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An Overview of Biosimilars and the Biosimilar Pathway in India

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India is one of the most densely populated countries in the world. According to the World Bank (2012), 1.237 billion people live in India, accounting for about 17.5% of the world's population. India has risen from the 15 largest **pharmaceutical market** in 2007 to 12 in 2011 and is expected to become the 8 largest by 2015. In fact, India's pharmaceutical market has a compound annual growth rate of 12% post price controls. Some of this growth is driven by:

1. Increased accessibility and affordability of prescription drugs.

2. An increase in the diagnosis and treatment of chronic diseases.

3. Mergers, acquisitions and partnerships with big pharma.

4. High growth in the hospital sector.

Since its independence, India has struggled to provide its people with universal health care. India's health industry arose in 1986. However, very few people today have health insurance. As a result, approximately 70% of Indians pay for health care expenses out of their own pockets and this is one of the important causes of poverty in the country today.

Presently, the current health insurance system comprises stand alone health insurers along with government sponsored health insurance providers. Of the policies currently available, most only cover inpatient hospitalization and treatment in hospitals. Outpatient services are not covered. Nonetheless, over the last five years, government-sponsored healthcare schemes (GSHISs) have

contributed to a significant increase in the population being covered by health insurance, scaling up at a pace possible unseen elsewhere in the world. Over 300 million people, or more than 25 percent of India's population, gained access to some form of health insurance in 2010, up from 55 million in 2003-04. More than 180 million of these were people below the poverty line.

Given that most Indians pay for healthcare expenses out of their own pockets, drug pricing is a major concern of the government. In fact, the government believes that the prices of lifesaving drugs should not be set by market forces. As a result, the Indian government has attempted to control drug prices in several different ways. These include:

1. Denying patent protection for certain drugs (Glivec (treatment for leukemia) – which was being supplied by Novartis free of charge to 16,000 patients – roughly 95% of those who needed it via the Novartis "Glivec International Patient Assistance Program").

2. Issuing compulsory licenses (e.g., Bayer's Nexavar).

3. The Drug Price Control Order (DPCO) of 2013. The DPCO applies to both brand name and generic drugs and lists 348 drugs as "essential" and subject to price control. The DPCO places 50% of the market under price controls, which results in a price reduction of up to 80% for these essential drugs. However, drugs that have some form of innovation that can be attributed to Indian researchers may be immune from price controls for a period of five years. Specifically, three types of innovation qualify: (a) drugs resulting from indigenous R&D; (b) improvements by an Indian company on a process for making an existing drug; and (c) development of a new drug delivery system by Indian R&D. As one government official explained, this policy "…would spur innovation and make sure the price-control regime doesn't dissuade pharma firms from research and development."

Biologics are an important component of the pharmaceutical industry and have grown exponentially in the last decade. In recent years, the pharmaceutical industry has placed greater and greater emphasis on developing biopharmaceutical-based drugs (biologics). As a result, the global biologics market is expected to reach $220 billion by 2019.

By 2020, patents on several biological products with global sales of more than US$67 billion will expire. The patent expiration dates for some of the best-selling biologics are provided in the tables 1-3.

Table 1: Humanized Antibodies

Table 2: Non-humanized Antibodies

Table 3: Non-antibody Molecules

Biologics have shown huge potential in curing the unmet demand of small drug molecules. These factors have caught the attention of the global pharmaceutical industry and have polarized the industry towards biologic products. Given this, biosimilars, or “similar biologics” are expected to become an important economic and therapeutic driver of the Indian pharmaceutical market.

In India, similar biologics are regulated by the:

1. Drugs and Cosmetics Act, 1940 (Drugs and Cosmetics Act);

2. Drugs and Cosmetics Rules, 1945 (as amended from time to time);

3. Rules for the Manufacture, Use, Import, Export and Storage of Hazardous Microorganisms and Genetically Engineered Organisms or Cells, 1989 (Rules 1989) notified under the Environment (Protection) Act, 1986;

4. Recombinant DNA Safety Guidelines, 1990;

5. Guidelines for Generating Preclinical and Clinical Data for rDNA Vaccines, Diagnostics and other Biologicals, 1999;

6. The Central Drugs Standard Control Organization (CDSCO) Guidance for Industry, 2008 (including: (a) Submission of Clinical Trial Application for Evaluating Safety and Efficacy; (b) Requirements for Permission of New Drugs Approval; (c) Post Approval Changes in Biological Products: Quality, Safety and Efficacy Documents; and (d) Preparation of the Quality Information for Drug Submission for New Drug Approval: Biotechnological/Biological Products); and

7. Guidelines and Handbook for Institutional Biosafety Committees (IBSCs), 2011.

CDSCO and Department of Biotechnology (DBT) through the Review Committee on Genetic Manipulation (RCGM), approve similar biologics using an abbreviated version of the pathway applicable to new drugs. CDSCO is the highest regulatory authority in India, addresses issues and challenges for ensuring the safety and efficacy of similar biologics and establishes the appropriate regulatory pathways. Specifically, with respect to similar biologics, CDSCO is responsible for granting import/export licenses, clinical trial approvals and permission for marketing and manufacturing. The RCGM is responsible for monitoring all research scale activity and the approval of nonclinical studies. The DBT is responsible for overseeing the development and preclinical evaluation of recombinant biologics.

In 2012, CDSCO, in collaboration with the DBT, issued the (Guidelines). The Guidelines detail the regulatory requirements, such as data requirements for the manufacturing, characterization, preclinical studies and clinical trials, for receiving marketing authorization of similar biologics. The Guidelines are applicable for similar biologics developed in or imported into India.

According to the Guidelines, similar biologics are developed through a sequential process designed to demonstrate the similarity, by extensive characterization studies, of the molecular and quality attributes of the similar biologic with a reference biologic. The extent of the testing of the similar biologic is likely to be less than that required for a reference biologic; however, it is essential that the testing of the similar biologic be sufficient to ensure that the product meet acceptable levels of safety, efficacy and quality to ensure public health. Generally, a reduction in data requirements is possible for preclinical and or clinical components of the development program by demonstrating comparability of the product (to the reference biologic) and consistency in the production process. If any significant differences in safety, efficacy and quality between the similar biologic and the reference biologic are identified, more extensive preclinical and clinical evaluation will be necessary. It is quite likely in this instance that the product may not qualify as a similar biologic.

A “similar biologic” is defined as:

> “A biological product/drug produced by genetic engineering techniques and claimed to be ‘similar’ in terms of safety, efficacy and quality to a reference biologic, which has been granted a marketing authorization in India by the Drug Controller General of India (DCGI) on the basis of a .”

A “reference biologic” (which is an innovator product) is defined as:

> “A comparator biological product/drug used for head-to-head comparability studies with a similar biologic in order to show similarity in terms of safety, efficacy and quality. Only a biological product that was licensed on the basis of a full registration dossier can serve as reference biologic.”

A similar biologic can only be developed against a licensed reference biologic that has been approved using a complete data package in India. However, if a reference biologic is not authorized in India, it must have been licensed and widely marketed for at least four years (post-marketing) with significant safety and efficacy data in a country with an established regulatory framework. Nonetheless, this four year period can be waived or reduced in the event that no medicine or palliative therapy is available or in the event of a national healthcare emergency.

Other important points:

1. The rationale for the choice of the reference biologic should be provided by the manufacturer of the similar biologic in the submissions to DBT and CDSCO.

2. A similar biologic cannot be used as a reference biologic.

3. The reference biologic must be used in all comparability testing.

4. The dosage form, strength and route of administration of the similar biologic must be the same as that of the reference biologic.

5. The active ingredient of the reference biologic and the similar biologic must be shown to be similar.

Approval of a similar biologic is a multi-step process involving several government agencies such as CDSCO, RCGM, DCGI, IBSC, the Genetic Engineering Advisory Committee (GEAC), the Food & Drugs Control Administration (FDCA) and the Institutional Animal Ethics Committee (IAEC). The DCGI is responsible for product safety and efficacy and clinical trial and marketing approval for biotech drugs. The IBSC is responsible for training personnel on biosafety and instituting health monitoring programs for laboratory personnel. The GEAC is involved with environmental safety for large scale operations of live modified organism (LMO) based products. The FDCA approves plants and ensures current good manufacturing practices (cGMP).

The first step in the biosimilar approval process involves an Applicant submitting an application and requesting approval from RCGM and CDSCO to begin conducting studies with the similar biologic. Upon receipt of approval, the Applicant can begin to generate the following information:

1. Manufacturing Process Information. The manufacturing process for a similar biologic should be highly consistent and robust. If the host cell line used to produce the reference biologic is known, it is preferable to use the same cell line to manufacture the similar biologic. If such a host cell line is not available, any cell line that is adequately characterized and appropriate for intended use can be used to develop the similar biologic. The Applicant will need to describe the steps taken to minimize the potential for significant changes in critical quality attributes of the product and to avoid introduction of process related impurities that could impact clinical outcomes and cause immunogenicity issues.

The data requirements for review of the manufacturing process at the preclinical submission include a complete description of the manufacturing process from development and characterization of cell bands, stability of the clone, cell culture/fermentation, harvest, excipients, formulation, purification,

primary packaging interactions (if different from the reference biologic), etc. and the consequences on product characteristics based on the below:

a. Molecular biology considerations – Applicant will need to provide information regarding the host cell cultures, vectors, gene sequences, promoters, etc., used in the production of the similar biologic. Details regarding post-translational modifications, if any (e.g., glycosylation, oxidation, deamination, phosphorylation) should be explained.

b. Fermentation Process Development – Applicant will need to supply at least three batches of reproducible fermentation data at pilot scale (batch is adequate to give enough purified product to generate preclinical data). Fermentation must be carried out in a controlled and monitored environment and details of fermentation kinetic data from a representative batch (indicating such things as cell growth, product formation, pH temperature, dissolved oxygen, major nutrient consumption pattern and agitation rate) should be provided. Additionally, an Applicant will need to supply data verifying that the specific protein yield (amount of protein per unit cell mass) remains constant for all fermentation batches. Finally, the Applicant must demonstrate that the overall productivity is reproducible and scalable.

c. Downstream Process Development – Applicant will need to include information such as the steps involved in the purification of protein, batch size for protein purification and consistency of recovery in three consecutive batches of purification from three independent batches of fermentation.

Additional information on the manufacturing process will be required when submitting an application for clinical trials (Phase III). Specifically, the Applicant must include a description of a well-defined manufacturing process with its associated process controls that assure that an acceptable product is produced on a consistent basis in accordance with good manufacturing practice (GMP). Data for submission should include: a detailed description of the drug substance and drug product processes, critical quality attributes of the product, manufacturing process controls, critical process parameters, stability data, comparability of the product manufactured on a commercial scale against the reference biologic and data from consistency batches and/or process validation batches, as applicable.

2. Product Characterization Information. Characterization studies should be performed using analytical methods in order to establish product comparability for the key quality attributes of the product. State of the art analytical methods should be used to detect whether any “slight differences” exist in any of the relevant quality attributes. Such studies should involve the use of appropriately qualified reproducible and reliable assays. Such studies should include samples of the Applicant’s recombinant product, the reference biologic as a control, known positive and negative controls, when relevant. Each quantitative experience should be done at least three times and data should be represented in terms of mean and standard deviation. The Indian Pharmacopoeia Monograph should be followed, if available.

Product characterization studies which should be conducted include:

a. Structural and Physicochemical properties: The primary and higher order structure of the product as well as other significant physicochemical properties should be determined. Specifically, the target amino acid sequence of the similar biologic should be confirmed to be the same as the reference biologic. If any post-translational modifications exist, these should be identified and quantified. In the event any significant differences exist, these should be scientifically justified and critically examined in preclinical studies and clinical trials.

b. Biological activity: Appropriate biological assays should be used to characterize the activity and establish the product's mechanism of action and clinical effects (in units of activity). It is important that the assays employed be calibrated against an international or national reference standard, where available and appropriate. If no standards are available, an international reference standard must be established pursuant to the ICH guidelines.

c. Immunological Properties: Because the manufacturing process of recombinant biologics is known to affect the level of process related impurities and post-translational modifications of such products, these characteristics may affect the immunogenicity of the product. In view thereof, a comparison to the reference biologic should be made with respect to specificity, affinity, binding strength and Fc function. In addition, animal studies should be performed.

d. Purity and Impurities: A similar biologic should be evaluated for the following: (i) product related variants (e.g., glycoforms, isomers, etc.); (ii) product related impurities (e.g., aggregated, oxidized or deaminated product); (iii) host cell related impurities (e.g., host cell protein, host cell DNA etc.); and (iv) process related impurities (residual media components, resin leachates, etc.). Any differences observed in the purity and impurity profiles of the similar biologic when compared to the reference biologic should be evaluated to assess its potential impact on safety and efficacy. If a similar biologic exhibits different impurities, those impurities should be evaluated to assess their potential impact on safety and efficacy. In contrast, if a similar biologic exhibits different impurities, those impurities should be identified and characterized, when possible. Depending on the type and amount of an impurity, preclinical and clinical studies will be used to confirm that there is no adverse impact on the safety and efficacy of the similar biologic.

e. Specifications: Acceptance limits should be set based on reference biological data and from data from a sufficient number of batches from preclinical or clinical batches.

f. Stability: Stability studies on the drug substance and drug product should be carried out using containers and conditions that are representative of the actual storage containers and conditions, according to relevant guidelines (e.g., ICH Q5C10, WHO TRS 82211). Side-by-side accelerated and stressed studies comparing the similar biologic to the reference biologic showing comparable degradation profiles are also useful in demonstrating the similarity of the products.

Once the Applicant generates the above information comparing the quality of the similar biologic with the reference biologic, this information is submitted along with basic clinical information and preclinical study protocols to the RCGM (using Form C3) requesting permission to conduct preclinical studies. The basic information about the reference biologic and similar biologic to be submitted may include the information contained in table 4:

Table 4:

The Applicant should also include approvals from the IBSC, IAEC, if available. Finally, the Applicant should also provide details regarding the proposed site for conducting toxicity testing and the personnel involved (e.g., the study direction, principal investigator, pathologist, other investigators and quality assurance officers at the site). The status of good laboratory practice (GLP) certification of the proposed facility should also be provided.

Once approval is received to conduct the preclinical studies, the studies should be comparative in nature and designed to detect differences, if any, between the similar biologic and reference biologic. The studies should be conducted with the final formulation of the similar biologic intended for clinical use unless otherwise justified. Additionally, the dosage form, strength and route of administration of the similar biologic should be the same as that of the reference biologic and any differences must be justified.

The following studies are required:

1. Pharmacodynamic studies:

a. studies: The comparability of the similar biologic and reference biologic should be established by cell based bioassay (e.g., cell proliferation assays or receptor binding assays).

b. studies: evaluation of the biological/pharmacodynamic activity of the similar biologic may not be necessary if assays are available which are known to reliably reflect the clinically relevant pharmacodynamic activity of the reference biologic. If such assays are not available, then studies should be conducted.

2. Toxicological Studies: At least one repeat toxicology study in a relevant species is required. The duration of the study should not be less than 28 days with a 14 day recovery period. However, the duration can vary depending on the dose and other parameters. The Applicant is required to provide a scientific justification for the choice of animal model used based on the data available in the scientific literature. In the event that a relevant animal species is not available but has been appropriately justified, the toxicity studies will need to be undertaken in two species (e.g., one rodent and the other non-rodent species) as per the requirements of Schedule Y of the Drugs and Cosmetics Act with due permission from the RCGM.

The dose should be calculated based on the therapeutic dose of the reference biologic. Other toxicity studies, such as safety pharmacology, reproductive toxicity, mutagenicity and carcinogenicity, are generally not required for evaluation of a similar biologic unless warranted by the results from the repeat dose toxicity studies.

Additionally, during this time, the Applicant should be collecting data comparing the antibody response of the similar biologic with the response generated by the reference biologic in a suitable

animal model. Specifically, test serum samples should be tested for reaction to host cell proteins.

After completion of the preclinical studies, the final reports should reflect all aspects approved in the protocol and include the following additional sections/documents: RCGM approval of protocol and test center, IBSC approval of report, IAEC approval for animal use and for the procedures, QA statement, signatures of study director and all investigators who were involved in the study, all quality analytical reports on the test material and vehicle, animal feed and animal health certifications, protocol deviations if any, discussion of the results, individual animal data, summary data and any other data (such as computer analysis outputs, etc) and conclusions. These reports are submitted to RCGM (using Form C5) for review and consideration.

Upon successful evaluation of the preclinical study reports, the Applicant submits Form 44 (an application for grant of permission to import or manufacture a new drug or to undertake a clinical trial) to the DCGI seeking permission to conduct the appropriate phase of clinical trials (Phase III trials) and the documents required per Schedule Y of the Drugs and Cosmetics Act. Further, the Applicant should submit an application for market authorization as per the CDSCO Guidance Document for Industry, 2008. For cases where commercial manufacturing is performed either at a different scale and/or with a different process as compared to that used for manufacturing the Phase III clinical trial batches, information on the comparability of quality also needs to be submitted with appropriate justification, which are dealt with on a case-by-case basis (see, page 22 of the Guidelines, guideline 9). A manufacturing license is also needed giving the Applicant authorization to manufacture clinical trial batches of the similar biologic (along with a WHO GMP certificate). The State Licensing Authority in Form 29 issues a manufacturing license after which a “no objection” certificate is provided by the Central License Approving Authority. Moreover, environmental clearance for clinical trials must also be received from the GEAC and RCGM (see, page 42 of).

For a similar biologic in which quality characterization, preclinical studies and clinical trials have been conducted outside India, an Applicant wishing to seek approval for the product in India must submit Form 44 to CDSCO seeking permission to conduct one or more clinical trials.

Once the necessary approvals are received, Applicant must conduct the following clinical studies:

1. Pharmacokinetic studies (Phase I Study): Comparative pharmacokinetic (PK) studies should be performed in healthy volunteers or patients to demonstrate the similarities in pharmacokinetic characteristics between the similar biologic and the reference biologic on a case-by-case basis. Factors that should be taken into consideration when designing a comparative PK study include: half-life, linearity of PK parameters, endogenous levels and diurnal variations of the biologic under study, conditions and diseases to be treated, route(s) of administration and indications.

In single dose comparative studies, the dose used in the PK study should be within the therapeutic dose range of the reference biologic, otherwise justification will be required. Additionally, the route of administration should be the one where the sensitivity to detect differences is the largest. Any differences in elimination kinetics between the similar biologic and reference biologic (e.g., clearance and elimination half life) should be explored.

Multiple-dose, comparative, parallel arm studies are required for a similar biologic used in a multiple dose regimen, where markedly higher or lower concentrations are expected at steady state than that expected from single dose data PK measurements and where time-dependence and dose-dependence of PK parameters cannot be ruled out.

2. Pharmacodynamic studies (Phase I study): Comparative, parallel or cross-over, pharmacodynamic (PD) studies in the most relevant population (patients or healthy volunteers) is required for the purpose of detecting differences between the reference biologic and similar biologic. If a PD marker is available in healthy volunteers, PD in healthy volunteers can be done. Comparative PD studies are recommended when the PD properties of the reference biologic are well characterized with at least one PD marker being linked to the efficacy of the molecule. The relationship between dose/exposure, the relevant PD marker(s) and response/efficacy of the reference biologic should be well established and used to justify the design. The parameters investigated in PD studies should be clinically relevant and surrogate markers should be clinically validated. PD studies may be combined with PK studies provided that the PK/PD relationship is characterized. Finally, a PD study can be part of a Phase III clinical trial, when applicable.

3. Confirmatory Safety and Efficacy Studies (Phase III studies): Comparative clinical trials to demonstrate the similarity in safety and efficacy of the similar biologic and reference biologic are required except in a few exceptions (namely recombinant human soluble insulin products for which comparative clinical safety studies are all that are required). One or more adequately powered, randomized, parallel group, blinded confirmatory clinical safety and efficacy trials are desirable based on the comparability established during preclinical and PK/PD studies. More than one safety and efficacy study may be required if the similar biologic is not comparable to the reference biologic in all preclinical evaluations conducted and/or the PK/PD studies have not demonstrated comparability.

A similar biologic can be approved without conducting a confirmatory clinical safety and efficacy trial (phase III study) if the following conditions are met:

a. The structural and functional comparability of a similar biologic and the reference biologic is characterized to a high degree of confidence using physicochemical and techniques;

b. The similar biologic is comparable to the reference biologic in all the preclinical evaluations conducted;

c. The PK/PD study has demonstrated comparability of the similar biologic and the reference biologic and has preferentially been done in an in-patient setting with a safety measurement (including testing for immunogenicity) for adequate period of time; and

d. A comprehensive post-marketing risk management plan is presented (for the purpose of gathering additional safety and immunogenicity data).

However, the confirmatory clinical safety and efficacy study cannot be waived if there is no reliable and validated PD marker. Additionally, comparative pre-approval safety data including immunogenicity data, is required for all similar biologics including those for which confirmatory clinical trials have been waived. Pre-approval safety data is intended to provide assurance of the absence of any unexpected safety concerns.

Safety and efficacy data for a particular clinical indication (for which clinical studies have been conducted) of a similar biologic can be extrapolated to other clinical applications provided that the following are met:

a. Similarity with respect to quality has been proven to the reference biologic;

b. Similarity with respect to preclinical assessment has been proven to reference biologic;

c. Clinical safety and efficacy is proven in one indication;

d. Mechanism of action is the same for the other clinical indications; and

e. The receptor(s) involved are the same for the other clinical applications.

Once all the clinical studies have been successfully completed, the Applicant submits an application for market authorization to DCGI. As described in the , the application must contain the following five modules:

1. Module I: Administrative/Legal Information

2. Module II: Summaries

3. Module III: Quality Information (Chemical, Pharmaceutical and Biological)

4. Module IV: Non-clinical information

5. Module V: Clinical Information

Once the Applicant receives marketing authorization, the similar biologic can be sold in India. Once such marketing authorization is received, the Applicant is required to submit a post-marketing risk management plan. The purpose of the risk management plan is to monitor and detect known inherent safety concerns and potential unknown safety signals that may arise from similar biologics. The risk management plan must include:

1. Pharmacovigilance Plan: A comprehensive pharmacovigilance plan must prepared to further evaluate the clinical safety of the similar biologic in all approved indications post-approval. The plan must include the submission of periodic safety update reports (PSURs). The PSURs must be submitted every 6 months for the first two years after approval to CDSCO. After the first two years, the PSURs are submitted to DCGI.

2. Adverse drug reaction reporting: All cases involving serious and unexpected adverse reactions must be reported within 15 days of initial receipt.

3. Post-marking studies: At least one post-marketing safety and immunogenicity study (non-comparative) is required. The study must be designed to confirm that the similar biologic does not have any concerns with regards to the therapeutic consequences of unwanted immunogenicity. The post-marketing study should be submitted to CDSCO.

According to GaBI Online, in 2000, the first “similar biologic” was approved and marketed in India for a hepatitis B vaccine. In recent years, over 50 biopharmaceutical products have been approved for marketing in India, with more than half of them being “similar biologics”. Table 5 lists some of the similar biologics approved in India.

Table 5: “Similar Biologics” Approved in India

In addition, Bicon reported in its April 2014 investor report that it is working on biosimilar versions of Bevacizumab (Avastin), Adalimumab (Humira), Etanercept (Enbrel), Peg-filgrastim (Neulasta), rh-insulin, Glargine, Lispro and Aspart.

Roche's block buster drug Herceptin (trastuzumab) is used to treat HER2+ breast cancer. Generally, it is prescribed during post-surgery chemotherapy for women suffering from metastatic breast cancer and has been sold in India under the international brand name Herceptin as well as under a second off-brand name, Herclon. The cost of Herceptin in India is 15 times the per capital monthly income. The maximum price of lower cost Herclon is $75,000 rupees (US$1249.00) for a 440-mg vial.

While there is no compound patent covering trastuzumab (It was a pre-1995 compound and Indian patent law at the time did not allow product patent applications to be examined), Roche received Indian Patent No. 205534 (the '534 patent) claiming a formulation containing trastuzumab. The patent issued on April 6, 2007 with an expiration date of May 3, 2019. Specifically, the patent claims "a composition comprising a mixture of an anti-HER2 antibody and one or more acidic variants thereof, wherein the amount of acidic variants(s) is less than about 25%".

Roche filed three divisional patent applications: (a) 1638/KOLNP/2005 (a divisional of the '534 patent) filed August 16, 2005; (b) 3272/KOLNP/2008 a divisional application off of (a) and filed February 12, 2009; and (c) 3273/KOLNP/2008, a divisional off of (a) and filed February 12, 2009.

A post-grant opposition was filed by Glenmark Pharmaceuticals. During the opposition, it came to light that Roche had failed to pay the 15 annuity on the '534 patent and as a result, the patent lapsed. There is speculation that Roche did not pay the annuity because the Ministry of Health was poised to issue a compulsory license for Herceptin pursuant to Section 92 of the Indian Patents Act, 1970. Roche avoided the issuance of the compulsory license by abandoning its patents and patent applications.

With respect to the divisional applications, the Controller found that a request for examination had been filed in 1638/KOLNP/2005 on March 17, 2006, one month later than the due date of February

16, 2006 (the request for examination had to be filed within 6 months of its filing date). As a result, the application was deemed to be withdrawn. With respect to the remaining two divisional applications, the Controller found that these applications had been filed after the grant of the first filed application and were not permissible. Thus, these applications were also deemed to be withdrawn.

In December 2013, Biocon announced that it had received authorization from the DCGI to market its jointly developed (with Mylan) trastuzumab similar biologic (under the name CANMAb) for the treatment of breast cancer. However, in early 2014, Roche sued Biocon and Mylan in the Delhi High Court over the impending launch of its trastuzumab similar biologic. Roche made two arguments. First, Roche argued that Biocon and Mylan were misrepresenting their drugs as “trastuzumab”, “biosimilar trastuzumab” and a “biosimilar version of Herceptin” without following the due process for their drugs being approved as biosimilars in accordance with the Guidelines issued in 2012. The second argument accused Biocon and Mylan of passing off their goods as “trastuzumab”, “biosimilar trastuzumab” and a “biosimilar version of Herceptin”. The DGCI was also made a party to the suit for giving permission to Mylan and Biocon to launch their generic versions of the drug. Moreover, Roche argued that that the approvals received by Biocon and Mylan could not have satisfied the requirements for a biosimilar drug under the Guidelines, because the protocol and design study for CANMAb was filed and approved prior to the Guidelines becoming effective. Furthermore, the approval had been granted very quickly which made a weak case for compliance with the Guidelines.

The Court issued an injunction in early February 2014 against Biocon and Mylan stating that the companies were “not entitled to introduce or launch the drug” until they persuaded the Court that their product had undergone sufficient testing and attained requisite approvals.

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