Citizens for Affordable,
Safe & Effective Medicine
CASEM

To,

June 17, 2020

Under Secretary (Drugs),
Ministry of Health and Family Welfare
Government of India,
414-A, D Wing Nirman Bhavan,
Maulana Azad Road,
New Delhi – 110011.
Email: drugsdiv-mohfw@gov.in

Dear Sir,

SUB: Comments on the draft New Drugs & Clinical Trials (Amendment) Rules, 2020

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). Since the end of my whistle-blower lawsuit against Ranbaxy in 2013, I have been engaged in advocacy aimed at strengthening the drug regulatory framework in India.

2. On behalf of CASEM, I would like to thank you for inviting comments on the proposed New Drugs & Clinical Trial (Amendment) Rules, 2020. However, we must add that a mere 15 days to review the proposed amendments and offer considered comments on this amendment is inadequate. The issue of allowing unapproved experimental drugs to be used for compassionate use is rather complicated from a legal and ethical perspective and the Ministry of Health must not rush the proposed reforms. Despite the challenge of making meaningful submissions within such a short period, we would like to submit our comments on this issue to the Ministry, with the caveat that we reserve our right to make additional comments over the coming weeks.

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3. The use of unapproved experimental drugs outside the setting of a controlled clinical trial has always been a controversial issue from a bioethics perspective. For a long time, drug regulation has revolved around the fact that drugs can be accessed by the general population only after pharmaceutical companies have carried out rigorous clinical trials on potential drug candidates in a controlled setting, in order to generate the required safety and efficacy data that is needed to evaluate the risk-benefit ratio of approving the treatment.. Such rigorous testing was felt necessary after the Thalidomide tragedy which resulted in the birth of babies with severe deformities in the 1960s. Rigorous clinical trials were meant to prevent a repeat of such tragedies. At the same time, it was also felt that since clinical trials take a long time to complete, a new regulatory pathway should be created to provide access to experimental medicine for terminally ill patients who lack any treatment alternatives. Such treatment was usually offered under strict guidance of the prescribing physicians. This gave rise to the 'expanded access' (also called the 'compassionate use') program of the United States Food & Drug Administration (USFDA) in the late 1970s, which has been revised every few years.[1] This program allows patients to access experimental medicine after going through a process that is subject to the rigorous oversight of institutional review boards (IRBs) and the USFDA. More recently, the American Congress has enacted the very controversial Right to Try Act, 2018 which has significantly diluted the USFDA oversight of access to experimental medicine.[2] This legislation has been the subject of heated debate in America with medical associations opposing the new law.[3]

4. In this backdrop, we welcome the government's proposal to put in place a new regulatory framework to allow patients to access experimental, unproven therapies subject to appropriate ethical, clinical and regulatory oversight. We are however skeptical of the capacity of the office of the Drug Controller General of India (DCGI) to execute such a policy transparently and efficiently given the

[1] 'Expanded Access to Investigational Drugs for Treatment Use – Questions and Answers: Guidance for Industry', October 2017 available at https://www.fda.gov/media/85675/download.
[2] Public Law 115-176 can be accessed at https://www.congress.gov/115/bills/s204/BILLS-115s204enr.pdf.
[3] James Hamblin, 'The Disingenuousness of 'Right to Try', *Atlantic* June 2, 2018 *available at* https://www.theatlantic.com/health/archive/2018/06/right-to-try/561770/; Letter from a group of medical associations to the Speaker of the House of Representatives in February 6, 2018 *available at* https://www.asco.org/sites/new-www.asco.org/files/content-files/February-2018-Right-to-Try-Coalition-Letter.pdf.

number of controversies over the grant of drug approvals in India. The 59th report of the Parliamentary Standing Committee on Health and Family Welfare[4] and the subsequent inquiry conducted by the Mahapatra Committee[5] are reminders of how several former DCGIs have illegally and unethically approved drugs for the Indian market which have not been approved by the more experienced regulators in developed countries. This unfortunate history must be kept in mind while creating a new pathway for patients to access unproven experimental drugs. With this background, we propose a list of recommendations which we hope are incorporated into the law.

5. The proposed New Drugs & Clinical Trial (Amendment) Rules, 2020 offer the possibility of two types of licenses to access unproven drugs for compassionate use. The first licence is for the import of an unproven drug by a medical institution. We refer to this as an 'Import Licence'. The second licence is for the manufacture of an unproven drug by a pharmaceutical manufacturer within India. We refer to this as a 'Manufacturer's License'. We will critique each of these licences in the following sections.

6. **The import licence for a medical institution:** As per the proposed amendment, an unapproved drug can be imported into the country for the purpose of treating "life threatening disease or disease causing serious permanent disability or disease requiring therapy for unmet medical needs" if the drug is at Phase III stage of clinical trials in India or any other country, if an application to that effect has been submitted by a medical institution. The application, which has to be certified by the head of the institution, is required to be accompanied by several details which include the medical rationale for use of the drug, criteria for selecting patients for administration of this drug, the method of administration, pharmacology and toxicology data etc. If this application is approved by the Central Licensing Authority (usually the DCGI) the medical institution can import the drug subject to the conditions of the licence. These

[4] 59th Report of the Department Related Parliamentary Standing Committee on Health and Family Welfare on 'The Functioning of the Central Drugs Standard and Control Organisation (CDSCO)' (2012) *available at* http://164.100.47.5/newcommittee/reports/englishcommittees/committee%20on%20health%20and%20family%20welfare/59.pdf;

[5] Prabha Raghavan, "CDSCO faces CIC ire over 'misplaced' 2013 report on 'irregular' approval to drugs', *Indian Express* June 2, 2020 *available at* https://indianexpress.com/article/business/cdsco-faces-cic-ire-after-2013-report-on-irregular-approval-to-drugs-goes-missing-6437906/.

conditions include maintenance of records of usage of the drugs etc. In our opinion, the following are the serious deficiencies with the proposed regulatory framework:

(a) As of now Rule 96A does not require the Ethic Committee of the medical institution to oversee the process of recommending the use of unapproved experimental drugs on patients. In our opinion, the medical institution which is submitting the application to the Central Licensing Authority should be required to have its Ethics Committee (as defined in Rule 7 of the New Drugs & Clinical Trial Rules, 2019) oversee the process by which an application for the compassionate use of drugs is processed by the administration of the medical institution treating the patient in question. We believe this is a very crucial requirement because terminally ill patients or patients with serious conditions are a particularly vulnerable class. It is thus necessary for the State to take special care to protect their interests and guarantee them the highest level of ethical protections. This necessarily requires some amount of external scrutiny from outside the medical institution. An ideal Ethics Committee will usually have such external representation.

(b) Rule 96A is silent on the need for the medical institution to record the informed consent of the patient prior to filing a request on behalf of the patient to import the drug. In our opinion, there should be a requirement for the medical institution to record the informed consent of the patient before administration of the experimental drug on the patient and such records should be maintained for a period of 5 years. Ideally the Rules should prescribe the format and requirements for such an informed consent process.;

(c) The Medical Institution should be under a legal obligation to disclose to its Ethics Committee, the Central Licensing Authority and the Patient, any financial linkages that it (or its staff) may have with the pharmaceutical company supplying the unproven, experimental drugs for compassionate use. Such disclosures should ideally also include the profits/margins being made by the Medical Institution on the sale of such experimental drugs to the patient. This is of particular importance in a country like India where hospitals generally make some profit on the sale of drugs to their patients.

(d) Rule 96B states that the application once submitted must be decided by the Central Licensing Authority which is the DCGI. In our opinion, given the observations of the Parliamentary Standing Committee on Health in its 59th report and the manner in which past DCGIs have abused their discretion, it would be prudent to first refer the Medical Institution's application to a "Subject Expert Committee" for their written opinion on whether the application should in fact be approved This is the process currently being followed for approving new drugs. This written opinion must be published in the *Gazette of India* for public comments (except in the case of emergency) and thereafter the Central Licensing Authority may either accept the decision of the SEC or if he disagrees provide reasons for such disagreement. The final approval or disapproval granted by the Central Licensing Authority should be published in the *Gazette of India* in order to guarantee transparency.

(e) Once the application is allowed, in addition to the existing conditions of the licence mentioned in the draft rules, the Medical Institution should be required to report any adverse events related to the administration of the experimental drug, to both the Central Licensing Authority and the manufacturer of the drug. Currently, there is no such requirement mentioned in Rule 96C. Ideally the Rules should provide a format/timeline for such reporting.

7. **The manufacturing licence issued to the domestic manufacturer:** As per the draft Rule 96D, a new unproven drug may also be manufactured within India if permission is granted by a Central Licensing Authority. For such permission to be granted, the rules require the manufacturer to seek informed consent of the patient seeking such experimental drug on prescription of a doctor.Once such consent is secured from the patient, the Ethics Committee of the medical institution is required to give its approval. The application is then required to be submitted to the Central Licensing Authority along with other information such as the rationale for use, criteria for patient selection, pharmacology and toxicology data etc. The Central Licensing Authority may then allow or reject the application subject to the conditions of the licence which are outlined in Rule 96F. These conditions include maintenance of records of usage of the drugs etc. In our opinion, the following are the serious deficiencies with the proposed regulatory framework:

(a) Our first and foremost concern regarding the process for the issuance of a manufacturing licence for experimental drugs as per Rule 96D, is the complete silence in the rules onthe manner in which the Central Licensing Authority is going to validate the manufacturing process for the new unapproved drug. For example, in the case of approval of the generic versions of already approved drugs, there are well established parameters to judge the quality of the manufacturing process. These parameters include bioequivalence studies and stability testing. However with unproven, experimental drugs, there is usually very little published information to assist the regulator in establishing the quality of the drug manufactured by a pharmaceutical company. Unless the Ministry of Health is able to clarify this point, it may be a prudent policy to allow such applications for manufacture of experimental unproven drugs to be filed only by the pharmaceutical company that is currently manufacturing the drug for the purpose of clinical trials being conducted either in India or in other countries.

(b) Our second concern pertains to the requirement in the rules for the manufacturer to seek informed consent of the patient and approval from an Ethics Committee of the medical institution where the patient is being treated.[6] In our opinion this is a baffling requirement because the informed consent process is usually administered by a medical doctor under the oversight of an Ethics Committee of a medical institution. We do not see how a representative of a pharmaceutical company can be trusted with the ethical administration of an informed consent process when such a representative has a direct financial incentive to ensure sale of the drug. This rule must absolutely be amended to require the prescribing doctor to administer the informed consent process. In our opinion, the application process for the manufacturing licence must focus only on issues of safety, efficacy and the manufacturing process. A Subject Expert Committee (SEC) must be required to opine on the issue of safety and efficacy of the experimental unproven drug, while the Central Licensing Authority can vet the manufacturing process prior to granting any approval. The manufacturer should not have any interaction with the patient.

[6] Rule 96D(2)

8. **Standardising protocols for use of experimental unproven medical drugs at government medical institutions and private medical institutions:** Prior the proposed amendments which are under comment, the New Drugs and Clinical Trial Rules, 2019 already provided a route for import and manufacture of unproven drugs for use by patients in India.[7] However those rules applied only to government medical institutions. The present amendments intend to bring in a regulatory framework for non-governmental medical institutions to achieve the same objective. In our opinion, it makes little sense for the law to create two different regulatory frameworks for patients being treated in governmental medical institutions and non-governmental medical institutions. The patient should be at the centre of any such regulatory process and the law cannot vary depending on the type of medical institution where the treatment is being administered. To this end we recommend an amendment that ensures the same process is followed by all medical institution regardless of whether they are run by the government or the private sector.

9. **Labelling and packaging requirements:** The draft rules are entirely silent on the labelling and packaging requirements for experimental unproven drugs. In our opinion this is a serious omission. It is a common practice in developed countries to mandate special labelling and packaging requirement for experimental unproven drugs. Given the special nature of these experimental unproven drugs, they cannot be labelled and packaged in the same manner as other drugs that have gone through a rigorous clinical trial process. In our opinion the rules under comment should mention special labelling and packaging requirements for experimental, unproven drugs. These requirements should include an explanation that the drug in question is in fact experimental and not clinically proven, its intended dosage, warnings of potential serious adverse events and perhaps results of earlier clinical trials. A special package insert that includes pharmacokinetic, pharmacodynamic and toxicological information should be required to be packaged along with every single dose of the experimental drug. Further, the contact information for the National Pharmacovigilance Cell and an emergency contact for the medical institution where the experimental therapy is being administered should be clearly printed on the packaging.

[7] Rules 86 to 89.

10. **Privacy of patient data:** A critical question on which the draft rules are silent is the question of privacy of patient data. This is an important question given the experience with Janssen and Janssen's donation of Bedaquiline, a new experimental and unproven drug for the treatment of multi-drug resistant tuberculosis. This drug was given for free to hundreds of patients being treated in Indian government hospitals in exchange for the treatment data. A specific data transfer agreement was entered into between the Government of India and Janssen for this purpose.[8] We are unable to confirm whether patients were informed that their information was being shared with a for-profit pharmaceutical company. The draft rules must create a legal framework to protect the privacy of patients in such conditions consistent with the guidelines laid in the Supreme Court judgement on protection of individual privacy.[9]

11. **Compensation for patients:** One particularly prickly issue regarding the use of experimental and unproven drugs is regarding the liability and compensation in case the drug causes unexpected injury to patients. These patients are technically on par with patients enrolled in a clinical trial. The patients in a clinical trial are guaranteed compensation under the New Drugs & Clinical Trial Rules, 2019 in case the drug causes patients any injury. Schedule VII of these rules even lay out a formula to calculate compensation. If patients enrolled in a clinical trial are entitled to compensation, it is but fair for patients receiving a similar drug outside a clinical trial setting to also qualify for compensation in case the experimental unproven drug causes them injury. There is however a danger that such a requirement may scare away companies from providing such experimental drugs for an unmet clinical need unless they are willing to assume the risk because they want to sell their drugs as well as collect data on how the drug is behaving on patients in India. This is a sensitive issue that requires further discussion with all stakeholders.

[8] Prashant Reddy and Balaji Subramaniam, 'RTI Replies Reveal The Deal Between Janssen And The Ministry of Health On Bedaquiline', *SpicyIP*, March 8, 2018 *available here* https://spicyip.com/2018/03/rti-replies-reveal-the-deal-between-janssen-and-the-ministry-of-health-on-bedaquiline-access-and-data-sharing-from-govt-run-clinical-trials.html.

[9] *Puttaswamy* v. *Union of India* 2017 (10) SCALE 1.

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We hope that the Ministry of Health and Family Welfare finds these comments helpful. Please feel free to contact me at dinesh@casemindia.org for any queries.

Regards,

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