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Bioequivalence

Definition

Two pharmaceutically equivalent drug products are considered to be bioequivalent (BE) when the rates and extents of bioavailability (BA) of the active ingredient in the two products are not significantly different under suitable test conditions.[1] Different pharmaceuticals having same active ingredient, in equal strength or concentration, same dosage form and route of administration are known as pharmaceutical equivalents.[2]

How did the concept emerge?

When a medicine is discovered for the first time, it must undergo preclinical and clinical studies before it is marketed for public use.[3] Formulation prepared by the discovering company, known as innovator drug, is expensive and is patented.[4] Once the patent expires, various pharmaceuticals can produce generic drugs.[4] The World Health Organization (WHO) defines a generic product as "a pharmaceutical product, usually intended to be interchangeable with an innovator product, that is manufactured without a license from the innovator company and marketed after the expiry of the patent or other exclusive rights."[5]

Before 1962, pharmaceutical companies only required submitting safety data in their application (New Drug Application, NDA) to get approval.[4] This requirement was enforced by Food, Drug and Cosmetic Act of 1938, brought in response to a series of deaths from Elixir Sulfanilamide containing diethyl glycol.[6] Later, issues like thalidomide tragedy, in concert with concerns raised by various officials (Miss Kelsey, Senator Estes Kefauver and President Mr. Kennedy) in 1962, made data on efficacy of drug mandatory for approval for which elaborate pre-clinical and clinical testing have to be repeated even for the generics.[4,7] This resulted into longer period of drug testing time, associated with raised economic burden. Thus, there was decrease in submission of NDAs. Drug Price Competition and Patent Restoration Act, also known as Hatch-Waxman Act was then enacted in 1984 that required submission of Abbreviated New Drug Application (ANDA), which required generic manufacturers to submit only the manufacturing process and assure its product's quality by bioequivalence.[4, 8]

Why is it necessary?

The global escalation of healthcare costs over decades has drawn significant attention and effort to control them in various countries.[9] Due to their low cost, nations across the globe rely on multisource

(generic) pharmaceutical products to ensure affordable healthcare costs without sacrificing their public health goals.[10] A pharmaceutical formulation contains active pharmaceutical ingredient as of innovator drug but may contain different excipients (inactive ingredients).[6] This requires that the performance of the formulations in terms of safety and efficacy is unchanged. Various studies (comparative pharmacokinetic studies, comparative pharmacodynamics studies, comparative clinical trials, in vitro studies) are used to benchmark the performance of a generic formulation (bioavailability) and to understand that this performance is unchanged (bioequivalence) in the presence of change in components/ composition and/or method of manufacture.[11] Global acceptance of concept of BE has resulted in availability of high quality generic medicines at every corner.

Biopharmaceutical Classification System (BCS) and BE

Drugs requiring BE studies is dictated by BCS and dissolution profile of drug. According to BCS, drugs are classified into 4 classes based on their solubility and permeability as shown below.[12]

Solubility \ Permeability	High	Low
High	I	III
Low	II	IV

Similarly, according to dissolution profile, drugs are classified as having rapid or slow dissolution. These three parameters govern the rate and extent of drug absorption. Based on these parameters, WHO mandates BCS class IV drugs to undergo BE studies before its marketing but drugs having rapid dissolution and falling in class I of BCS does not require BE studies provided their excipients used do not interfere with the absorption of the active pharmaceutical ingredient. Considerations for biowaiver (i.e. no requirement of BE studies) varies among different drug regulating authorities.

Harms of not having BE studies

The sole purpose of Hatch-Waxman Act is to allow drug regulating authorities approve generic formulation for marketing on the basis of BE.[6] Not having BE studies affects healthcare services as emphasized by discovery of broad variability of digoxin products in the past.[6] Patients are prone to bear the burden of expensive medications, which might contribute to non-compliance (modification of therapy or discontinuation at their will). Prescribing generics of uncertain quality could also expose them to unfavourable effects/adverse drug reactions and/or sub-therapeutic effect. Prescriber's on the other hand, lack faith over the generics, resulting in prescription of brand drugs. Quality of medicine availed by government health services (hospital pharmacy) as per government rule cannot be assured in the absence of BE studies. Absence of BE studies also cost dearly to the pharmaceutical industry in terms of finance and more over in terms of their reputation. The issue of counterfeit medicine has prevailed, more in the developing countries. This can be addressed with stringent BE studies requirement of generic products.

Status in Nepal

Medicine Registration Guidance (Drug Registration Regulation 2038) does not mandate bioequivalence of generics produced by Nepal based pharmaceutical companies. However, requirement for BE studies for registration of imported medicines exists. Import drugs fulfilling the criteria mentioned in box below require submission of BE report for registration in Nepal.[13]

Conditions requiring BE study (Medicine Registration Guidance, 2016):

1. Drugs with narrow therapeutic index, low bioavailability, non linear kinetics, poor dissolution profile
2. Oral products intended to be absorbed in the oral cavity
3. Locally applied, but systemically acting products
4. Non-oral immediate release forms with systemic action
5. Modified release products; e.g. sustained release tablet
6. Transdermal products

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Brief Information

Safety of intravenous iron

Intravenous iron should be considered as second-line therapy for patients who do not respond to oral iron or require rapid iron replacement. Hypersensitivity reactions, which can be fatal, can occur with all intravenous iron formulations and the patient should be made aware of it while taking consent. The risk of hypersensitivity

is substantially lower with nondextran formulations (ferric carboxymaltose, iron polymaltose and iron sucrose). Ferric carboxymaltose has been shown to be safe and effective that can deliver a large dose of iron in a short time. The estimated risk of serious anaphylactic reactions and infusion site reaction with ferric carboxymaltose is 0.1% and 1.6% respectively. The European Medicines Agency recommended that all intravenous iron preparations should only be given in an environment where resuscitation facilities are available. The common adverse effects associated with iron infusion are tabulated below.

Adverse effects of intravenous iron preparations

Adverse Effects	Symptoms/Signs
Immediate adverse effects	Headache, Nausea, Vomiting, Dysguesia, Arthralgia, Myalgia
Anaphylactoid reaction	Wheezing, Flushing, Dyspnoea, Dizziness
Infusion site reaction	Localised pain, Discolouration of skin
Delayed adverse effects (1-2 days post infusion)	Mild fever, Headache, Arthralgia, Myalgia

Drug Monitoring and Toxicology Laboratory

Total number of patients who received TDM services from this laboratory in 2016 was 1125. The summary of samples received by this laboratory during 1 year period is as follows:

Drug/Enzymes	Referenece Range	Total Samples	Results Within Normal Limit	Result beyond normal limit	Not Detected
Cholinesterase	5400-13200 U/L	793	137	656	0
Paracetamol	10-20 µg/ml	118	3	44	71
Phenytoin	10-20 µg/ml	141	34	80	27
Carbamazepine	04-12 µg/ml	67	30	16	21
Phenobarbitone	15-40 µg/ml	6	0	5	1
	Total	**1125**	**204**	**801**	**120**

"Drug and Therapeutics Letter" is also available in the following website:
http://www.teachinghospital.org.np/diu.html

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