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Research Article

INTRA/INTER SUBJECT VARIABILITY OF VARIOUS ANTI-CANCER DRUGS

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ABSTRACT

Cancer is the second most common cause of death in India (after cardiovascular disease). Cancer burden in India has more than doubled over the last 26 years. Oral Cancer is among the top three cancers in India, number one among all cancers in men and number three among female cancers. Treatment of cancer is limited by affordability of patients in India. Generic drug manufacturers have responded to this scenario by making drugs available at affordable costs, often at less than 10% the cost of the original brand. Bioequivalence (BE) studies are an integral component of the development, approval and marketing of generic drug products globally and are commonly accepted method to demonstrate therapeutic equivalence between two medicinal products. Savings in time and cost are substantial when using bioequivalence as an established surrogate marker of therapeutic equivalence. For this reason the design, performance and evaluation of bioequivalence studies have received major attention from academia, the pharmaceutical industry and health authorities. Keeping in view of this, minor efforts were made to collect the intra/inter subject variability of various anti-cancer drugs, which helps in deciding the appropriate study design and sample size to establish the bioequivalence of generic drug with innovator.

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INTRODUCTION

Cancer is the name given to an accumulation of related sicknesses. In a wide range of growth, a portion of the body's cells start to partition without ceasing and spread into encompassing tissues. Tumor can begin anywhere in the human body, which is comprised of trillions of cells. In India, there are many types of cancer treatment available. The line of cancer treatment depends on the type & stage of cancer, location of the cancerous cells, growth of the tumor, affected organs, pre-existing medical conditions of the patient, age, gender and other parameters that can only be gauged by a cancer specialist¹.

Cancer is among the leading causes of death worldwide. In 2012, there were 14 million new cases and 8.2 million cancer-related deaths worldwide. The number of new cancer cases will rise to 22 million within the next two decades. More than 60% of the world's new cancer cases occur in Africa, Asia, and Central and South America; 70% of the world's cancer deaths also occur in these regions¹.

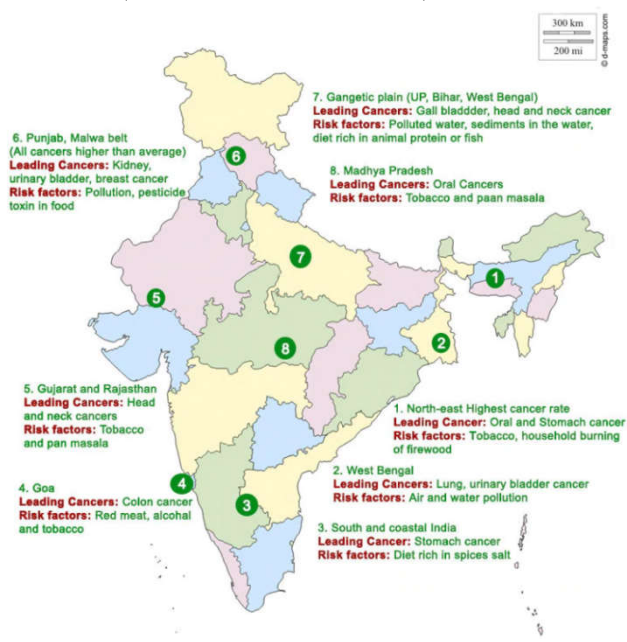
In early stages of cancer, the patient can have only one form of treatment and will be cured. However, in most of the patients, a combination of treatments (from surgery, chemotherapy,

radiation therapy, hormone therapy, proton therapy, etc.) is used for cancer treatment. The cost of cancer treatment could be as low as Rupees 2.5 lakh for six months of treatment, with some of the lowest priced generic drugs in the world, to as high as Rupees 20 lakh, with novel drugs and targeted medicines. The cost of lung cancer in India varies from \$10000 to \$12000, the cost of chemotherapy vary from \$250 to \$700 per session, the cost of blood cancer vary from \$20000 to \$25000, the cost of breast cancer varies from \$6,000 to \$9,000 in top hospitals in India. More than 20 tumor types are being treated with one or more of the 70 new cancer treatments that have been launched in the past five years, with the sustained surge in innovative therapies driving the global oncology market to \$107 billion in 2015. An annual global growth in the oncology drug market is expected to be 7.5 - 10.5 percent through 2020, reaching \$150 billion². In India the following cancer statistics are identified, one woman dies of cervical cancer every 8 minutes, for every 2 women newly diagnosed with breast cancer, one woman dies of it. As many as 2,500 persons die every day due to tobacco-related diseases. Tobacco (smoked and smokeless) use accounted for 3,17,928 deaths (approx.) in men and women in 2018. Estimated number of people living with the disease are around 2.25 million. Every year, new cancer patients registered over 11,57,294 lakhs. Risk of

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developing cancer before the age of 75 years in males and females was found to be 9.81% 9.42% respectively. Total deaths due to cancer in 2018 are 7,84,821 lakhs, out which 4,13,519 are men and 3,71,302 are women. The risk of dying from cancer before the age of 75 years is 7.34% in males and 6.28% in females. Cancers of oral cavity and lungs account for over 25% of cancer deaths in males and cancer of breast and oral cavity account for 25% cancers in females. The top five cancers in men (lip, oral cavity, lung, stomach, colorectal and esophagus) and women (breast, lip, oral, cervix, lung and gastric) account for 47.2% of all cancers; these cancers can be prevented, screened for and/or detected early and treated at an early stage. This could significantly reduce the death rate from these cancers³.

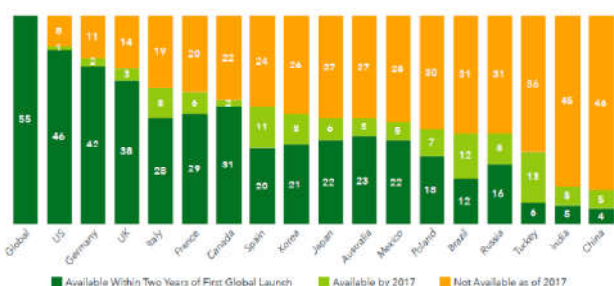
Cancer burden in India has more than doubled over the last 26 years. Oral Cancer is among the top three cancers in India, number one among all cancers in men and number three among female cancers. Nearly 60 per cent patients with breast cancers are diagnosed in advanced stages. Breast cancer burden is not only limited to disease burden and mortality but also leads to an economic loss for the nation. India lost nearly 6.7 billion USD in 2012 due to cancer, amounting to 0.36 per cent of the total GDP. Cancer is the second most common cause of death in India (after cardiovascular disease)⁴.



The below mentioned picture depicts that many new oncology medicines are not available beyond the largest developed markets⁶.

Many new oncology medicines are not available beyond the largest developed markets

Chart 18: Year 2017 Availability of 55 Oncology Medicines First Launched Globally 2012-2016



Source: KIVA MEDAS, Dec 2017

Treatment of cancer is limited by affordability of patients in many developing countries including India. Producing a generic drug will reduce the costs, often at less than 10% the cost of the original brand. In India, it is found that there is a three-fold higher prescription of generic brands compared to innovator, accompanied by cost savings of up to 80% per prescription. Unfortunately, the regulatory environment prevailing in India is not geared to ensure satisfactory quality of generic products. The standards set by the regulatory agencies for establishing equivalence of generics vis-à-vis the innovator product allow anticancer generics to enter markets without undergoing clinical evaluation. To ease the access to the cheaper and quality medicines, bioequivalence testing should be made mandatory for all oral formulations in India. Unless these measures are rigidly implemented, the benefits of generic substitution would be seriously undermined. The below emtnioend tables depicts the percentage savings from generic substitution and the prevalence of generic substitution respectively⁷.

Name of the drug	Brand name	Cost* (INR)		% savings [‡]
		Innovator	Generics	
Cisplatin	Platinol-AQ	\$	350-511	-
Carboplatin	Paraplatin	2,030	950-990	53.20
Oxaliplatin	Eloxatin	10,349	3420-6300	53.20
Imatinib	Glivec	12,456.00	3000-10350	75.91
Gemcitabine	Gemcite	8,622.00	5460-6201	36.67
Docetaxel	Taxotere	43,333.33	8138-10979	81.21
Rituximab	Mabethra	104,000.00	39,996	61.54
Anastrozole	Arimidex	2400.00	734.30	69.41
Bortezomib	Velcade	60,360.00	17,640	70.77
Fludarabine	Fludara	10,764.20	5,780	46.30
Gefitinib	Iressa	34,860.00	10,200	70.74
Pemetrexed	Alimta	79,050.00	25,500	67.74
Temozolamide	Temodal	34,947.00	9,450	72.95
Zolendronate	Zometa	15,213.00	2,940	80.67
Irinotecan	Camto	18,000.00	4,195	76.69

*Cost of the drug is obtained from the hospital formulary of tata memorial hospital; [‡]Percentage savings calculated based on difference in costs of the innovator and the lowest priced generic; [§]Innovator not available; INR=Indian Rupees

Name of the drug	Number of brand prescription	Number of generic prescription	Total number of prescription	% of generics
Cisplatin	0	405	405	100
Carboplatin	75	206	281	73.30
Oxaliplatin	50	90	140	64.28
Imatinib	0	100	100	100
Gemcitabine	121	92	213	43.19
Docetaxel	37	15	52	28.84
Rituximab	38	23	61	37.70
Anastrozole	51	74	125	59.20
Bortezomib	10	6	16	37.50
Fludarabine	7	0	7	0.0
Gefitinib	8	50	58	86.20
Pemetrexed	16	0	16	0.0
Temozolamide	5	16	21	76.19
Zolendronic acid	21	243	264	92.04
Irinotecan	8	17	25	68.00
Total	447	1337	1784	74.94

Bioequivalence (BE) studies are an integral component of the ANDA (Abbreviated New Drug Application) approval and marketing of generic drug products.

Molecule Name	Inter/Intra CV%
Abiraterone Acetate 250 mg tablets ⁹	Intra CV - 31% for AUC _{0-∞} & 42% for C _{max}
Methotrexate sodium 2.5 mg tablets ¹⁰	Intra CV - 16.4% for C _{max} .
Methotrexate sodium 50mg/2mL injectable injection ¹¹	Intra CV - 24.6% for C _{max} .
Brentuximab Vedotin injectable injection 50mg/vial ¹²	Intra CV - 33%
Ado-trastuzumab emtansine Injection 160 mg lyophilized single use vial (20 mg/ml afterreconstitution) for intravenous infusion ¹³	Intra CV - 15% for AUC _{0-∞} .
Doxorubicin Hydrochloride Liposome 50mg/m ² ¹⁴	Intra CV of total doxorubicin – 14.05% for AUC _{0-∞} . Intra CV of encapsulated Doxorubicin 14.56% for AUC _{0-∞} and 18.61% for AUC _{49-337hr} . Intra CV of free (un-encapsulated) doxorubicin – 51.52% for C _{max} , 32% for AUC _{0-∞} , 30.3% for AUC ₀₋₁ , 38.40% AUC ₀₋₄₈ and 31.57% for AUC ₄₉₋₃₃₇
Afatinib Dimaleate 40 mg tablets ¹⁵	Intra CV - 22.2% to 67.5% for C _{trough} . Inter CV - 57.1 to 105%.
Everolimus 10 mg tablets ¹⁶	Inter CV for C _{max} ranged from 27.6% to 31.2% and for AUCs from 32.4% to 38.7%.
Alectinib 150 mg capsule ¹⁷	Intra CV-17% for AUC and 19% for C _{max}
Amifostine injectable injection 500mg/vial ¹⁸	Intra CV-18.7% for C _{max} and 22.5% for AUC
Anastrozole 1 mg tablets ¹⁹	Interoccasion variability in plasma 19% and in whole blood 33%.
Aprepitant 125 mg capsule ²¹	Intra CV-7.8% for AUC _{0-∞} and 7.3% for C _{max}
Asparaginase Erwinia chrysanthemi for injection, intramuscular 10,000 IU ²³	Inter CV for AUC about 30% and for C _{max} about 23%
Atezolizumab Infusion: 60 mg/mL solution in a single use 20 mL vial ²⁴	Inter CV for CL about 14.8% and for Vd about 66.6%
Axitinib 1mg and 5 mg tablets ^{25& 58}	Inter CV for CL about 29% and for Vd about 34%
Azacitidine 100mg/Vial injectable suspension ²⁶	Inter CV for AUC about 70%, for CL about 60% and for Vd about 40%. Intra CV 27%.
Belinostat for injection, for intravenous 500 mg/vial ²⁷	Inter CV <50%.
Bendamustine Hydrochloride Injection 120 mg/m ² for intravenous Infusion ²⁸	Inter CV for CL about 27% and for Vd 69%.
Bevacizumab (ruhMab VEGF) 400mg/vial solution for intravenous infusion ³⁰	Residual variability 36%.
Bexarotene 75 mg capsule ³¹	Inter CV for CL about 30.8% and for Vd 18.7%. Residual variability 12.7%.
Bicalutamide 50 mg tablets ^{32&33}	Intra CV 40% for C _{max} and 37% for AUC _{0-∞}
Blinatumomab injectable injection 35 mcg ³⁴	Intra CV 13% for C _{max} , 20% for AUC _{0-72hr} and 15% for AUC _{0-120hr}
Bortezomib injectable injection 3.5 mg/Vial ³⁵	Inter CV for CL about 41.9%
Bosutinib 100 and 500 mg film coated tablets ³⁶	Within the observed variability (CV%) = 36-55%.
Brigatinib 30 and 90 mg tablets ³⁸	High PK variability (CV%) 58 - 73% in the patient population PK model. Intra CV 34.2 for AUC _{0-t} and 25.8% for C _{max} ³⁷
Busulfan 2 mg tablets ³⁹	Following brigatinib 90 mg QD, the inter-subject variability (CV%) of steady-state AUC _{0-tau} was 57% and C _{max} was 65%.
Busulfan 6mg/mL intravenous injectable Injection ⁴⁰	Following brigatinib 180 mg QD, the CV% of steady-state AUC _{0-tau} was 56% and C _{max} was 60%.
Cabazitaxel injection, for intravenous 60 mg/1.5mL (40mg/mL) ⁴¹	Intra CV - 47 % to 103 %
Cabozantinib-S-Malate Oral Capsules (20 mg and 80 mg) ⁴²	Inter CV for AUC 20% . Intra-patient CV on AUC 10%.
Capecitabine film-coated tablets 150, 500 mg ⁴³	Inter CV for CI 15% . Intra-patient CV on CI 14%.
Carfilzomib powder for Intravenous injection, 60 mg/vial ⁴⁴	Intra-patient variability of 23% for AUC ₀₋₄₈ . Inter CV for CI 48% and 94% for Vd.
Ceritinib 150 mg capsules ⁴⁵	Intra CV 34% for C _{max} and 25% for AUC. Inter CV 38-61% for C _{max} and 27-55% for AUC
Cetuximab 100mg/Vial injection for intravenous infusion ⁴⁶	Intra CV 50.2% for C _{max} and 22% for AUC in patients with colon, colorectal or breastcancer under fed condition with 4 x 500 mg tab dose.
Chlorambucil 2mg tablets ⁴⁷	Intra CV for log transformed carfilzomib concentrations was 0.937. Inter CV for CL about 25% and for Vd 88%.
Cisplatin injectable injection for intravenous infusion 1mg/mL ⁴⁸	Inter CV for 42-74% for AUC _{inf} and 35-94% for C _{max} (single oral doses of 450 to 750 mg) Inter CV in steady state AUC and C _{max} at the dose of 750 mg is 74% and 76%, respectively.
Cladribine injectable injection for intravenous infusion 1mg/mL ⁴⁹	Inter patient CV ranged from 6 to 40%.
Cladribine 10 mg tablets ⁴⁹	The CV of AUC was 31%
Clofarabine 1 mg/mL solution for injection ⁵⁰	Inter CV for Vd 27.4% and CI 39.1%.
Cobimetinib Fumarate 20 mg tablets ⁵¹	Inter CV 28%. CV for AUC 38% for intravenous formulation.
Crizotinib 250 mg capsules ⁵²	Inter CV for AUC 36% for oral formulation
Cyclophosphamide 50 mg capsules ⁵³	Inter CV 27% and 56%, for CL and V ₁ respectively.
Cyclophosphamide 250 mg/m ² IV infusion ⁵⁴	Inter CV 26% and 52%, for AUC _{0-∞} and C _{max} respectively in healthy subjects. Inter CV 61% and 60%, for AUC and C _{max} respectively in patients at steady state.
Dabrafenib mesylate capsule 75 mg ⁵⁵	CV ranges from 36-38% and 38-44% for AUC _τ and C _{max} respectively over steady state.
Daratumumab Injection for intravenous infusion: 100 mg/5mL and 400 mg/20 mL single use vial ⁵⁶	CV% values in AUC _{inf} and C _{max} range from 28% to 34% for oral administration. And 18% to 19% following intravenous infusion
	Inter CV 41%, 51% and 91% for C _{max} , AUC _τ and C _{min} respectively.
	Estimates of inter Occasion Variability were CL 18% and V ₁ 21%.
	Inter CV 37% for C _{max ss} and 38% for AUC _(0-τ) . Inter CV for CL/F and V _e /F is 59% and 53%, respectively.
	Inter CV 19% to 114% for AUC _{0-8days} and from 13% to 59% for C _{max} .

Dasatinib 140 mg tablets ^{57& 58}	Intra CV AUC _{0-t} and C _{max} were 67.33 % and 84.44 %. Intra CV 80%.
Decitabine IV injection 50mg/vial ^{59& 60}	Intra CV 31.6%. Inter CV 37% for CL and 68% for Vd.
Defibrotide lyophilized powder, 200 mg/vial, 80 mg/mL solution ^{61, 62 & 63}	Intra CV 25% for C _{max} and 26% for AUC _{0-∞} . Intra CV 29.3 for AUC _{0-τ} . Inter CV 25% for CL and 44% for Vd. Inter occasion variability 18% for CL and 20.2% for Vd. 15-20% variability observed in healthy subjects.
Degarelix 120mg base/vial powder for SC injection ⁶⁴	34-83% in patients. CV % ranges from 20-48% for C _{max} and AUC.
Denosumab 70mg/mL or 60 mg/mL subcutaneous injection ⁶⁵	and residual variability high and low concentrations are 26 and 81% respectively.
Dexamethasone 40 mg tablets ⁶⁶	Intra CV 12% for C _{max} .
Dexrazoxane Hydrochloride 1000 mg/m ² i.v. infusion ⁶⁷	Intra CV 13.6%, 14.9% and 38.0% for CL, AUC and Vd respectively. Inter CV 30.4%, and 35.6% for CL and Vd respectively.
Dinutuximab injectable injection 17.5mg/5mL ⁶⁸	Inter CV 62% for CL and 36% for Vd.
Docetaxel injectable injection 160mg/8mL (20mg/mL) ⁶⁹	Intra CV 44.3% for C _{max} and 48% for AUC _{0-t} .
Durvalumab injectable injection 50mg/mL ⁷⁰	Inter CV 29.3%, 21.2%, and 39.9% for CL, V1, and V2 respectively.
Eltrombopag Olamine 100 mg tablets ⁷¹	Inter CV 30%, and 40% for AUC and C _{max} respectively.
Enzalutamide 40 mg capsule ⁷²	Inter CV for AUC and C _{max} ≤ 31% respectively.
Epirubicin Hydrochloride injectable injection 200mg/100mL (2mg/mL) ⁷³	Inter CV 53.3%, and 44% for CL, and Vd respectively.
Eribulin mesylate intravenous solution 1mg/2mL(0.5mg/mL) ⁷⁴	Inter CV 54% for CL.
Erlotinib Hydrochloride 150 mg tablets ⁷⁵	Intra CV 30% for C _{max} and 29.6 for AUC _{0-t}
Etoposide 50 mg and 100 mg capsule ⁷⁶	Inter-patient variability of AUC 25% for the IV route and 35% after oral intake.
Everolimus 5mg and 10 mg tablets ⁷⁷	Inter CV for C _{max} ranged from 27.6% to 31.2% and for AUCs from 32.4% to 38.7%.
Everolimus tablets for oral suspension, 2mg, 3mg and 5mg ⁷⁸	Intra CV% 17% for AUC and 19% for C _{max} . Inter CV 51.2% for C _{max} and 36.0% for AUC _{0-t} in patients with renal cell carcinoma at steady-state.
Everolimus Tablets, 0.25 mg, 0.5 mg, and 0.75 mg ⁷⁹	Intra CV 22.4 % for AUC and 20.2% for C _{max} .
Exemestane 25 mg tablets ⁸⁰	Intra CV% 44 %, 26% and 24% for C _{min} , C _{max} and AUC _{0-τ} respectively in De Novo Kidney Transplant patients. Intra CV% 38 %, 30% and 30% for C _{min} , C _{max} and AUC _{0-τ} respectively in De Novo Heart Transplant patients.
Filgrastim 300 µg/0.5 mL and 480 µg/0.8 mL single use prefilled syringe ⁸¹	Intra CV 40.25%, 40.47% and 40.25% for C _{max} , AUC _{0-t} and AUC _{0-∞} respectively.
Filgrastim-SNDZ IV and SC injectable injection 480 mcg/0.8 mL ⁸²	Variability (% CV for C _{max} and AUC) 5µg/kg SC dosing in healthy subjects 40%, breast cancer 35%, lung cancer 60% and non-Hodgkin's Lymphoma 23%.
Fludarabine Phosphate Injectable Injection 50mg/2mL(25mg/mL) ⁸³	Inter CV 40% in patients and 20% in healthy subjects.
Flutamide 125 mg capsule ⁸⁴	Residual unexplained variability is 22.36%
Fulvestrant intra muscular injectable injection 50 mg/mL ⁸⁵	Inter CV 22-51% in patients with renal insufficiency
Gefitinib 250 mg tablet ^{86& 87}	Inter CV 25 and 70% for AUC _{0-28d} and between 28 and 83% for C _{max} , steady state, CV% about 15%.
Gemtuzumab Ozogamicin injectable injection 5mg/vial ⁸⁸	Inter CV for AUC was 66-67% and for C _{max} was 52-55%.
Goserelin Acetate implantation implant 3.6mg base ⁸⁹	Intra CV 17-30%
Hydroxyurea 500 mg capsules ⁹⁰	Inter-subject CV was very large: %CV was 62% and 136% for C _{max} and AUC of hP67.6 (antibody)
Ibrutinib 140 mg Capsules ^{91& 92}	Intra CV 30.9 % for AUC _{0-∞} and 14.4% for C _{max} in healthy young women
Idelalisib 100 mg and 150 mg tablets ⁹³	Intra CV 3.0 % for AUC _{0-∞} and 16.5% for C _{max} in healthy subjects.
Imatinib Mesylate 100 mg and 400 mg tablets & capsules ^{94& 95}	Intra CV were approximately 61% for C _{max} and 47% for AUCs of ibrutinib. Inter CV % ranged from 58.5% to 136% for C _{max} and 60.1% to 107% for AUC _{0-24h}
Ipilimumab 50 mg/10 mL (5 mg/mL) and 200 mg/40 mL (5 mg/mL) in a single use Vial ⁹⁶	Intra CV 53%. Inter CV for CL/F to be 38% and in Vc/F to be 85%.
Irinotecan Hydrochloride 2 mL-fill vial (40mg), 5 mL-fill vial (100mg), 15 mL-fill vial (300mg) vials ⁹⁷	Intra CV 13.6%, 12.8% and 12.3% for C _{max} , AUC _{0-t} and AUC _{0-∞} respectively.
Irinotecan Hydrochloride Liposome 43 mg/10 mL single dose vial ⁹⁸	18.2%, 11.6% and 11.8% for C _{max} , AUC _{0-t} and AUC _{0-∞} respectively.
Ixabepilone for intravenous Injection 15 mg/vial, 45mg/vial ⁹⁹	Inter CV 39.5% for CL and 22.9% for Vd.
Lanreotide Acetate Depot Injection 60mg base/0.2mL, 90mg base/0.3mL, 120mg base/0.5mL ¹⁰⁰	Inter CV 13.5% for CL and 37.9% for AUC.
Lapatinib Ditosylate 250 mg tablets ¹⁰¹	Inter CV 77%, 49% and 88% for AUC _{0-∞} , Vd, and CL respectively.
Lenalidomide 25 mg capsules ¹⁰²	The variability in PK parameters ranged from 47-55%.
Lenvatinib Mesylate 10 mg capsules ^{103& 104}	PK: Inter CV 19%, and 44% for CL and Ka respectively
Letrozole 2.5 mg tablet ¹⁰⁵	PD: EC50, E0 and Emax is 43%, 85% and 14% respectively.
Leuprolide Acetate 7.5 mg SC injection ¹⁰⁶	Overall variability ranges from 39 to 79%, for C _{max} , from 31 to 90% for AUC.
Megestrol Acetate 125mg/mL suspension ¹⁰⁷	Intra CV% 9% and 18% for C _{max} s and AUC _{0-t}
Melphalan 2 mg tablets ¹⁰⁸	Inter CV 36%, and 78% for Cycle 1, Day 1, C _{max} and AUC _{0-τ} respectively.
Melphalan Hydrochloride ¹⁰⁹	Inter CV 19%, and 54% for Cycle 2, Day 1, C _{max} and AUC _{0-τ} respectively.
	Inter CV 25.5% for CL.
	%CV of AUC in healthy subjects ranged from about 8% to 20%.
	Intra CV% 14% and 6% for C _{max} s and AUC _{0-∞}
	Inter CV 24.7% in AUC _{0-tldc}
	Intra CV% 21.4%, 19.7% and 41% for C _{max} s, AUC _{0-t} and AUC _{0-∞} respectively.
	Total melphalan Inter CV 59.5% and 33.6% for Vd, and CL respectively. Unbound melphalan Inter CV 57.2% and 41.7% for Vd, and CL respectively.
	Inter CV 37% and 21% for Vd, and CL respectively.

Mercaptopurine 50 mg tablets ¹¹⁰	Inter CV 68.8% 39.5% and 38.5 for C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ respectively.
Mercaptopurine 20 mg/mL oral suspension ¹¹⁰	Inter CV 45.8% 30.1% and 30.1 for C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ respectively.
Mesna 400 mg tablets ¹¹¹	Inter CV 34% and 23% for C_{max} and AUC_{0-t} respectively.
Methylglutathione Bromide 150 mg tablets ¹¹²	Inter CV 55-85% for C_{max} and AUC 27%-56% respectively.
Methylglutathione Bromide 12mg/0.6mL SC injection ¹¹³	Inter CV 30% for C_{max} and AUC 20% respectively.
Midostaurin 25 mg capsules ¹¹⁴	Intra and inter CV 61% and 61% respectively for 50 mg BID and Intra and inter CV 32% and 54% for 100 mg BID.
Necitumumab IV injection 800 mg/50 mL (16 mg/mL) vial ¹¹⁵ .	Inter CV ranged from 21% to 55% for Vd and 25.5%-31.9% for CL.
Nelarabine IV injection 250mg/50mL (5mg/mL) ¹¹⁶	Inter CV ranged from 42-115% for Nelarabine, 20-39% for deoxyguanosine analogue 9- β -Darabinofuranosylguanine (ara-G) and 87-93% for deoxyguanosine analogue 9- β -Darabinofuranosylguanine 5-triphosphate (ara-GTP).
Netupitant 300 mg and Palonosetron Hydrochloride 0.5 mg capsule ¹¹⁷	Inter %CV ranges from 25-60% in for netupitant for helathy subjects. Fed: Intra CV% 30.9%, 19.4% and 20.1% for C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ respectively for netupitant and Fed: Intra CV% 12.0%, 10.0% and 9.0% for C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ respectively for Palonosetron.
Fosnetupitant chloride hydrochloride 235 mg; Palonosetron hydrochloride 0.5 mg IV injection ¹¹⁷	The CVs of about 37%, 23%, and 32% for the netupitant 50 mg, 75 mg and 100 mg doses, respectively for netupitant.
Nilotinib 200 mg capsules ¹¹⁸	Inter CV in patients ranges from 30-70% for C_{max} and AUC , in healthy subjects inter CV ranges from 30-50% for C_{max} and AUC .
Niraparib Tosylate Monohydrate 100 mg capsule ¹¹⁹	The inter CV% for CL and Vd 38.7% to 103%.
Nivolumab 40 mg/4 mL injectable injection single-use vial ¹²⁰	The inter CV% for CL and Vd 50% and 30.4% respectively.
Obinutuzumab intravenous injection for infusion 1000 mg/40mL (25 mg/mL) single use vial ¹²¹ .	Inter patient variability for AUC_{7d} ranges from 28 to 144% and for C_{max} : 21 to 74%.
Ofatumumab intravenous injection 100 mg/5 mL and 1000 mg/50 mL single-use vial ¹²²	The inter CV% for Vd 6% and CL 31%.
Olaparib 50 mg capsule ¹²³	High PK variability: Single dose 65% and for multiple dose 74%.
Olaparib 150 mg tablets ¹²⁴	The inter CV% for CL-45%, V1-70% and V2-73% at steady state.
Olaratumab injectable injection 500mg/50mL ¹²⁵	The inter CV% for CL-38.2% and V1-22.2%.
Omacetaxine Mepesuccinate 3.5mg/vial SC injection ¹²⁶	Inter CV% for AUC is 70%.
Osimertinib 40 mg and 80 mg tablets ¹²⁷	Inter CV% for Cycle 1, Day 1, C_{max} and $AUC_{0-\tau}$ ranges from 36% to 78% and for Cycle 2, Day 1, C_{max} and $AUC_{0-\tau}$ ranges from 19% to 54%.
Paclitaxel Protein-Bound (albumin-bound) Particles Injectable Suspension 100mg/vial ¹²⁸	Intra CV in breast cancer patients it is 21.3% for total paclitaxel and unbound paclitaxel.
Palbociclib Capsules: 125 mg, 100 mg, and 75 mg ¹²⁹	Fasting: Inter CV is 39% for AUC_{inf} and 73% for C_{max} ; Fed: Inter CV is 23% to 27% for AUC_{inf} and 21% to 24% for C_{max} .
Palifermin injectable injection 60mcg/kg/day ¹³⁰	The inter CV% for CL-40% and Vd-70%.
Palonosetron Hydrochloride IV injection 0.25 mg/5 mL ¹³¹	The inter CV% for CL-88.8% and Vd-35.8%.
Panitumumab 5ml/100mg, 10ml/200mg 20ml/400mg vials (20 mg/mL) injectable injection ¹³² .	The inter CV% for CL-54% and Vd-25%.
Panobinostat 10 mg, 15 mg 20 mg capsules ¹³³	Intra CV for C_{max} -52% and AUC_{0-inf} -38% in patients with oral administration. Intra CV for C_{max} -34% and AUC_{0-inf} -17% in patients with IV administration. The inter CV% for CL-65%.
Pazopanib Hydrochloride 200 mg, 400 mg tablets ^{134, 135& 136}	The mean intra-patient CV in AUC_{0-24} was 24.7% (range, 8.3 - 48.7%). The inter CV% for CL-52.3 and for Vd-67.1%. Inpatient CV in PK (25-27%).
Pegaspargase solution for injection or infusion 750 U/mL ¹³⁷ .	Inter-patient CV for AUC : between 22.2% and 120.2% and for C_{max} : between 19.7% and 62.1%.
Peginterferon Alfa-2a ¹³⁸	Variability in PK parameters ranges from 50-80%
Peginterferon Alfa-2b ¹³⁹	Inter-patient CV for AUC : 36.8%
Pembrolizumab 50mg IV injection ¹⁴⁰	The inter CV% for CL and Vd 28.1% and 13.5% respectively.
Pemetrexed Disodium for injection 500mg base/vial ¹⁴¹	The inter CV% for CL, V1 and V2 25.8%, 13.5% and 26.0% respectively.
Pertuzumab 420mg/14ml single use vial ¹⁴²	Inter CV of CL and Vd are 34.9% and 18.7%, respectively.
Plerixafor 24mg/1.2ml (20mg/ml) subcutaneous Solution for Injection ¹⁴³	PK variability in different cancer types ranged between 14-24%. For healthy volunteers the CV% for C_{max} and AUC ranged from 11-16%.
Pomalidomide 4 mg capsules ¹⁴⁴	Inter CV for AUC was between 13.5% to 39.4% in healthy subjects and 20.5% to 55.4% in multiple myeloma patients, respectively. Intra CV for AUC ~10% in healthy subjects. Intra CV for C_{max} ranged from 11.3% to 26.2% and 11.1% to 40.6% in healthy subjects and multiple myeloma patients, respectively
Pralatrexate 20mg/ml (20mg/ml) and 40mg/2ml (20mg/ml) IV injection ¹⁴⁵	PK inter CV >50%.
Raloxifene Hydrochloride 60 mg tablets ¹⁴⁶	Intra CV ~30%.
Regorafenib 40 mg tablets ¹⁴⁷	Intra CV for $C_{max,ss}$ is 32% and $AUC_{0-24hrs,ss}$ is 34%. Inter CV for C_{max} is 44% and AUC is 35% in solid tumor patients. Inter CV in solid tumor patients $C_{max,ss}$ is 44% and $AUC_{0-24hrs,ss}$ is 43%. Intra CV in metastatic colorectal cancer for $C_{max,ss}$ is 63% and $AUC_{0-24hrs,ss}$ is 86%.
Ribociclib succinate 200 mg tablets ¹⁴⁸	In patients with cancer after 600 mg multiple doses, CV% for C_{max} : 66.0 % and AUC_{0-24} : 62.4%
Rolapitant Hydrochloride 90 mg tablets and injection ¹⁴⁹	The variability in exposure (C_{max} and AUC) was low to moderate with coefficients of variation ranging from 10% to 47%.
Romidepsin injection for intravenous infusion 10mg/vial ¹⁵⁰	Intra CV in refractory neoplasm patients for C_{max} and AUC ranges from 30-80%. Inter CV in T cell lymphoma patients ranges from 50 to 70%.
Rucaparib Camsylate Tablets: 200 mg and 300 mg ¹⁵¹	CVs of $C_{max,ss}$ and AUC_{0-12SS} ranged from 43% to 72% and 58% to 73%, respectively.
Ruxolitinib Phosphate Tablets: 5 mg, 10 mg, 15 mg, 20 mg and 25 mg ¹⁵²	Fed: CVs of $C_{max,ss}$ and AUC_{0-12SS} ranged from 73% to 84% and 74% to 76%, respectively. In healthy volunteers inter CV%, ranging from 19.0% (200 mg) to 55.9% (25 mg) for C_{max} and from 8.59% (200 mg) to 34.0% (25 mg) for $AUC_{0-\infty}$. 21.7 to 35.8% for $C_{max,ss}$ and from 27.0 to 31.3% for $AUC_{0-\tau,ss}$ at steady state. In myelofibrosis patients, the inter CV%, ranging from 2.2-44.1% for ruxolitinib $C_{max,ss}$ and from 20-57% for $AUC_{0-\tau,ss}$.

Siltuximab Injection for Intravenous infusion 100 mg & 400 mg of lyophilized powder in a single-use vial ¹⁵³	Single-dose intersubject variability in AUC_{0-inf} and C_{max} were 39% and 27% (%CV), respectively. Multiple-dose (Day 43) intersubject variability in AUC_{0-t} and C_{max} were 39% and 30% (%CV), respectively.
Sonidegib Phosphate 200 mg capsules ¹⁵⁴	Inter CV of CL and Vd are 67% and 213%, respectively.
Sorafenib Tosylate tablets 200 mg ¹⁵⁵	Inter CV in pharmacokinetics ranges from 36% to 91%.
Sunitinib Malate Capsules 12.5 mg, 25 mg and 50 mg capsules ¹⁵⁶	Variability in PK parameters in healthy subjects ranges from 15-36% for C_{max} and AUC and in patients ranges from 25-60% for C_{max} and AUC.
Tamoxifen Citrate 40 capsules and tablets ¹⁵⁷	Intra CV% 10.3%, 7.4% and 12.5% for C_{max} , AUC_{0-72} and $AUC_{0-∞}$, respectively.
Temozolomide 250 mg capsules ^{158& 159}	Intra CV% 17.7%, 12.9% and 12.2% for C_{max} , AUC_{0-t} & $AUC_{0-∞}$, respectively. The inter-subject variability in clearance was 15%, and the residual variability was 26%
Temsirolimus injection for intravenous infusion 25 mg/mL ¹⁶⁰	PK Variability in cancer patients ranges from 20-40% and in healthy subjects ranges from 2-20% for C_{max} and AUC.
Thalidomide 50mg Hard Capsules ¹⁶¹	Coefficients of variation (CV%) for $AUC_{(0-∞)}$ and C_{max} were low suggesting a low inter-individual variability.
Thioguanine 40 mg tablets ¹⁶²	Intra CV% 71.3% and 56.1% for C_{max} and AUC_{0-t} , respectively.
Thiotepa for injection, 15 mg and 100 mg lyophilized white powder in single-dose vial for reconstitution ¹⁶³	CV% for C_{max} : 6-74% and AUC_{0-t} : 10-25% (Thiotepa). CV% for C_{max} : 8-19% and AUC_{0-t} : 11-22% (TEPA).
Topotecan Hydrochloride 0.25 mg and 1 mg capsules and 4mg base/vial IV injection ¹⁶⁴	Intra CV% 43% for oral administration and 22.5% after IV administration.
Toremifene 40 mg tablets ¹⁶⁵	Intra CV% 8.3% for AUC and inter CV% 25.3 for AUC.
Trabectedin IV injection 1 mg sterile lyophilized powder in a single-dose vial ¹⁶⁶	The inter and intra CV in clearance of trabectedin were 50% and 31%, respectively in patients with cancer.
Trametinib Tablets 0.5 mg, 1 mg, and 2 mg ¹⁶⁷	Inter-patient variability at steady state (on day 15) is 22% in AUC and 28% in C_{max} . Inter CV of CL and Vd are 24% and 77%, respectively.
Uridine Triacetate 10gm/packet oral granules ¹⁶⁸	The inter-CV of uridine concentrations ranged from 44% to 65% for 10 gram dose.
Vandetanib 100 mg and 300 mg tablets ¹⁶⁹	In healthy subjects inter CV% for AUC and C_{max} ranged from 8.4% to 25.8%. Intra CV% within 20% for AUC and within 10% for C_{max} . In patients inter CV% of 40% to 77% for C_{max} and 57.44% to 175.9% for AUC at a single dose, and 60.7% for C_{max} and 58.4% for AUC at Day 29.
Vemurafenib 240 mg tablets ¹⁷⁰	The inter-subject variability was relatively small at 37% for C_{max} and 32% for AUC_{0-8h} on Day 15 at the 960 mg bid dose. Inter CV of CL and Vd are 31.9% and 65.7%, respectively.
Venetoclax Tablets 10 mg, 50 mg, 100 mg ¹⁷¹	Inter CV of CL and Vd are 40.7% and 47.7%, respectively.
Vincristine sulfate liposome injection for intravenous Infusion 5mg/5ml (1mg/ml) ¹⁷²	Inter CV for C_{max} , AUC_{0-t} , $AUC_{0-∞}$ and CL are 18.8%, 41.3%, 43.7% and 51% respectively.
Vismodegib 150 mg capsule ¹⁷³	The inter CV for CL and Vd was 49% and 46%, respectively. Intra CV% for total and unbound concentrations was 27% and 42%, respectively.
Vorinostat 100 mg capsule ¹⁷⁴	The variability in $AUC_{0-∞}$ and C_{max} ranges from 35-54%.
Ziv-Aflibercept 25 mg/mL solution for IV infusion ¹⁷⁵	The inter CV% for CL and Vd was 28% and 20%, respectively.
Aldesleukin (Interleukin-2) ¹⁷⁶	The variability in $AUC_{0-∞}$ and C_{max} ranges from 15.23-62.21% and -23.9%-66.42% respectively.
Alemtuzumab IV injection 30 mg/1 mL single use vial ¹⁷⁷	The inter CV alemtuzumab pharmacokinetics was large (>30% for all PK parameters). Inter CV for V1 and V2 was 84% and 179%, respectively.
Avelumab IV injection weight-based (10 mg/kg Q2W) and flat (800 mg Q2W) dosing regimen ¹⁷⁸	The overall variability 27.1% vs 29.0% for AUC_{0-336h} ; 38.6% vs 41.2% for AUC _{ss} for weight-based (10 mg/kg Q2W) and flat (800 mg Q2W) dosing regimen.
Carboplatin Aqueous Solution Injection 50mg, 150 mg, and 450 mg and carboplatin 50 mg/m ² /day i.v. ^{179& 180}	Inter-patient variability in PK pharmacokinetics ranges from 15% to 21%. Interpatient variability for $AUC_{0-∞}$ is 68.6%. Inpatient variability for CL is 40%.
Cytarabine Liposome injection 10mg/mL ¹⁸¹	Inter-subject variability was 52% for CL and 117% for liposomal Vd for cytarabine
Daunorubicin Hydrochloride injectable injection 5mg ¹⁸¹ base/mL	Inter-subject variability was 44% for CL and 146% for liposomal Vd for daunorubicin.
Elotuzumab 400 mg injectable injection ¹⁸²	Inter-subject variability was 31.6% for CL, 20.3% for V1 and 34.6% for V2.
5-Aminolevulinic acid hydrochloride crystalline powder for oral solution 30mg/mL ¹⁸³	Inter CV 4-13%.
Lomustine 100 mg capsules ¹⁸³	Inter CV 51-62%.
Vinorelbine Ditartrate capsules 20 mg and 30 mg ¹⁸³	Intra CV 19% and inter CV 20%.
Procarbazine Hydrochloride 50 mg capsules ¹⁸³	Inter CV 38-106%.
Nilutamide 150 mg tablet ¹⁸⁴	Oral bioavailability 97%. Low intra CV is expected
Rituximab Hydrochloride 10 mg/vial ¹⁸⁵	The inter-patient variability for CL, V1 and V2 was 29.3% (estimation of CV = 4.74%), 10.7% (estimation of CV = 14.0%), and 22.5% (estimation of CV = 15.3%) respectively
Zoledronic Acid for Injection Concentrate 4 mg/5 mL zoledronic acid (as zoledronic acid monohydrate) ¹⁸⁶	Inter-patient variability of clearance was 36%.
Ramucirumab 500mg/50mL injectable injection ¹⁸⁷	The inter-patient variability for CL, V1 and V2 was 32.3%, 22.9% and 54.0% respectively.
Rasburicase ¹⁸⁸	Total patient variability in C_{ei} and AUC_{0-24} was 21.8 and 42.6%, respectively.
Pegfilgrastim subcutaneous Injection: 6 mg/0.6 mL solution in a single-dose prefilled syringe ¹⁸⁹	The inter-patient variability for CL, Vd was 50.5% and 53.1% respectively.

V1=Central volume of distribution, V2=Peripheral volume of distribution, CL= Clearance, Vd: volume of distribution; PK: Pharmacokinetics, C_{ei} =Plasma concentration observed at the end of IV infusion.

BE studies are generally designed to determine if there is a significant difference in the rate and extent to which the active drug ingredient, or active moiety, becomes available at the site of drug action.

According to the criteria developed by the U.S. (United States) Food and Drug Administration (FDA) and generally applied by other regulatory agencies, two pharmaceutically equivalent products are judged bioequivalent if the 90% confidence

interval of the geometric mean ratio (GMR) of AUC and C_{max} fall within 80.00-125%.00⁸.

An effort was made to compile the data of inter/intra-subject variability of various anti-cancer drugs for ready reference in order to determine the appropriate study design and sample size, which is an important component to determine the cost of the bioequivalence studies while conducting the pivotal studies, which in turn may help in producing more generic anti-cancer drugs globally including in India.

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