

**Fordham IP Conference**  
**9 April, 2015 - Cambridge**

# **Biosimilar Patent Litigation – UK Perspective**

Dr Penny Gilbert  
Powell Gilbert LLP

**EPLAW**  
European Patent Lawyers Association

Powell   
Gilbert

# A changing landscape.

- The landscape of blockbuster medicines in Europe has been changing: small molecule drugs to biologics →
- The patents on many blockbuster biologics have already expired or will expire around 2020 making them targets for “biosimilar”
- Biosimilars (or follow-on biologics) are subsequent versions of originator biopharmaceutical products
- Impending “Patent cliff” but secondary patents might provide a “Soft landing” →
- Few biosimilars on the European market at present.
- Growing interest as a number of top selling biologics about to come off patent in the next five years.
- Only a few manufacturers, but most of them are well-established companies in the pharma/ biotech field with recombinant protein manufacturing expertise.

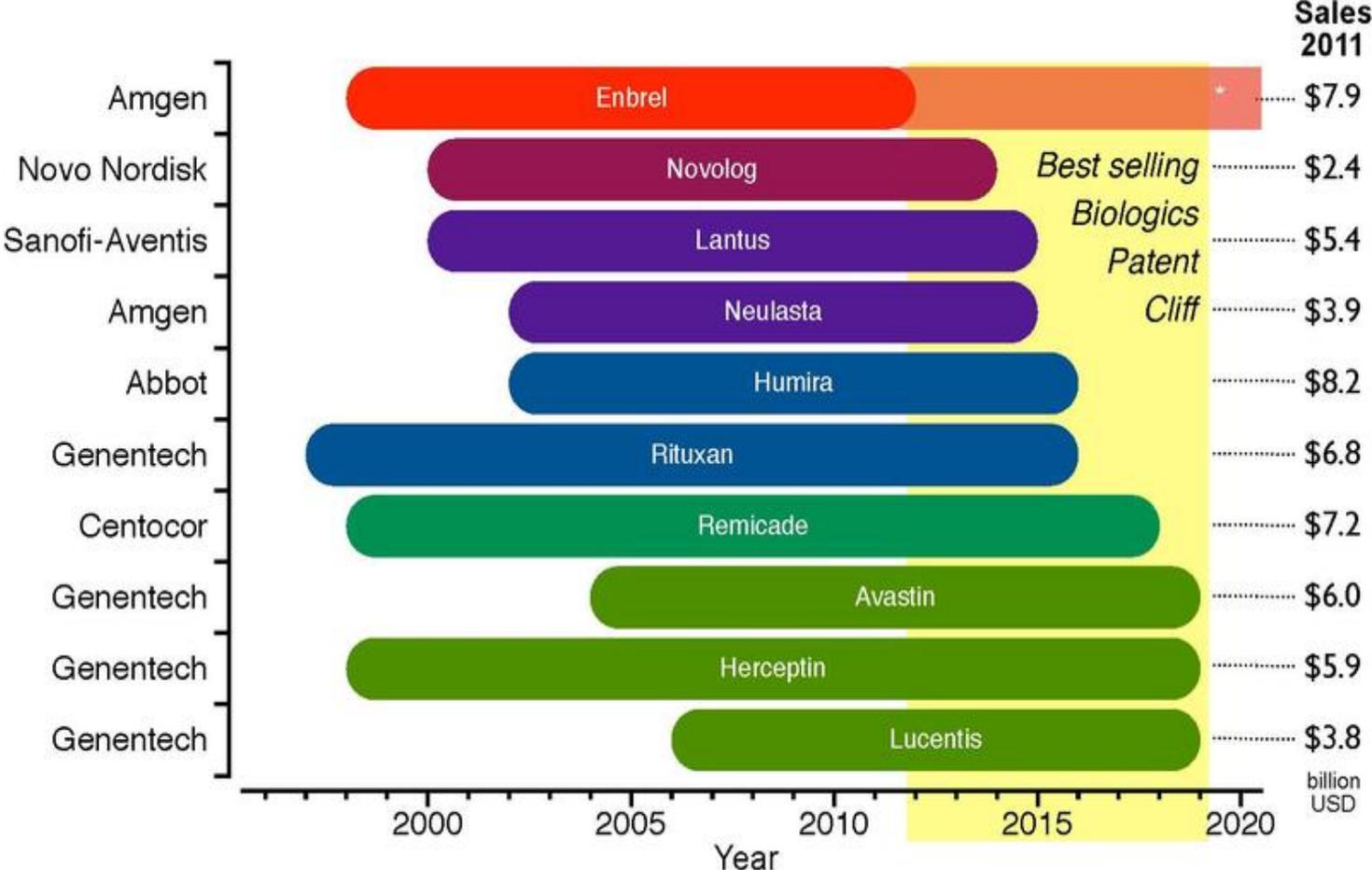
# Top 10 best-selling drugs in Europe 2008–2013



Source: IMS Health, MIDAS, MAT June 2013

	2008	2009	2010	2012	2013
1	Lipitor (atorvastatin)	Lipitor (atorvastatin)	Seretide (fluticasone/ salmeterol)	Humira (adalimumab)	Humira (adalimumab)
2	Seretide (fluticasone/ salmeterol)	Seretide (fluticasone/ salmeterol)	Lipitor (atorvastatin)	Seretide (fluticasone/ salmeterol)	Seretide (fluticasone/ salmeterol)
3	Plavix (clopidogrel)	Plavix (clopidogrel)	Humira (adalimumab)	Herceptin (trastuzumab)	Enbrel (etanercept)
4	Herceptin (trastuzumab)	Enbrel (etanercept)	Enbrel (etanercept)	Enbrel (etanercept)	Herceptin (trastuzumab)
5	Enbrel (etanercept)	Herceptin (trastuzumab)	Herceptin (trastuzumab)	Lipitor (atorvastatin)	Mabthera (rituximab)
6	Zyprexa (olanzapine)	Humira (adalimumab)	Lovenox (enoxaparin)	Mabthera (rituximab)	Remicade (infliximab)
7	Lovenox (enoxaparin)	Lovenox (enoxaparin)	Mabthera (rituximab)	Lovenox (enoxaparin)	Lovenox (enoxaparin)
8	Glivec (imatinib)	Glivec (imatinib)	Avastin (bevacizumab)	Remicade (infliximab)	Avastin (bevacizumab)
9	Pantozol (pantoprazole)	Zyprexa (olanzapine)	Remicade (infliximab)	Avastin (bevacizumab)	Lucentis (ranibizumab)
10	Symbicort (budesonide/ formoterol)	Mabthera (rituximab)	Glivec (imatinib)	Spiriva (tiotropium)	Lyrica (pregabalin)
Biological					

# Top 10 best-selling drugs in Europe 2008–2013



# Biosimilar players include:

## Generics

- Sandoz
- Mylan/ Biocon
- Hospira / Celltrion
- Actavis
- Merck Serono / Dr Reddys
- Stada / Gedeon Richter
- Synthron

+ China, India and other local manufacturers

## Large Pharma / Biopharma

- Boehringer Ingelheim
- Samsung / Biogen
- Pfizer
- Amgen

▪+ non-pharma including Samsung and LG

# Biosimilars v Generics

- **Small molecule generic drugs**
  - Chemically based compounds – easily replicated identically and considerably less expensive to reproduce.
  - Generic regulatory approval generally based on *in vitro* release data with minimal clinical work required.
- **Biologics**
  - Complex proteins/antibodies derived from living organisms that are genetically modified
  - Difficult and costly to produce
  - Regulatory approval pathway is more complex for Biosimilars requiring more extensive testing than for a small molecule generic.

# Regulatory hurdles



- The regulatory body for approval of medicines in the EU is the European Medicines Agency (EMA).
- All medicines for human and animal use derived from biotechnology and other high-tech processes (including biosimilars) must be approved via the centralised EMA procedure.
- The complexity of biological products makes the standard generic drug procedure, based on **bioequivalence** to innovator product, not applicable.
- Procedure is based on a thorough demonstration of "comparability" of the "similar" product to an existing approved product.

# Biosimilar Authorisation

- EMA has well established procedure:
  - **Overarching Guidelines:** covering all biosimilar products
  - **Specific Guidelines:** specific to the type of biosimilar product.
  
- 1. Non-clinical comparability (comparative non-clinical studies)
- 2. Clinical comparability (comparative clinical studies)
- 3. Quality comparability is established with regard to
  - the molecular structure
  - the functionality and
  - must be demonstrated with rigorous comprehensive analytical characterisation of the reference medicinal product in a rigorous comparative manner.

# Patent hurdles



- After the regulatory hurdle, patents may lie in the way.
- No Orange Book or the like for biologics.
- No EU “Patent Dance”.
- Identification of relevant patents for biologics is not straightforward – and there may be many!
- Secondary patents will be relevant:
  - medical uses
  - dosage regimens
  - manufacturing methods
  - Devices.
  
- Do special considerations arise for enforcement against biosimilars?

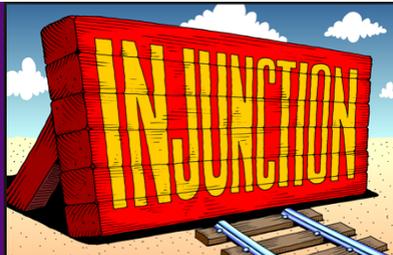
# Availability of Preliminary Injunctions?

- Particular relevance to generic cases – disruption of originator monopoly can have dramatic and irreversible effects on price due to the reimbursement system for medicinal products.
- Established UK case law doctrine that generic market entrants should ‘clear the way’ by seeking revocation or declaratory relief. If they do not, they are at risk of being restrained from launch pending full trial (SKB v Apotex, followed in many cases subsequently).
  - minimise the risk of injustice in the interim, pending resolution of the dispute at trial.
  - Injunction backed by a cross-undertaking in damages, which may be significant.
  - Potential for cross-undertaking to extend to the NHS (as the ultimate payer for the products) - little case law on this aspect.



# Clearing the way – *SKB v Apotex*

- Generics lined up pre-patent expiry regulatory approval to launch
- SKB originally heard of launch plans and applied for interim injunction
- *American Cyanamid* principles applied and injunction granted
  - Is there a serious issue to be tried? – agreed
  - Would damages be an adequate remedy?
  - SKB – Expected price downward spiral
  - Apotex – Value in being 1<sup>st</sup> to market and lost opportunity unquantifiable?
    - Where does the balance of convenience lie?
- Clear the way to market or face an injunction
  - Preliminary injunction
  - Trial on the merits on both infringement and validity within 12-18 month (appeal 12 months later) NB *Hospira v Novartis* re timing
  - *Cephalon v Orchid* – there may be factors where the balance of convenience does not favour an injunction



# Are considerations different for biosimilars?

- Complex manufacturing process and regulatory approval requiring extensive clinical testing makes cost of bringing biosimilar to market much higher than small molecule generic.
- Innovators may face one or two competitors per product (not 10-20 as for generic small molecules).
- May be an initial reluctance to prescribe biosimilars (issues including INN naming and confidence of medical professionals/ patients to switch)
  - Price reduction / market penetration following biosimilar launch may be less than for a generic; and
  - Fewer competitors may mean no/less dramatic downward price spiral on launch.
- How will these factors affect risk of patent litigation?

# Clearing the way for Biosimilars?

- As yet no case law.

## But:

- *Eli Lilly v Sanofi*

Biosimilar insulin glargine. Patent relates to delivery device. Defendant brought proceedings to clear the way. Judge ordered speedy trial so that patents could be dealt with (to appeal level) before planned launch to avoid PI risk.

- *Hospira v Genentech*

Multiple patent revocation/ DNI proceedings to clear the way for launch of biosimilar trastuzumab / Herceptin.

# Nature of Validity Challenges

- Most likely secondary patents at issue
- All grounds of invalidity available:
  - Lack of sufficiency
    - eg clinical data for proof of new medical use / dosing regimen *Hospira v Genentech I*
  - Prior disclosure
    - eg Phase II trials for new use *Hospira v Genentech II*
  - Lack of inventive step
    - eg known purification steps for other molecules *Hospira v Genentech I*; known excipients and formulation methods *Hospira v Genentech II*
- SPC challenges?

# More patent litigation?



- Valuable market - blockbuster biologics
- Incentive to litigate to clear the way – or enforce monopoly – will be high
- Cost of bringing product to market already high, more to lose if cannot sell!
- Will we see these cases in the UPC if launch timings approach start of unitary patent package (late 2015+)?
- Revocation and DNI cases will be brought in London = Central Division for Life Sciences.
- An opportunity to try to beat EPO opposition proceedings to a final decision on central revocation.

# Thank you!

penny.gilbert@powellgilbert.com

