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REGULATORY CHALLENGES IN GLOBAL PHARMACEUTICAL MARKET

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ABBREVIATIONS:

AUC- Area under the concentration, **ANDA**-
Abbreviated New Drug Application

CRESCENDO- Comprehensive Rimonabant
Evaluation Study of Cardiovascular
Endpoints and Outcomes, **C_{max}** -peak
concentration, **GCP**- Good Clinical Practices,

ICH- International Conference on
Harmonization, **NDA** -New Drug
Application, **PMDA** -Pharmaceutical and
Medical Devices Agency, **SCOUT**-
Sibutramine Cardiovascular Outcome Trial

t_{max}- Time to peak concentration, **USFDA**-
United State Food and Drug Administration

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ABSTRACT

The global pharmaceutical industry “looks like the epitome of a modern, mature industry that has found a comfortable way to make profits by the billion: it’s global, hi-tech, and has the ultimate customer, the health care budget of the world’s richest countries. A number of factors contributed to the globalization of the pharmaceutical industry. Chief among these are the convergence of medical science and practice under the influence of modern communication technology and increased and information exchange. The global success of the Swiss pharmaceutical industry is only due to the high level of investment in research and development and the other fact is the favorable regulatory frame work. For the development of a new drug and generics pharmaceutical company have to face number of regulatory challenges such as bioequivalence, patent expiry, newer antibiotics ,and the complexity involved in the regulated market etc. Regulatory processes are also undergoing international harmonization. As international market becomes more important, pharmaceutical companies will require greater corporation among national regulators to get life saving products which will help them to market faster and reduce regulatory compliance.

INTRODUCTION: Regulatory challenges in global pharmaceutical market lead to the new drug, and generics development to a large extent. For the globalization at the international level regulatory challenges contribute a great extent. As there are too many similarities around the world in concern with drug safety and availability, differences and similarities in regulatory system and drug markets continue to significantly impact firm strategy and the relative

performance of pharmaceutical or biotechnology companies of different countries.

A report was calculated that one third of new drug were invented by Germany in the 1960s and 1970s, this figure was dropped to thirteen percent in the 1990s and also further declined since time to time but united state and Europe drug development rate was grown up because of excellent innovation to regulations.

METHODOLOGY: The new drug development as well as the generic drug availability is well balanced by the current regulations. The fundamental objective of the regulatory harmonization¹ is to improve the efficiency of national economics and their ability to adopt to change and remain competitive. The complicated regulatory landscape can be a barrier to success for foreign companies that do not have the experience or resources that are essential to overcome the obstacles in countries such as China, Japan, Korea, and Taiwan. Regulatory processes were also undergoing international harmonization. As international market becomes more important, pharmaceutical companies will require greater cooperation among national regulators to get life saving drug which will help them to market faster and reduce regulatory compliance costs.

Regulatory challenges^{2, 3} that involved in the development of a new drug and generics are as follows:

1. Generics
2. Patent expiries
3. Newer antibiotics
4. Clinical trials
5. Consumer risks
6. Medical devices

Generics: Bioequivalence is the major regulatory challenge for the development of a new generic^{4, 5}. According to the regulation a generic should have parameters like area under the concentration (AUC) time curve, the peak concentration (C_{max}), and the time to peak concentration (t_{max}). Statistically, geometric mean ratio of the test to the reference drug for AUC and C_{max} must fall within 90% confidence limits of 80 and 125. Within this statistical limit, these particulars parameters will be sufficient for bioequivalence.

Patent Expiries: The second major regulatory challenge is patent and intellectual property rights. In US the patent and trademark office is the regulatory agency that grants patents which permit the patent holder to assert their rights to exclude others from making, using or selling the patented invention or process. The new drug development, as well as the generic drug availability is well balanced by the current regulations in the USA through implementing the

HATCH-WAXMAN^{5, 6} act. The Drug Price Competition and Patent Term Restoration Act⁵ of 1984, usually referred to as the Hatch-Waxman Act, were designed to promote generics in the USA while leaving intact a financial incentive for R&D. It allows generics to win FDA marketing approval by submitting bioequivalence studies. Approvals were generally provided with the following certifications

- Paragraph I Certification: The generic applicant certifies that there are no patents listed in the orange book. "Orange book" being a publication of USFDA, lists the patents relating to drugs approved for marketing and sale in the USA, including patents that protect active ingredients.
- Paragraph II Certification: In case any listed patents have previously expired, the applicant may enter the marketplace immediately upon FDA approval.
- Paragraph III Certification: The applicant certifies that any listed patent has not yet expired but will expire on a particular date. The FDA may approve the Abbreviated New Drug Application (ANDA) and make it effective as of the patent expiration date.
- Paragraph IV Certification: The applicant for generic approval intends to market the drug prior to expiration of any patent(s) listed in the orange book; the applicant makes a certification that the patent(s) are not infringed or are invalid and FDA notifies the New Drug Application (NDA) holder and patent owner accordingly. It also grants a period of additional marketing exclusivity to make up for the time a patented pipeline drug remains in development. This extension cannot exceed 5 years, and it is in addition to the 20 years exclusivity granted by the issuance of a patent.

Another provision of the Hatch-Waxman Act is that it grants a 30-month stay to drug companies that file suits against generic manufacturers who challenge their patents. Thus the act maintains a fair balance between the innovator of a new drug and the generic drug producers.

Newer Antibiotics: The history of antibiotic⁷⁻¹⁶ regulation clarifies the relationship between regulatory plan and the scientific/ regulatory constraints and the marketing condition in which they operate. Antibiotics and insulin containing drugs were added to the regulatory scheme beginning with a series of steps in 1941. However, the procedure, for establishing safety and efficacy applicable to other “new drug” antibiotics were subject to a far different regulatory scheme. Finally, in 1982 the batch certification program for antibiotic was eliminated entirely but was considered and regulated as for any other drug to comply with the monograph. In 1986, over the counter antibiotic that complied with the applicable monograph were excluded from the batch certification process. In contrast to the earlier times only penicillin was the available antibiotic in the market, several hundreds of antibiotic started getting approval from the agency. As a result of 1962 Amendments, the FDA required the submission for several antibiotics of scientific evidence of substantial well controlled clinical studies demonstrating the effectiveness of the product; In contrast to the earlier those product that failed to provide such evidence had their certifications overturned. In addition, the FDA cancelled approval of several antibiotics that did not have substantial scientific evidence.

Clinical Trials: FDA regulations that specify methods for clinical trials¹⁸⁻²¹ requires each new drug application to include data from at least two controlled clinical trials.

Consumer Risks: Regulatory environment for drugs and the spectrum of indications for which they will be approved and marketed would change dramatically if positive data from either the SCOUT²¹ or CRESCENDO^{22, 23} outcome trials.

Medical Devices: Since the beginning of 1980s, the regulatory world for medical has changed dramatically. From few countries, there are now 60-65 countries which have implemented regulations for medical devices²⁴⁻²⁸. After considering all of the above mentioned issues, we can say that when harmonized regulation of medical device comes in to existence and consequently a uniform adaptation of harmonized regulation takes place, then there is an availability of quality product. If by any reason, the regulation of

medical is not harmonized and consequently, the harmonized regulation is not adopted, then it leads to serious concerns like delayed or absent access to innovative technology, continue rise in the cost of medical therapies, *etc.*

Regulatory challenges in the Asia-pacific Region: The Asia pacific region is becoming increasingly attractive for global clinical development activities. Asia is the fastest growing pharmaceutical market in the world, providing significant opportunities for drug development and marketing. At the same, the Asia-pacific region presents major challenges: a complex and continually evolving regulatory environment. The complicated regulations can be a barrier to success for foreign companies that do not have the experience or resources that are essential to overcome the obstacles in the countries such as China, Japan, and Korea.

China: China’s growing economic strength and population of more than a billion people hold tremendous potential for global pharmaceutical companies – both as a location for clinical trials and a market for novel therapies. That potential is tempered by the daunting regulatory requirements for pharmaceutical products in China – requirements that have only recently begun to improve. One of the major drawbacks is the time it takes to receive regulatory approval for a clinical trial³¹: an average of 9-12 months, plus 1-2 months for Independent Review Board (IRB) approval.

In October 2007, China’s State Food and Drug Administration (SFDA) issued a new guidance that established timetables for some parts of the review process – a change that has reduced the average review time by 1-2 months. Another important change involves China’s requirements for locally generated Certificates of Analysis (COA) for ingredients in drugs to be tested in the country. For multinational trials that include Chinese patients, the COA requirement can now be waived if a chemical-based product is not going to be registered for sale in China. This is a major change from past practice, when separate Phase III trials in China were required – a change that should encourage global pharmaceutical companies to include Chinese patients in multinational trials so they can bring their products to the Chinese marketplace more quickly.

Japan: The challenging regulatory environment in Japan has improved substantially in the last decade. The adoption of the International Conference on Harmonization (ICH) "Guideline on Ethnic Factors in the Acceptability of Foreign Clinical Data" (E5) in 1998, and the approval by Japan's Pharmaceutical and Medical Devices Agency (PMDA) of a new guideline called "Basic Concepts for International Joint Clinical Trials" in 2007, have eased the country's strict restrictions on accepting clinical data from non-Japanese patients. These changes resulted from public health concerns about the "drug-lag" challenge facing Japan, where new biopharmaceutical products^{33, 34} typically enter the market more than four years after their approval in the U.S. or Europe because of the difficulty of conducting trials in Japan.

The PMDA requires most of the pivotal Phase II/III studies to be conducted in Japan. This requirement will continue to cause delays in conducting trials and submitting regulatory filings in Japan because of the high cost of conducting trials and the shortage of available volunteers.

Another regulatory challenge in Japan³⁶ is the relatively slow review and approval process, which takes an average of 2.5 years longer than in the U.S. Part of that delay is the result of a shortage of reviewers.

Korea: Until a few years ago, obtaining approval to import a foreign investigatory new drug³⁸ (IND) into Korea was very difficult. In most cases, an IND could be submitted only after a drug had received market approval in the U.S. or Europe. Since 2002, however, companies conducting multinational studies³⁹ have been allowed to include Korean patients in clinical trials at the same study stage as trials being conducted elsewhere. This change has greatly improved the regulatory climate in Korea, and is paving the way for Korean patients to have access to novel therapies much more quickly than in the past. It has also provided new opportunities for global pharmaceutical companies looking to expand their multinational trials.

Other significant changes in the regulatory environment in Korea include:

- Implementation of GCP standards at major health centers across the country
- Changes in FDA regulations that now require INDs to be approved within 30 working days (if no additional information or clarifications are necessary)
- Significant reductions in the requirements for translating regulatory documents into Korean⁴⁰.

Taiwan: Like other countries in the Asia-Pacific region, Taiwan has implemented a number of changes in recent years to improve the regulatory environment for clinical trials involving foreign pharmaceutical companies. The Department of Health and its Center for Drug Evaluation are working closely with the FDA to share knowledge and opinions aimed at bringing Taiwan's regulations⁴¹ more closely in alignment with those of the U.S. and Europe. Taiwan has also established a program that allows its regulatory reviewers to receive training from FDA officials on best practices and procedures for reviewing IND and NDA submissions.

Additional changes to improve the regulatory process in Taiwan include:

- Shorter timelines for regulatory reviews and approvals
- New procedural regulations that are bringing greater transparency to Taiwan's regulatory processes^{42, 43}.

CONCLUSION: The Asia-Pacific region is one of the most vibrant and rapidly growing areas in the world. China is expected to become the fifth largest global pharmaceutical marketplace within the next few years. The environment surrounding the regulation of pharmaceutical products has shown steady improvement since the beginning of the new century, with significant changes over the last five years. These changes have brought greater transparency and professionalism to the regulatory arena, and increased the opportunities for the pharmaceutical industry to conduct clinical trials and introduce novel therapies.

However, major regulatory challenges remain for pharmaceutical companies looking to expand their clinical trial programs into this region. Equally important, the challenges are different for each country. The Asia-Pacific region²⁵ cannot be treated as a single market, but must be approached with an abundance of local knowledge. Success is contingent upon understanding the regulatory – as well as medical and social – nuances that characterize each country. With the right combination of local knowledge, perseverance, and flexibility, sponsors can overcome most of the challenges and take advantage of the opportunities to expand their clinical development programs in this dynamic part of the world.

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