Citizens for Affordable,
Safe & Effective Medicine
CASEM

To,
Dr. Harshavardhan
Union Minister for Health,
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June 7, 2020

Dear Minister,

Petition to setup Expert Committee to amend the bioequivalence framework put in place by the Drugs & Cosmetics (Ninth Amendment) Rules, 2017

1. By way of introduction, I am a public health activist and the Founder of Citizens for Affordable, Safe & Effective Medicine (CASEM) which aims to be a collective of like- minded individuals working towards ensuring that the medicines supplied to India and other countries are affordable, safe and effective. I have formerly worked in the Indian pharmaceutical industry and was responsible for exposing the regulatory violations at Ranbaxy Laboratories after which the company was prosecuted and fined $500 million dollars by the United States Food and Drug Administration (USFDA).[1] Since the end of my whistleblower lawsuit against Ranbaxy in 2013, I have been engaged in advocacy aimed at strengthening the drug regulatory framework in India. This includes a report that I submitted to the Ministry on measures to improve drug regulation in India[2], a petition to the Prime Minister's Office[3] requesting a prohibition on certain harmful drugs, as well as an ongoing writ petition before the Delhi High Court[4] requesting directions to the Central Government to prohibit certain drugs that were red flagged by a Parliamentary Standing Committee on Health.

[1] 'Ranbaxy pleads guilty, to pay $500 mln in settlement', *Reuters*, May 13, 2013.
[2] Dinesh Thakur & Prashant Reddy, 'A report on fixing India's broken drug regulatory framework' (June, 2016) *available here*: ; https://dineshthakur.com/wp-content/uploads/2016/06/CDSCO-Reform.pdf Dinesh Thakur, 'India needs strict prosecution laws to fix drug regulatory system: Ranbaxy whistleblower Dinesh Thakur', *Economic Times*, June 24, 2016.
[3] Prabha Raghavan, 'Ranbaxy whistleblower petitions PMO to investigate 'illegal' drug approvals', *Economic Times*, May 21, 2018. The text of the petition can be accessed over here: https://dineshthakur.com/wp-content/uploads/2018/05/Petition-to-the-Prime-Minister.pdf
[4] Dinesh Thakur v. Union of India, W.P. No. 11107 of 2018 before the High Court of Delhi at New Delhi.

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2. On behalf of CASEM, I kindly request you to please consider favourably our petition to setup an Expert Committee to amend the regulatory framework put in place by the Drugs & Cosmetics (Ninth Amendment) Rules, 2017 with the aim of ensuring mandatory bioequivalence studies for all generic medicines manufactured and marketed in India. These rules were drafted under the Drugs & Cosmetics Act, 1940. In this petition, we outline the importance of bioequivalence studies in ensuring the quality of generic medicines, the history of the Indian position on mandatory bioequivalence studies for generic medicines and finally, the loopholes in the framework put in place by the Drugs & Cosmetics (Ninth Amendment) Rules, 2017. In our opinion, these well-intentioned and much required amendments in 2017, fail to do justice to their stated objective of improving the quality of generic medicines in India. In this petition, we list the loopholes with the present legal framework. We have also taken the liberty of proposing certain recommendations to ensure the creation of a truly effective and transparent regulatory framework, which we hope will ensure that only the best quality generic medicines are approved not just for Indian citizens but also for our trading partners across the world whose citizens rely upon Indian generic medicines to meet their public health objectives.

A. The importance of bioequivalence studies in ensuring effective generic medicines

3. The birth of the modern drug regulatory framework can be traced to the Thalidomide tragedy when a drug which was otherwise safe caused the birth of babies with severe deformities. The tragedy served as an eye-opener to the potential dangers of modern medicines leading to the enactment of modern regulatory laws such as the Kefauver-Harris Drug Amendments Act, 1962.[5]

[5] Jeremy A. Greene & Scott H. Podolsky, "Reform, Regulation and Pharmaceuticals – The Kefauver-Harris Amendments at 50", 367(16) *New England Journal of Medicine*, 1481-1483 (2012) *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4101807/.

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4. The new regulatory framework required pharmaceutical companies to adequately test all drugs for both safety and efficacy in clinical trials before they could be approved and marketed to patients. These clinical trials are both risky and expensive because they are conducted on hundreds or thousands of patients, typically, in a double blind controlled format, in order to generate quality clinical data on therapeutic efficacy and safety. The primary aim of these trials is to generate clinical data which demonstrates that the drug has justifiable therapeutic benefit for patients and that the risk from the drug, in the form of side-effects, does not cause unreasonable harm to patients. The cost of these trials is estimated to run into millions of US dollars and is usually conducted by the company that owns the patents over the new drug. A study conducted by John Hopkins University reported that the cost of clinical trials, depending on the nature of the drug, can range from $6 million to $157 million dollars with the median being $19 million dollars.[6]

5. Typically, once the innovator is able to establish the safety and efficacy of a new drug before the regulators and the patent for that drug expires, other companies that want to manufacture a generic version of the drug are not required to repeat the same clinical trials since that would be both expensive and unethical, given that some patients have to necessarily be given a placebo to reestablish therapeutic benefit. As a result, after significant political pressure[7], the United States Food and Drug Administration (USFDA), published the first draft regulations, in 1975, proposing the introduction of bioequivalence testing in order to establish whether generics were equivalent to the innovator drug formulation.[8] These regulations, which were finalized in 1977[9] were central to the Drug Price Competition and Patent Term Restoration Act, 1986 (a.k.a. Hatch

[6] Moore T.J. et.al., "Estimated Costs of Pivotal Trials for Novel Therapeutic Agents Approved by the US Food and Drug Administration, 2015-2016," 178(11) *JAMA Intern. Med.* 1451-1457 (2018) *available at* https://www.ncbi.nlm.nih.gov/pubmed/30264133.
[7] Jeremy A. Greene, "When is a Medicine Good Enough?: Science, Similarity, and the History of Generic Drugs", 105(2) *Clinical Pharmacology & Therapeutics* 290-291 (2019) *available at* https://www.ncbi.nlm.nih.gov/pubmed/30703267.
[8] Jerome P. Skelly, "Bioavailability and Bioequivalence", 16(10) *The Journal of Clinical Pharmacology* 539-545 (1976) *available at* https://accp1.onlinelibrary.wiley.com/doi/10.1177/009127007601601013.
[9] 21 C.F.R. 320;

Waxman Act) which incentivized the launch of generic drugs with the promise of limited exclusivity on the basis of bioequivalence studies without conducting de-novo clinical trials.

6. According to the American regulations[10], the definition of bioequivalence is as follows:

   "*Bioequivalence* means the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study. Where there is an intentional difference in rate (e.g., in certain extended release dosage forms), certain pharmaceutical equivalents or alternatives may be considered bioequivalent if there is no significant difference in the extent to which the active ingredient or moiety from each product becomes available at the site of drug action. This applies only if the difference in the rate at which the active ingredient or moiety becomes available at the site of drug action is intentional and is reflected in the proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug."

7. In simple English, the above definition means that a generic drug is considered to be bioequivalent to the innovator drug when there is evidence to confirm the former is dissolving in the bloodstream of a patient at the same rate as the innovator drug, thereby indicating that it will become bioavailable in a concentration similar to the innovator formulation and therefore have the same therapeutic effect as the innovator drug. These bioequivalence studies are important because although different generic drug manufacturers may use the same active pharmaceutical ingredient (API), they are likely to formulate those

[10] 21 C.F.R. 314.3

APIs into tablets or capsules which are solid oral dosage solutions, or syrups and injectables using different manufacturing processes. Thus although all generic drugs will have the same active ingredient as the innovator drug, each of these drugs, depending on their manufacturer, are likely to have different excipients and be made through a manufacturing process that is different from the one that is followed by the manufacturer of the innovator drug. For example, the use of different binding agents, stabilizing agents or mechanical equipment as tablet punching machines with differing punching strength may influence the manner in which a drug dissolves into the bloodstream. Certain binding agents may lead to an improper dissolution of the drug in the bloodstream. Similarly, if a tablet is punched incorrectly by a tablet punching machine, it may not dissolve adequately in the bloodstream. In both scenarios, the generic drug is not likely to have the same therapeutic effect on the human body as the innovator drug. In this backdrop, the bioequivalence testing requirement is essentially a test of the manufacturing process adopted by a pharmaceutical company.

8. In order to establish that a generic drug is bioequivalent to an innovator drug, most jurisdictions require that the generic drug be administered on a group of healthy volunteers over a study period. Their blood or urine samples are drawn at regular intervals to determine the rate at which the drug is dissolving into the bloodstream. The concentration of the drug in the blood of the volunteers for the study, over a period of time is plotted on a graph and compared to that of the innovator drug. If the graphs are equivalent (measured by the maximum concentration of the drug in the blood stream C_{max})[11] and the total bioavailable drug in the body before it is excreted AUC[12], even with minor deviations, the generic drug can be considered to be bioequivalent to the innovator drug. Once declared bioequivalent to the innovator drug formulation, the generic drug can

[11] C_{max} refers to the level of maximum concentration of the drug being tested in the bloodstream of the patient post its administration. The concentration of the drug increases with time post administration until it peaks and the body begins to excrete the drug via kidneys and other organs

[12] AUC stands for Area Under the Curve and refers to the total amount of drug that is metabolized by the body before it is excreted through kidneys and other organs.

be used as a substitute for the former in clinical practice meaning that doctors can prescribe a generic drug as a substitute for an innovator drug.[13]

9. These bioequivalence studies are usually conducted by external Clinical Research Organisations (CRO) on behalf of generic pharmaceutical companies seeking to launch their generic drugs in the market. By their very nature, the cost and complexity of these bioequivalence studies is far less when compared to full-fledged clinical trials conducted by innovator companies new untested drugs. The lower cost of bioequivalence studies in contrast to a full-fledged clinical trial is one of the reasons that generic drugs usually cost a fraction of innovator drugs. It is thus good policy for more countries to allow generic drugs to be used to treat their patient population on the basis of bioequivalence studies. Europe and other jurisdictions have followed the American regulatory framework by allowing for generic drugs to be sold in their markets on the basis of bioequivalence studies. There are some variations in how each jurisdiction regulates the standards for such studies but the underlying logic usually remains the same.[14]

B. The history of the bioequivalence requirement in India under the Drugs & Cosmetics Act, 1940

10. For more than 40 years, after bioequivalence studies became compulsory in the United States for all generic drugs, India did not require bioequivalence studies for all generic drugs sold in the Indian market. At most, India required bioequivalence studies only for "new drugs" which has its own connotations under Indian law. Originally under the Drugs & Cosmetics Rules, 1945 a drug maintained a "new drug" status for the first 4 years after it was approved by the central licensing authority for the Indian market.[15] During this period, all generic

[13] *See generally* Mei-Ling Chen et. al., "Bioavailability and Bioequivalence: An FDA Regulatory Overview", 18(12) *Pharmaceutical Research* 1645-1650 (2001).
[14] *See generally* Roger Nation & Llyod N. Sansom, "Bioequivalence Requirements for Generic Products", 62(1-2) *Pharmacology & Therapeutics* 41-55 (1994).
[15] Originally defined in Rule 122E of the Drugs & Cosmetics Rules, 1945 this definition has been replaced by Rule 2(w) of the New Drugs and Clinical Trial Rules, 2019. The definition remains substantially the same save for two categories of new drugs.

manufacturers who wanted to introduce their generic copies in the Indian market were required to conduct a bioequivalence study and submit the data from such studies to the central licensing authority as a condition of the approval process.[16] However after the 4 year period was exhausted, when the drug lost its "new drug" status, generic drug manufacturers were required to submit their applications to manufacture the drug to the state licensing authorities.[17] Shockingly, till 2017 there was no requirement in the law to demonstrate bioequivalence in applications filed with state licensing authorities. At most, these generic pharmaceutical companies would conduct bioequivalence studies, if it was required by the laws of an export market that they supplied to and even then, there have been several instances of data manipulation at clinical research organisations (CROs) which conduct these studies.[18] These manufacturing plants supplying drugs for the export market, rarely supply drugs to the Indian markets.

11. The lack of a requirement to establish bioequivalence for generic drugs entering the market after the initial 4 year period was alarming since it meant that Indian patients were being given drugs that would not have been accepted in any of the better regulated markets because of the lack of a guarantee that they would have the same therapeutic efficacy as the innovator drug.

12. However in the last decade, a series of events have led to a gradual change in the law. In 2013, an expert committee headed by Dr. Ranjit Roy Chaudhry had made the recommendation that all new generics in India should necessarily undergo bioequivalence studies before being approved for use in patients.[19] This

[16] Originally this process was governed by Rule 122B of the Drugs & Cosmetics Rules, 1945 which has subsequently been replaced by Rule 80 of the New Drugs and Clinical Trial Rules, 2019.
[17] Rule 69 of the Drugs & Cosmetics Rules, 1945.
[18] *See generally* Madhuri Patel, "Misconduct in Clinical Research in India: Perception of Clinical Research Professional in India", 8(2) *Journal of Clinical Research and Bioethics* 1-9 (2017); PTI, "GVK Bio manipulated clinical trials of generic drugs: Reports", *Economic Times*, December 5, 2014 *available at* https://economictimes.indiatimes.com/industry/healthcare/biotech/pharmaceuticals/gvk-bio-manipulated-clinical-trials-of-generic-drugs-reports/articleshow/45385764.cms?from=mdr; E.J. Lane, "India's drug and CRO manufacturing travails gather pace as New Delhi calls on diplomats to help", *Fierce Pharma,* July 23, 2015 *available at* https://www.fiercepharma.com/manufacturing/india-s-drug-and-cro-manufacturing-travails-gather-pace-as-new-delhi-calls-on.
[19] Report of the Prof. Ranjit Roy Chaudhary Expert Committee to Formulate Policy and Guidelines for Approval of New Drugs, Clinical Trials and Banning of Drugs at p. 38, 39 (July 2013).

recommendation was discussed in 2014 at the 47th meeting of the Drugs Consultative Committee (DCC), comprising of central and state drug controllers, as well as representatives from the Ministry of Health.[20] Quite astonishingly, the DCC while concluding that bioequivalence studies were important and would be insisted upon for drugs with variable bioavailability, determined that the same could not be "implemented as a rule" because India allegedly lacked the infrastructure to facilitate the conduct of such studies on a large scale. The same committee however supported the idea of the pharmaceutical industry conducting such studies for exports to jurisdictions that mandatorily required such testing.

13. In June, 2016 I submitted a report to the Ministry of Health where I raised the issue of the lack of bioequivalence testing in India. I also met with a Joint Secretary in the drug regulation section of the Ministry of Health who assured me that action would be taken on the basis of my report.

14. Just a few weeks after the submission of my report, at the 72nd meeting of the Drugs Technical Advisory Board (DTAB), it was decided that since several concerns were being raised regarding the lack of mandatory bioequivalence studies, these tests would be made mandatory for all generics drugs, save for a few exceptions.[21]

15. Thereafter, on April 3, 2017 the Ministry of Health exercised its powers under the Drugs & Cosmetics Act, to enact the Drugs and Cosmetics (Ninth Amendment) Rules, 2017 to make it mandatory for all generics, even those approved by state licensing authorities, to mandatorily conduct bioequivalence studies as a requirement to getting approval for sale in the Indian market. There are however serious lacunae in the wording of these rules, with regard to the waivers that have been permitted. The overall lack of transparency in how this

[20] Report of the 47th Meeting of the Drugs Consultative Committee held on 30th and 31st July, 2014 at New Delhi at p. 8-10 *available at* https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/common_download.jsp?num_id_pk=ODA5.
[21] Report of the 72nd Meeting of the Drugs Technical Advisory Board (DTAB) held on June 27, 2016 at New Delhi at p. 8-9 *available at* https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/common_download.jsp?num_id_pk=Nzcy.

new regulatory framework is being implemented will also undermine confidence in its efficacy. The precise problems with the wordings and exemptions, allowed under these rules, are described in more detail below.

C. The exceptions to bioequivalence tests under the Drugs & Cosmetic (Ninth Amendment) Rules, 2017 and their shortcomings

16. The amendments in 2017 adopted a bio-pharmaceutical classification system (BCS) which classifies all drugs into four classes based on their solubility and permeability. Of these four classes, the amendments of 2017 required mandatory bioequivalence testing for only two classes.[22] The four classes as per the BCS are as follows:

	Solubility	Permeability
Class I	High	High
Class II	Low	High
Class III	High	Low
Class IV	Low	Low

17. The BCS methodology owes its existence to research by Professor Gordon Amidon and his colleagues while working for the USFDA Division of Biopharmaceutics in 1990 to reduce and simplify regulatory requirements. Their key contribution was in discovering a co-relation between in-vitro drug product dissolution and in-vivo bioavailability of the drug formulation.[23] In simple English, this meant that the rate of bioavailability of a particular drug in the human body was linked to its permeability and the rate at which the drug dissolved in a laboratory setting. Towards this end, they created what is now the

[22] Rule 2(a) of the Drugs & Cosmetics Rules, 1945;
[23] G. L. Amidon et. al., "A Theoretical Basis for a Biopharmaceutic Drug Classification: The Correlation of In-Vitro Drug Product Dissolution and In Vivo Bioavailability, Pharma Res 12, 413-420, 1995 – Backstory of BCS", 16(5) *The AAPS Journal* 894-898 (2014).

BCS to classify different drug formulations based on their solubility and permeability.

18. The importance of establishing this co-relation was that it opened the door to the concept of bio-waivers wherein certain generic drugs, displaying high solubility and permeability, could get a waiver from conducting studies on human volunteers to collect bioequivalence data by relying instead on data generated from in-vitro studies in the laboratory. Such a measure would reduce the cost and time of generating data necessary to establish the bioequivalence of generic drugs.

19. In such cases of in-vitro testing, for the purpose of establishing bioequivalence, the solubility of the drug is to be tested in an aqueous media that has the pH range expected in the human stomach and permeability is to be tested either, on animal models or epithelial cells in the laboratory setting. If the generic drug meets the same parameters as the reference product (usually the innovator product), it can be presumed that bioequivalence has been established. As mentioned earlier, the advantage of this approach is that in-vitro tests significantly reduce the costs of proving the bioequivalence of a generic formulation to a reference product because unlike in-vivo testing that is conducted on humans in-vitro testing is conducted in a laboratory setting. Obviously not all drugs will qualify for bio-waivers. As per one published study, which attempted to classify the top 200 selling drugs in the US, EU and Japan, according to the BCS methodology, it was found that more than 55% fell within Class I and Class III, meaning that they qualified for bio-waiver.[24] An earlier study by the same authors, found a similar percentage of drugs on the WHO's Essential Drug List qualifying for bio-waivers.[25]

[24] Toshihide Takagi et. al., "A Provision Biopharmaceutical Classification of the Top 200 Oral Drug Products in the United States, Great Britain, Spain, and Japan", 3(6) *Molecular Pharmaceutics* 631-643 (2006) doi.org/10.1021/mp0600182.
[25] Kasim N.A. et. al., 1(1) "Molecular Properties of WHO Essential Drugs and Provisional Biopharmaceutical Classification", *Molecular Pharmaceutics* 85-96 (2002). doi.org/10.1021/mp034006h .

20. Although the research by Amidon and his colleagues was originally published in 1995, it was adopted by the USFDA only in 2000 in a guidance document that introduced the concept of bio-waivers for the first time.[26] The World Health Organisation (WHO)[27] and the European Medical Agency (EMA)[28] followed suit, in 2006 and 2010 respectively. These guidance documents have undergone significant revisions in the last few years. Over time, the BCS system of bio-waivers has been adopted by more regulatory agencies for certain drugs. There is however, no uniform global standard for granting bio-waivers and variations existing between different regulatory systems.[29]

21. Despite the possibility of significant savings by requesting bio-waivers, studies have reported that relatively few generic manufacturers have been seeking bio-waivers.[30] Instead most generic pharmaceutical companies appear to prefer the option of conducting in-vivo bioequivalence studies on human volunteers. This may be due to the uncertainty surrounding the bio-waiver system since it involves a case-by-case approval based on each drug and even then the approval will depend on the quality of the in-vitro study that was conducted. On the other hand, the standards of in-vivo bioequivalence testing appear to be standardized across most regulatory jurisdictions, with fewer variations. Since the latter offers greater certainty to generic drug manufacturers, most of them do not bother seeking bio-waivers,

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[26] Office of Medical Products and Tobacco, Centre for Drug Evaluation and Research, (2017): "Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. Guidance for Industry", Docket No. FDA-2015-D-1245, United States Food and Drugs Administration (USFDA) *available at* https://www.fda.gov/media/70963/download.

[27] Proposal to Waive in Vivo Bioequivalence Requirements for WHO Model List of Essential Medicines Immediate-release, Solid Oral Dosage Forms. WHO Technical Report Series, No. 937, 2006, Annex 8 (2006) *available at* https://apps.who.int/medicinedocs/en/m/abstract/Js19640en/.

[28] Committee for Medicinal Products for Human Use, "Guidelines on the Investigation of Bioequivalence", CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** European Medicines Agency; January 20, 2010 *available at* https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf.

[29] Joy Van Oudtshoorn et. al., "A Survey of the Regulatory Requirements for BCS-Based Bio-waivers for Solid Oral Dosage Forms by Participating Regulators and Organisations of the International Generic Drug Regulators Programme", 21(1) *Journal of Pharmacy & Pharmaceutical Sciences* 27-37 (2018). doi.org/10.18433/j3x93k.

[30] Lorena Barbosa Arrunátegu et. al, "Biopharmaceutics classification system: importance and inclusion in biowaiver guidance" 51(1)*Brazilian Journal of Pharmaceutical Sciences,* (2015) ("Although there was an increase in the number of applications of biowaiver based on BCS, this progress has been tempered by the lack of international harmonization and the reluctance of companies to adhere to the methodology due to fears raised by a possible delay in the registers.") *available at* http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1984-82502015000100143; Ines Lenic et. al. "Overview of the European Medicines Agency's Experience With Biowaivers in Centralised Applications", 12 *Clinical and Translational Sciences* 490-496 (2019) doi: 10.1111/cts.12642. Barbara Davit et. al., "BCS Biowaivers: Similarities and Differences Among EMA, FDA and WHO Requirements", *The AAPS Journal* (2016) doi.org/10.1208/s12248-016-9877-2

22. Further, some drugs are entirely excluded from the possibility of being granted bio-waivers because of their peculiarities. For example, drugs with a Narrow Therapeutic Index (NTI) or drugs designed to be absorbed in the oral cavity are excluded from bio-waivers in most jurisdictions.[31] For drugs falling in Class III, regulators may also review the type of excipients that are being used since it directly affects the dissolution profile of the drug formulation.[32] Therefore it is necessary for regulators to critically review each application for bio-waivers and the process can take time and involve uncertainty since regulators can reject such requests for bio-waivers based on the data presented with the application.

23. Unlike the process described above in other jurisdictions wherein each application for a bio-waiver is scrutinized on its individual merits, the process put in place by the Drugs & Cosmetics (Ninth Amendment) Rules, 2017 grants a blanket bio-waiver for drugs in Class I & III of the BCS, from supplying any data to show in-vitro bioequivalence and does not lay down any specific data requirements for even Class II & IV drugs, which are required to demonstrate in-vitro bioequivalence. Overall, the amendments of 2017 were poorly drafted and must be amended to fix the following lacunae/errors:

    (a) Conflicting legal definitions of the phrase "bioequivalence": The Drugs & Cosmetics (Ninth Amendment) Rules, 2017 did not lay down a definition of "bioequivalence". Instead, it required applicants to supply bioequivalence data as per the requirements laid down in Schedule Y to the Drugs and Cosmetics Rules, 1945. The problem however, is that Schedule Y does not really have a definition of "bioequivalence" and for most part, Schedule Y has been rendered virtually redundant when the government brought in the New Drugs and Clinical Trial Rules, 2019. The latter rules define clearly, the terms "bioequivalence" and "bioavailability".[33] It would

[31] Supra 26; USFDA Guidelines at p.12.
[32] Supra 26; USFDA Guidelines at p.10.
[33] Rule 2(e) and 2(f) of the New Drugs and Clinical Trials Rules, 2019.

be prudent to incorporate the same definition into the Drugs & Cosmetics Rules, 1945 as amended in 2017 in order to ensure consistency and legal clarity.

(b) **No parameters laid down for defining "high solubility" and "permeability":** Another worrying omission in The Drugs & Cosmetics (Ninth Amendment) Rules, 2017 is the lack of parameters to define high solubility and high permeability. Should it be 85% or 90% or should it be some other figure? Similarly, there is currently no guidance in the law on how solubility or permeability, are to be tested in in-vitro conditions. For example, can permeability be established through testing on animal models and what should be the pH range of the solutions in which solubility is being tested? The rules are currently silent on this aspect. It was necessary for the rules to define these parameters and lay down testing protocols, so as to prevent the 29 different state licensing authorities from interpreting these rules differently. In all other countries which follow the BCS, there are extensive regulations or guidance documents explaining the manner in which high solubility and high permeability are to be established, as well as the many exceptions to bio-waivers. The Indian regulations are entirely lacking in this regard despite the fact that there are 29 different state licensing authorities that will be considering applications for bio-waivers

(c) **The absence of regulations mandating the submission of in-vitro bioequivalence data in case a bio-waiver is granted:** It is important for applicants, seeking a bio-waiver for drugs falling within Class I and Class III, to submit data collected through in-vitro testing, demonstrating high solubility and permeability. After all, the science behind bio-waivers is that data that can be collected through the in-vitro route (laboratory testing), need not be collected through the in-vivo route (human testing). Surprisingly, there is no requirement in the Drugs & Cosmetics (Ninth Amendment) Rules, 2017 for submission of such in-vitro data when

granting a bio-waiver to a manufacturer of a generic drug. This omission appears to be a drafting error because bio-waivers make sense only where there is a legal requirement for the manufacturers of generic drugs in this category to submit in-vitro test data to the regulator certifying that the drug is bio-equivalent to the reference product despite being manufactured through a different process. It is important for regulators to scrutinize the in-vitro data because the use of different excipients can affect the dissolution profile of an otherwise highly soluble drug. For example, a recent peer-reviewed paper demonstrates that despite high solubility, variation of excipients used in a formulation significantly affects permeability thereby making the formulation, being studied, non-bioequivalent. This study demonstrates that despite high solubility, a variation in the excipients by the generic manufacturers can have a disproportionate effect on bioavailability.[34] It is therefore of utmost importance for the licensing authorities to review the in-vitro bioavailability data even when a bio-waiver is granted.

(d) Silence on the exceptions to the bio-waiver rule: There is no mention in the Indian rules of any exceptions to the rule of bio-waivers for drugs in Class I and Class III. As mentioned earlier in this petition, in other countries such as the United States, drugs that have a Narrow Therapeutic Index (NTI) or drugs that are designed to be absorbed in the oral cavity cannot qualify for bio-waivers. There are scientific reasons for these exceptions. For example, for NTI drugs, a slight change in the bioavailability can have significant implications for the clinical performance of the drugs. It is of utmost importance that similar exceptions are expressly mentioned in the Indian legal-framework regulating bio-waivers.

[34] Alejandro Ruiz-Picazo et. al., "Investigation to Explain Bioequivalence Failure in Pravastatin Immediate-Release Products", 11 *Pharmaceutics* 663 (2019).

(e) Lack of measures against data fabrication: Given the degree of data fabrication that has taken place amongst the pharmaceutical industry in India, it may be prudent for licensing authorities to verify the in-vitro data submitted by generic pharmaceutical companies by replicating the tests in government laboratories.

D. The lack of transparency regarding the manner in which reference products were selected by the CDSCO

24. Another important issue, with regard to the manner in which the bioequivalence criteria are being implemented, is the lack of clarity regarding the manner in which the "reference products" are being chosen by the CDSCO. In simple English, a "reference product" is the product to which the generic drug is compared for the purpose of bioequivalence studies. The generic drug has to prove it is bioequivalent to the "reference product" in order to get its approval. Usually, the reference product is the innovator product which has gone through a full-fledged clinical trial process to establish its therapeutic efficacy and safety profile. However some regulators do list even generic drugs as "reference products".

25. As per the minutes of the 72nd meeting of the Drugs Technical Advisory Board (DTAB) where it was decided to make bioequivalence studies a mandatory condition for approving all generic drugs, a "group" was to be constituted to "lay done the modalities for identification of the reference drug for the conduct of BE studies".[35] It is not clear whether such a group was ever setup because its details are unavailable on the website of the CDSCO.

26. On January 22, 2020 the CDSCO published a list of accepted "reference products" that are required to be used during the conduct of bioequivalence studies.[36] For

[35] Supra 20; DTAB Minutes at para 4.7.
[36] "List of Reference Products for conduct of BE Study", F. No. 12-32/2019-DC (Pt-Misc-SND), Central Drug Standard Control Organisation, January 22, 2020,

almost all drugs, the CDSCO has listed generic drug formulations as well as innovator drugs as the "reference products". While regulators may list generic drugs as "reference products", there needs to be some explanation as to why these drugs are chosen as "reference products". For example, if the innovator drug is no longer on the market, a regulator maybe constrained to choose a generic drug as a "reference product". Generic drug formulations which are designated as "reference products" must undergo additional scrutiny in order to ensure that the formulation selected behaves similar to the original innovator product in human physiology. Both, the World Health Organisation (WHO) and the USFDA do have guidelines in place for selection of the "reference product" to make matters more transparent.[37]

27. Unfortunately, there is little transparency regarding the manner in which the CDSCO has chosen these particular products as the "reference products" because it has not made public any studies or minutes of meetings where the list of these products was finalized. The government must guarantee transparency in this regard so as to bolster the confidence of the medical community in the regulatory process to approve generic drugs. The government must, in consultation with the medical community, consider formulating guidelines for the selection of reference products in a transparent manner.

E. The lack of clarity regarding the status of generic drugs approved for the Indian market, prior to 2017

28. One critical question that has remained unanswered in the Drugs & Cosmetics (Ninth Amendment) Rules, 2017 is the status of various generic drugs that were approved by State Licensing Authorities (SLA) prior to the amendments in 2017 that made bioequivalence testing compulsory for all generic drugs. Originally when the DTAB decided to make bioequivalence testing compulsory at its 72nd

available at https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=NTQ5Mg==

[37] Office of Medical Products and Tobacco, Centre for Drug Evaluation and Research, (2017): "Referencing Approved Drug Products in ANDA submissions: Draft Guidance for Industry", United States Food and Drugs Administration (USFDA) *available at* https://www.fda.gov/media/102360/download.

meeting, held on June 27, 2016, it had also recommended that "For the drugs already marketed in the country, three years time may be given of submission of BE study data."[38] This was an important recommendation because prior to 2017, India was flooded with generic drugs that were not tested for their bioequivalence with the innovator drugs. Subsequently at its 77th meeting, held on June 16, 2017 the DTAB reiterated this decision but extended the timeline for these drugs to a four year period.[39] However, shockingly, it does not appear that the Health Ministry has taken any steps to implement this decision.

F. Recommendations to strengthen the legal framework for bioequivalence studies in India for the domestic and export market

29. We request that the Ministry of Health constitute an expert committee of experienced doctors, pharmacologists, legal experts, experts from Public Health and representatives of the DCGI to make recommendations on the following issues:

(a) The requirement to insert a legal definition of "bioequivalence" in the Drugs & Cosmetics Rules, 1945;

(b) The precise scientific criteria required to classify a drug as per the BCS by clearly spelling out the criteria for dissolution, in-vitro permeability and the effect of excipients used to develop the formulation;

(c) An amendment to the existing rules to mandate the submission to the licensing authority of data based on in-vitro testing for drugs that qualify for bio-waivers (i.e. exemption from in-vivo testing), in order to establish bioequivalence to the reference product;

(d) Requiring the licensing authorities to verify the in-vitro data by replicating the tests in government laboratories;

[38] Supra 20; DTAB Minutes at para 4.7.
[39] Report of the 77th Meeting of the Drugs Technical Advisory Board (DTAB) held on June 16, 2017 at New Delhi at p. 7 *available at* https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/common_download.jsp?num_id_pk=NTcw

(e) Making public the data submitted by all generic drug manufacturers to establish the bioequivalence of their drugs, in order to ensure more transparency and boost public confidence in generic drugs;

(f) Making public, the process as per which reference products were selected and creating a searchable database listing all reference drugs for all generic drugs;

(g) The minimum criteria for carrying out a bioequivalence study – this should include the minimum number of volunteers required for a BE study, the batch size from which samples will be drawn for a bioequivalence study, whether manufactured under cGMP conditions and the parameters that are to be tested etc.;

(h) The drugs for which bio-waivers will not be allowed – e.g. Drugs with a narrow therapeutic index or drugs consumed through an oral cavity;

(i) A continuously updated list of drugs for which biowaivers are granted by the CDSCO;

(j) The need for a centralized database of volunteers for BE studies in order to prevent the possibility of the same volunteers enrolling in multiple BE studies since this is known to be an issue from past reporting[40];

(k) Measures to prevent data fabrication at CROs which conduct BE studies;

(l) Penalties in cases where data fabrication and intentional data integrity issues are verified by the CDSCO

I trust and hope the government will treat this petition with the urgency and speed that the situation demands. If required, I can be contacted at dinesh@casemindia.org.

Best Regards,

Dinesh Thakur,
Founder, CASEM

[40] Priyanka Pulla, "Lured by blood money: serial volunteers set disturbing trend", *Hindu*, December 30, 2017 *available at* https://www.thehindu.com/opinion/op-ed/lured-by-blood-money-clinical-trials/article22328296.ece.