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Azadi Ka Amrit Mahotsav

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राष्ट्रीय जैविक संस्थान
NATIONAL INSTITUTE OF BIOLOGICALS

NATIONAL INSTITUTE OF BIOLOGICALS
NEWSLETTER

April – June 2023 Issue #2

Director's Desk

National Institute of Biologicals is an Institute positioned to make key contributions to the advancement of technology solutions and sustainability research in quality control of Biologicals. The institution works very closely with the industry and actively seeks the participation of stakeholders in standardizing new Biologicals and to take up research in emerging areas. As a scientific institution our organization is well equipped but more importantly it is relevant, contemporary and also futuristic, keeping abreast with current and relevant needs of the Biopharmaceuticals industry.

NIB is the only platform where one can get opportunity for training in Quality Control of Biologicals, especially for various Medical Devices, Blood Products, Recombinant Products and Therapeutic Monoclonal antibodies along with a state of the art facility for hands-on trainings in various in-vivo tests. NIB creates unique and novel training programs to make significant contributions in the area of Science and Technology as a domain.

NIB hosted a Two-week training for two officials of National Drug Authority, Uganda in "Testing of Medical Devices", from 12th – 22nd June 2023 in Blood Reagent Laboratory, Immunodiagnostic Kit Laboratory and Biochemical Kit Laboratory of the institute. The training comprised theoretical sessions and Hands-on practice. Continuing with the tradition of Training the Trainers of the Blood Banks, NIB in collaboration with the Blood Cell-National Health Mission, conducted a six-day residential Hands-on training programme from 08- 13 May 2023 on "Training of Trainers for Strengthening of Blood Services" for 39 Blood Bank Officials (including 15 Doctors and 24 Lab Technicians) from Telangana.

I am immensely proud of our committed staff who continues to demonstrate their resilience and agility as we move to new ways of working.

I wish Good Luck to All!!

Anup Anvikar
Director

Contents In This Issue

Humira, the Top-Selling Pharmaceutical in The World: A Case Story Revealing Barriers for Biosimilars

Dr. Hemant Kumar Verma, Scientist Grade-II, NIB

Biologics are among the most expensive pharmaceuticals but have begun to lose their exclusivity rights over the past 15 years, opening avenues for biosimilars competition. Biosimilars are biological products that are highly similar to an already approved original product (the reference product) and can be manufactured once the innovator's patent and other exclusivity rights on the original biologic has expired.

In the conventional drug market, policy measures in many countries attempt to contain the growth of expenditure and improve efficiency through regulations. Policies to foster the uptake of generics have played an important role in this respect. However, compared to generics, there are substantial barriers to the ability of biosimilars to compete with branded biologics. These include factors associated with the manufacturing process, regulatory framework, intellectual property rights, limited interchangeability and substitution, innovators' reach (e.g., strong ties with physicians and patients) and a lack of incentive for payers, health care professionals and patients to foster uptake after marketing authorization, e.g., due to limited knowledge about biosimilars. Thus, it remains unclear to what extent biosimilars will promote competition in the off-patent biologic market.

The most important aspect is to highlight how the legal landscape enables incumbent manufacturers to block competition in the pharmaceutical market. Recently, a case study published in the American Journal of Managed Care described policy debates surrounding the highest-grossing drug, AbbVie's Adalimumab (Humira).

AbbVie's Adalimumab (Humira) is the top-selling pharmaceutical in the world, indicated for many autoimmune, rheumatologic, and gastrointestinal diseases. From 2011 to 2021, worldwide net revenues more than doubled from $7.9 billion to $20.7 billion. Due to concerns about Government health programmes spending on Humira, the US House Committee on Oversight and Accountability opened an investigation in 2019 to investigate AbbVie's pricing and marketing practices. Following a review of internal business documents, the Oversight Committee published majority staff reports identifying strategies that AbbVie used to extend market exclusivity for Humira beyond the usual US patent protection timeline (Figure 1). Tactics include patent thickets, evergreening, Paragraph IV settlement agreements, product hopping, and linking executive compensation to sales growth. These strategies are not unique to AbbVie and shed light on pharmaceutical market dynamics that may be hindering a competitive market.

Review of AbbVie's Pricing Tactics

A significant factor in Humira's success has been the absence of biosimilar competition. This is partially related to Paragraph IV settlement agreements negotiated between AbbVie and Adalimumab biosimilar manufacturers. Biosimilar manufacturers attempted to invalidate AbbVie's Humira patents so they could enter the US market before the technical end of its market exclusivity period, which in the United States was 2039. Biosimilar manufacturers ultimately dropped their patent cases and negotiated individual settlement agreements with AbbVie, in which they agreed not to contest AbbVie's patents in the United States and to delay US biosimilar Adalimumab entry to 2023 in exchange for AbbVie agreeing not to fight entry of Adalimumab biosimilars in the European Union. These agreements are often considered anti-competitive by regulators, as they are thought to extend market exclusivity of the biologic. Notably, although no Adalimumab biosimilars have launched in the United States as of the end of 2022, other therapeutic alternatives considered competition to Humira have been on the market for several years. Still, AbbVie successfully increased Humira net revenues and increased its list and net prices despite the presence of competitor products.

A key barrier to biosimilar entry for Humira is AbbVie's practices around patent protection. A review of AbbVie's materials revealed that they employed evergreening and patent thicket strategies to extend their product's patent life well beyond the originally granted exclusivity period. A patent thicket is when a manufacturer files many patents on one innovator product to deter competitors from legally challenging the patents of the innovator product. Since its original patent approval, AbbVie obtained or applied for 250 patents for Humira. Evergreening is when a manufacturer obtains secondary patents near primary patent expiration to extend market exclusivity.

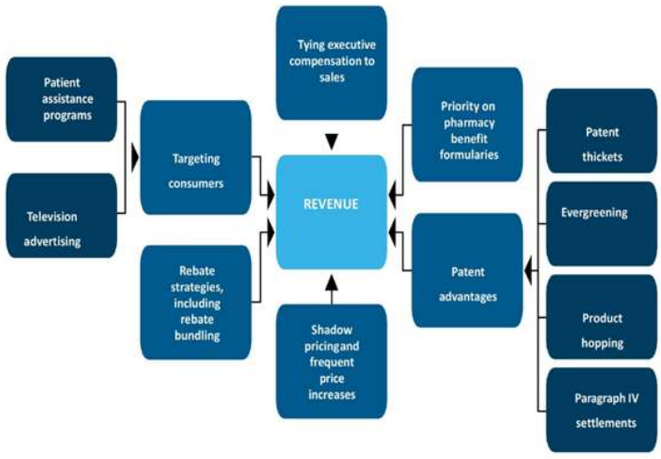

FIGURE 1. Factors That May Be Associated With Humira Revenue Between 2011 and 2020

Some secondary patents obtained were specific to orphan and pediatric designations, which offer extended patent protection periods. AbbVie also employed "product hopping," whereby providers were encouraged to prescribe a less painful high-concentration formulation that is slightly different from Humira. AbbVie also transitioned providers and patients to new formulations of Humira, the line-extended products Risankizumab (Skyrizi) and Upadacitinib (Rinvoq). As biosimilars launch in 2023, this product hopping may affect market penetration of Adalimumab biosimilars as patients transition to line-extended products that are considered imperfect substitutes.

AbbVie shifted patient and prescriber demand for Humira through its marketing tactics. In March 2021 alone, AbbVie spent $40.5 million in television advertising for Humira, Skyrizi, and Rinvoq. AbbVie promoted financial assistance programs to patients to maintain brand loyalty. Internal documents revealed that 40% of Humira revenues went to funding marketing costs and patient assistance programs and 3% went to research and development. Most notably, AbbVie increased the list price of Humira 27 times since 2003. Between 2009 and 2018, the annual price for a biweekly dose increased from $16,663 to $35,041. AbbVie engaged in a practice known as shadow pricing, when it increased prices alongside an alternative drug from another company. Specifically, AbbVie's Humira prices increased almost identically with prices of Etanercept (Enbrel), a drug manufactured by Amgen but in the same therapeutic category. AbbVie also leveraged rebating strategies and established priority tiering on pharmacy benefit manager formularies. This practice and other strategies such as rebate bundling have huge implications for the uptake of biosimilars across product classes because they increase use of brand biologics over biosimilars. The final tactic AbbVie used was linking executive compensation to sales growth. This created incentives for executives to engage in business practices to freeze out biosimilar competition and increase demand and prices for Humira in the United States.

Conclusion

To ensure sufficient competition in biologic markets, policy makers will need to carefully review the House Oversight Committee's 2021 majority staff report on Humira pricing and develop bipartisan legislation to protect market competition. More broadly, efforts are needed to shape regulatory landscapes that promote competition while encouraging innovation. Until congressional lawmakers find agreement on the path forward, decision-making power lies in the courts. Policy reform and legal initiatives may help reduce anticompetitive behaviours by pharmaceutical manufacturers and increase access to competitive therapeutic options such as biosimilars.

References

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2. Dunleavy K. Humira rings up $20.7 billion in 2021, but AbbVie still mum on post-biosimilar expectations. Fierce Pharma. February 2, 2022.

3. Drug pricing investigation: majority staff report. US House of Representatives Committee on Oversight and Reform. December 2021.

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PROFICIENCY TESTING (PT)/ EXTERNAL QUALITY ASSURANCE SCHEME (EQAS)

- Biochemical Kit Lab is enrolled into the Association of Clinical Biochemists of India/ Christian Medical College (ACBI/CMC) External Quality Assessment Scheme (EQAS) - 2023 for Chemistry II (Glucose, Cholesterol, Triglyceride, Creatinine, Uric acid & Albumin), conducted by the Department of Clinical Biochemistry, Christian Medical College, Vellore and the generated results were uploaded on the CMC-EQAS website.
- Recombinant Products Lab participated in the "LAL Proficiency Testing Program (PTP) for Bacterial Endotoxin test" by Gel clot Method and Kinetic Chromogenic method conducted by M/s Charles River Laboratories. Laboratory has secured a "PASS" result in this study.

TECHNICAL EXPERT COMMITTEE MEETINGS

- Dr. Harish Chander, Deputy Director (QC) and Sh. Harit Kasana, Scientist Gr. II, attended the meeting of National Technical Advisory committee on Rabies under National Rabies Control programme held on 18th April 2023 at CSR Room, National Centre for Disease Control (NCDC), New Delhi under the Chairpersonship of DGHS.
- Dr. Harish Chander, Deputy Director (QC) is designated as a member in the newly constituted sub-committee of Zoonosis Disease Programme, NCDC, New Delhi,to review the proposal for pilot project on Rabies Pre-Exposure Prophylaxis (PrEP) in children for selected states under National Rabies Control Programme.
- Dr. Meena Kumari, Scientist Grade-II & Head, BPL attended a meeting of the Regular Committee of the Board of Studies (BOS) in Biotechnology, University Institute of Engineering & Technology (UIET), Kurukshetra University, Kurukshetra on 06.04.2023 & 30.06.2023, to discuss the agenda of affiliated colleges.
- Dr. Gauri Misra, Scientist Grade-II & Head, CKTL attended the First Hub Meeting by BIRAC virtually on 21.04.2023 & 02.06.2023 to facilitate entrepreneurs, academia and SMEs by addressing their queries as external expert.
- Dr. Meena Kumari, Scientist Grade-II & Head, BPL, Ms. Y. Madhu, Scientist Grade-III, BPL and Ms. Apoorva, Junior Scientist, BPL attended the online meeting with M/s Alfa Drugs, Delhi and M/s Bio Products Laboratory, UK on 11.05.2023 to discuss the feasibility of testing of new product Human Coagulation Factor X.

- Dr. Meena Kumari, Scientist Grade-II & Head, BPL, Ms. Y. Madhu, Scientist Grade-III, BPL, Dr. Manoj Kumar, Scientist Grade-III, BPL and Mr. Tara Chand, Scientist Grade-III, BPL attended the meeting with M/s Bharat Serum and Vaccine Pvt. Ltd., Mumbai on 18.05.2023 to discuss the possibility of testing of Anti-T Lymphocytes Immunoglobulin for Human Use (Rabbit) product at NIB.
- The annual inspection of In Vivo Bioassay Laboratory and Animal Facility & 64th Institutional Animal Ethics Committee (IAEC) meeting of NIB was conducted by IAEC on 25.05.2023 to review and approve protocols for in-vivo QC testing of various Biologicals at NIB.
- Dr. Gauri Misra, Scientist Grade-II & Head, CKTL attended an online General Body Meeting as an IBS member on 27.05.2023 organized by TIFR, Mumbai.
- Ms. Rashmi Shrivastava, Scientist Grade-III, QMU was invited as an External Expert for the Technical Evaluation committee of ICMR-NICPR, Noida for the meeting held on 06.06.2023.
- Dr. Gauri Misra, Scientist Grade-II & Head, CKTL attended 12th Meeting of Medical Biotechnology and Nanotechnology Sectional Committee, MHD 20 through video conferencing on 26.06.2023 organized by the Bureau of Indian Standards (BIS).
- 14th Institutional Human Ethics Committee meeting at NIB was convened on 28.06.2023 for seeking approval on the protocols from various laboratories under the Chairpersonship of Dr. Neena Valecha.

INVITED TALKS/ LECTURES DELIVERED

- Dr. Shikha Yadav was invited as faculty to speak on "Post-Operative Care in Laboratory Rodents" in the Rodent Surgery Workshop held on 03.06.2023, organized by the Institute of Liver and Biliary Sciences (ILBS), Delhi.

WORKSHOPS/ CONFERENCES/ SEMINARS

- Ms. Kanchan Ahuja, Scientist Grade-III & Head, BRL attended CME on "Serological approach to red cell antibody identification" at the Department of Transfusion Medicine, Institute of Liver & Biliary Sciences, New Delhi on 19th & 20th, April 2023.

Mr. Harit Kasana, Scientist Grade -II & Head and Mr. Jaipal Meena, Scientist Grade –III, Vaccine and Antisera Laboratory attended one-week training Programme on "NRA-WHO Global Benchmarking Tool for vaccines" at Hyderabad from 10.04.23 to 14.04.23, organized by CDSCO.

- Dr. Manoj Kumar, Scientist Grade-III, Mr. Tara Chand, Scientist Grade-III and Mr. Anoop Kumar, Junior Scientist of BPL attended an online faculty development programme from 08.05.2023 to 12.05.2023 on "Development of Therapeutics using Bioinformatics: Recent trends and strategies" organised by NIT, Warangal.
- Ms. Kanchan Ahuja, Scientist Grade II& Head, BRL and Ms. Sudha V Gopinahth, Scientist Grade II& Head Training Division participated in an IPC interactive meeting on Pharmacopoeia Standards: Regulatory and Quality Considerations organized by the Indian Pharmacopoeia Commission with knowledge partner National Institute of Pharmaceutical Education and Research (NIPER), Mohali at NIPER Mohali on 09.06.2023.
- The scientific staff of the Enzymes & Hormones Laboratory & Recombinant Product Laboratory attended a seminar on Bacterial Endotoxin and microbial solutions by M/s Charles River Laboratories (I) Ltd, New Delhi at their facility on 10.05.2023.

- Dr. Hemant Verma, Scientist Grade-II & Head CFB, Dr. Saurabh Sharma, Scientist Grade-III T AL, and Dr Supriya Saini, Junior Scientist, MDL & COVID Kit Testing Laboratory attended the Training program on "Laboratory Quality Management System and Internal Audit as per IS/ISO/IEC17025:2017" from 06th - 09th June 2023 at National Institute of Training for Standardization (NITS), NOIDA.
- The scientific staff of the Enzymes & Hormones Laboratory & Recombinant Product Laboratory attended an On-site training on "Basics of Liquid Chromatography" for the laboratory analysts by M/s Waters (I) Pvt Ltd, New Delhi on 12.05.2023.

TRAININGS/ VISITS

- Ms. Aradhana Patnaik, IAS, Joint Secretary (Regulations), Ministry of Health & Family Welfare visited NIB facility on 13.04.2023 and interacted with senior scientists of the Institute on various aspects of Quality Control of Biologicals.
- Five days training course on "Ethical use & care of Laboratory Animals in Research and Regulatory Testing" (under newly Structured Training Courses) held from 17th – 21st April, 2023 in In-vivo Bioassay

Laboratory & Animal Facility, NIB. A total of 03 participants (01 Assistant Professor and 02 Associate Professors) attended this training course.

- Five days structured training course on "Basics of Cell Culture & Bioassays" (under structured Lab based training courses of NIB) held from 08th -12th May, 2023 in Centralised Facility for Bioassay. 02 participants (01 faculty & 01 PhD scholar) attended this training course.

- NIB in collaboration with the Blood Cell-National Health Mission, (Government of India) conducted a six-days residential Hands-on training programme on "Training of Trainers for Strengthening of Blood Services" for 39 Blood Bank Officials (including 15 Doctors and 24 Lab Technicians) from Telangana state held from 08th – 13th May, 2023 at NIB.

- NIB organized two-weeks National Skill Development and Hands on Training in Quality control of Biologicals for 30 M.Sc. Students (Biotechnology) students from Guru Ghasidas Vishwavidyalaya,, Bilaspur (Chhattisgarh) from 22.05.2023 to 02.06.2023.

Five days structured training on "Cell Culture-based Techniques for evaluation of Biologicals and Vaccines" in Vaccine and Antisera Laboratory held from 05th - 09th June, 2023. A total of 05 participants (01 faculty, 01 PhD scholar & 03 PG Students) attended this training course. The training comprised theoretical sessions and Hands-on practical sessions.

- Two-weeks training on "Testing of Medical Devices" from 12th – 22nd June, 2023 organized for two officials of National Drug Authority, Uganda, at NIB by Blood Reagent Laboratory, Immunodiagnostic Kit Laboratory and Biochemical Kit Laboratory of the Institute. The training comprised theoretical sessions and Hands-on practice.

- A Guest Lecture Session on "Recent developments in Bioprocessing of Recombination Proteins" by Prof. Anurag S. Rathore, Department of Chemical Engineering, Indian Institute of Technology, Delhi organized at NIB on 15.06.2023.

PUBLICATIONS

- World Health Organization. (2023). Monoclonal antibodies for malaria prevention: preferred product characteristics and clinical development considerations. World Health Organization. https://apps.who.int/iris/handle/10665/367044. License: CC BY-NC-SA 3.0 IGO. (Subhash Chand, Scientist Grade -III, CFB, NIB contributed as a member of the scientific development committee on monoclonal antibodies for malaria prevention under WHO Global Malaria Programme).
- Girija LV, Priyanka Singh, Dr Varun Singh, Apoorva Anand Talwar, Y. Madhu, Harish Chander, Anup Kumar Anvikar & Dr Meena Kumari*. A simple, effective and inexpensive method to estimate IgA content in Human Immunoglobulin for intravenous use preparations based on ELISA Technique. IOSR Journal of Biotechnology and Biochemistry (IOSR-JBB) ISSN: 2455-264X, Volume 9, Issue 2 (Mar- Apr 2023), PP 38-46 www.iosrjournals.org.
- Gauri Misra*, Sandhya Hora, Sanjana Ginwal, Neeraj Singh, Anup Anvikar, SARS-CoV-2 Variants Impact on Key Signaling Pathways Metamorphoses into Severity. Brazilian Archives of Biology and Technology. Vol.66: e23220261, 2023. https://doi.org/10.1590/1678-4324-2023220261. ISSN 1678-4324 Online Edition.

SPORTS DAY CELEBRATIONS

- NIB celebrated Sports Day on the occasion of its 30th Foundation Day. Prizes were distributed to all winners on 07.06.2023



INTERNATIONAL YOGA DAY CELEBRATIONS

NIB celebrated International Yoga Day with Ms. Aradhana Patnaik, Joint Secretary (Regulations), Ministry of Health and Family Welfare under the guidance of Yogacharya Vijay Ji and NIB staff on 21.06.2023.




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