taken the brave step and become the first
  - v. More countries are likely to follow
- c. More US states are approving interchange biosimilar substitution laws that will allow pharmacy level substitution of biosimilars (e.g. California, North Carolina).
  - i. A step in the right direction, but will only have a material impact on products reimbursed via Medicare Part D (specialty pharmacy) as Part B drugs (infused products) administered in physician offices.