BIOINFORMATICS
Life Science Industry Market Research

Manufacture of Biosimilar Drugs for the U.S. Market: Defining the Market Opportunity for Life Science Suppliers

Multi-Sponsor Research Prospectus 13-003
Prepared for Life Science Manufacturers & Suppliers

May 2013

BioInformatics LLC
2111 Wilson Boulevard
Suite 250
Arlington, VA 22201
703.778.3080 x 13 phone
703.778.3081 fax

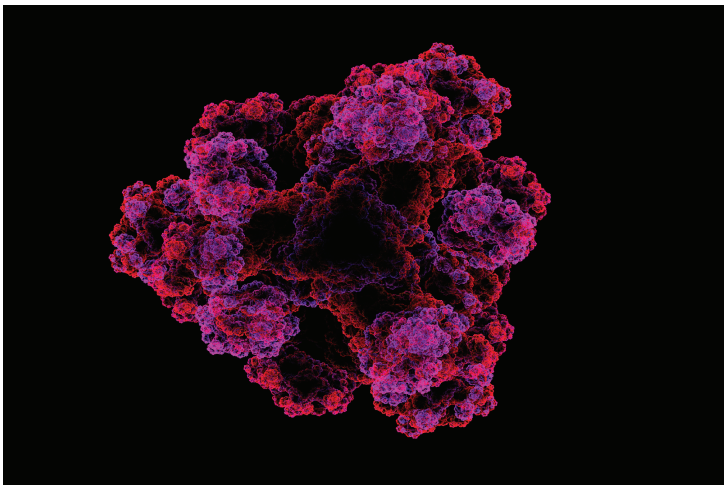
Objectives

In response to our clients' needs to better understand the opportunity for life science instrument suppliers in the U.S. market with regards to the development of biosimilar drugs, BioInformatics LLC is proposing to conduct a multi-sponsored study to conduct in-depth research with key stakeholders in the biosimilar drug discovery and development industry.

To provide insights to life science suppliers who stand to benefit from the introduction of biosimilars development in the U.S. market, in this study we will explore the following objectives:

- Describe the scale of the opportunity presented by biosimilars for analytical instrumentation manufacturers.
- Identify best practices at European pharmaceutical companies to demonstrate comparable physicochemical characteristics, molecular characteristics, purity, biological activity and stability.
- Understand how US pharmaceutical companies are planning to demonstrate biosimilarity and what affect these strategies will have on their choice of analytical instruments and consumables.
- Explore how different classes of biosimilars (monoclonal antibodies vs. other protein therapeutics) will influence the selection of tools necessary for establishing biosimilarity.
- Determine whether existing analytical instrumentation is sufficient for the needs of biosimilar manufacturers and what improvements to sensitivity, specificity, precision and accuracy may be required.
- Highlight what pharmaceutical customers expect from their analytical instrumentation vendors in terms of partnerships, services and support.

The Situation



Establishing a regulatory pathway for pharmaceutical companies in the U.S. to manufacture biosimilar drugs presents a much anticipated new market opportunity for life science analytical instrument suppliers. Suppliers who are monitoring this development closely are asking questions that are difficult to pin down. Will there be an increased need for instrumentation or instrumentation features to meet the demand for biosimilar drugs? What types of new instruments or features will be required to determine biosimilarity? How will the types of molecules targeted influence decision-making regarding pipeline prioritization and analytical instrumentation selection? *Manufacture of Biosimilar Drugs for the U.S. Market: Defining the Market Opportunity for Life Science Suppliers* will present an in-depth exploration of these questions—and more—to find out what this regulatory change could yield for suppliers of analytical instrumentation.

The Situation (continued)

The delivery of more cost-effective healthcare has become a worldwide challenge as the costs associated with healthcare continue to increase, driven by changing demographics, societal expectations and advances in medical technology. The introduction of alternative versions of biologic products, also known as biosimilars, into the United States market has been gaining increasing visibility as patents for many agents are nearing expiration and as the Food and Drug Administration (FDA) moves closer to establishing a regulatory pathway for these agents.

- Global sales of biosimilar drugs are expected to increase from $311 million in 2010 to an estimated $2-$2.5 billion in 2016 driven by (1) the availability of new biosimilar drugs and (2) opening of the U.S. market.

- Biosimilar drugs are typically less expensive (20% to 30% lower) than the branded biological, reducing healthcare costs in developed markets, improving the standard of care for some indications and providing greater accessibility of care to pharma-emerging markets.

- Lower costs and faster time to development is expected for biosimilar drugs. Estimates of about eight years and $100-$250 million are associated with development and testing of biosimilar drugs compared to $1 billion for a novel biological entity and $1-10 million for a generic small molecule drug.

Although less burdensome than the requirements for new pharmaceuticals of the same class, abridged regulatory pathways, well-established in Europe and pending in the United States, for authorization of biosimilars are underpinned by a science-based approach that reflects the complexity of the molecule in question. The process for developing monoclonal antibody biosimilars is expected to be much more complex than that associated with erythropoietin or G-CSF.

Below is a listing of the types of analysis that could be required during biosimilar drug development:

- Protein structure
- Drug-related substances and/or impurities
- Process-related substances and/or impurities
- Post-translational modifications
- Function/potency
- Stability
- General Methods
- Non-clinical analyses in relevant animal mode

The draft guidelines published by the FDA in February 2012 requires the manufacturer of a biosimilar product to find appropriate ways to analytically compare the biosimilar product to the original product in terms of structure and function. Thus, the initial investment in product development will be to find ways to perform this analysis. The observed analytical differences between products will drive what further testing needs to be done.

The draft guidelines are intended to assure that subtle structural and compositional differences do not impact the clinical performance of the biosimilar to its reference standard with regards to quality, safety and efficacy. That said, a high level of uncertainty remains for drug manufacturers with regards to the full extent of testing that will be required for a particular drug or class of drugs. Also unknown is how the FDA plans to evaluate "interchangeability"; that is, the ability of a pharmacist to substitute a biosimilar drug for the branded innovative product.

The Situation (continued)

Manufacturers of biosimilars do not have access to the originator's cell banks, exact fermentation and purification processes, or the active drug substance. The question of how biosimilars manufacturers can compare their product to originator products and prove similarity and indeed encourage interchangeability is therefore a hot issue for biosimilars research.

The market opportunity for biosimilar drug manufacturers is thought to be high, although not totally risk-free. The stage appears to have been set for a period of rapid biosimilar product development by drug manufacturers. In this rapidly changing landscape, *Manufacture of Biosimilar Drugs for the U.S. Market: Defining the Market Opportunity for Life Science Suppliers* will help life science suppliers clarify opportunities in the U.S. market.

Top Selling Biologic Drugs of 2011

Name	Lead Company	Approved Indications	2011 Worldwide Sales ($ millions)
Humira (adalimumab)	Abbott Laboratories	RA; juvenile rheumatoid arthritis; Crohn's disease; PA; psoriasis; ankylosing spondylitis	$7,932
Enbrel (etanercept)	Amgen	RA; psoriasis; ankylosing spondylitis; PA; juvenile rheumatoid arthritis	$7,367
Rituxan (rituximab)	Biogen Idec	Non-Hodgkin's lymphoma; RA; chronic leukocytic leukemia / small cell lymphocytic lymphoma; antineutrophil cytoplasmic antibodies associated vasculitis	$6,772
Remicade (inflixmab)	Johnson & Johnson	RA; Crohn's disease; psoriasis; ulcerative colitis; ankylosing spondylitis; Behçet syndrome; PA	$6,751
Avastin (bevacizumab)	Roche	Colorectal cancer; non–small cell lung cancer; renal cell cancer; brain cancer (malignant glioma; anaplastic astrocytoma, glioblastoma multiforme)	$5,968
Herceptin (trastuzumab)	Roche	Breast cancer; gastric cancer	$5,924
Neulasta (pegfilgrastim)	Amgen	Neutropenia/leukopenia	$3,952
Lucentis (ranibizumab)	Roche	Wet age-related macular degeneration; retinal vein occlusion	$3,769
Avonex (interferon beta 1-a)	Biogen Idec	MS	$2,687
Rebif (interferon beta 1-a)	Merck	MS	$2,354
TOTAL:			**$53,476**

RA, rheumatoid arthritis; PA, psoriatic arthritis; MS, multiple sclerosis. Source: BioMed Tracker.

Description of Work to be Performed

BioInformatics LLC will conduct dozens of in-depth interviews to understand how biopharmaceutical companies in the EU and the United States view the manufacture of biosimilars.

Representatives responsible for regulatory policy, intellectual property, regulatory compliance, preclinical research, business development, research and development, process development and/or bioproduction from the following companies may be interviewed:

Pharma/Biopharmaceutical Companies:

Abbott Bioresearch
Amgen
AstraZeneca
Baxter International
Biogen-Idec
Boehringer Ingelheim
Celltrion
Cook Pharma
Eli Lilly
GE Healthcare
Genzyme
Hospira, Inc.
Johnson & Johnson
Medice
Medimmune
Merck & Co.
Momenta Pharmaceuticals
Novartis
Pfizer
Roche Holding
Samsung Bioepis Co., Ltd.
Sandoz/Novartis
Seattle Genetics, Inc.
STADA Arzneimittel AG
Symphogen A/S
Teva Pharmaceutical Industries Ltd.
Watson Pharmaceuticals

Contract Research Organizations:

Covance
Karmic Lifesciences, Inc.
Parexel
Quintiles
BaroFold, Inc.

Interview Guide & Conducting Interviews

The key information objectives for this report are used to guide the discussion but are not intended to be a "script" because the research effort will be conducted in the form of a conversation rather than a traditional market survey interview. This technique allows the interviewer greater freedom, latitude, and flexibility when working with each respondent. This technique also allows the interviewer to steer the conversation to areas that the respondent may be more willing and open to discussing, while minimizing any perceived threats or concerns over confidentiality. In most cases, discussions average 20 to 30 minutes in length and in many cases no given individual will have opinions on all of the key information objectives being sought.

At no time will BioInformatics LLC ask a respondent to disclose any information that he/she declares is proprietary and/or confidential and, in fact, will explicitly explain to said individual that he/she is only being asked to provide more general information or insight, and their opinions on market evolution and competitor activity.

BioInformatics LLC will follow a strict ethical methodology and process in conducting the telephone interviews. In addition, BioInformatics LLC will not engage in any coercion or coercive tactics to obtain participation by respondents, nor will it provide any financial or material compensation to entice a competitor's participation and/or disclosure of confidential/proprietary information. That said, BioInformatics LLC may share information that it has obtained from other sources with respondents as a means to obtain their participation in the discussion. Throughout the interviews, BioInformatics LLC will continually attempt to challenge and corroborate data, information, and opinions obtained from other respondents.

The Advantages of Participating in Multi-Sponsor Research Include:

Considerations	BioInformatics LLC Advantages:
Sart-up Time	BioInformatics LLC has a multidisciplinary team of scientists, industry veterans and market research experts who will begin work immediately upon receipt of your Sponsorship Agreement.
Expertise	BioInformatics LLC has unmatched expertise in the life science market and has delivered market studies to more than 500 unique suppliers.
Objectivity	BioInformatics LLC Multi-Sponsor Research Projects are unbiased and provide a fresh perspective on your strategies.
Efficiency	There is no need for the pre-publication sponsors to disrupt their routine activities. BioInformatics LLC will achieve the sample quota and deliver the final report within the required time frame.
Cost Control	To commission a custom study on biosimilar development at this level of effort would cost approximately $50,000-$60,000.

BioInformatics LLC will deliver an in-depth analysis of the study's significant findings and their implications regarding the market opportunity for life science suppliers in the development of biosimilars. An electronic version (PDF) of the final report will be provided to each sponsor. The final report will consist of the following sections:

Section 1. Executive Summary and Key Findings.
Section 2. The Biosimilar Market Opportunity
Section 3. European Best Practices for Establishing Biosimilarity
Section 4. US Pharmaceutical Company Strategies & Implications for Vendors
Section 5. Selecting Analytical Tools to Establish Biosimilarity
Section 6. Customer Unmet Needs
Section 7. Customer Expectations of Vendors
Section 8. Company Profiles of Five Leading Biosimilar Manufacturers
Section 9. Interview Notes & Supporting Data

Categories of biological drugs to be considered in this report:

G-CSF (Granulocyte-Colony Stimulating Factor)

Somatropin

LMWH (low molecular weight heparin)

Monoclonal antibodies

FSH (follicle-stimulating hormone)

Insulin

Interferon-alpha

Erythropoietin

Interferon-beta

References

Blackstone EA, Fuhr JP. Innovation and Competition: Will Biosimilars Succeed? *Biotechnology Healthcare*. 2012 Spring 9(1): 24-27.

FDA, *Guidance for Industry: Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009* (Draft Feb. 2012), *available at* http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm25979 7.htm. Accessed January 10, 2013.

FDA, *Guidance for Industry: Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product* (Draft Feb. 2012), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/ Guidances/UCM291134.pdf. Accessed January 10, 2013.

FDA, *Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (Draft Feb. 2012), *available at* http://www.fda.gov/ downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ UCM291128.pdf. Accessed January 10, 2013.

Gravel P, Naik A, Le Cotonnec, J-Y. Biosimilar rhG-CSF: How Similar Are They? *Targ Oncol* 2012. 7 (Suppl 1): S3-S16.

Haag T, Krattinger C. The Emergence of Biosimilars - *How are they Different from Generics and What are the Implications for Marketing?* EphMRA 2011 Conference Plenary Presentation June 29, 2011. http://www.ephmra.org/pdf/EphMRA%202011%20Conference%20Haag%20&%20Krattiger%20Plenary%2029th%20June%202011.pdf Accessed on January 14, 2013.

Huggett B , Lähteenmaki R. Public biotech 2011—the numbers. *Nature Biotechnology*. 2012 30: 751–757. http://www.nature.com/nbt/journal/v30/n8/fig_tab/nbt.2320_T5.html. Accessed January 14, 2013.

IMS Health. *Shaping the biosimilars opportunity: A global perspective on the evolving biosimilars landscape*. 2011 IMS Health Incorporated. http://www.imshealth.com/ims/Global/Content/Home%20Page%20Content/IMS%20News/Biosimilars_Whitepaper.pdf. Accessed January 10, 2013.

Kozlowski S, Woodcock J, Midthun K, Sherman RB. *Developing the Nation's Biosimilars Program*. N Engl J Med 2011. 365(5): 385-388. Accessed January 16, 2013.

Malkin BJ. *Challenges to the Development of a Biosimilars Industry in the United States in Recent Developments in Food and Drug Law* 2013 Edition ©2012 Thomson Reuters/Aspatore. Accessed January 16, 2013.

Questions and answers on biosimilar medicines (similar biological medicinal products). EMA/837805/2011. http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/12/WC500020062.pdf. Accessed December 5, 2012.

These fees are calculated based on the nature and scope of the project, the level of detail, the objectives and the relative difficulty of obtaining the information. The delivery of the final report will mark the end of this assignment.

Task	Timing
Due date for signed agreement	3/15/13
Email report delivered in PDF format	5/31/13
TOTAL	***$15,000/sponsor***

General Terms

BioInformatics LLC is unable to guarantee the participation of any specific individual and will seek to obtain the participation/opinions of specific individuals on a **"best efforts"** basis only.

Fee includes *all* costs associated with the production of this report.

In order to successfully undertake this engagement, we understand that we will be exposed to highly confidential and proprietary information about your company. Therefore, BioInformatics LLC promises not to disclose, reveal or share any confidential or proprietary information about your company that we learn during the duration of this engagement and for three years thereafter. Confidential and proprietary information covered by this agreement includes, but is not limited to, information relation to your personnel, operations, methodologies, products, pricing, strategies, financing and customers. Every BioInformatics LLC employee and analyst is required to sign a strict confidentiality agreement and copies of these agreements will be made available to each sponsor.

BioInformatics LLC also pledges to uphold the highest of ethical standards. BioInformatics LLC will pursue research engagements with zeal and diligence while avoiding all unethical practices.

BioInformatics LLC will neither seek, nor provide, competitor trade secrets (as defined by law).

Payment Terms

For this engagement, BioInformatics LLC's billing procedures are as follows:

- 50% of the total engagement cost is due upon receipt of your signed Authorization Letter.
- Balance due upon receipt of the final authorized task.
- The delivery dates and fees contained in this proposal will remain in effect until March 15, 2013.
- A minimum of six (6) companies must participate, or BioInformatics LLC reserves the right to cancel the project. If the project is canceled by BioInformatics LLC, sponsor fees will be refunded.

Our Valued Clients

Biotechnology/Life Science

AbCam
AbD Serotec
AB SCIEX
Accelrys
Adnavance Technologies
Affymetrix
Agilent Technologies
Alcott Chromatography
Alfa Wassermann
American Type Culture Collection
Anachem
Apple Computer
Applied Precision
ART Advanced Research Technologies
Asterand
Axxora
Barr Laboratories
BD Biosciences
Beckman Coulter
BIA Separations
Biocept
BioGenex
Bioneer
Bio-Rad Laboratories
Biotage
Bio-Tek Instruments
Blue Heron Biotechnology
BTF - Precise Microbiology
Carl Zeiss
Cell Signaling Technology
Cepheid
Charles River Laboratories
CIS bio
CLC bio
Clontech Laboratories
Corning
CyBio
DAKO
Dharmacon
DNAStar
DxS
Edge Biosystems
Eksigent Technologies
EMD Millipore
Entelechon
Epigenomics
Epitomics
Eppendorf
Eurogentec
Expression Analysis
Expression Pathology
Fermentas
Fine Science Tools
Fluidigm
Fluorous Technologies
Fujirebio Diagnostics
GE Healthcare
Gene Codes
Gene Therapy Systems
Genomic Solutions
Gen-Probe
GenVault Corporation
Glycominds
Helicos BioSciences
Hitachi Instruments
Hybrigenics
IBM Life Sciences
Illumina
Instron
Integrated DNA Technologies
Interagon
Irvine Scientific
Kirkegaard & Perry Laboratories
Kodak Scientific Imaging
Leica Microsystems
LI-COR
Life Techonologies
Luminex
Macherey-Nagel
MDL Information Systems
Mettler-Toledo AutoChem
MiraiBio
Mo Bio Laboratories
Molecular Devices
MP Biomedicals
New England Biolabs
Nonlinear Dynamics
Novozymes
NuGEN Technologies
OligoEngine
OpGen
Osmonics
Ovid Technologies
Ozyme
Pall Life Sciences
PamGene
Pel-Freez
Percival Scientific
PerkinElmer Life Sciences
PetaGen
Photometrics
Photon Technology International
PhyNexus
Plexagen Diagnostics
Post Genome Institute
PPD
Promega
Proteome Systems
Qbiogene
QIAGEN
R & D Systems
Ribomed Biotechnologies
Sachem
Sandia National Laboratories
Sarstedt
Schott Nexterion
Sigma-Aldrich
SomaLogic
Source Precision Medicine
Strand Genomics
SurModics
Takara Mirus Bio
Talent S.r.l.
Targeted Genetics
Tecan
TEF LABS
The Jackson Laboratory
Thermo Fisher Scientific
Thomas Scientific
Transgenomic
Universal Imaging
UVP
Virginia Bioinformatics Institute
Vision BioSystems
VWR International
Waters

Medical Diagnostics

Applied Imaging
Dade Behring
Diametrics Medical
Guidant
Hewlett-Packard Medical Products
LifeScan
Ortho-Clinical Diagnostics
Radiometer
Tektronix
Varian

Pharmaceuticals

Abbott Laboratories
Allergan
Amgen
AstraZeneca
Aventis
Baxter Healthcare
Bayer
Boehringer Ingelheim Pharmaceuticals
Cardinal Health
Genzyme
Janssen Pharmaceuticals
Merck
Novartis Pharmaceuticals
Novo Nordisk Pharmaceuticals
Pfizer

Professional Services & Finance

Audacity Group
Bain & Company
Gerson Lehrman Group
McKinsey & Co.
OCC Strategy Group
PJ+A
PureTech Ventures

Publishers & Associations

Academic Press
C&EN
Elsevier
Informa Life Sciences
John Wiley & Sons
Nature Publishing Group

Authorization Letter

Project No.: 13-003
Please remit to:
BioInformatics LLC
2111 Wilson Boulevard
Suite 250
Arlington, VA 22201
(703) 778-3080 *phone*
(703) 778-3081 *fax*

Purchase Order Number: _____

Please sign, date and complete the Accounts Payable details and REMIT TO:
accounting@gene2drug.com, or
703.778.3081 (fax)

_____ Yes, my company wishes to participate as a pre-publication sponsor of BioInformatics LLC's study, *Manufacture of Biosimilar Drugs for U.S. Market: Defining the Market Opportunity for Life Sciences Suppliers*.

I understand that the budget for this project is $15,000 including expenses, for delivery of the final report on May 31, 2013.

A non-refundable payment of $7,500 is due from each sponsor before the start of the project. The balance of $7,500 is due upon delivery of the final report.

Payment method for initial deposit: (please select one option)

☐ Charge my credit card
Type: _____ (American Express, MasterCard, Visa) Number: _____
Security/CSC:_____ Name on card: _____
__ Expiration Date (MM/YY): _____

☐ Bank wire/ACH payment (if selected, we will send our bank details)

☐ Invoice me referencing Purchase Order #: _____

Authorized by:

_____ _____
(Signature) (date)

_____ Billing Address

_____
Street Address

_____
City, State/Province, Postal Code

_____
Country

BioInformatics LLC's Federal Tax Identification Number is 54-2001907