



**ECRON ACUNOVA**

*Accelerating Pharma time-to-market, cost effectively*



Asia



Europe



Americas

# **Biosimilars Clinical Development: Opportunity & Challenges**

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## EA Biosimilars Opportunity



- Biosimilars mkt estimated (PWC 2009) at \$40B in 2020 from \$2B in 2010. 10 (12) year exclusivity granted to innovators US/EU expiring by 2015.
- Diabetes (Insulin), cancer (interferon Alfa, epoetin), MS (interferon Beta) and HGHD (somatropin) treated successfully with biological drugs.
- Monoclonal Antibody treatment can cost up to \$100k/year
- Chronic nature of diabetes, cancer, MS..... Makes lifetime treatment with biological drugs high cost and out of reach for many patient groups.
- Patient advocacy groups and governments have interest in Biosimilars, to lower health care cost and make these wonderful drugs accesible.
- More innovators enter Biosimilar space. Novartis, Pfizer, Merck, Hospira have been joined by BI, GSK, Amgen, Biogen in 2011!

***Amgen, Biogen join Biosimilar race in 2011!***



## Challenges in Biosimilars introduction



- Economics of introduction has to be a fraction of the cost of biological drug near patent expiry
- Production cost, clinical development cost and market access costs have to be comparatively less.
- Ambiguous regulatory pathway adds significantly to introduction cost
- Biosimilar co's & regulators are challenged with issues of patient safety, efficacy & follow up, to find an optimal pathway.

***Biosimilar co's & regulators challenged for the right pathway***



## Production and market access



- Biologics are made in living systems as micro-organisms, plants or animal cells. Minor change in raw material, process impacts end product.
- Control on source & initial material is required for stable process over time
- Biologics are difficult to characterize unlike chemical entities.
- Biosimilar makers for consistency, quality & purity follow same process as reference product. <100 tests on small molecule vs. >2000 tests on biologics. Govt's like India are subsidizing characterization labs.
- Biosimilars need significant mfg investment. Teva has a JV with Lonza.
- Asian Biosimilar co's through 'frugal innovation' have partly overcome!
- To access physicians in G8 mkt , Biosimilar Cos work with local partners.
- Biosimilar co's prefer entry, where government buys in bulk thro' tenders

***Frugal innovation & simultaneous entry into multiple markets***



## Clinical Development challenges



- Convince regulators to abridge toxicology and pre clinical studies
- Biosimilars are injectibles. Emergency response time available in an AE is much less. Study design/ site selection to anticipate and mitigate risk.
- Biologics elicit immune response.-sometimes life-threatening. Immune response can also manifest as reduced efficacy.
- If subjects become immune, can they switch to reference product ?
- Safety issues call for luminary tertiary care sites. Luminaries prefer to work on innovator drugs, than on Biosimilars
- Long term follow up of trial subjects is a requirement for Biosimilars
- Merck -Parexel & Samsung - Quintiles tie-up indicate need for a long term association of CRO with Biosimiliars company.

***Sponsors & regulators look for a credible & competent CRO***

# EA Pharmacovigilance



- Essential to monitor immunogenicity with a long incubation period.
- Continued benefit-risk assessment is sought by some Regulators.
- Pharmacovigilance system to include services of a qualified physician
- Necessary means for notification of AE's in all countries marketed.
- System to ensure specific identification of the SBPs (*i.e. traceability*).
- PV and PSUR after launch needed similar to biologics.

***Choose a CRO with capability in PV & safety services***

## EA Country selection for Biosimilar studies



- Marketing authorization in large markets is essential to lower cost/dose
- US, EU, Japan, India, Korea are key markets. Govt. of Malaysia and South Africa have shown keenness to authorize Biosimilars.
- Unclear Regulatory pathway, slows clinical development & increases cost
- Let us examine the pathway in key markets.

***Country selection for Biosimilars study is influenced by a clear regulatory pathway (other factors being common)***

## EA US FDA pathway for Biosimilars (follow-on biologics)



- Largest potential market.
- For applications for 2013-17, FDA public hearings on Nov 2<sup>nd</sup> and 3<sup>rd</sup>
- FDA's plan, process, recommendation is going to congress on Jan 15, '12.
- Process patent information exchange proving patent expiry or challenge
- Biosimilars managed by FDA section dealing with innovator biologics.
- Abridged routes planned in principle under Sec 505(b)(2)
- Obama administration prioritized to improve access at economical cost
- In March 2010 Health Canada released Govt guidelines on Biosimilars.

***US lacks clear regulatory pathway for Biosimilars  
Wise to design CDP to comply with draft FDA guidelines  
Conducting study in USA not currently advisable***

# EMA EMEA's pathway for Biosimilars



- Guidelines provide clear pathway. Guidelines by protein class issued.
- Clear comparability of quality, safety & efficacy to reference product.
- Minor structural differences in active substance acceptable
- Step wise demonstration of similarity
- Study conduct with an optimal mix of western and eastern European countries reduces time to market at optimal cost
- Long term follow up of study participants is required.
- Substitution by prescribing physician and not Pharmacist
- Provides market access to 27 EU, 3 EEA-EFTA countries, Japan, ANZ.  
Data is also helpful to enter Swiss and Turkish markets. (34 nations)

***Clear guidelines & attractive market – Co's choose Europe***



## WHO (Geneva CH) guidelines for Biosimilars



- Globally harmonized framework for licensing in multiple countries.
- Global standard against which experimental values can be compared.
- Stepwise comparability exercise: 1.Quality 2.Non-clinical 3.Clinical data
- Differences in quality attributes known to have potential impact on clinical activity is not acceptable e.g. glycosylation patterns
- Immunogenicity- should always be investigated in humans
- Extrapolation of efficacy and safety data to other indications possible
- WHO approval provides a low cost access to markets:
  - No profit sharing with local partners due to WHO tendering process
  - Access to Korea, Malaysia which have harmonized with WHO
  - Malaysian approval provides access to middle east & gulf countries
  - India, S Africa etc using abbreviated guidelines likely to adopt WHO

***WHO approval provides advantages of market access and product extension . Should be seriously evaluated***

## In summary.....



### Key factors for CRO Selection

1. CRO who understands Biosimilars industry dynamics
2. Conversant with regulatory pathways including WHO
3. Who can recruit from western and eastern Europe, Korea, Malaysia , South Africa and India.
4. Relationship with tertiary care luminary sites interested in conducting Biosimilar studies.
5. Can select sites with emergency response.
6. Has a competent PV service

***Ecron Acunova CRO meets above criteria***



## Experience in Biosimilar Studies

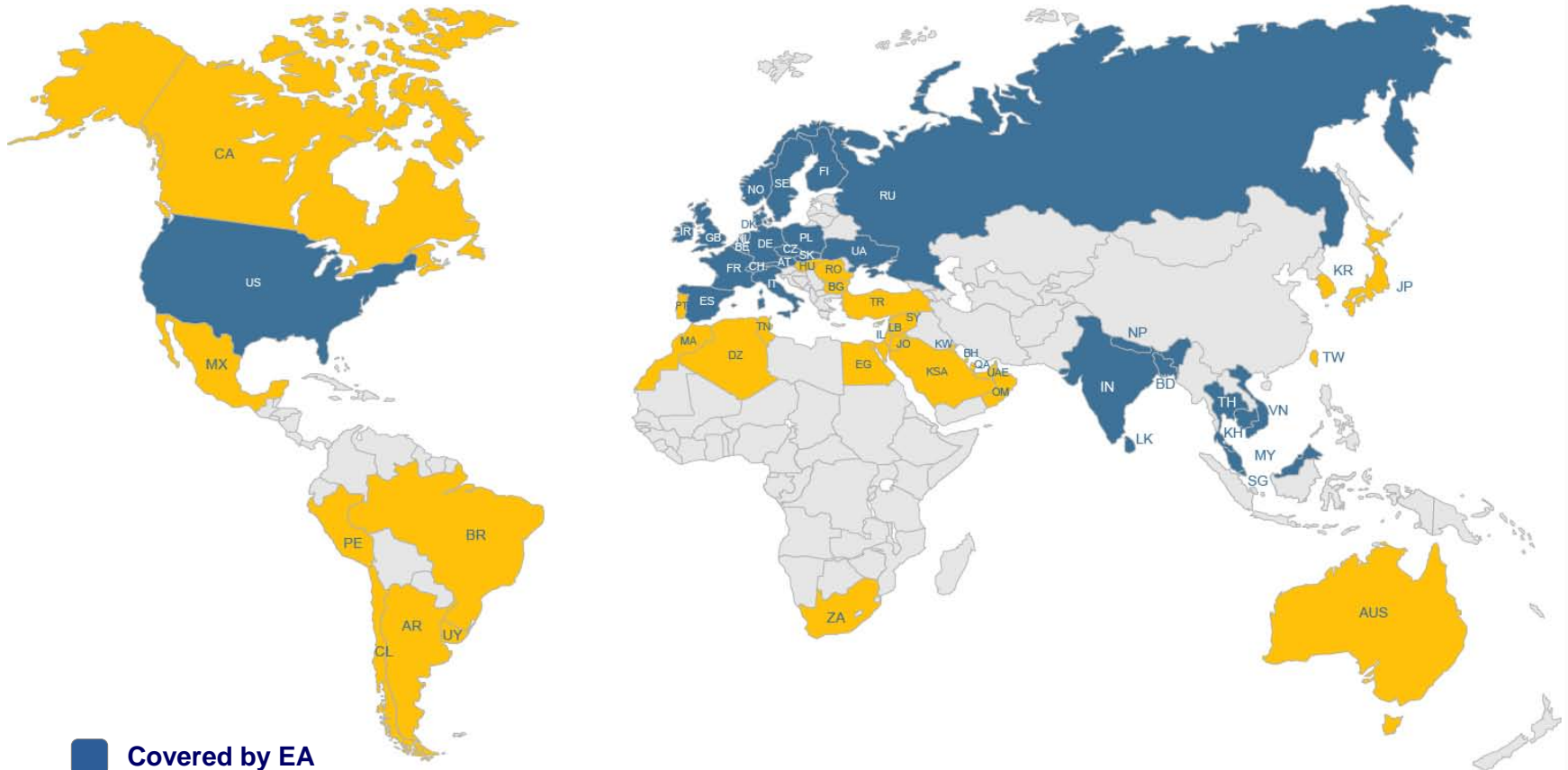


#	Indication	Sponsor	Drug	Patients	Services	# of Sites
1	Breast Cancer	Biocon	BIOMab EGFR	43	Clinical Operations	02
2	Breast Cancer	Celltrion	Trastuzumab	-	Regulatory Consulting	-
3	Percutaneous Coronary Intervention	Lupin	Abciximab	210	All	13
4	Rheumatoid Arthritis	Biotrion	Etanercept	224	All	10
5	DVT Prophylaxis (PMS)	Lupin	Enoxaparin	450	Clinical Operations	27
6	Deep Vein Thrombosis	Sanofi Aventis	Enoxaparin	200	Clinical Operations	10



# Studies for marketing authorization in key markets

*Meeting guidelines of WHO, US FDA, EMA, Health Canada, MHW, DCGI ....*



## Covered by EA

Austria, Bangladesh, Belgium, Cambodia, Czech Republic, Denmark, Finland, France, Germany, India, Ireland, Italy, Malaysia, Nepal, Netherlands, Norway, Poland, Russia, Singapore, Slovakia, Spain, Sri Lanka, Sweden, Switzerland, Thailand, UK, Ukraine, US, Vietnam



## Covered through Co-operations

Algeria, Argentina, Australia, Bahrain, Brazil, Bulgaria, Canada, Chile, Egypt, Hungary, Israel, Japan, Jordan, KSA, Kuwait, Lebanon, Mexico, Morocco, Oman, Peru, Portugal, Qatar, Romania, South Africa, South Korea, Syria, Taiwan, Tunisia, Turkey, UAE, Uruguay

# EA Recent Biologic studies



SI No	Product	SI No	Product	SI No	No. of Projects
1	Intraocular lenses	6	Herbal medicine	11	Hormone
2	Hormone	7	Interferon	12	Collagen-based biomatrices
3	Intra articular injection compound	8	Hormone	13	Monoclonal AB
4	Monoclonal AB	9	Antibiotic	14	Antibiotic
5	Bispecific AB	10	Amino Acid	15	Inhaling agent
				16	TTS



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*Thank You*