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Quantitative Pharmacovigilance Modeling for TCM Injections Adverse Event Reporting

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Abstract

For a long time, traditional Chinese medicine in clinical practice has been considered to be safe, low toxicity of drugs. In recent decades, with the listing of the many independently developed traditional Chinese medicine injections, compared traditional Chinese medicine, traditional Chinese medicine injections has accurate dose, quick, and other advantages, increasingly widespread clinical application. But in recent years to adverse reactions happened frequently, especially traditional Chinese medicine injection adverse events happened at Honghe Prefecture, Yunnan Province, Datong County, Qinghai Province, Zhongshan City, Guangdong Province in 2008 and 2009.Pharmacovigilance issues of traditional Chinese medicine injection became increasingly serious. Adverse information notification system as established by the State Food and Drug Administration in 2001, making the last decade, the adverse reaction reporting database can be formed. This article is based on the database, because the foreign series of pharmacovigilance data method, preliminary mining of TCM injections pharmacovigilance signal.

Adverse reaction database is broadly divided into epidemiological databases and adverse reactions spontaneous reporting database. Principle, different databases need different pharmacovigilance data mining method, the State Food and Drug Administration's adverse reaction databases are spontaneous reporting database. The existing signal mining methods are based on the fourfold table; make use of the relative proportions of imbalance in principle to explore the warning signs of adverse reactions. Relative proportions of imbalance also have different angles to measure. This article summarizes the nine existing research point of view, and aims to propose the specific range of these methods, comparative nine kinds of methods of statistical theory and calculation process. As for the method of choice in the practice of pharmacovigilance, this article does not involve.

Keywords: Traditional chinese medicine injection; Pharmacovigilance; Data mining

Overview of the Security Problems of the Traditional Chinese Medicine Injections

Form of traditional Chinese medicine preparations were pellet, cream, pill, powder and soup. Traditional Chinese medicine injection is developed on the basis of traditional Chinese medicine preparations, retaining the characteristics of traditional Chinese medicine and injection, which applies to a patient in critical characteristics, developed quickly in recent years in drug development. TCM injections can be traced back to the 1940, in the base areas behind the enemy lines Eighth Route Army division built "the field Material Factory of Health Ministry" Shanxi Wuxiang (later renamed as Lihua pharmaceutical), which developed Bupleurum injection.

After using it in influenza symptoms, it appears have a significant effect, and no side effects. It's the fact that the traditional Chinese medicine pharmacy lagged far behind in the performance of Pharmacology, many of the traditional Chinese medicine research only exist in literature. Bupleurum injection was born in war for clinical urgency. After the liberation, Wuhan Pharmaceutical Factory carried on re-efficacy studies in this species and then put into production in December 1954, became the first industrial production of traditional Chinese medicine injections. From 1950s to 1960s, there has been the development of the Great Leap Forward of traditional Chinese medicine injections, in 1970s,there is the "all-out Chinese herbal medicine movement", and there have been over one thousand kinds of traditional Chinese medicine injection since then. In addition to the Chinese Pharmacopoeia Collection, lots of provinces occasional formulated "herbal preparations norms". Data reported by more than 700 species, more than 700 species used reported in the literature.

TCM injections have backward production technology have been eliminated in clinical practice slowly. In 1977 "Chinese Pharmacopoeia" contains 23 kinds, such as Dinggongteng injection, Ilex pubescence injection."TCM injections research techniques guiding principles "introduced in 1980s, make management more scientific and traditional Chinese medicine injections varieties which do not meet modern medical technology have eliminated."Chinese Pharmacopoeia" in 1985 only collected a variety ephedrine hydrochloride injection, "Chinese Pharmacopoeia" in 1990 collected none traditional Chinese medicine injections.105 varieties has production approval number so far, 40 varieties have been mass-produced. With the progress of the manufacturing process, the traditional Chinese medicine active ingredients and effective parts has the concept of digitization, played a good clinical efficacy, such as Salvia, Shenmai injection for cardiovascular and cerebrovascular diseases, Houttuynia Shenqi Fuzheng injection fortumors; Qingkailing injections for medicine emergency. In the fight against SARS period, Xingnaojing, Shenmai and Qingkailing injections, also gained huge success.

But the traditional Chinese medicine injection adverse events

increases progressively year by year. From 1960 to 1993, 3009 adverse reactions cases of traditional Chinese medicine were reported in 780 reports, traditional Chinese medicine injections accounted for 6.3%. From 1990 to 1999, 1291 adverse reactions cases of traditional Chinese medicine were reported in 460 reports, traditional Chinese medicine injections accounted for 55.62%, followed by the establishment adverse reaction center of State Food and Drug Administration in 2001. Among the spontaneous reporting of adverse events, TCM injections also showed increasing in recent years. For example, in the year 2005, the Chinese medicine had adverse reaction accounting for 16.7%, traditional Chinese medicine injection account for 14.3%, accounting for 83.7% in adverse reactions of traditional Chinese medicine. In 2011, FDA received a total of 852,799 copies of the number of reports of adverse drug reactions / events, including 65,572 cases of TCM injections reports, a 35% increase over 2010 [1,2]. In 2011,top three TCM injections with most number of adverse reaction / event reports were Qingkailing injections SHL injection and Shenmai injection. Recent years, the National Adverse Drug Reaction Center released phytotoxicity event of Qingkailing, Shuanghuanglian, Shenmai and Houttuynia, which make TCM injections of medication security issues have become increasingly prominent.

Pharmacovigilance Data Mining Algorithms apply to Traditional Chinese Medicine Injections

Before listing, clinical test is the most effective detection methods of adverse reactions. But unfortunately, many small probabilities of adverse events in clinical trials are not easy to be detected. The reasons of causing such a situation has a lot of, for example the adverse reaction is only applied to a certain part of the specific crowd, or adverse reaction latent time longer, more than temporary test period. Object of pharmacovigilance study is the side effects which didn't found before listing, including drug post-marketing adverse events spontaneous reporting system. Adverse reaction self-reporting system (SRS) provide reports of some drugs suspected related adverse reactions, this system's largest defect is lots of omission, adverse reactions report also cannot prove the causal relationship between drugs and adverse reaction. But, SRS provides huge adverse reaction report database. For example, in 1997 alone, the WHO will increase35000 new reports each quarter. In 1999, the United States Food and drug administration has 1200000 copies of reports of adverse reactions. As of 2000 January, Holland pharmacovigilance tissue (LAREB) has 26555 reports contains 17330 drug combination – events [3]. At the end of 2001, the French pharmacovigilance database contains 200000 reports, involved 185000 drug combinations of events [4]. China State Food and Drug Administration published 690000, reports of adverse reactions in 2010, 630000 in 2009, showed the increasing tendency year by year. Such a large database is not possible using artificial methods to drug warning, so recently several warning signal automatic generation system was introduced to assist in pharmacovigilance experts to find accurate drug warning signal.

The main purpose of pharmacovigilance is to detect the occurrence of unknown clinical principles of adverse events, severity and frequency of occurrence after use of drugs. Also includes early warning of adverse events. WHO spontaneous reporting system, drug warning signal is defined as, 'reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to detect a signal depending on the seriousness of the event and the quality of the information [5]. A warning signal does not necessarily mean that the inevitable association between the drug and

	ADR = j	ADR ≠ j	Total
drug = I	N_{ij} = a	b	a+b
drug ≠ i	c	d	c+d
Total	a+c	b+d	a+b+c+d

Table 1: SRS two dimensional projection fourfold table.

the adverse reactions, but further observation is needed. Warning signal can come from a variety of adverse reaction databases, more stringent warning signal can be defined as in known risk level, drugs and adverse reactions come with a greater number or more serious adverse effects were reported. Warning signal algorithm for adverse reactions of listed traditional Chinese medicine injection is based on the same principle.

Different signal detection methods require different database, during the early time people use the drug use database or observation epidemiological database, by the proportion fluctuations of adverse reactions occurrence of the exposed population, discover the early warning signal. Compared with western countries, our country medical treatment system for drug of marketed medicines population statisticsis not complete, it is still no uniform database [6]. The existing HIS system generally no accurate fills in adverse reaction. The only complete database of adverse reactions is the adverse reactions adverse reaction center database of State Food and Drug Administration [7]. The type of database applicable to calculate the relative imbalance warning method, the type of method first calculates the following fourfold table (Table 1).

Assumed there are A kinds of drugs, B kinds of adverse reactions in the database of the adverse reactions, The number of combinations of drugs - adverse reactions is $M = A \times B$.When focus on relations of the drug i and adverse reaction j, it can get two dimensional projections fourfold table. The letter 'a' records count when an interaction between drug i and adverse reaction j. The letter 'b' records count when an interaction between drug i and adverse reaction except j. Total reports number is N=a+b+c+d.

$$E = \frac{(a+b)(a+c)}{N}$$

Reporting odd ratio (ROR)

$$\text{ROR} = \frac{a/c}{b/d} = \frac{ad}{bc}, \quad Se = e^{\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}}, \quad 95\%CI : e^{\ln(ROR)\pm 1.96 \cdot Se}$$

The generation criterion is lower bound of the 95% confidence interval $e^{\ln(ROR)-1.96.Se}>1$.

Proportional reporting ratio (PRR)[8]

$$\text{PRR} = \frac{a(a+b)}{c(c+d)}, \quad Se = e^{\sqrt{\frac{1}{a}+\frac{1}{a+b}+\frac{1}{c}+\frac{1}{c+d}}}, \quad 95\%Cl : e^{\ln(PRR)\pm 1.96.Se}$$

The generation criterion is lower bound of the 95% confidence interval $e^{\ln(PRR)\pm 1.96.Se}>1$, Adverse reactions proportion can be different between the target drugs and other drugs, suggesting a signal.

Yule's Q,Q is defined as

$$Q = \frac{ROR-1}{ROR+1}$$

When LI_{95} (Q)>0, Adverse reactions proportion can be different between the target drugs and other drugs, suggesting a signal, i.e.

$$\frac{ROR-1}{ROR+1} - 1.96\left(\frac{1}{2}\left(1-Q^2\right)\right)\exp\left[\ln(PRR) - 1.96\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}\right] > 0$$

E is obtained from the equation

$$E = \frac{(a+b)(a+c)}{N}$$

Chi-Square with Yate's Correction

$$\chi^2 = \sum_{a,b,c,d} \frac{\left(\left|a-E\right|-\frac{1}{2}\right)^2}{E}$$

The generation criterion is

$$\Pr\left(\chi_1^2 > \chi^2\right) \le 0.05$$

Poisson distribution method

This method assumes that the Poisson distribution for the combination of certain drugs and some kind of adverse reaction, the number of reports satisfied Poisson distribution. The generation criterion is:

$$\Pr\,(Pois\,(E){>}a)\le 0.05 \text{ with } 1-\sum_{k=1}^{a}\frac{\exp^{-E}\cdot E^k}{k!} \le 0.05$$

Sequential probability ratio test (SPRT)

SPRT is applicable in the case of cumulative adverse reactions occurred in Pharmacovigilance the number of reports satisfied Poisson distribution [9].

The "real" of drugs and adverse reactions associated relative risk $SPRT_2$ is twice unrelated risk, the generation criterion of $SPRT_2$ is $\ln(2)\cdot a-E \ge \ln(B)$ with $B=\ln\left(\frac{1-\beta}{\alpha}\right)$

α and β are the risk of a false positive generating signal and a false negative signal.

α = β =0.05, the generation criterion is:

ln (2).a-E≥2.94

Information Component (IC)

The method belongs to Bayesian approach. IC is defined as:

$$IC = \log_2\left(\frac{2}{p\cdot q}\right)$$

p, q, and γ are the probabilities of being exposed to the drug, of the observing the aimed adverse reaction, and of the drug-adverse association. At the same time p, q, and γ satisfied β distribution.

β distribution parameter selection has the following two ways:

Orre et al. [10] and Bate et al. [11] explained for p,q on-informative prior distribution $\beta\left(p_1^0=1, p_2^0=1\right)$ and $\beta\left(q_1^0=1, q_2^0=1\right)$. When the observed number of reports tends toward zero. The posterior expectation (Post-Expect) of the information component tends toward zero. Define prior distribution of r is β distribution $\beta\left(r_1^0=1, r_2^0=1/\,PostExpect(p)\cdot PostExpect(q)-1\right)$ introduced knowledge on the observed data in the prior parameters, and this method belongs to semi-empirical Bayesian method.

Gould [12] proposed p, q for this distribution, but for distribution for, without consider the observed number of reports. Define prior distribution of r to β distribution $\beta\left(r_1^0=1, r_2^0=1/\,PostExpect(p)\cdot PostExpect(q)-1\right)$

For example: $\beta\left(r_1^0=1, r_2^0=3\right)$

So, prior distribution of $p, q, and\,\gamma$ is:

$$p_1 = p_1^0 + (a+b) = 1 + a + b\,;$$
$$p_2 = p_2^0 + N - (a+b) = 1 + N - a - b\,;$$
$$q_1 = q_1^0 + (a+c) = 1 + a + c\,;$$
$$q_2 = q_2^0 + N - (a+c) = 1 + N - a - c\,;$$

$$r_1 = r_1^0 + a = 1 + a\,;$$
$$r_2 = r_2^0 + N + a$$

Assuming a normal distribution for IC, the generation criterion is: $LI_{95}\,(IC) > 0$, with:

$$LI_{95}(IC) = Expect\,(IC) - 1.96.SD(IC)$$

Expect and SD is the posterior expectation and standard deviation

$$E(IC) = \frac{1}{\ln(2)}\cdot\left(\psi(r_1)-\psi(r_1+r_2)-\left(\psi(p_1)-\psi(p_1+p_2)+\psi(q_1)-\psi(q_1+q_2)\right)\right)$$
$$(SD(IC))^2 = \frac{1}{=}(\ln(2))^{-2}\cdot\left(\psi'(r_1)-\psi'(r_1+r_2)+\left(\psi'(p_1)-\psi'(p_1+p_2)+\psi'(q_1)-\psi'(q_1+q_2)\right)\right)$$

Ψ, Ψ are digamma, trigamma functions, can be tabulated in statistical software such as SPSS, SAS.

Empirical bayes method (EBAM)

Dumouchel et al. [13] assumed Poisson distribution of mean μ_i and n order to describe, make $E_{ij} = E(a) = \frac{(a+b)\cdot(a+c)}{a+b+c+d}$.

Assume N_{ij} comes from Poisson distribution of mean, define $\lambda = \mu_{ij}/E_{ij}$ distribution of λ is a mixture of two priorΓdistributions. The calculation process is as follows:

First, Estimate the parameters of the prior distribution.

Because N_{ij} satisfied mixed negative binomial distribution,

$$P(N_{ij}) = P.f\,(N_{ij}; \alpha_1,\beta_1, E_{ij}) + (1-P).f\,(N_{ij}; \alpha_2, \beta_2, E_{ij})$$

With f (n; α, β, E) = (1+ β/E)⁻ⁿ.(1+ β/E)⁻ᵅ.Γ(α+n)/Γ(α).n! Mixed negative binomial distribution.

Structure the maximum likelihood function to estimate prior distribution parameters

θ= (α₁,α₂,β₁,β₂,P)γ

$$L(\theta) = \prod\left\{P\cdot f\left(N_{ij}; \alpha_1, \beta_1, E_j\right)+(1-P)\cdot f\left(N_j; \alpha_2, \beta_2, E_j\right)\right\}$$

Second step, Estimate the parameters of the post distribution $\lambda\mid N_{ij}, E[\lambda\mid N_{ij}], E[\log(\lambda)\mid N_{ij}]$

For λ satisfies mix γ distribution, then π (λ; α₁, β₁, α₂, β₂, P) = P. gamma (λ; α₁, β₁) + (1-P).gamma(λ; α₂, β₂).

λ comes from Γ distribution of parameters (α₁, β₁) with the probability P, parameters (α₂, β₂) with the probability (1-P).

Subsequent posterior distribution:

$$\lambda\mid N_{ij} \sim \pi(\lambda; \alpha_1 + N_j, \beta_1 + E_j, \alpha_2 + N_j, \beta_2 + E_j, Q_j)$$

With: $Q_{ij} = \dfrac{P\cdot f(N_j; \alpha_1, \beta_1, E_j)}{P\cdot f(N_j; \alpha_1, \beta_1, E_j)+(1-P)\cdot f(N_j; \alpha_2, \beta_2, E_j)}$

Then:

$$E(\lambda\mid N_{ij}) = Q_{ij}\frac{(\alpha_1 + N_j)}{\beta_1 + E_j}+(1-Q_{ij})\frac{(\alpha_2 + N_j)}{\beta_2 + E_j}$$

$$E[\log(\lambda)\mid N_{ij}] = Q_{ij}[\psi(\alpha_1 + N_{ij})-\log(\beta_1 + E_{ij})]+(1-Q_{ij})[\psi(\acute{a}_2 + N_{ij})-\log(\beta_2 + E_{ij})]$$

With $\psi(.)$ represent digamma function, $\psi(x) = \log[\Gamma(x)]$

Third step, Calculate $EBGM_{ij}$ (Empirical Bayesian Geometric Mean) at 95% confidence interval.

$$EB\log 2_{ij} = \frac{E[\log(\lambda)\mid N_{ij}]}{\log 2}$$
$$EBGM_{ij} = 2^{EB\log 2_{ij}}$$

Based on lognormal approximation principle, variance of Posterior parameters λ is V (λ) = 1/(N_{ij} + 1), 95% confidence interval of $EBGM_{ij}$

is:

$$(EBGM_j \cdot \exp(-2\sqrt{N_j + 1}) \quad EBGM_j \cdot \exp(2\sqrt{N_j + 1})$$

When lower bound of the 95% confidence interval is more than 2, it suggests a signal.

Alternative Generation Criterion for the Empirical Bayes Method

Using Empirical Bayes methods, λ is in one drug adverse reaction comes from the first part with probability P, and the second part with probability 1-P.

Consider the two Γ distribution, Consider Γ distribution, in which λ has the mean is greater than 1, then calculate empirical Bayesian probability (EBp). Actually, the more probability λ is more than 1, the larger EBp is for a drug-adverse event which λ is larger than 1. If the number of reports of adverse reactions observed is greater than expected number of reports of adverse reactions, det ermined to be a drug warning signal.

EBp is defined as:

EBp = Q.δ_1+(1-Q).δ_2

When posterior mean of kth part is larger than1, δ_k=1. If the opposite is δ_k=0 that is:

$$k = \{1,2\} \begin{cases} \delta_k = 1, when \frac{\alpha_k + \alpha}{\beta_k + E} > 1 \\ \delta_k = 0, otherwise \end{cases}$$

EBp exceeds a warning value, pharmacovigilance signal is generated, usually generation criterion EBp>0.5.

Pharmacovigilance on TCM injections

Using the Adverse reaction self-reporting system (SRS) of CFDA [1] for example, this system provides reports of some drugs suspected related adverse reactions.

In this article, there are ten kinds of TCM injections as database, Shen fu, Xiyanping, Ginkgo Biloba Leaves, Shenqi Fuzheng, Shenmai, Shuxuetong, Tanreqing, Dengzhanxixin, Kudiezi and Salvianolic acid injection.

The most ten ADR of Ginkgo Biloba Leaves injection are Rash, Itching, Suffocation Palpitations, Dizziness, Chills, Allergic-like reaction, Nausea, Phlebitis and Vomiting. Pharmacovigilance signal is generated every season from 2005 to 2012 using 9 methods. The result of PRR and IC (Information Component) are shown in Figures 1 and 2.
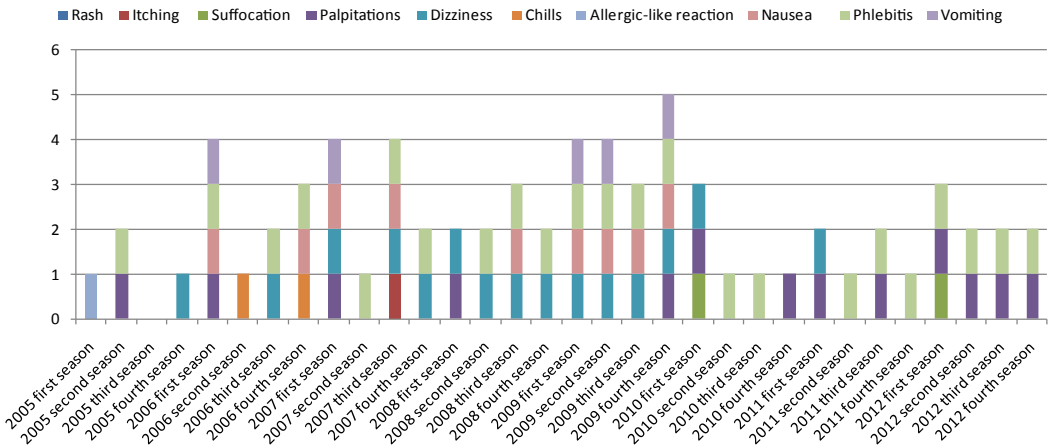

Figure 1: PRR pharmacovigilance signal of Ginkgo Biloba Leaves injection (2005-2012).
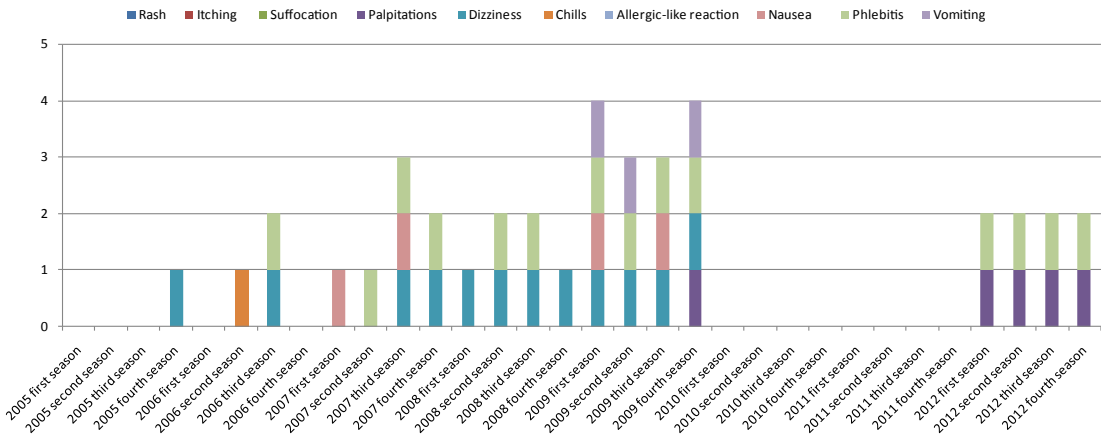

Figure 2: IC pharmacovigilance signal of Ginkgo Biloba Leaves injection (2005-2012).

PRR seems mean to find more signals than IC, in other words methods based on frequency seems to generate more signal than methods based on Bayesian Principle. There are no better methods or worse methods. The only golden gold standard is different medicine using different method, which seems didn't answer the key question. One suggestion is making these 9 methods work out at hospital computer system, when doctor prescribes, the system will Automatically prompt ADR pharmacovigilance signal in recent days, doctor can decide whether prescribe or not though the signal and other information such as clinical experience.

Discussion

From simple and intuitive frequency ratio imbalance method to Bayesian methods, there are nine kinds of methods above, statistical theory and computing have become increasingly complex. Different country has different database and different data mining method, so there is no golden standard for signal. In fact, the various unknown characteristics of the data, including detailed background of adverse events, medication total number and unreported adverse reactions, are the factors that are affecting [4,14].

Evans et al. [15] pointed out that "to compare the validity and applicability of the various data mining method, you need to measure three aspects of the sensitivity, specificity and predictive accuracy. But there are no completely reliable databases". For Chinese medicine injections database, two aspects need to focus on, First, how to control confounding factors is a real problem, confounding factors affecting adverse reactions include with physical of patients, mode of administration, dose and concomitant medications. If it is assumed that confounding factors in the database is random, the warning signal will not be affected. But it is obviously difficult to make this assumption .in reality it was difficult to remove confounding factors in adverse reactions database, currently it seems no literature in this area. Propensity score can be considered a method in the future research. Second, imbalance of spontaneous reporting system report sources [16]. In 2011, adverse reaction monitoring reports of the discovery procedure center in Food and Drug Administration, according to the source statistics, from medical institutions accounted for 84.7%, from the pharmaceutical enterprises accounted for 12.7%, and 2.5% from individuals. Compared with Western countries, the pharmaceutical production enterprises significantly seem less, and this may also hide important information of the adverse reactions [3].

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