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Use of a Bayesian approach in the design and evaluation of NCE2s

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ABSTRACT

Taiwan's regulatory agency defines New Chemical Entity 2 (NCE2) as a compound drug that has been approved and marketed for ten years in a top-ten pharmaceutically-advanced country but which is new in Taiwan. To apply for registration of NCE2 in Taiwan, a clinical trial may be conducted in Taiwan to evaluate the efficacy and safety. Since the NCE2 has been approved in at least one of the top-ten pharmaceutically-advanced countries, we can borrow the information from all of the observed data from other countries to synthesize the data from both Taiwan and other countries to assess the NCE2 efficacy. In this paper, we propose a Bayesian approach that uses a mixture of prior information to help evaluate an NCE2's efficacy. Numerical examples illustrate applications of the proposed approach in different scenarios. A method for sample-size determination for such trials is also proposed.

1. Introduction

New drug registration has a pivotal role in pharmaceutical affairs. It can serve as a measure of a central health authority's competence and ability to ensure the quality, safety, and efficacy of new drugs for use by the public. The health regulatory agency in Taiwan defines a New Chemical Entity 2 (NCE2) as a "compound drug that has been approved and marketed for ten years in a top-ten pharmaceutically-advanced country but which is new in Taiwan" [1]. This refers to those drugs that, during time of the application for new drug inspection and registration, are without counterparts containing the same compound approved for sale in Taiwan. Article 7 of the "Regulations for Registration of Medicinal Products" defines the ten advanced pharmaceutical countries as Germany, the United States, Britain, France, Japan, Switzerland, Canada, Australia, Belgium, and Sweden [2]. For these kind of new drugs to be

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marketed in Taiwan, evidence or prescription data must be enclosed as the supporting materials, except for biological agents. Biological agents are defined as "serums, antitoxins, vaccines, toxoids, and bacteria liquids manufactured following microbiology and immunology theories." In addition, according to the Regulations for Registration of Medicinal Products announced by the Department of Health on September 12, 2008, biological agents also include genetically engineered drugs, vaccines, human plasma drugs, allergen drugs, and others. All new compound drugs applicable under this requirement may not infringe upon the patent rights of other drugs. The manufacturer must submit an affidavit while applying for new drug inspection and registration as a guarantee. Article 97 of the Pharmaceutical Affairs Act [3] also applies.

Because drugs that are new to Taiwan are generally from the top-ten pharmaceutically-advanced countries, technical information about their characteristics is easily accessible, and such drugs have been recognized for quality, safety, and efficacy by the regulatory agencies of the respective countries. The adoption evidence shall be issued by the highest health regulatory authority in the adopting country and authenticated by our government agency overseas. It may be substituted with photocopies of a collection of medicinal products containing the prescription compound in the country of origin and package inserts of prescription drugs containing the compound in the country of origin. The collection of medicinal products used shall be limited to that with the version number specified and that of the version from the most recent five years. Domestic manufacturers may enclose prescription criteria while applying for inspection and registration. Consequently, drugs made available for purchase in such countries have undergone extensive human trials, and their safety and efficacy can be confirmed. In order to promote public health and improve drug accessibility, Taiwan's regulatory agencies will use published research and literature as important information for NCE2 registration [4].

This idea introduces the concept of "global generic drugs." When regulatory agencies decide whether a drug — especially a new drug or one with new ingredients — should be allowed to enter the market, technical information and authorization of human drug trials using similar ingredients in other countries may be brought into consideration when assessing the drug's safety and efficacy. Although drug research and development have followed this global trend, some listed NCE approved drugs in advanced countries have yet to be introduced in Taiwan. Taiwanese pharmaceutical companies are smaller and therefore not as able to develop new drugs as larger and more advanced countries. Therefore, the research and development of new pharmaceuticals is more of a market niche. Regulatory agencies' policies support such research, and they guide Taiwanese pharmaceutical companies toward a higher level of development and drug technology.

The fact that such drugs have entered the market in other countries affirms that the technical information of these drugs has been recognized for safety and efficacy by the regulatory agencies of that country. Since these drugs have been on the market, they have been tested by a considerable number of human trials. To apply registration to Taiwan, a NCE2 trial needs to be conducted. Since the NCE2 has been approved in at least one of the top-ten pharmaceutically-advanced countries, we should therefore borrow "strength" from the information on efficacy and safety from previous trials and incorporate them into the analysis of the additional data obtained from the NCE2 trial. Therefore, in this paper, we propose a Bayesian approach with the use of mixed prior information suggested by Hsiao et al. (2007) [5,6] to assess an NCE2's efficacy. In Section 2, a Bayesian approach with mixture prior information for evaluating an NCE2's efficacy is established and the method for determining sample size is also presented. Section 3 supplies an example to illustrate the Bayesian approach. And Section 4 provides discussion and final remarks.

2. Method

2.1. *Information needed*

We assume that an NCE2 trial is conducted in Taiwan to compare an NCE2 and a placebo control. Let X_i and Y_j be efficacy responses for patients i and j receiving the NCE2 and the placebo control, respectively. We further assume that the primary endpoint is a continuous variable. Therefore, we can assume that $X_i \sim N(\mu_T, \sigma^2)$ and $Y_j \sim N(\mu_P, \sigma^2)$, where $N(\mu, \zeta^2)$ represents a normal distribution with mean μ and variance ζ^2. We assume that higher values of μ represent a preferable outcome. Here we assume that σ^2 is known. Let $\Delta = \mu_T - \mu_P$ be the treatment difference in the NCE2 trial. The hypothesis for testing the NCE2 treatment effect can be given as

$$H_0: \Delta \leq 0 \text{ vs. } H_A: \Delta > 0. \tag{1}$$

Since the NCE2 has been approved in at least one top-ten pharmaceutically-advanced country, we can borrow "strength" from previous trials' information on efficacy and safety, incorporating this into the analysis of the additional data obtained from the NCE2 trial. Therefore, we propose a Bayesian approach to synthesize the data generated by the NCE2 trial and the clinical data generated in the previous trials for assessing the efficacy of the NCE2 over a placebo control.

The proposed prior information for Δ is a weighted average of two priors:

$$\pi(\Delta) = \gamma\pi_1(\Delta) + (1-\gamma)\pi_2(\Delta), \tag{2}$$

where $0 \leq \gamma \leq 1$. In (2), $\pi_2(.)$ is a normal prior with mean θ_0 and variance σ_0^2 summarizing the clinical data about the treatment difference provided in previous clinical trials, whereas $\pi_1(.) = 1$ represents a non-informative prior. Here a γ value of 0 indicates that the prior π all comes from the information derived from the clinical data in the previous trials, while γ being 1 indicates that no strength of the evidence for the efficacy of the NCE2 relative to the placebo would be borrowed from the clinical data of previous trials.

The Bayesian approach proceeds as follows. Based on the NCE2 trial, Δ can be estimated by

$$\hat{\Delta} = \bar{x} - \bar{y},$$

where $\bar{x} = \sum_{i=1}^{n_T} x_i/n_T$, $\bar{y} = \sum_{j=1}^{n_p} y_j/n_P$, and n_T and n_P represent the numbers of patients recruited for the NCE2 group and the placebo, respectively. First, the marginal density of $\hat{\Delta}$ is

$$m(\hat{\Delta}) = \gamma + (1-\gamma)\frac{1}{\sqrt{2\pi(\sigma_0^2+\tilde{\sigma}^2)}}\exp\left\{-\frac{(\hat{\Delta}-\theta_0)^2}{2(\sigma_0^2+\tilde{\sigma}^2)}\right\}, \quad (3)$$

where $\tilde{\sigma}^2 = \sigma^2/n_T + \sigma^2/n_P$. With the prior information, once we derive the results from the NCE2 trial, the posterior distribution of Δ can be derived by the following calculation

$$\pi\left(\Delta\middle|\hat{\Delta}\right) = \frac{1}{m\left(\hat{\Delta}\right)}\left\{\gamma\frac{1}{\sqrt{2\pi}\tilde{\sigma}}\exp\left[-\frac{\left(\Delta-\hat{\Delta}\right)^2}{2\tilde{\sigma}^2}\right] + (1-\gamma)\frac{1}{2\pi\sigma_0\tilde{\sigma}}\exp\left[-\frac{\left(\Delta-\theta_0\right)^2}{2\sigma_0^2}-\frac{\left(\Delta-\hat{\Delta}\right)^2}{2\tilde{\sigma}^2}\right]\right\}.$$

Let P_{SP} be the posterior probability of superiority of the test drug to the placebo. Consequently,

$$P_{SP} = P(\mu_T - \mu_P > 0 | \text{tNCE data and prior}) = \int_0^\infty \pi(\Delta|\hat{\Delta})d\Delta$$

The NCE2 efficacy can be concluded if

$$P_{SP} > \tau$$

for some pre-specified $\tau > 0$. Here τ should generally be greater than 0.8. The value of 80% can be thought of as mimicking frequentist statistical power.

2.2. *Determination of sample size*

Suppose that in the NCE2 trial the numbers of patients required per treatment group is n. The marginal density of $\hat{\Delta}$ in (3) can be re-expressed as

$$m(\hat{\Delta}) = \gamma + (1-\gamma)\frac{1}{\sqrt{2\pi(\sigma_0^2+2\sigma^2/n)}}\exp\left\{-\frac{(\hat{\Delta}-\theta_0)^2}{2(\sigma_0^2+2\sigma^2/n)}\right\}. \quad (4)$$

Consequently, the posterior distribution of Δ is given by

$$\pi(\Delta|\hat{\Delta}) = \frac{1}{m(\hat{\Delta})}\left\{\gamma\frac{1}{\sqrt{4\pi\sigma^2/n}}\exp\left[-\frac{(\Delta-\hat{\Delta})^2}{4\sigma^2/n}\right] + (1-\gamma)\frac{1}{2\pi\sqrt{2\sigma_0^2\sigma^2/n}}\exp\left[-\frac{(\Delta-\theta_0)^2}{2\sigma_0^2}-\frac{(\Delta-\hat{\Delta})^2}{4\sigma^2/n}\right]\right\}.$$

Given τ, θ_0, σ_0^2, and σ^2, and replacing $\hat{\Delta}$ by the expected Δ, we can determine the sample size n by finding the smallest n, such that the equation

$$P_{SP} = \int_0^\infty \pi(\Delta|\hat{\Delta})d\Delta > \tau$$

is satisfied.

To determine the expected Δ, the "worst outcome criteria" approach developed by Lawrence and Belisle (1997) [7] can be used. To proceed, we assume that n^* represents the numbers of patients studied per treatment group in the previous clinical trial. Also, for the previous clinical trial we assume that the efficacy endpoints of both the NCE2 group and the placebo group have the same variance σ^2. Subsequently, θ_0 can be estimated by the difference in sample means of the previous trial and $\sigma_0^2 = 2\sigma^2/n^*$ can be estimated by the pooled sample variance of mean difference. Once θ_0 and σ_0^2 are determined, σ^2 in (4) can be derived by $n^*\sigma_0^2/2$. Because the NCE2 by definition showed significant efficacy in previous trials, the ratio of θ_0 to σ_0 should be greater than 1.96. By Lawrence and Belisle (1997) [7], the estimate of the treatment difference, $\hat{\Delta}$, is chosen to be the lower bound of a 95% confidence interval for Δ constructed from θ_0 and σ_0^2. In Table 1, the ratio of the sample size per treatment group for the NCE2 trial to that of the previous trial (i.e., n/n^*) for various combinations of θ_0 and variance σ_0^2 is provided with $\tau = 0.8$ or 0.9.

As shown in Table 1, an increase in τ or γ, or a decrease in the ratio θ_0 to σ_0 would increase the sample size required per group in the NCE2 trial. However, it is clear that for a given value of θ_0/σ_0, with proper choices of γ and τ, reduction of the total sample size for the NCE2 trial compared with the total sample size for previous trial is possible. Especially notable is that the required sample size for the NCE2 trial is much smaller than that of the previous clinical trial when $\gamma = 0$ — that is, when all information from the previous trial is used.

3. Results

In this section we provide an example to illustrate our approach. Earlier clinical trials provided the results of three randomized, placebo-controlled trials for a new anti-hypertension (test drug) conducted among the top-ten pharmaceutically-advanced countries. The design, dose, duration, and inclusion/exclusion criteria of these three trials are similar; hence, those three can be seen as pivotal trials for previous approval elsewhere. The primary endpoint is the change from baseline of sitting diastolic blood pressure (mmHg) at week 12.

An NCE2 trial was conducted in Taiwan to show the NCE2's efficacy. Using the technique of meta-analysis from Petitti (2000) [8] to integrate the results from the previous clinical trials, we derive that $\theta_0 = -13.28$ and $\sigma_0^2 = 0.51$. In this example, five scenarios for the results from the NCE2 trial were considered. Table 2 provides the number of patients and mean reduction and standard deviations of sitting diastolic blood pressure for all previous trials and for the five scenarios for the NCE2 trial.

The first scenario presents a situation where no statistically significant difference in the primary endpoint exists between the NCE2 and a placebo (2-sided p-value = 0.7188). It is clear that the difference in mean reduction of sitting blood pressure between the NCE2 and placebo is 0.7 mmHg, which is strikingly different from the relative levels obtained from the three previous clinical trials. However, as shown in Table 3, $P_{SP} \approx 1.00$ if all information from the previous clinical trials is used (i.e., $\gamma = 0$); in this case, efficacy of the NCE2 is claimed even if the primary endpoints of the NCE2 and the placebo are not shown to be significantly different. Thus, when all information from previous clinical trials is used, the results of the NCE2 trial will be overwhelmingly dominated by those results. On the other

Table 1 – The ratio of the sample size per treatment of the NCE2 trial to that of the previous trial with $\tau = 0.8$ or 0.9 and different combinations of θ_0 and σ_0^2.

γ	$\theta_0 = 4, \sigma_0^2 = 2$	$\theta_0 = 4, \sigma_0^2 = 2$	$\theta_0 = 5, \sigma_0^2 = 2$	$\theta_0 = 5, \sigma_0^2 = 3$	$\theta_0 = 6, \sigma_0^2 = 3$
	$\tau = 0.9$	$\tau = 0.8$	$\tau = 0.8$	$\tau = 0.8$	$\tau = 0.8$
0.0	<0.01	<0.01	<0.01	<0.01	<0.01
0.1	1.29	0.20	0.09	0.24	0.12
0.2	1.75	0.51	0.16	0.51	0.19
0.3	1.92	0.68	0.20	0.63	0.24
0.4	2.01	0.77	0.23	0.70	0.26
0.5	2.06	0.82	0.25	0.74	0.28
0.6	2.10	0.86	0.26	0.77	0.29
0.7	2.13	0.89	0.27	0.79	0.30
0.8	2.15	0.91	0.28	0.80	0.30
0.9	2.17	0.93	0.28	0.81	0.31
1.0	2.18	0.94	0.29	0.82	0.31
γ	$\theta_0 = 6, \sigma_0^2 = 3$	$\theta_0 = 7, \sigma_0^2 = 2$	$\theta_0 = 7, \sigma_0^2 = 3$	$\theta_0 = 7, \sigma_0^2 = 4$	$\theta_0 = 7, \sigma_0^2 = 5$
	$\tau = 0.8$	$\tau = 0.8$	$\tau = 0.8$	$\tau = 0.8$	$\tau = 0.8$
0.0	<0.01	<0.01	<0.01	<0.01	<0.01
0.1	0.12	0.04	0.07	0.12	0.21
0.2	0.19	0.05	0.11	0.20	0.35
0.3	0.24	0.06	0.13	0.23	0.41
0.4	0.26	0.07	0.14	0.25	0.45
0.5	0.28	0.07	0.15	0.27	0.47
0.6	0.29	0.08	0.15	0.28	0.48
0.7	0.30	0.08	0.16	0.29	0.50
0.8	0.30	0.08	0.16	0.29	0.50
0.9	0.31	0.08	0.16	0.29	0.51
1.0	0.31	0.08	0.16	0.30	0.52

hand, if $\gamma \geq 0.1$, then P_{SP} always drops to around 0.6411. In this situation, we would reject the NCE2 if τ is set at 80%. Therefore, our proposed procedure reaches a conclusion that is more consistent with the evidence provided by the NCE2 trial.

Table 2 – Descriptive statistics of reduction from baseline in sitting diastolic blood pressure (mmHg).

Region	Statistics	Treatment group	
		Test drug	Placebo
Original 1	N	138	132
	Mean	−18.1	−3.1
	Standard deviation	11.1	12.2
Original 2	N	185	179
	Mean	−17.2	−2.3
	Standard deviation	10.2	11.2
Original 3	N	141	143
	Mean	−15.3	−5.2
	Standard deviation	13.1	14.2
Scenario 1	N	64	65
	Mean	−4.6	−3.9
	Standard deviation	11	11
Scenario 2	N	64	65
	Mean	−15.1	−2.2
	Standard deviation	11	11
Scenario 3	N	64	65
	Mean	−12.5	−4.3
	Standard deviation	18	18
Scenario 4	N	24	23
	Mean	−11.1	−4.3
	Standard deviation	13	13
Scenario 5	N	24	23
	Mean	−11.1	−4.3
	Standard deviation	18	18

The second scenario is that the mean reduction of sitting diastolic blood pressure at week 12 of the NCE2 is statistically significantly greater than that of the placebo group (2-sided p-value < 0.0001). From Table 2, the difference in mean reduction of sitting blood pressure between the NCE2 and placebo is 12.9 mmHg, which is consistent with the differences obtained from the three previous trials. As expected, the values of P_{SP} in Scenario 2 appear to be close to 1.00 regardless of the choice of γ. We can therefore conclude NCE2 efficacy. Our procedure definitely obtains a conclusion that is consistent with the evidence provided by the results of the NCE2 trial. For the third scenario, again the mean reduction of sitting diastolic blood pressure at week 12 of the NCE2 is statistically significantly greater than that of the placebo group (2-sided p-value = 0.0048). However the standard deviations from both groups were larger than that from previous trials. It can be seen that the values of P_{SP} are all greater than 0.9 regardless of the choice of γ.

The fourth scenario shows the magnitude of the mean difference is 6.8, or close to half that of the results from the previous trials. However, the difference is not statistically significant at the 5% level due to the smaller sample size and the larger variability in the NCE2 trial (2-sided p-value = 0.0732). As shown in Table 3, the values of P_{SP} are all greater than 0.96 for all values of γ between 0 and 1. Consequently, NCE2 efficacy is concluded if τ is set at 90%. With the strength of the substantial evidence of efficacy borrowed from the data of the previous clinical trials, our procedure can demonstrate an NCE2's efficacy when a non-significant efficacy result but with around half magnitude of treatment difference is observed in the NCE2 trial. For the fifth scenario, the magnitude of the mean difference is similar to the fourth

Table 3 – Values of P_{SP} derived from Scenarios 1, 2, and 3 with various values of γ.

γ	P_{SP}				
	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
0.0	≈1	≈1	≈1	≈1	≈1
0.1	0.64109	≈1	0.99976	0.969002	0.95520
0.2	0.64109	≈1	0.99950	0.966160	0.91093
0.3	0.64109	≈1	0.99920	0.965094	0.86718
0.4	0.64109	≈1	0.99886	0.964535	0.82395
0.5	0.64109	≈1	0.99846	0.964191	0.78121
0.6	0.64109	≈1	0.99799	0.963958	0.73898
0.7	0.64109	≈1	0.99745	0.963789	0.69722
0.8	0.64109	≈1	0.99679	0.963662	0.65595
0.9	0.64109	≈1	0.99598	0.963563	0.61514
1.0	0.64109	≈1	0.99497	0.963482	0.57480

scenario with larger standard deviation. Again the difference is not statistically significant at the 5% level (2-sided p-value = 0.0985). In this case, if γ is greater than 0.4, the values of P_{SP} will be less than 0.8. Since the population variation for the NCE2 trial is different from that for the previous trials, there may exist ethnic difference.

4. Discussion

With increasing globalization in the development of medicines, new approaches to addressing geographic variations in efficacy and safety for product development are inevitable [9,10]. Previously conducted NCE2 clinical trials already provide some information on efficacy, safety, dosage, and dose regimen. NCE2 also has human use experience, to support safety and efficacy. As a rule, pharmaceutical companies engaged in the research and development of new drugs focus mainly on their manufacture and development. Normally, applications for the registration of a new drug are accompanied by information related to relevant information pertaining to both clinical and non-clinical research. Information on NCE2s already approved abroad can serve as published studies, saving both time and money in the new-drug-development process.

Here, a Bayesian method that uses a mixture of prior information has been suggested to synthesize data from both NCE2 trials and previous trials for assessment of NCE2 efficacy in Taiwan. The proposed prior information is a weighted average of a non-informative prior and a normal prior. The choice of weight γ can help demonstrate efficacy results that are consistent among the integrated results of the NCE2 trial and those from the top-ten pharmaceutically-advanced countries. However, the ethnic difference may not be quantified before the NCE2 trial properly conducted, therefore before that, it mat be difficult to choose an appropriate weight to calculate the sample size required for the NCE2 trial.

Selection of weight γ may be critical, since it determines how much information is borrowed from the results of previous trials. The regulatory agency and the trial sponsor should balance consideration of potentially relevant differences between Taiwan and the top-ten pharmaceutically-advanced countries (e.g., ethnic differences) with belief in the evidence of efficacy provided in previous trials. However, from Example, weighting has a minimal effect on P_{SP} once it is greater than 0.2. If an NCE2 is sensitive to ethnic factors — such as drug metabolism, sex, body size, and medical practice — we suggest that weight γ be greater than 0. In addition, in the design stage, to calculate the sample size required for the NCE2 trial we may consider either maximum possible values of the expected Δ or a set of the expected Δ values.

Conflicts of interest

The authors disclose no potential conflicts of interest.

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