Who Develops Innovations in Medicine for the Poor? Trends in Patent Applications Related to Medicines for HIV/AIDS, Tuberculosis, Malaria and Neglected Diseases

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This paper sought to answer this question by collecting and analyzing patent data of medicines and vaccines for diseases using the database of the Japan Patent Office. Results indicate that private firms have led in innovation not only for global diseases such as HIV/AIDS but also diseases such as malaria that are spreading exclusively in low income countries. Innovation for the three infectious diseases is diverse among firms, and frequent patent applications by high-performing pharmaceutical firms appear prominent even after R&D expenditure, economies of scale, and economies of scope are taken into account.

Keywords: HIV/AIDS; malaria; tuberculosis; neglected diseases; patent; medicine; knowledge production

JEL classification: I19, L65, O31, O34

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1. Introduction

Infectious diseases are a serious concern to many people in developing countries. Among all, the damage caused by HIV/AIDS[4], tuberculosis, and malaria is the most severe. As seen in Table 1, the WHO [2002] estimates that three million, 1.9 million and more than 1 million people died in 2000 due to AIDS, tuberculosis, and malaria respectively. Further, a far greater number of newly infected people were added to those living with HIV, tubercle bacillus and malaria parasite. The number of newly infected people in 2000 was 5.3 million for HIV, 8.8 million for tuberculosis, and 300 million for HIV. Table 1 further shows that within the context of international development, most people with the virus, bacterium, or parasite, are living in developing countries.

While AIDS was discovered in 1981, developments in diagnosis, medicine, and vaccine seem to have been greater for tuberculosis and malaria, diseases which have been prevalent for a long time. Above all, one of the most promising inventions for HIV/AIDS has been the antiretroviral (ARV) that prevents HIV by using an enzyme called reverse transcriptase to convert RNA into DNA. Taking antiretroviral drugs regularly in appropriate combinations prevents destruction of the immune system of people living with HIV. However, patent holders have monopolized sales and distribution of the antiretroviral drugs where the substance patent system has been applied to pharmaceuticals.[5] Thus, drugs have been prohibitively expensive for people living in developing countries.

In November 2001, an epoch-making breakthrough took place at the Fourth Ministerial Conference of the World Trade Organization (WTO) in Doha, Qatar.[6] At the conference, a Declaration on the TRIPS[7] Agreement and Public Health was released, and this stated that patents should not be applied in cases where keeping the TRIPS Agreement would result in serious damage

[4] AIDS is the abbreviation of Acquired Immune Deficiency Syndrome. It is caused by the Human Immunodeficiency Virus (HIV). Infection of HIV gradually destroys the immune system, and infected people become susceptible to "opportunistic illness," *such as* tuberculosis, Pneumocystis carinii pneumonia, Kaposi's sarcoma, and Candidiasis. People living with HIV are more likely to be infected due to destruction of the immune system than those without HIV. Infection with any of the opportunistic illnesses is very dangerous for people living with HIV.

[5] In many countries, there is an inclination for patents on medicines to be waived on the grounds of public health. Even at the end of the 1980's, forty countries, including developed countries, did not admit substance patents on medicines but only process patents (Lanjouw and Cockburn [2001], p. 265).

[6] One thing that drove the conference forward to the declaration was a rise in public sentiment supporting people living with HIV rather than pharmaceutical companies owning patents of antiretroviral drugs. This issue was pushed in order to persuade companies to lower their prices below the level at which drugs would be affordable to people with HIV who are living in developing countries, and it resulted in concessions of companies relative to trials on patents of the drugs in Brazil and South Africa in 2001. Bio-terrorism, which included the case of anthrax in North America in October 2001 (right after the September 11), also helped raise concerns about the importance of public health over intellectual property rights of delegates, not only in developing countries but also in developed countries. See *Economist* [2001a, b, 2002a] and Cassier and Correa [2003].

[7] This is the abbreviation of trade-related aspects of intellectual property rights.

to public health.[8] More concretely, clause No. 4 of the declaration states the following:

> *We agree that the TRIPS Agreement does not and should not prevent members from taking measures to protect public health. Accordingly, while reiterating our commitment to the TRIPS Agreement, we affirm that the Agreement can and should be interpreted and implemented in a manner supportive of WTO members' right to protect public health and, in particular, to promote access to medicines for all.*
> *In this connection, we reaffirm the right of WTO members to use, to the full, the provisions in the TRIPS Agreement, which provide flexibility for this purpose.*

The agreement incorporated into the declaration in Doha heightened the bargaining power of low income countries over multinational pharmaceutical companies in determining prices of antiretroviral drugs and those for tuberculosis and malaria (which were explicitly mentioned in the declaration). As a result, costs for treatment with antiretroviral drugs declined from around thirty US dollars per day per person in the middle of 1998 to one dollar in the beginning of 2002 (*Economist* [2002]). This was a revolutionary achievement for people living with HIV, even though only around 30,000 people out of 25 million people living with HIV in Sub-Saharan Africa in 2003 received antiretroviral therapy.

In terms of wide distribution of drugs, the decline in prices of antiretroviral drugs is undoubtedly favorable when seen as a measure against HIV/AIDS. However, the same decline in prices may be potentially harmful to further development of innovations in medicines, therapies, and vaccines for HIV/AIDS, because low prices reduce profits of pharmaceutical firms, and these firms may lose their incentive to make innovations. This is a concern not only HIV/AIDS but also any disease that is prevalent in low-income countries. Pharmaceutical firms may expect to be forced by the government and by international organizations to reduce prices of any medicines, therapies and vaccines which are helpful and critical to either prevention, cure, or treatment in low income countries, even though governments and international organizations have promised that they will not do so. That is, *ex ante* governmental commitment can be withdrawn once the medicine, therapy or vaccine has been developed. This is known as "the time inconsistency problem" in the context of game theory (Chari, Kehoe and Prescott [1989]; Kremer [2000a]; Kremer and Glennerster [2004]). Thus, cautious pharmaceutical companies, without declaring that they will do so, may not want to participate in such a risky field of diseases and may shift resources toward innovations in medicines for diseases for which the demand will be sure and great in developed countries. They may pretend to have lost advantages in innovation of medicines and vaccines for diseases prevalent in developing countries, and nobody can disprove this statement.

[8] See Lippert [2002] among others. The whole declaration is available at the WTO's homepage (http://www.wto.org/english/thewto_e/minist_e/min01_e/mindecl_trips_e.htm).

In fact, pharmaceutical companies and their industrial associations have serious worries regarding public sentiment that may be against them. They lobby, publicizing their philanthropic activities, and try to persuade the public that the prevalence of HIV/AIDS is not due to patents but rather to poverty.[9] However, some leaders within the society of pharmaceutical companies have already avowed that the industry will retrench R&D for antiretroviral drugs because of price constraints (Lanjouw [2002a], p. 109). It is noteworthy that as shown in Table 1, there are a number of people living with HIV in rich countries, while the number of people with the malaria parasite is almost zero. When pharmaceutical firms lose incentives to create medicines and vaccines for HIV/AIDS, they lose even more when it comes to malaria, because the demand based on purchasing power for medicines and vaccines for malaria is far smaller than that of HIV/AIDS. There are a number of other "neglected diseases" in low income countries.

That pharmaceutical companies appear to shrink from innovation in low income countries, the question of who will lead in innovation for the poor must be raised. In order to predict who will lead in the future, it is important to explore who led in the past. For example, who has invented medicines and vaccines for malaria and other neglected diseases? Which sector, public institutions or private pharmaceutical firms, invested and invented more for medicines and vaccines for diseases prevalent in developing countries? What type of institutions and/or firms devoted themselves to such unprofitable R&D activities? Answers to these questions will help in the design of schemes to stimulate innovation for the poor.[10] If public institutions have made the most innovations for the poor, then there is no point in discussing the incentive problem caused by the opportunistic behavior of governments and international organizations. However, if pharmaceutical companies have committed themselves to innovation for the poor, the incentive problem becomes more important, and determining the types of companies that make innovation becomes more important in order to determine policy measures to promote companies of such types.

What kinds of entities have led innovation of medicines and vaccines for diseases prevalent in low-income countries so far? This is the question addressed in this paper. Viewing the characteristics and attributes of entities that contributed to innovation of medicines for the poor in the past gives us hints as to what should be done to promote innovation.

Findings are threefold: First, private pharmaceutical firms have led in the innovation of medicines, for not only HIV/AIDS and tuberculosis that are currently prevalent in developed countries, but also malaria, which is rare in developed countries. Second, performance among firms

[9] These tendencies can be seen on the web sites of pharmaceutical company, Pfizer, and an industrial association of pharmaceutical companies in the United States, the International Federation of Pharmaceutical Manufacturers Associations (IFPMA). See http://www.pfizerforum.com/english/lippert.shtml, and http://www.ifpma.org/.

[10] Proposals that would stir innovation of medicines and vaccines for the poor have already been publicized. See Kremer [2000a, b, 2002]; Kremer and Glennerster [2004]; Lanjouw [2002b], and Pilling [2000].

in innovation for the three infectious diseases is diverse. Third, the number of patent applications of medicines made by GlaxoSmithKline for HIV/AIDS and neglected diseases is outstanding. In addition to trends over time, a substantial part of this performance is explained by the scale of GlaxoSmithKline's total R&D stock, sales, and economies of scope that are incorporated by the variety of diseases for which pharmaceutical companies made patent applications of medicines and vaccines.

This paper is organized as follows: Section 2 includes a brief description of the general facts related to the influence of the three infectious diseases and the trends in innovation of medicines and vaccines for them. It appears that private pharmaceutical firms outperform public institutions in terms of the number of patent applications for medicines and vaccines for the three infectious diseases. Section 3 includes an empirical study with data to find determinants of the magnitude of patent applications. Due to constraints related to sample size, focus is placed primarily on HIV/AIDS and the "neglected diseases" that cause serious problems in some developing countries, but seem not to be of concern in the rest of the world. Poisson regression and associated applications are used as analytical methods. Conclusions are given in the final section.

2. General Facts Regarding the Influence of Infectious Diseases and the Development of Innovations in Medicines to Treat Them

This section includes a discussion of general facts related to the influence of the three infectious diseases and the development of innovations in medicines and vaccines for their treatment. First, the burden imposed on people in the world by these diseases is discussed. This issue is important because those who are influenced by a disease affect incentives for coping with the disease. People who are seriously affected by a disease are probably more likely to work for innovation of medicines than those who are not.

2.1. Burdens of Diseases

There are two types of infectious diseases. One is widespread in both low and high income countries; examples include HIV/AIDS and tuberculosis. The other is rampant only in low-income countries; an example is malaria. As shown in Table 1, most casualties for both types of infectious diseases are found in low-income countries. Even if infected people survive, they are destined to face various difficulties in their life. Obviously, different infectious diseases create different kinds of burdens on infected people. In order to evaluate the magnitude of burdens caused by various diseases and injuries, a measure called the Disability Adjusted Life Years (DALYs) was developed. This measure incorporates various kinds of damages imposed by diseases and injuries such as death and

disability.[11] It is tabulated by the factors of disease and injury. Table 2 shows the number of deaths (upper row) and the share of DALYs lost due to each disease (lower row) tabulated by region. It is evident from the table that the burden of disease varies from region to region. The first column indicates that HIV/AIDS accounts for 5.8 percent of the total DALYs lost in the world; this value is twice as high as the value for both tuberculosis and malaria. Similar dominance of HIV/AIDS is found in terms of the number of deaths. At the regional level of DALYs of HIV/AIDS, tuberculosis and malaria, Africa suffers the most with East and South Asia following. It is particularly remarkable that the share of DALYs lost due to the three diseases accounts for more than 30 percent in Africa. It is also noteworthy that the Americas and Europe, parts of developed world, have only negligible burdens due to malaria. Table 2 thus suggests that people living in Africa should have more incentive to cope with the three diseases than those living in more developed regions such as the Americas and Europe.

2.2. Patent Applications by Disease

There is an argument that the number of patents is a good proxy for the number of innovations in pharmaceuticals. While R&D activity for medicines costs a large amount of money, manufacturing costs are extremely low. Using reverse engineering, imitating an original is very easy (Kremer [2002]). Therefore, obtaining patents are the most important way to secure profits from R&D investments in the pharmaceutical industry (Scherer [1996], p. 362, Table 9.1, Levin, *et al* [1987], Cockburn and Griliches [1987]). To investigate the tendency of R&D efforts aimed at infectious diseases, a database of the Japan Patent Office was examined, and patent applications for medicines to be used against HIV/AIDS, tuberculosis and malaria were retrieved. Due to the Paris Convention and the Patent Cooperation Treaty, key patent applications are likely to be made at patent offices of major countries at about the same time. Therefore, as far as important patent applications are concerned, a database of any particular country suffices for the analysis of tendencies in patent applications.[12] The Japan Patent Office maintains a patent data retrieving system that is available to anyone through the Internet. Appendix 1 explains how samples were retrieved. It should be noted that the number of patent applications for tuberculosis and malaria might be overestimated.

Figure 1 shows trends in patent applications related to medicines for HIV/AIDS, tuberculosis and malaria that were submitted to the Japan Patent Office from 1980 to 1998.[13] There

[11] See Murray and Acharya [1997], World Bank [1993], Appendix B in details.
[12] It is noteworthy that a commercial database named Derwent World Patent Index integrates information on patents and citations from the major patent offices in the world. The database is not easily available, as it is owned by a private company.
[13] Taking into account the fact that patent applications became open after one and a half years have passed since filling, data until 1998 are considered reliable.

appears to be a significant difference in the number of patent applications found among the three diseases. For example, there was a sharp increase in the number of patent applications related to HIV/AIDS for the decade after the first case of AIDS was reported in 1981. The number has continued to be higher than that of tuberculosis and malaria in the 1990's. Although tuberculosis and malaria attracted attention as re-emerging infectious diseases because of the emergence of drug-resistant types, R&D activities resulting in patent applications seemed to be extremely slow. There seem to be two factors that can potentially explain the difference in the number of innovations between HIV/AIDS and the other two diseases. First, it may be that demand is more important than necessity. As Schmookler [1966] pointed out, market size is an important determinant of the intensity of innovation in general. Even though the necessity of creating medicines to cope with malaria in developing countries is very high (see Table 1), the purchasing power of people in these countries is weak on average. Thus, the development of innovations in medicines for malaria is slower than that of HIV/AIDS, a disease that is also spreading in developed countries. Second, since HIV was discovered only recently, it is seen as an unexploited frontier in research and is deemed to be of greater interest than tuberculosis and malaria, diseases that were discovered some time ago and have been studied for a long time. Both factors seem to be at work in accounting for a difference of ten times the number of patent applications for HIV/AIDS innovations and those for the other two diseases.

2.3. Patent Applications by Country of Origin and Status of Firm

These days, patent application is so internationalized that many rely on either the Paris Convention or the Patent Cooperation Treaty. Figure 2 illustrates shares of the cumulative number of patent applications for medicines related to the three infectious diseases. These are organized by origin of applicant, and the Figure indicates that applicants from the United States, Japan, and European countries account for 90% of total for each disease.[14] The United States has a large share of the total number of applications, not only for HIV/AIDS (a serious influence in the country), but also for malaria (except for military needs, meets a thin demand in the home market). This shows that the United States is a leader in this field of research. It is interesting that the number of applications by Japan is roughly equal to that of the United States with respect to tuberculosis, while the share of Japan for malaria is small. In terms of innovation by the Japan, the difference between tuberculosis and malaria is due to two facts: First, Japan has directed its efforts to the treatment of tuberculosis from World War II until the present. Second, there is no mosquito transmitting malaria on the mainland of the country, so malaria has not been a serious concern in Japan. There are some differences with regard to the type of infectious diseases, but innovations in medicines for the three

[14] In the case of multiple applicants, the first applicant on the list is adopted.

diseases are dominated by the three poles: the United States, Japan, and European countries.

It is notable that medicines are likely to be exempt from protection by patent in many countries. For example, patent law started covered medicines in 1975, even in Japan, where the law had been stipulated long ago. Since then, both public and private entities have applied for and owned patents of medicines in Japan. Now, which sector, public or private, leads in the innovation of medicines for the poor? Consumption of medicine is likely to have an external impact (externality) by reducing the rate of infection moving from infected persons to others (Philipson [2000]). The private sector is unwilling to work on unprofitable medicines for which the market is small because of low purchasing power of people in poor countries. Under these circumstances, the public sector is expected to play a key role in R&D activity for infectious diseases. However, Table 3 shows that a majority of patent applications are filed by the private sector for all the three diseases (see Table 4 for the classification of public, university, and private entities). As for HIV/AIDS, the private sector accounts for more than three fourths of total applications. In contrast to expectation relative to the externality of infectious diseases and the unprofitable nature of medicines for the poor, it is evident that the private sector also leads in the innovation of medicines in developing countries..

Figure 3 shows trends in patent applications by sector. Regarding HIV/AIDS, private entities increased applications drastically in the middle of the 1980's, while the growth of applications by the public entities and universities was very modest. With tuberculosis, there is no upward trend in applications by public entities, but universities and private entities gradually increased the number of patent applications over time. Private entities had a surge in applications in 1998. With respect to malaria, private entities again showed an strong increase in the middle of the 1980's and maintained the level of innovation until 1995 when the next rise in applications started. It seems in terms of innovations in medicine, that public entities and universities cannot perfectly substitute functions of private entities. Cockburn and Henderson [2000] showed that there is a complementary relationship between the public and private sectors in R&D activity for medicines in the United States. They described a division of labor in which the public sector covered basic research while the private sector engaged primarily in applied research in order to make results from basic research practical and commercialized.[15] Since scientists in universities and public research institutes may be more like to publish results of their research in scientific journals rather than apply for a patent, estimations in the data of this study may underestimate the contribution of public entities and universities to the innovation of medicines.

[15] Evidence for estimating this cross correlation comes from data in this study and implies existence of a complementary relationship where private patent applications pick up after public ones become active. For example, in the case of malaria, the number of public applications three or four years ago correlates positively with present private applications.

2.4. Patent Applications by Firm

Which entities in the public and private sectors filed the most patent applications? Who make innovations in medicine for diseases in developing countries when such innovations do not seem to make great profit? Actually, the motivation for innovation is not necessarily related to profit. A private firm may have a philanthropic mind. It may want to enhance its reputation, or it may use the experience of innovation as an investment for innovation in the development of another more profitable medicine. In any case, determination of which types of firms filed many patent applications may provide useful information for identifying factors that determine performance in innovation of medicines for the poor.

From this perspective, data for patent applications by firm is analyzed below. Table 5 shows the cumulative number of patent applications related to HIV/AIDS, tuberculosis, malaria, and the neglected diseases,[16] the four disastrous diseases that are rampant in low income countries. These applicants are arranged in descending order based on number of applications for HIV/AIDS. It appears that most major applicants are pharmaceutical firms such as GlaxoSmithKline, Aventis, Merck, Bristol Myers Squibb Co., and others. The number of patent applications for medicines related to HIV/AIDS that GlaxoSmithKline filed during the period is remarkable. The number for GlaxoSmithKline is almost twice that of the second firm, Aventis. What is even more surprising is that GlaxoSmithKline is also the top applicant for malaria and the neglected diseases, and it is ranked second for tuberculosis. GlaxoSmithKline is the top innovator for development of medicines to fight serious infectious diseases spreading in low-income countries. The prominence of GlaxoSmithKline contributes to a positive correlation in patent applications among the three diseases, as shown in Table 6.[17] Are there any factors explaining the outstanding performance of this firm, and if so, what are they?

3. Empirical Analysis

What are the determinants of the large variation in patent application? Do common determinants of innovation in general explain the high performance of GlaxoSmithKline? Among major pharmaceutical companies, GlaxoSmithKline is relatively large in terms of sales and R&D expenditure. This could completely explain the prominent performance of the company. Since these medicines are unlikely to be profitable, ordinary variables that explain the extent of innovation may not significantly affect that of medicines for the diseases. Is there any firm-specific factor, other than controlling variables that are considered to affect invention of medicines in general, that leads

[16] Details for this category of diseases are given in section 3.
[17] Once GlaxoSmithKline is dropped from the sample, the correlation coefficients become small and statistically insignificant.

GlaxoSmithKline to invent medicines for developing countries?

3.1. Model

The equation for estimation is one commonly used as a knowledge production function (see Jones [1995] among others):

$$Y_{it} = e^{\gamma \mathbf{Z}_i + u_{it}} K_{it}^{\beta_1} S_{it}^{\beta_2} . \quad (1)$$

where *i* is the index of firms, and *t* is an index of years. Y_{it} is an indicator of knowledge produced; K_{it} and S_{it} are measures of the stock of knowledge and production of the firm *i*. $\mathbf{Z}_{it}$ is a vector consisting of other explanatory variables representing economies of scope, firm dummies, time trend, and a constant. $\boldsymbol{\gamma}$ is a corresponding vector of parameters. β_1 and β_2 are parameters of the elasticity of Y_{it} with respect to K_{it} and S_{it}, respectively. Finally, u_{it} is the error term.

Griliches[1984], and Hausman, Hall and Griliches[1984] assume a Poisson distribution for the error term, with a similar representation of the equation in order to investigate the relationship between the number of patents and R&D. In this paper, the output of the knowledge production function, Y_{it}, is measured by the number of patent applications of medicines and vaccines for the diseases. Success in innovation is a rare achievement that takes place after long R&D activity. The number of patent applications is a non-negative integer and takes on values as a discrete dependent variable. Therefore, the Poisson distribution is appropriate for the error term. The probability density function of a stochastic variable (Y_{it}) following the Poisson distribution is:

$$P(Y_{it}) = f(Y_{it}) = \frac{\lambda_{it}^{Y_{it}} e^{-\lambda_{it}}}{Y_{it}!}, \quad (2)$$

where λ_{it} is the Poisson parameter standing for the arrival rate of success in innovation per year per firm. Note that the conditional mean is identical to the conditional variance according to the probability density function. The conditional mean is expressed as:

$$E[Y_{it} | \mathbf{X}_{it}] = \lambda_{it} = \exp[\mathbf{X}_{it}\boldsymbol{\beta}'], \quad (3)$$

where $\mathbf{X}_{it}$ and $\boldsymbol{\beta}$ are $(1 \times k)$ vectors of regressors and parameters, respectively. The term *k* is the number of explanatory variables. Parameters are estimated by the maximum likelihood estimation method. Plugging equation (1) into equation (3), conditional expectation (4) below is derived.

$$\lambda_{it} = \exp[\beta_1 \ln K_{it} + \beta_2 \ln S_{it} + \boldsymbol{\gamma}\mathbf{Z}_{it}] = K_{it}^{\beta_1} S_{it}^{\beta_2} \exp[\boldsymbol{\gamma}\mathbf{Z}_{it}]. \quad (4)$$

As in other studies, explanatory variables are divided into two classes: variables entered in logarithms and variables entered in levels. It is notable that while the parameters of elasticity with respect to K_{it} and S_{it} are β_1 and β_2, respectively, elasticity with respect to the *j*-th explanatory variable contained in $\mathbf{Z}_{it}$ is $\gamma^j Z_{it}^j$.[18]

The equalization feature of a conditional mean and variance is rarely satisfied with data. Variance is often greater than the mean of a discrete variable, and this feature is called "over-dispersion" in a Poisson regression model. In order to cope with the non-equalization problem between mean and variance, two methods have been developed. One is the Negative Binomial model (NB), and the other is the Zero Inflated Poisson model (ZIP).

In order to derive the NB model, a stochastic variation in the Poisson parameter, ε_{it}, is used, and the Poisson model is modified as follows:

$$\lambda_{it} = \exp[\mathbf{X}_{it}\boldsymbol{\beta}' + \varepsilon_{it}] \equiv \lambda' \exp(\varepsilon_{it}), \tag{5}$$

where $\exp(\varepsilon_{it})$ is assumed to follow a gamma distribution, $\Gamma(\bullet)$, with mean of 1 and variance of α. The probability density function is thus

$$g(\varepsilon_{it}) = \frac{\theta^\theta}{\Gamma(\theta)} \exp[-\theta\varepsilon_{it}]\varepsilon_{it}^{\theta-1}. \tag{6}$$

where $\theta = 1/\alpha$. The conditional probability density function is then

$$f(Y_{it}|\mathbf{X}_i) = \frac{\Gamma(\theta + Y_{it})}{\Gamma(Y_{it}+1)\Gamma(\theta)} \left(\frac{\lambda'_{it}}{\lambda'_{it}+\theta}\right)^{Y_{it}} \left(\frac{\theta}{\lambda'_{it}+\theta}\right)^{\theta}. \tag{7}$$

The conditional mean of Y_{it} is no longer equal to its variance.

$$E[Y_{it}|\mathbf{X}_{it}] = \lambda'_{it}, \text{ and } \operatorname{var}[Y_{it}|\mathbf{X}_{it}] = \lambda'_{it}(1+\alpha\lambda'_{it}). \tag{8}$$

Unless the parameter α, which is called the "over-dispersion parameter",[19] is equal to zero, the mean and variance of the dependent variable in this model are distinct.

The second model that takes account of the over-dispersion problem is the Zero Inflated

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[18] This is derived as follows: $\frac{Z_{it}^j}{\lambda_{it}} \frac{\partial \lambda_{it}}{\partial Z_{it}^j} = \frac{Z_{it}^j}{\lambda_{it}} \cdot \lambda_{it}\gamma^j = \gamma^j Z_{it}^j$.

[19] This formula is referred to as the Negbin2 model in Cameron and Trivedi [1986].

Poisson (ZIP) model. This is designed to incorporate the feature of many zero counts in the dependent variable (Lambert [1992]). When a large number of zeros is observed for the dependent variable, the Poisson regression model underestimates the probability of zeros, and this may cause over-dispersion. The ZIP model allows for "excess zeros" by assuming that the data generating process is characterized by two regimes: one where the value always takes a zero count and one where it takes zero or positive counts generated by the Poisson process. These two regimes are described as follows:

$$Y_{it} \sim \begin{cases} 0, & \text{with probability} \quad p_i \\ \text{Poisson}(\lambda_i) & \text{with probability} \ 1-p_i \end{cases} \tag{9}$$

Estimation with this model takes two stages. A probability density function of the logit model is applied to the first stage estimation. The second regime follows the ordinary Poisson model. Synthesizing the two stages of estimation, the probability density functions are as follows:

$$\begin{aligned} &\Pr(Y_i = 0) = p_i + (1-p_i)e^{-\lambda_i} \\ &\Pr(Y_i = j) = (1-p_i)\frac{e^{-\lambda_i}\lambda_i{}^j}{j!}, \qquad j = 1,2,3\cdots \end{aligned} \tag{10}$$

For the Zero Inflated Poisson model, the conditional mean and variance are described as follows:

$$\begin{aligned} E[Y_i] &= p_i \times 0 + (1-p_i) \times E[Y_i | Y_i > 0], \\ &= (1-p_i)\frac{\lambda_i}{1-e^{-\lambda_i}}, \end{aligned} \tag{11}$$

$$\text{var}[Y_i] = \frac{\lambda_i}{1-e^{-\lambda_i}}(1-p_i)[1+\frac{\lambda_i}{1-e^{-\lambda_i}}p_i]. \tag{12}$$

This model is thus able to incorporate the over-dispersion feature.

It should be noted that the NB and ZIP models are not mutually exclusive. On the contrary, the features of two models can be integrated, and the Zero Inflated Poisson model with negative binomial distribution is called the Zero Inflated Negative Binomial model (ZINB). The Vuong test is available for testing the validity of the ZIP model against the alternative model (Vuong [1989]). Suppose that the probability density function of the ZIP (or ZINB) model is denoted by $f_1(Y_i|\mathbf{X}_i)$, and that of the ordinary Poisson (or NB) model is denoted by $f_2(Y_i|\mathbf{X}_i)$. A test statistic is the log likelihood ratio,. $m_i = \log\left(f_1(Y_i|\mathbf{X}_i)/f_2(Y_i|\mathbf{X}_i)\right)$. More precisely, the Vuong statistic for testing the Zero Inflated Poisson model against the Poisson model is:

$$v = \frac{\sqrt{n}\left[\frac{1}{n}\sum_{i=1}^{n} m_i\right]}{\sqrt{\frac{1}{n}\sum_{i=1}^{n}(m_i - \overline{m})^2}}. \qquad (13)$$

If v is greater than 2, the ZIP (ZINB) model is accepted. If v is smaller than -2, the Poisson (NB) model is accepted. If v falls in the range between -2 and 2, the test is indeterminate.

3.2. Data Sets

Diseases studied

The knowledge production function can be estimated with the specification expressed in equation (1). Two data sets are used: one for HIV/AIDS and one for the neglected diseases. The former is the most acute and serious disease in contemporary developing countries, while the latter is a group of diseases that is also very serious and spreads exclusively in developing countries. For HIV/AIDS, a panel data set running from 1981 to 1998 was made up for 9 major pharmaceutical companies, *i.e.* Abbott Laboratories, Bristol-Myers Squibb Company, Eli Lilly, F. Hoffmann - La Roche, GlaxoSmithKline, Merck, Novartis, Pharmacia, and Pfizer. The sample size of the panel data for HIV/AIDS was 162. Abbott Laboratories and Pharmacia were dropped from the data set for neglected diseases because each of the two firms has only a single patent application of medicine for the diseases. As a result, the sample size of panel data for the neglected diseases covering 1980-1998 was 133.

The category of “neglected diseases” was used as a dataset because of the small sample size for malaria. Since the number of patent applications of medicines for malaria was relatively small, the sample size of the panel data was also small. This was not the case for HIV/AIDS. Malaria is a representative disease among those that spread exclusively in developing countries, but HIV/AIDS is a global disease in the sense that many people with HIV/AIDS live in rich countries. Since it is important to study determinants of innovations in medicines for diseases spreading only in developing countries, and to compare them with global diseases, patent applications of medicines for other important and influential infectious diseases that are prevalent exclusively in developing countries were added to those for malaria. A new category called “neglected diseases” was thus created.

The category of “neglected diseases” was “borrowed” from the homepage of a renowned non-government organization, Médecins Sans Frontières (MSF). MSF is an organization known to be a forerunner of international aid in medical activities. It undertakes activities to diffuse knowledge and information in medicines used in developing countries. In order to facilitate innovation of medicines for diseases which are rampant and very serious in low income countries, MSF designates

and publicizes information about the "neglected diseases": malaria, human African trypanosomiasis (alias sleeping sickness), leishmaniasis and meningitis.[20] This category suits the present analysis and is juxtaposed with HIV/AIDS.

Patent application

As explained in subsection 3.1, the proxy for knowledge produced is the number of patent applications (*PATENT*). Each application is dated by a priority date.[21] However, the number of patent registrations is not suitable for this empirical analysis due to small sample size. Adoption of patent applications as a proxy for innovation can be used because the protection of an invention comes into effect on the date of the application (according to the first-to-file principle of the Japan Patent Office).[22]

R&D stock

Explanatory variables are identical between the two sets (one for HIV/AIDS and one for the neglected diseases), even though the sample periods and the number of firms are different due to the availability of the dependent variable.

R&D stock is used as a proxy for the stock of knowledge which each firm utilizes in order to make innovative activities. The R&D stock is constructed as the deflated and depreciated sum of R&D expenditure for all innovative activities of the firm according to the perpetual inventory method using a depreciation rate of 10%. The data were collected from either the Form 10-K or the annual report directed to stockholders of sample firms. All values were converted to U.S. dollars using the annual average exchange rate against U.S. dollar. The R&D expenditures are deflated with the biomedical research and development price index (BRDPI)[23] that is constructed by the National Institute of Health in the United States. Sales are deflated with the pharmaceutical price index in the United States (See Appendix 2 for details).

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[20] Human African trypanosomiasis is a fatal parasitic disease carried by tsetse flies that affects about 3-5 hundred thousand people in 36 countries of sub-Saharan Africa. Leishmaniasis is another fatal parasitic disease transmitted to humans through the bite of infected tsetse flies. Currently, at least twelve million people in the world are infected. The most serious type of disease is the visceral leishmaniasis known as "Kala azar". This mainly spreads in five developing countries: Bangladesh, Brazil, India, Nepal and Sudan. Meningitis is transmitted through coughing and sneezing of infected people. It prevails particularly in the area referred to as the African meningitis belt which ranges from Senegal to Ethiopia.

[21] The priority date is the first filing date of a patent application to the patent office of a country. If the applicant submits the same application to another country for a suspended period (one year in most cases), the latter application is treated as if it is filed in the second country on the priority date.

[22] There are some studies that use indicators of the number of patents weighted by intensity of citations in order to take into account the quality of innovation (Jaffe and Trajtenberg [2002]). Unfortunately, contrary to the US Patent office, there is no citation system in the Japan Patent office.

[23] This index is available on the web (http://www1.od.nih.gov/osp/ospp/ecostudies/economic_studies.htm).

There are two caveats for this variable: First, there have been frequent mergers and acquisitions in the pharmaceutical industry. In order to handle this problem, a base year is set. The status for each sample company as of December 2002 is applied to the whole sample period. In other words, multiple firms that merged before December 2002 are treated as a single firm, and the number of patent applications, R&D expenditures, and sales are added respectively among the firms. Second, for any given firm, it is not possible distinguish R&D expenditures directed to development of innovations in medicines for the infectious diseases from those for other diseases and injuries. In other words, this variable captures only the general scale of R&D for each pharmaceutical firm.

Economies of scale

It is often hypothesized that large companies have an advantage over small ones in developing innovations. A justification for this hypothesis is that under the circumstance of imperfect financial markets, an invention is financed by profits and larger companies are good at exercising market power to raise profits. This justification was proposed by Schumpeter [1942]. On the other hand, the opposite view is that overall productivity should be lower for a large firm because of the diminishing marginal productivity of investment. In short, scale economy may or may not work for knowledge production. The economies of scale are estimated by the elasticity of knowledge production with respect to production within the threshold of the elasticity of unity. As a matter of fact, there is little general empirical evidence that supports economies of scale in innovation. As for innovation in medicines, Jensen [1987], Graves and Langowitz [1993], and Cockburn and Henderson [1996, 2001] report that they did not find economies of scale. The present research tests the hypothesis with the data set that includes medicines for the infectious diseases spreading in low-income countries.

Economies of scope

The performance of an R&D activity may depend on the intensity of similar activity in neighboring areas. Some knowledge drawn from research in adjacent fields may be beneficial. In other words, diversification in R&D within a group of medicines may positively affect the innovation of a certain medicine classified within that group. Generally speaking, an ascendancy associated with conducting variety in production is known as “economies of scope”. This can be interpreted to mean that conducting multiple research projects together by a single firm is more efficient than carrying out the same projects by various firms. For example, it is known that an important antiretroviral that is widely used as a medicine for AIDS was invented by applying knowledge gained from development of an anticancer drug. Engaging in developing an innovation in medicine for cancer enhanced productivity of innovations in medicines for HIV/AIDS. There is empirical evidence supporting the hypothesis of “economies of scope” in the area of pharmaceutical innovations. Cockburn and Henderson [1996, 2001] found positive and significant returns to scope

in research for ten major pharmaceutical companies. The same hypothesis for the infectious diseases spreading in developing countries is tested in this research.

For proxies of economies of scope, the precedent of Okada and Kawahara [2004] is used. These researchers measured the breadth of R&D activities using the number of therapeutic classes where the firm has at least applied for a patent.[24] There are 13 therapeutic classes and subcategories under each class. These are called "facets" in the International Patent Classification (IPC).[25] In this study, the number of IPC facets where the firm files at least one patent application in a year (*SCOPE*) is used as a proxy for economies of scope. In order to elucidate the effect of economies of scope among medicines for infectious diseases, *IDSCOPE* is defined as the number of IPC facets with at least one patent application among the facets for all infectious diseases. The squared *IDSCOPE*, which is denoted by *IDSCOPE-SQ*, is also used to take account of non-linearity in economies of scope.

Time trend and dummies

The time trend (*TREND*) and firm dummies are added to the equation. Regarding firm dummies, GlaxoSmithKline is set to be the benchmark. The sample firms are numbered as follows:

1. GlaxoSmithKline,
2. Bristol-Myers Squibb (BMS),
3. Pfizer,,
4. Merck,
5. Abbott Laboratories,
6. Novartis,
7. Roche,
8. Pharmacia,
9. Eli Lilly.

As a result, the general form of equation for estimation is the following:

$$\ln\left(PATENT_{it}\right) = \gamma_0 + \beta_1 \ln\left(R\,\&\,DStock_{it}\right) + \beta_2 \ln\left(SALES_{it}\right) + \gamma_1\left(SCOPE_{it}\right) + \gamma_2\left(IDSCOPE_{it}\right) + \sum_{j=2}^{9} \gamma_{3j}\left(FIRMDUMMY_j\right) + \gamma_4\left(TREND_t\right) + u_{it}\,. \quad (14)$$

[24] Cockburn and Henderson [1996, 2001], who explored the effect of economies of scope, used ,the number of research programs which were kept ,inside each firm and not open to the public. Even though the approach is interesting, it is not feasible in the present research.
[25] See Table A for details of the 13 therapeutic classes.

3.3. Results of Estimation

Table 7 displays summary statistics for the two data sets. It should be noted that the standard deviation is far greater than the mean of the dependent variable (*PATENT*) for both HIV/AIDS and the neglected diseases. These observations suggest over-dispersion. The Negative Binominal (NB) model, the Zero Inflated Poisson (ZIP) model, and the Zero Inflated Negative Binomial model (ZINB) were then applied for estimation in addition to the standard Poisson (POIS) model. Results of estimation with the HIV/AIDS data are displayed in Table 8, while those of the neglected diseases may be seen in Table 9. The four combinations of explanatory variables, which deserve particular attention, are selected and numbered [1]-[4] in the tables.

(1) Estimation for HIV/AIDS

The logarithm of R&D stock, firm dummy variables, and time trend were used for all estimations, but the remaining explanatory variables, such as logarithm of sales and the measures of economies of scope, are included as ,explanatory variables in order to examine the effect of those variables on innovation. The estimation results of the standard Poisson model are shown in the first four columns. The coefficients of most of the explanatory variables maintain expected signs, and these are statistically significant (Table 8). An exception is the logarithm of sales; here, the coefficient is negative and statistically insignificant.

There is some doubt about the validity of the standard Poisson model due to over-dispersion. Results of a Lagrange multiplier test for over-dispersion leads to rejection of the null hypothesis of equality between conditional mean and variance. In addition, over-dispersion is detected as a result of the NB estimation. A likelihood-ratio test of the over-dispersion parameter of the NB model with null hypothesis of $\alpha = 0$ (bottom of the second four columns in Table 8) indicates that for the four combinations of explanatory variables, the alternative hypothesis of the over-dispersion may be accepted. Thus the negative binomial model is judged to be more appropriate than the Poisson model for this data set.

It turns out that over-dispersion is perhaps better explained by the “excess zeros” feature of the Zero Inflated Poisson model than by the NB model. The Vuong statistics and their *p*-values are displayed in the second row at the bottom of Table 8. All values of the Vuong statistics are far greater than 2 for the eight patterns of estimation by the ZIP and ZINB models. This suggests that the ZIP and ZINB models that incorporate the “excess zeros” assumption are favored over the Poisson and NB models, respectively. Hence, the ZINB model appears to be the most consistent with regard to the over-dispersion feature of the data.

All estimates obtained through the estimation are in general, appropriate. As expected, the signs of coefficients on ln(*R&Dstock*) are all positive, and estimates are all significantly greater than zero (except for those from the NB model). The values of estimated elasticity of patent applications,

with respect to R&D stock, exhibit relatively wide variation ranging from 0.55 to 1.93. However, the null hypothesis that the elasticity is unity is in no case rejected because of the large standard errors of estimates.

Estimates of the coefficient on ln(*SALES*), which is a proxy for a firm's scale, are negative but statistically insignificant for all specifications. This lack of significance is reinforced by the fact that the log-likelihood does not change greatly by adding ln(*SALES*) in all specifications (see Table 8 for differences in log-likelihood between explanatory variable sets [1] and [2] using all estimation methods).[26] This absence of scale effects for innovations in medicines for HIV/AIDS is consistent with the findings of Jensen [1987], Graves and Langowitz [1993], and Cockburn and Henderson [1996, 2001] in their studies on medicines in general. Because of its insignificance, ln(*SALES*) was dropped from the remaining estimations.

Economies of scope are incorporated in two indicators: *SCOPE* and *IDSCOPE*. The former embodies the scope effect among all diseases and injuries, while the latter does so only among infectious diseases. As seen in Table 8, the estimates of coefficients for *SCOPE* are significantly positive for the standard Poisson and NB models while not significant for the zero inflated models (ZIP and ZINB).[27] Estimates of the coefficient of *IDSCOPE* are always significantly positive irrespective of the combination of explanatory variables. The smallest estimate of the coefficient among all estimations is 0.247 for ZINB [4] where the equivalence of elasticity is 1.163. In summary, a positive impact of economies of scope on innovations in medicines for HIV/AIDS is detected among medicines for infectious diseases, but the same impact among medicines for all diseases and injuries is not confirmed.

Another noteworthy finding on innovations in medicines for HIV/AIDS is the diminishing nature of economies of scope within medicines for infectious diseases. The explanatory variable set [4] for all estimation methods includes a quadratic term for *IDSCOPE* in order to account for non-linearity in the relationship between scope of R&D and innovations. Viewing results using the explanatory variable (set [4] in Table 8), the estimated coefficient of *IDSCOPE-SQ* is significantly negative. There is precedence for this result. When looking at R&D in pharmaceutical firms, Cockburn and Henderson [1996, 2001] found a similar relation between diminishing returns and scope for innovation of medicines in general.

The sign and significance of the coefficient of *TREND* is altered according to the estimation method and model used. However, this instability may not matter; dropping *TREND* does not

[26] There is some reservation regarding multicolinearity between *R&D stock* and *SALES* where the correlation coefficient is 0.77. However, *SALES* is not significant due to its correlation with Trend, even when *R&D stock* is dropped.

[27] Note that the inverse of the Herfindahl index was used as another proxy for economies of scope. This index incorporates information about how equally patent applications are distributed across all 13 therapeutic classes (see Appendix 2 for details). However, the coefficient on this index does not reach significance for any specified equation and combination of variables.

dramatically affect the results mentioned above. As pointed out by Mairesse and Sassenou [1991] and Bassant and Fikkert [1996], it should be noted that R&D stock is likely to be correlated with time. Thus, it may be observed that the introduction of *TREND* somewhat lowers the coefficient of *R&D stock*.

The impact of firm dummy variables is a major concern of this experiment. GlaxoSmithKline was set to be the benchmark used for comparison with other pharmaceutical firms. As seen in the first column of Table 8, even after the magnitude of cumulative R&D expenditure is controlled, the prominence of GlaxoSmithKline in the number of patent applications of medicines for HIV/AIDS is apparent. This is reflected by negative coefficients on all firm dummy variables when the standard Poisson model is used without any proxies for economies of scope (see POIS [1] in Table 8). Further, six out of eight firms have coefficients that are significantly negative. This result remains consistent when ln(*SALES*) is added as an explanatory variable (see the second column labeled POIS [2]).

The prominence of GlaxoSmithKline is attenuated by either introducing proxies for economies of scope as explanatory variables (explanatory variable sets [3] and [4]) or by taking account of the possibility of "zero inflation" with ZIP and ZINB models. However, coefficients on dummy variables for three giant firms in terms of R&D stock,[28] specifically Novartis, Roche and Pharmacia, tend to remain significantly negative. This empirical observation implies that the prominence of GlaxoSmithKline in innovation of medicines for HIV/AIDS is remarkable among pharmaceutical giants, even after the variable of economies of scope is taken into account and the probability of failure in innovation is augmented by adoption of the ZIP model.

In fact, the significance of proxies for economies of scope and adoption of zero inflated models do not aid in understanding the mechanisms that led to the higher performance of GlaxoSmithKline. The strong and positive association between the number of patent applications of medicines for HIV/AIDS and the width in innovation of medicines for infectious diseases (incorporated in *IDSCOPE*) is consistent with the observation that GlaxoSmithKline files patent applications for medicines not only related to HIV/AIDS but also tuberculosis and malaria. It is a challenge for future studies to treat *IDSCOPE* as an endogenous variable and to explain the variation in the number of patent applications and *IDSCOPE* jointly. Further, "zero inflation" successfully reduces negative significance of dummy variables for relatively small firms for which the number of successful innovations is more likely to be zero. However, that methodology seems incapable changing the negative insignificance for larger firms. Although the prominence of GlaxoSmithKline is explained by introducing proxies for economies of scope and adopting the zero inflation models, the factors that explain the performance of this company, both for scale and scope in innovation of medicines for the poor, are still open for investigation.

[28] Refer to Table 10 for the scale in R&D stock for each sample firm.

(2) Estimation for the neglected diseases

Another fundamental concern for this analysis is determining whether the mechanisms that affect performance in innovation of medicines is different between HIV/AIDS, which is a global disease, and the neglected diseases that are spreading only in low income countries Table 9 displays results for estimations related to the neglected diseases. In general, it may be concluded that almost all findings mentioned above for HIV/AIDS are applicable to innovations in medicines for the neglected diseases. In general tendencies differences between the two are rarely found.

The same explanatory variables are used for estimations of HIV/AIDS and the neglected diseases, but the sample size is less for the neglected diseases due to the decline in the number of sample firms. As in the case of HIV/AIDS, the over-dispersion parameter is significantly different from zero (except for ZINB[4]), and the zero inflation hypothesis may be accepted using the Vuong test.

Estimates of elasticity of patent applications with respect to *R&D stock* are distributed in a reasonable range between 1.16 and 1.43, unless *IDSCOPE* is introduced as an explanatory variable. The corresponding estimates of the standard errors are distributed between 0.55 and 0.75. Thus, estimates of elasticity are judged to be statistically significant only for some models, unless *IDSCOPE* is used. It is evident from the estimation results for HIV/AIDS that once *IDSCOPE* is introduced, the signs of estimates of elasticity turn negative, even though the negative difference from zero is not statistically significant. The scale effect, which is embodied in the coefficient for ln (*SALES*), is negative and statistically insignificant, as in the case for HIV/AIDS.

An interesting difference from the results for HIV/AIDS is that the estimates of coefficients for *IDSCOPE-SQ* are significantly positive, while those for *IDSCOPE* are insignificant. This implies increasing returns to scope. However, this feature appears at the cost of an unreasonable value for the elasticity of patent applications with respect to *R&D stock*. Thus, the increasing returns to scope feature must be treated with skepticism.

The effects of firm dummies are similar to those for HIV/AIDS. If only *R&D stock* is included as an explanatory variable, the coefficients of all firm dummy variables are estimated to be negative, and the impact of five out of six firm dummies are judged to be significantly negative. This significance becomes weak when proxies for economies of scope and adoption of the zero inflation models are introduced. However, such significance tends to consistently show up for large firms such as Novartis and Roche, unless *IDSCOPE* is introduced. Thus, the prominence of GlaxoSmithKline among large firms in the development of innovations in medicines for the neglected diseases is apparent, as it is in the case of HIV/AIDS.

(3) Discussion

Results of estimations show that economies of scope are exhibited in relations that exist

between research in medicines for the infectious diseases featured in the estimations and that for all other infectious disease. Firms that work with infectious diseases in general are superior in innovation for HIV/AIDS and the neglected diseases. For example, as seen in Table 10, the average values of *SCOPE* and *IDSCOPE* of GlaxoSmithKline over the sample period are the greatest among sample firms. GlaxoSmithKline has worked intensively on infectious diseases for many years, an outstanding achievement that currently gives it status in the field of innovations in medicines for the poor. This is reflected in Table 11, which shows the development pipeline of GlaxoSmithKline as of the end of 2003. Among all, it is remarkable that there are many medicines for tropical diseases such as dengue fever, leishmaniasis, meningitis, malaria, and rotavirus that are in the process of development at GlaxoSmithKline. Note that leishmaniasis and malaria are treated as neglected diseases in this paper. All told, these are reasons why the chief executive officer of GlaxoSmithKline is proud of the company's supremacy in accumulated resources for invention of medicines for infectious diseases in low income countries (GlaxoSmithKline [2003]).

What enabled the firm to succeed with such strength and depth of innovation? A key is mergers and acquisitions (M&A) that have resulted in the current form of GlaxoSmithKline. It is widely known that most large pharmaceutical multinationals have expanded their scale of business through M&A. As shown in Figure 4, GlaxoSmithKline is an integration of several companies resulting from a series of M&A that took place for last two decades. Among all, because of its excellence in the field, the addition of Wellcome in 1995 was crucial in development of further innovations in medicines for infectious diseases. However, study of the background of M&A in pharmaceutical companies in detail is beyond the scope of this paper. In this study, a firm formed through M&A during the sample period was treated as if the firm in December 2002 had its form from the beginning. Exploration of the effect of M&A on innovations in medicines for infectious diseases that are spreading in low income countries must await future study.

It is interesting that GlaxoSmithKline did not resort to a system of preferential treatment granted for developing innovations in medicines for serious diseases contracted by a small number of people. This is known as the "orphan drug" system and provides various incentives for sponsors to develop products for rare diseases in some countries (Thamer, Brennan and Semansky [1998]). The Orphan Drug Act of the United States, which came into effect in 1983, grants: (1) seven years of marketing exclusivity after approval of its orphan drug product, (2) tax credits for clinical research, and (3) funding for sponsors.[29] Diseases treated by orphan drugs include tropical diseases that are hardly contracted by U.S. nationals. Some argue that the orphan drug system could work internationally to promote innovation of medicines and vaccines for diseases which are neglected but

[29] The system is considered a great success. The cumulative number of designated orphan drug products is 1432, and 265 of these products received marketing approval as of December 2004. The Food and Drug Administration of the United States publishes data regarding designations and approval of orphan drugs on its web site (http://www.fda.gov/orphan/).

serious (Grabowski [2002]; Kremer [2000b]).

GlaxoSmithKline did not aggressively use the above system. Only two medicines were approved as orphan drugs in the U.S, *Retrovir* for HIV/AIDS and *Halfan* for malaria (see Table 11). Thus, the orphan drug system does not seem to have created momentum for GlaxoSmithKline to develop medicines for low-income countries. It is difficult to determine why GlaxoSmithKline succeeded in filing an extraordinary number of patent applications related to medicines for the three killer diseases found in low income countries.

4. Concluding Remarks

Now that there is consensus regarding lenient application of TRIPS for low-income countries, the price of medicines for diseases that are prevalent in low-income countries is gradually declining. The focus of institutional change, which are requested as a long-term solution to the problem of rampant infectious diseases, shifts to a problem of how to encourage the development of innovations in medicine for the diseases. There has been an expectation that the public sector leads such innovation because it is a matter of the "public good" to develop medicines for diseases when people have low purchasing power and live in low-income countries where they are susceptible to such diseases. Results of this research indicate that private companies have been dominant in applying for patents in that category of medicines. It seems that the private sector played a major role in the development of innovation in medicine, not only for patients in developed countries, but also for those in developing countries. As stated in Introduction, patents on medicines have been exempt from protection by patent (Lanjouw and Cockburn [2001]). This makes the above find particularly striking. Even in unfavorable circumstances described above, private pharmaceutical companies have contributed to developing medicines for the diseases.

On the other hand, it is well known that public research institutes and universities have contributed to both critical and fundamental innovations in the prevention and cure of HIV/AIDS, tuberculosis, and malaria (Cockburn and Henderson [2000], Seytre [1995]). Dominance of private firms in patent applications combines with essential contributions of public institutions form a complementary relationship. As suggested by Cockburn and Henderson [2000], those in the public sector are likely to engage in upstream and scientific discoveries while those in the private may tend to deal with downstream and applied inventions. Rather than be filed as patents, discoveries made by scientists in the public sector are more likely to be published in scientific journals such as *Nature* and *Science* in order to improve researcher's reputation.

Results indicate that there is a great variation in the number of patent applications filed by pharmaceutical firms. In particular, GlaxoSmithKline, a giant pharmaceutical firm, is distinguished in its innovation of medicines for HIV/AIDS, tuberculosis, and malaria. The prominence of

GlaxoSmithKline, which in this study is incorporated into firm dummies, is attenuated when the variable of economies of scope is introduced as an explanatory variable. However, if in addition to the number of patent applications, development of innovations in a wide variety of medicines is also used as a performance indicator of pharmaceutical companies, the good performance of GlaxoSmithKline becomes even more pronounced.

GlaxoSmithKline had been criticized by NGOs for interfering in the access to medicines where patents were owned by the firm, and it started cutting prices of medicines for patients in low-income countries in 2001 (Oxfam [2001]). In a sense, however, GlaxoSmithKline was criticized because it developed many inventions in medicine for the treatment of infectious diseases spreading in low-income countries, and it kept a number of patents resulting from these achievements. Other companies could not be criticized since they did not have patented medicines for the diseases.

Finally, it must be stressed that the mechanisms of innovation for HIV/AIDS and the neglected diseases are quite similar, even though there could be a difference in incentive for innovation due to a difference in purchasing power of respective patients. This research confirms that there is nothing special in the development of innovations of medicine for low income countries as compared with that for high income countries. As discussed in section 2, the development of innovations in medicine for low-income countries has been led by the private sector. Further, empirical analysis shows that innovation is closely associated with R&D and that the scale effect is invisible in innovation of medicines for the poor. These conclusions imply that the disincentive problem related to the lenient application of TRIPS, should be taken seriously. Otherwise, pharmaceutical firms may quietly retreat from what they see as unprofitable business.

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Appendix 1: The method of collecting patent application data from JPO

The Industrial Property Digital Library (IPDL) is provided by the Japan Patent Office (JPO) which releases various information on the World Wide Wed.[30] There are three main classification systems used to organize patent documents: (1) the International Patent Classification (IPC), (2) FI and (3) F-terms (File Forming Terms). IPC is an internationally uniform patent classification system formulated from a technological viewpoint. The FI system was originally developed originally by JPO in order to elaborate on the IPC so that an IPC search would become more efficient and convenient. FI includes some Japan-specific classifications. The F-terms system has a more detailed classification than the others, not only from a technological viewpoint, but also from a variety of viewpoints (objective, application, structure, material, manufacturing process, processing and operation method, control method, *etc.*). Combining FI with F-terms enables users to effectively extract more detailed data than in an IPC search.

In order to retrieve patent application data on medicines and vaccines by disease, FI and F-terms systems were used jointly. First, a conventional formula for combination of FI and F-terms for HIV/AIDS in JPO was used.[31] The authors adjusted the formula of HIV/AIDS for analysis. Second, some experimentation was conducted to determine appropriate FI and F-terms for each disease. The following formulas[32] were constructed, and data were retrieved according to these formulas.

Data for tuberculosis and malaria may include medicines and vaccines for other diseases because the formula for tuberculosis is based on “mycobacterium” which is a larger class of bacterium that includes tubercle bacillus, and the formula for malaria is based on “plasmodium” which contains the malaria parasite. There are no finer subcategories beyond mycobacterium and plasmodium.

[30] http://www.ipdl.ncipi.go.jp/homepg.ipdl.
[31] The authors are grateful for instruction given by Haruo Matsumura and Ken Takeda.
[32] The plus sign “+” indicates a union of sets before and after the sign.

HIV/AIDS: 4B024BA35+4C084DC43+4C084ZC55+4C085BA69+4C086ZC55+4C087ZC55 +4C088ZC55+4C206ZC55+C07K14/16+A61P31/18

	F-terms or FI	
1	4B024BA35	Mutation or genetic engineering for human immunodeficiency virus
2	4C084DC43	HIV protease inhibitors including enzyme-related protein substances
3	4C084ZC55	Anti-AIDS drugs including enzyme-related protein substances
4	4C085BA69	Bacterial antigens of HIV
5	4C086ZC55	Anti-AIDS drugs that contain other organic and inorganic compounds
6	4C087ZC55	Anti-AIDS drugs containing material from animals or micro-organisms
7	4C088ZC55	Anti-AIDS drugs containing plant substances
8	4C206ZC55	Anti-AIDS drugs including acyclic and carbocyclic compounds in medicinal compositions
9	C07K14/16	Peptides having more than 20 amino acids and origin in HIV-1
10	A61P31/18	Anti-HIV drugs

Tuberculosis: 4C085BA09+4C087BC29+C07K14/35+A61K39/04+A61P31/06

	F-terms or FI	
1	4C085BA09	Medicines containing mycobacterium for use as internal diagnostic agents
2	4C087BC29	Medicines for mycobacterium containing material from animals or micro-organisms
3	C07K14/35	Peptides having more than 20 amino acids with origin in mycobacterium
4	A61K39/04	Medicinal preparations containing mycobacterium
5	A61P31/06	Medicines for tuberculosis

Malaria: 4C085BA06+ C07K14/445+ A61K39/015+A61P33/06

	F-terms or FI	
1	4C085BA06	Medicines containing Haemosporidia antigens for use as internal diagnostic agents
2	C07K14/445	Peptides having more than 20 amino acids with origin in Plasmodium
3	A61K39/015	Medicinal preparations containing Plasmodium antigens
4	A61P33/06	Anti-malarial drugs

Neglected Diseases: (Malaria) + 4C085BA03+4C085BA04+4C085BA16+ A61K39/008 +A61K39/095 +A61P33/02

	F-terms or FI	
1	4C085BA03	Medicines containing Trypanosoma antigens for use as internal diagnostic agents
2	4C085BA04	Medicines containing Leishmania antigens for use as internal diagnostic agents
3	4C085BA16	Medicines containing Neisseria for use as internal diagnostic agents
4	A61K39/008	Medicinal preparations containing Leishmania antigens
5	A61K39/095	Medicinal preparations containing Neisseria
6	A61P33/02	Antiprotozoals, e.g., for leishmaniasis, trichomoniasis, toxoplasmosis

Appendix 2: Data sources and variable construction

(1) R&D stocks

R&D stocks are constructed using a perpetual inventory method. The stock at time *t* is equal to knowledge flow at time *t* plus the stock at time *t*-1 with depreciation:

$$R_t = RF_t + (1-\delta)R_{t-1}, \tag{A-1}$$

$$RF_t = \sum_{i=1}^{n} \mu_i E_{t-i}, \tag{A-2}$$

where R_t is R&D stock at *t*, RF_t is knowledge capital flow at *t*, E_{t-i} is real R&D expenditure at *t*-*i,* and δ is the depreciation rate (given at 10%).

Let R&D expenditures transform into knowledge capital flow with a time lag θ. Define μ_i in equation (A-2) as:

$$\mu_i = \begin{cases} 1, & \text{if } i = \theta, \\ 0, & \text{otherwise.} \end{cases} \tag{A-3}$$

Then, equation (A-2) is re-written as

$$RF_t = E_{t-\theta}. \tag{A-4}$$

In this paper, time lag is set to be one year. The benchmark of knowledge capital stock, R_{tb}, is constructed by assuming that real R&D expenditures in previous years have grown at an average annual rate of growth, *g*, for the sample period.

$$\begin{aligned} R_{tb} &= E_t + (1-\delta)E_{t-1} + (1-\delta)^2 E_{t-2} + \cdots \\ &= E_t + \left(\frac{1-\delta}{1+g}\right)E_t + \left(\frac{1-\delta}{1+g}\right)^2 E_t + \cdots \\ &= \frac{E_t}{1-\left(\frac{1-\delta}{1+g}\right)} \\ &= \frac{E_t(1+g)}{g+\delta} = \frac{E_{t+1}}{g+\delta} \end{aligned} \tag{A-5}$$

(2) Scope indexes

The Japan Patent Office provides sub-categories of the International Patent Classification

(IPC) as shown in Table A, this sub-category is called the IPC facet. Referring to Okada and Kawahara [2004], 13 therapeutic classes are defined as seen in Table A.

Three scope indexes were used in this paper: (1) *SCOPE* is the number of IPC facets for which at least one patent application is filled in a year. It is designed to capture the width of innovation activities of a firm for medical science as a whole. (2) *IDSCOPE* is the number of IPC facets in which at least one patent application is filled within the group of infectious diseases (displayed in the rows entitled "3. Anti-Infective Agents" in Table A). (3) To measure how equally R&D resources are allocated over IPC facets, the inverse of the Herfindahl index was constructed using the number of patent applications across 13 therapeutic classes.

$$HERINVRS_t = 1 \Big/ \sum_{i=1}^{13} s_{it}^2 , \qquad \text{(A-6)}$$

where $s_{it} = q_{it} \Big/ Q_{it}$, $Q_{it} = \sum_{i=1}^{13} q_{it}$ and q_{it} is the number of patent applications to the therapeutic class *i* at time *t*.

Table A: Definition of 13 Therapeutic Classes and IPC Facet Classification

Therapeutic class	Facet	Definition
1. Respiratory Agents	ABF	Antiallergic
	ACD	Respiratory active
	ACE	Respiratory stimulant
	ACF	Bronchodilator
	ACG	Antitussive
	ACH	Expectorant
2. Anti-cancer/tumor Agents	ADS	Cellular tissue active
	ADT	Cell-activating
	ADU	Tumor inhibitor
	ADV	Antileukemic
3. Anti-Infective Agents	ABH	Interferon
	ADW	Pathogenic organism active
	ADX	Antipathogen
	ADY	Antiviral
	ADZ	Antimicrobial
	AEA	Antipathogenic-parasite
	AEB	Antiparasitic
	AEC	Anthelmintic
4. Blood Agents	ABY	Hematopoietic
	ABZ	Blood substitutes
	ACA	Hemostatic
	ACB	Anticoagulant
	ACC	Antianemic
5. Cardiovascular Agents	ABN	Cardiovascular active
	ABP	Cardiac muscle stimulant
	ABQ	Myocardial depressant
	ABR	Vasodilator
	ABS	Coronary vasodilator
	ABT	Vasoconstrictor
	ABU	Hypoglycemic
	ABV	Hypotensive
	ABW	Capillary stabilizers
	ABX	Antithrombolytic
6. Gastrointestinal Agents	ACJ	Gastrointestinal active drug
	ACK	Agents for oral use
	ACL	Antiulcer
	ACM	Stomachics and digestives
	ACN	Antiobesity
	ACP	Emetic
	ACQ	Lexative
	ACR	Antidiarrhoeal
	ACS	Hepatic/bile duct active drug
	ACT	Cholagogues
	ACU	Dissolving of a gallstone
7. Central Nervous System Agents	AAA	Nervous system active drug
	AAB	Central nervous system active drug
	AAC	Central nervous depressant
	AAD	Anaesthetic
	AAE	Hypnotic
	AAF	Convulsant
	AAG	Antipyretic
	AAH	analgesic
	AAJ	Central stimulant
	AAK	Antidepression
	AAL	Antiemetic
	AAM	Improving brain function
	AAN	Antipsychotic
	ABE	Antiinflammatory
8. Metabolic/ Endocrine Agents	ADD	Metabolic active drug
	ADE	Vitamine preparations
	ADF	Vitamine A, D preparations
	ADG	Vitamine B preparations
	ADH	Vitamine B? preparations
	ADJ	Vitamine B? preparations
	ADK	Vitamine C, P preparations
	ADL	Vitamine E, K preparations
	ADM	Urea metabolic active
	ADN	Fatty metabolic active
	ADP	Antidiabetic
	ADQ	Antidote
	ADR	Agents for habitual-poisoning
9. Hormonal Agents	AED	Biologically active substances agents
	AEE	Hormones for medical purposes
	AEF	Pituitary hormone preparations
	AEG	Thyroid and para-thyroid hormone preparations
	AEH	Adrenal hormone preparations
	AEJ	Androgen preparations
	AEK	Estrogen preparations
10. Immune Agents	ABA	Agents for innate immunity
	ABB	Agents for antibody production
	ABC	Immune suppressant
	ABD	Adjuvant
11. Bone/Joint disorder Agents	ABG	Antirheumatic
12. Genitourinary Agents	ACV	Genitourinary active drug
	ACW	Urinary system agent
	ACX	Diuretic agent
	ACY	Hysterotonic
	ACZ	Contraceptive
13. Peripheral Nervous System Agents	AAP	Peripheral nervous system active drug
	AAQ	Agents for sensory nervous system
	AAR	Agents for motor nervous system
	AAS	Skeletal muscle relaxants
	AAT	Autonomics agents
	AAU	Sympathomimetic
	AAV	Sympatholytic
	AAW	Parasympathomimetic drug
	AAX	Parasympatholytic drug
	AAY	Spasmolytic
	AAZ	Hidrotic

Table 1: Infections of HIV, Tuberculosis and Malaria in 2000

	Number of Deaths in 2000	Number of Newly Infected Persons	Share of Infected People Living in Developing Countries in Total Infections
HIV/AIDS	3 million	5.3 million	92%
Tuberculosis	1.9 million	8.8 million	84%
Malaria	More than 1 million	300 million	Almost 100%

Source: World Health Organization [2002], Introduction.

Table 2: Damages of HIV/AIDS, Tuberculosis and Malaria in 2002

		World	Africa	The Americas	Eastern Mediterranean	Europe	East and South Asia	Western Pacific
HIV/AIDS	A)	2821	2204	103	50	43	375	46
	B)	5.8%	18.3%	2.2%	1.1%	1.1%	2.5%	0.7%
Tuberculosis	A)	1605	305	44	131	74	691	360
	B)	2.4%	2.3%	0.6%	2.1%	1.1%	3.7%	2.2%
Malaria	A)	1222	1088	1	57	0	65	11
	B)	3.0%	10.8%	0.1%	1.6%	0.0%	0.6%	0.2%
Total	A)	5648	3597	148	238	117	1131	417
	B)	11.2%	31.4%	2.9%	4.8%	2.2%	6.9%	3.2%

Note: A) The number of deaths due to each disease (unit: thousand).
B) Share of total DALYs lost in each region due to each disease.
Source: World Health Organization [2002b].

Table 3: Cumulative Numbers and Shares of Patent Applications by Innovator for 1980-98

		Public	University	Private	Total
HIV/AIDS		176 (5.0%)	497 (14.2%)	2835 (80.8%)	3508 (100%)
Tuberculosis		20 (5.8%)	102 (29.8%)	220 (64.3%)	342 (100%)
Neglected diseases		80 (6.3%)	271 (21.3%)	920 (72.4%)	1271 (100%)
	Malaria	34 (8.7%)	95 (24.2%)	267 (67.2%)	396 (100%)

Note: “Neglected diseases” consist of leishmaniasis, trypanosomiasis, meningitis, and malaria.

Table 4: Classification of Innovators

Notation	Definition
Public	Government and public institutions
University	Private universities and non-profit research institutes
Private	Private companies

Table 5: Cumulative Numbers by Applicants

Applicant	HIV/AIDS	Tuberculosis	Malaria	Neglected Diseases
GlaxoSmithKline	277	12	53	115
Aventis	139	9	12	79
Merck	107	5	6	46
Pfizer	93	3	2	46
the USA	72	6	13	23
Bristol-Myers Squibb	64	2	2	6
Roche	61	6	12	37
Int. Pasteur	51	8	12	15
Abbot Laboratories	50	0	0	1
Sankyo	48	6	0	4
Novartis	46	2	0	18
Takeda	39	8	4	24
Pharmacia	37	1	0	1
Chiron	35	4	15	27
Bayer	33	1	7	31
Astra Zeneca	30	5	1	2
Boehringer Ingelheim	27	1	2	3
Eli Lilly	27	1	1	13
Wyeth	25	3	9	31
Human Genome Sciences	15	2	8	10
Corixa Corporation	0	22	0	4

Note: See note in Table 3 for neglected diseases.

Table 6: Correlation Coefficients among Applications of Medicines for HIV/AIDS, Tuberculosis and Malaria

	HIV/AIDS	Malaria	Tuberculosis
HIV/AIDS	1		
Malaria	0.831	1	
Tuberculosis	0.676	0.705	1

Table 7: Descriptive Statistics

(1) HIV/AIDS : 162 observations

variable	Mean	Std. Dev	Min	Max
PATENT (AIDS)	4.71	7.27	0	56
R&Dstock	9268.4	5387.6	1446.1	25135.0
SALES	15506.7	6885.4	5647.6	35052.0
SCOPE	31.14	10.15	7	56
IDSCOPE	4.71	2.91	0	14
IDSCOPE-SQ	30.62	37.88	0	196
variable(Log)				
ln(R&Dstock)	8.96	0.61	7.28	10.13
ln(SALES)	9.55	0.46	8.64	10.46

(2) Neglected Diseases : 133 observations

variable	Mean	Std. Dev	Min	Max
PATENT (ND)	1.89	2.75	0	19
R&Dstock	9534.3	5504.5	3095.1	25135.0
SALES	15954.1	7232.1	5647.6	35052.0
SCOPE	33.02	9.95	9	56
IDSCOPE	4.72	2.73	1	14
IDSCOPE-SQ	29.67	35.40	1	196
variable(Log)				
ln(R&Dstock)	9.01	0.56	8.04	10.13
ln(SALES)	9.57	0.46	8.64	10.46

Table 8: Estimates of the Patent Production Function of Medicines for HIV/AIDS (N=162)

	POIS[1]	POIS[2]	POIS[3]	POIS[4]	NB[1]	NB[2]	NB[3]	NB[4]	ZIP[1]	ZIP[2]	ZIP[3]	ZIP[4]	ZINB[1]	ZINB[2]	ZINB[3]	ZINB[4]
Constant	-7.314*	-4.648	-9.797**	-11.667**	-4.346	-1.324	-9.728	-10.645	-12.879**	-11.441**	-13.723**	-15.005**	-12.584	-11.577	-13.928*	-15.988**
	(3.361)	(3.796)	(3.404)	(3.477)	(8.156)	(9.354)	(7.971)	(7.172)	(3.960)	(4.712)	(4.058)	(4.186)	(6.583)	(7.443)	(6.700)	(6.145)
ln(R&Dstock)	0.981*	1.083**	1.056**	1.110**	0.551	0.680	0.865	0.865	1.747**	1.747**	1.800**	1.834**	1.707*	1.734*	1.793*	1.931**
	(0.391)	(0.399)	(0.393)	(0.396)	(0.955)	(0.971)	(0.921)	(0.825)	(0.464)	(0.464)	(0.468)	(0.475)	(0.769)	(0.774)	(0.771)	(0.698)
ln(SALES)		-0.370				-0.427				-0.151				-0.129		
		(0.243)				(0.633)				(0.270)				(0.445)		
SCOPE			0.042**	0.040**			0.062**	0.057**			0.008	0.007			0.013	0.011
			(0.008)	(0.008)			(0.017)	(0.015)			(0.009)	(0.009)			(0.013)	(0.012)
IDSCOPE				0.407**				0.371**				0.259**				0.247**
				(0.057)				(0.105)				(0.058)				(0.083)
IDSCOPE-SQ				-0.019**				-0.018**				-0.010**				-0.009
				(0.003)				(0.007)				(0.003)				(0.005)
Firm 2: BMS	-0.868**	-0.975**	0.091	0.620	-1.158*	-1.274*	0.317	0.778	-0.330	-0.402	-0.122	0.413	-0.348	-0.395	-0.034	0.543
	(0.278)	(0.288)	(0.333)	(0.344)	(0.608)	(0.633)	(0.703)	(0.653)	(0.313)	(0.339)	(0.380)	(0.395)	(0.502)	(0.527)	(0.592)	(0.557)
Firm 3: Pfizer	-0.690**	-0.742**	-0.201	0.085	-1.142**	-1.214**	-0.306	0.026	-0.293	-0.337	-0.186	0.172	-0.374	-0.403	-0.212	0.216
	(0.202)	(0.206)	(0.222)	(0.223)	(0.465)	(0.477)	(0.495)	(0.459)	(0.226)	(0.239)	(0.252)	(0.256)	(0.365)	(0.378)	(0.398)	(0.371)
Firm 4: Merck	-0.410	-0.510*	-0.105	-0.056	-0.594	-0.789	-0.114	-0.116	0.052	-0.017	0.135	0.218	0.041	-0.012	0.150	0.244
	(0.246)	(0.256)	(0.253)	(0.254)	(0.545)	(0.616)	(0.548)	(0.502)	(0.281)	(0.307)	(0.294)	(0.297)	(0.450)	(0.485)	(0.462)	(0.425)
Firm 5: Novartis	-2.233**	-2.209**	-1.858**	-1.179**	-1.916**	-1.876**	-1.459**	-0.835	-2.453**	-2.414**	-2.394**	-1.737**	-2.428**	-2.409**	-2.340**	-1.731**
	(0.239)	(0.237)	(0.253)	(0.281)	(0.653)	(0.659)	(0.630)	(0.598)	(0.276)	(0.283)	(0.283)	(0.311)	(0.458)	(0.462)	(0.464)	(0.439)
Firm 6: Roche	-1.457**	-1.659**	-0.696**	-0.091	-1.076**	-1.334**	-0.113	0.273	-1.343**	-1.430**	-1.193**	-0.638**	-1.302**	-1.378**	-1.080**	-0.573
	(0.143)	(0.195)	(0.205)	(0.221)	(0.338)	(0.509)	(0.413)	(0.401)	(0.143)	(0.212)	(0.211)	(0.228)	(0.226)	(0.346)	(0.317)	(0.311)
Firm 7: Eli Lilly	-1.591**	-1.925**	-1.004**	-0.610	-1.928**	-2.322**	-0.651	-0.382	-0.657	-0.832	-0.507	-0.111	-0.680	-0.810	-0.437	0.028
	(0.358)	(0.421)	(0.378)	(0.379)	(0.733)	(0.943)	(0.796)	(0.723)	(0.407)	(0.512)	(0.435)	(0.442)	(0.624)	(0.769)	(0.668)	(0.615)
Firm 8: Abbott	-0.674	-0.872	0.424	1.287*	-0.973	-1.212	0.980	1.375	0.408	0.281	0.658	1.302*	0.450	0.366	0.852	1.506
	(0.442)	(0.462)	(0.485)	(0.512)	(1.072)	(1.132)	(1.148)	(1.021)	(0.510)	(0.558)	(0.571)	(0.606)	(0.845)	(0.892)	(0.935)	(0.868)
Firm 9: Pharmacia	-1.964**	-2.067**	-1.099**	-0.896**	-2.042**	-2.155**	-0.747	-0.545	-1.768**	-1.818**	-1.595**	-1.401**	-1.772**	-1.815**	-1.509**	-1.321**
	(0.176)	(0.190)	(0.243)	(0.251)	(0.353)	(0.394)	(0.478)	(0.448)	(0.177)	(0.198)	(0.253)	(0.263)	(0.254)	(0.294)	(0.366)	(0.351)
TREND	0.071*	0.078**	0.054	0.012	0.163*	0.168**	0.120	0.071	-0.056	-0.049	-0.060	-0.098**	-0.050	-0.047	-0.055	-0.104
	(0.031)	(0.031)	(0.031)	(0.030)	(0.072)	(0.072)	(0.069)	(0.062)	(0.038)	(0.039)	(0.038)	(0.038)	(0.059)	(0.060)	(0.059)	(0.055)
Over-dispersion parameter					0.684**	0.681**	0.605**	0.468**					0.198**	0.198**	0.196**	0.132**
					(0.133)	(0.133)	(0.122)	(0.108)					(0.051)	(0.051)	(0.051)	(0.040)
Vuong test of zip(zinb) vs. Poisson(nb)									z = 6.52 Pr>z = 0.000	z = 6.44 Pr>z = 0.000	z = 6.27 Pr>z = 0.000	z = 6.15 Pr>z = 0.000	z = 8.90 Pr>z = 0.000	z = 8.77 Pr>z = 0.000	z = 8.26 Pr>z = 0.000	z = 7.84 Pr>z = 0.000
Log-likelihood	-433.0	-431.9	-419.6	-388.4	-350.9	-350.7	-343.5	-336.0	-304.6	-304.5	-304.2	-284.4	-275.5	-275.5	-275.0	-265.2

Note: Standard errors in parentheses. * Statistically significant at the .05 level, ** at the .01 level. Over-dispersion parameter tested using the likelihood-ratio test of $\alpha = 0$.

Table 9: Estimates of the Patent Production Function of Medicines for the Neglected Diseases (N=133)

	POIS[1]	POIS[2]	POIS[3]	POIS[4]	NB[1]	NB[2]	NB[3]	NB[4]	ZIP[1]	ZIP[2]	ZIP[3]	ZIP[4]	ZINB[1]	ZINB[2]	ZINB[3]	ZINB[4]
Constant	-9.114*	-6.198	-11.323**	-4.471	-7.794	-5.900	-9.645	4.985	-9.127	-6.225	-11.725*	3.095	-8.560	-6.694	-11.022	3.145
	(4.650)	(5.524)	(4.766)	(5.684)	(6.319)	(7.340)	(6.267)	(6.388)	(5.142)	(6.284)	(5.358)	(6.331)	(6.075)	(7.268)	(6.232)	(6.446)
ln(R&Dstock)	1.224*	1.316*	1.345**	-0.443	1.074	1.146	1.173	-0.514	1.225*	1.258**	1.432*	-0.241	1.162	1.191	1.358	-0.250
	(0.547)	(0.560)	(0.552)	(0.658)	(0.743)	(0.754)	(0.728)	(0.742)	(0.606)	(0.613)	(0.619)	(0.732)	(0.717)	(0.719)	(0.722)	(0.746)
ln(SALES)		-0.389				-0.262				-0.336				-0.223		
		(0.397)				(0.521)				(0.415)				(0.478)		
SCOPE			0.029**	0.009			0.026	0.011			0.021	0.005			0.020	0.006
			(0.012)	(0.012)			(0.015)	(0.014)			(0.012)	(0.012)			(0.013)	(0.012)
IDSCOPE				-0.021				-0.003				-0.061				-0.056
				(0.086)				(0.099)				(0.085)				(0.089)
IDSCOPE-SQ				0.013**				0.012*				0.014**				0.014**
				(0.005)				(0.006)				(0.005)				(0.005)
Firm 2: BMS	-2.169**	-2.268**	-1.479**	-2.135**	-2.243**	-2.304**	-1.638*	-2.127**	-0.681	-0.821	-0.058	-0.665	-0.697	-0.780	-0.095	-0.657
	(0.519)	(0.530)	(0.594)	(0.608)	(0.603)	(0.614)	(0.690)	(0.652)	(0.539)	(0.569)	(0.641)	(0.657)	(0.600)	(0.627)	(0.714)	(0.667)
Firm 3: Pfizer	-0.606*	-0.650*	-0.232	-0.589	-0.670*	-0.691	-0.336	-0.603	-0.332	-0.390	-0.167	-0.374	-0.353	-0.385	-0.048	-0.372
	(0.291)	(0.295)	(0.329)	(0.347)	(0.379)	(0.380)	(0.418)	(0.384)	(0.307)	(0.316)	(0.353)	(0.369)	(0.354)	(0.360)	(0.402)	(0.375)
Firm 4: Merck	-0.262	-0.428	0.004	-0.908*	-0.318	-0.434	-0.114	-0.956*	-0.004	-0.166	0.239	-0.673	-0.030	-0.140	0.189	-0.675
	(0.322)	(0.365)	(0.340)	(0.386)	(0.425)	(0.483)	(0.433)	(0.433)	(0.344)	(0.399)	(0.369)	(0.423)	(0.397)	(0.461)	(0.419)	(0.430)
Firm 5: Novartis	-2.495**	-2.429**	-2.308**	-0.636	-2.390**	-2.352**	-2.223**	-0.563	-1.826**	-1.739**	-1.772**	-0.295	-1.784**	-1.731**	-1.728**	-0.283
	(0.432)	(0.433)	(0.446)	(0.556)	(0.565)	(0.567)	(0.565)	(0.628)	(0.429)	(0.443)	(0.434)	(0.565)	(0.506)	(0.518)	(0.505)	(0.577)
Firm 6: Roche	-1.106**	-1.311**	-0.652**	-0.122	-1.080**	-1.220**	-0.701*	-0.094	-0.989**	-1.162**	-0.687**	-0.233	-0.978**	-1.094**	-0.696*	-0.226
	(0.197)	(0.287)	(0.275)	(0.293)	(0.270)	(0.386)	(0.344)	(0.337)	(0.202)	(0.294)	(0.265)	(0.290)	(0.238)	(0.343)	(0.300)	(0.297)
Firm 7: Eli Lilly	-1.621**	-1.964**	-1.023	-1.885**	-1.708**	-1.931**	-1.172	-1.897**	-0.739	-1.058	-0.235	-1.082	-0.775	-0.979	-0.279	-1.079
	(0.506)	(0.617)	(0.564)	(0.594)	(0.616)	(0.759)	(0.680)	(0.645)	(0.526)	(0.661)	(0.597)	(0.632)	(0.588)	(0.735)	(0.669)	(0.640)
TREND	-0.049	-0.040	-0.072	0.003	-0.044	-0.039	-0.065	0.004	-0.048	-0.036	-0.075	-0.001	-0.047	-0.040	-0.074	-0.001
	(0.041)	(0.042)	(0.042)	(0.046)	(0.054)	(0.055)	(0.054)	(0.051)	(0.046)	(0.049)	(0.049)	(0.053)	(0.054)	(0.056)	(0.056)	(0.054)
Over-dispersion parameter					0.275**	0.271**	0.244**	0.101*					0.110**	0.107**	0.101**	-0.012
					(0.101)	(0.101)	(0.095)	(0.070)					(0.054)	(0.054)	(0.052)	(0.041)
Vuong test of zip(zinb) vs. Poisson(nb)									z = 6.71 Pr>z = 0.000	z = 6.70 Pr>z = 0.000	z = 6.65 Pr>z = 0.000	z = 7.62 Pr>z = 0.000	z = 8.03 Pr>z = 0.000	z = 8.01 Pr>z = 0.000	z = 8.26 Pr>z = 0.000	z = 7.81 Pr>z = 0.000
Log-likelihood	-219.3	-218.8	-216.5	-199.2	-209.0	-208.8	-207.5	-197.5	-165.3	-164.9	-163.6	-150.3	-161.3	-161.2	-163.6	-150.3

Note: Standard errors in parentheses. * Statistically significant at the .05 level, ** at the .01 level. Over-dispersion parameter tested using the likelihood-ratio test of $\alpha = 0$.

Table 10: Characteristics of Sample Firms

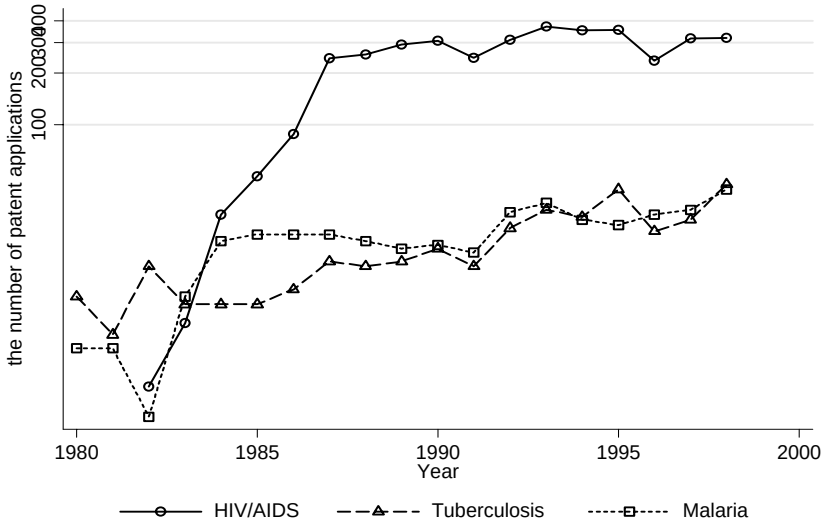
Code	Name	HIV/AIDS	ND	R&D stock			Sales			R&Dstock ／Sales	Average SCOPE	Average IDSCOPE	AIDS／ R&Dstock	ND／ R&Dstock
				Minimum	Mean	Maximum	Minimum	Mean	Maximum					
Firm1	GSK	277	115	5064.5	11273.4	21386.1	11195.5	11313.8	28702.9	99.6%	45.5	7.4	2.46%	1.02%
Firm2	BMS	64	6	3345.1	6349.2	10179.4	12351.7	14126.7	18495.0	44.9%	23.7	3.2	1.01%	0.09%
Firm3	Pfizer	93	46	3613.2	7587.1	14377.4	14139.7	16942.8	22890.7	44.8%	33.5	4.7	1.23%	0.61%
Firm4	Merck	107	46	3818.0	6760.3	11052.9	7052.7	12933.5	26898.2	52.3%	37.4	6.7	1.58%	0.68%
Firm5	Novartis	46	18	15274.5	19264.3	25135.0	20953.1	27646.2	35052.0	69.7%	36.2	3.4	0.24%	0.09%
Firm6	Roche	61	37	7894.3	11397.5	16279.2	8913.5	12254.4	17510.0	93.0%	29.4	3.7	0.54%	0.32%
Firm7	Eli Lilly	27	13	3270.4	5580.7	8862.1	5647.6	7257.4	9432.6	76.9%	25.4	4.0	0.48%	0.23%
Firm8	Abbott	50	1	1446.1	3846.9	7814.7	6164.5	8984.2	13160.0	42.8%	19.1	2.9	1.30%	0.03%
Firm9	Pharmacia	37	1	6941.6	11355.9	16717.4	15406.0	18298.7	23500.7	62.1%	24.6	5.4	0.33%	0.01%

Table 11: GlaxoSmithKline's Development Pipeline for Infectious Diseases at the End of 2003

	PHASE Ⅰ ⇨	PHASE Ⅱ ⇨	PHASE Ⅲ ⇨	Marketed
Vaccines	HIV Dengue fever	Hepatitis E Malaria N. Meningitidis *Cervarix* (HPV)	*Rotarix* (rotavirus) *Streptorix* (S.pneumoniae)	*Havrix* (hepatitis A) *Engerix B* (hepatitis B) *Twinrix* (hepatitis A & B) *Infanrix* (diptheria, tetanus, acellular pertussis) *Tritanrix* (diptheria, tetanus, whole cell pertussis) Pollo Sabin (polio) *Priorix* (measles, mumps and rubella) *Typherix* (typhoid) *Hiberix* (haemophilus influenzae type b) *Mencevax ACW* (meningitis)
HIV/AIDS	Non-NRTI CCR5 antagonist Aspartyl protease inhibitor NRTI		*Ziagen & Epivir*	*Retrovir* *Epivir* *Combivir* *Ziagen* *Trizivir* *Agenerase* *Lexiva/Telzir*
Malaria		CDA (chlorproguanil, dapsone + artesunate)	Tafenoquine	*Malarone* *Halfan* *Lapda p*
Tuberculosis				
Other			Sitamaquine (visceral leishmaniasis)	*Zentel* (de-worming agent) *Pentostam* (visceral leishmaniasis)

Note: Italics indicate brand names of medicines and vaccines.
Source: GlaxoSmithKline [2004]

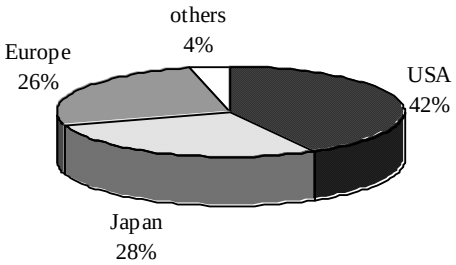
Figure 1: Trends in Patent Applications for Medicines for HIV/AIDS, Tuberculosis and Malaria for 1980-1998



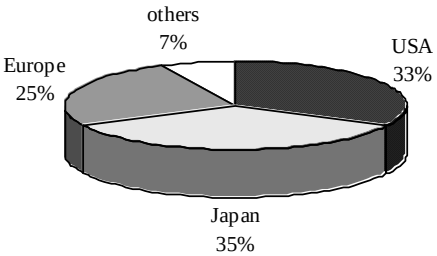
Notes: The vertical axis indicates a logarithmic scale.

Figure 2: Share of Cumulative Number of Patent Applications for Medicines for the Three Infections Diseases by Origin of Applicants

(1) HIV/AIDS



(2) Tuberculosis



(3) Malaria

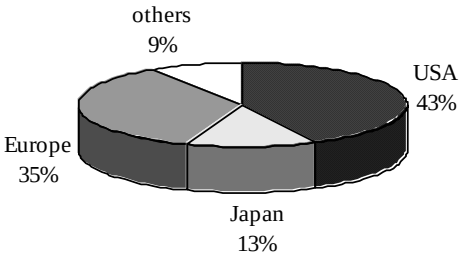
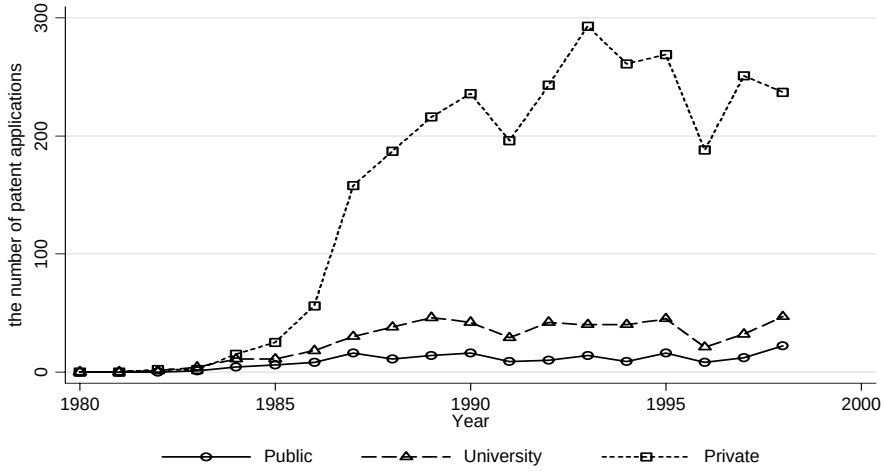
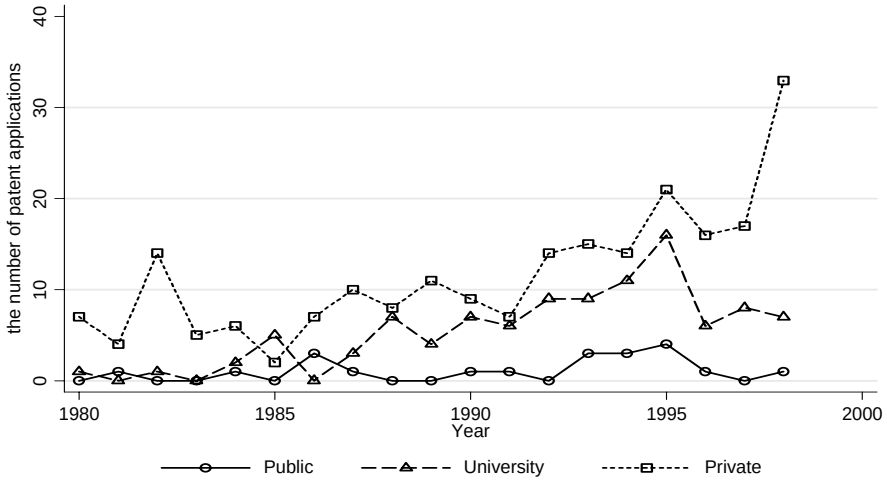


Figure 3: Trends in Patent Applications by Public and Private Organizations and Universities

(1) HIV/AIDS



(2) Tuberculosis



(3) Malaria

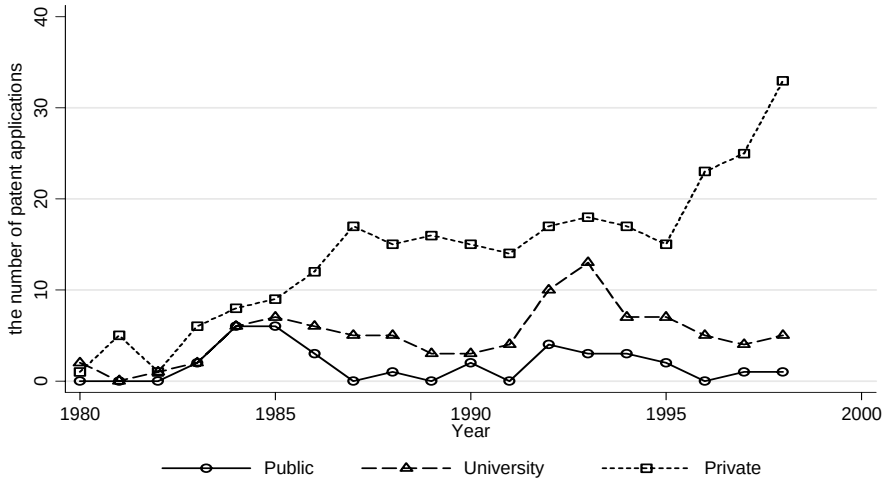


Figure 4: GlaxoSmithKline's M&A