Compassionate use (CU) provides an access mechanism to locally unlicensed treatments for patients with serious or life-threatening medical conditions when all available treatment options have been exhausted and enrollment into a clinical trial is not possible. Compassionate use is highly dependent on country regulations, which are evolving globally with varying levels of requirements. For the CU process to be effective and to adequately address patients’ needs, it requires comprehensive regulations and active involvement and collaboration of several stakeholders (requesting physicians, their patients, caregivers, and other health care professionals [HCPs], patient advocacy groups, health authorities [HAs], as well as pharmaceutical companies).1,2

The plurality of CU regulations or nonexistence of such regulations in some countries has resulted in disparity, delay, and lack of patient access to potentially life-saving therapies as well as access inequity across geographies globally.1,3,4 In some countries, the available regulations, though comprehensive, may be too stringent and hinder access for the potential CU population.5,6 Besides the risk of delayed or lack of access, for patients, there is the risk that the local CU framework may not provide adequate safeguards to ensure appropriate use and monitoring of the therapies.

We observed that unlike for clinical trials, a globally harmonized set of standards and principles is not available for CU.7 The adopted clinical trial framework enhances regulatory clarity, facilitates country adoption, and enables local conduct of studies irrespective of the level of regulatory maturity at a country level. As there are no globally agreed CU standards, stakeholders dealing with requests in some countries are faced with operational challenges and in some instances institutional and regional differences in how requests are handled locally. In addition, organizations dealing with CU across multiple countries experience similar challenges.4

Based on Novartis experience (approximately 10 000 CU requests per year) and our review of existing country CU regulations, we observed an association between CU request activity and local regulations. Notably, only a handful of requests were received from countries with no regulations, mostly lower-income and lower-middle income countries.1 The COVID-19 pandemic highlighted the challenging dynamics with accessing unlicensed therapies and vaccines, especially in countries where there were limited to no regulations in place, as in many instances CU was the only possible access mechanism.8

Even in instances in which overarching regional CU frameworks exist, eg, in the EU, individual member states develop and implement their own local regulations and procedures, which have substantial differences in terms of requirements, assessment time, and documentation, as well as in collection and use of data from CU programs.3 The access disparity to investigational antiretrovirals in Europe during the AIDS crisis in the 90s is well documented, largely based on the different local CU regulations and policies, which put patients in some countries at a huge disadvantage.3 In the US, a 2018 report commissioned by the US Food and Drug Administration (FDA) highlighted key pain points across the physician and patient journey in CU, with the absence of standard processes for request submission to the FDA, manufacturers, institutional review boards (IRBs), and payers, flagged as creating confusion for many stakeholders, causing administrative burden, and hindering access.9

Following our assessment of 199 UN states and territories (referred to as “countries”), we identified key regulatory factors, which could address the issues highlighted above and facilitate
patient CU access. We therefore present an 8-factor regulatory framework we deem to be essential at a country level for CU. This framework, developed in collaboration with our external independent Bioethics Advisory Committee,\textsuperscript{10} integrates governance, operational, and ethical factors. The 8 factors are enumerated in the Table. Our assessment is that the presence of all these factors would strengthen the CU process in a country, as it will provide direction to all involved stakeholders, enable faster patient access, and ensure that key ethical standards and adequate patient safeguards are implemented.

The 8 factors we posit here are useful indicators of the robustness of local CU regulations, as higher CU request rates were observed in countries where regulations fulfill most of these factors.\textsuperscript{1} A definition of the roles of involved stakeholders and the requirements for the overall CU request process including evaluation, documentation, and shipment would provide clarity to patients, treating physicians, and other involved stakeholders, potentially reducing the bureaucracy and burden of CU management. The involvement of HAs, ethic committee (EC)/IRB review, and requirements for informed consent would ensure adequate patient safeguards and holistic local oversight, hence mitigating the risks of potential CU misuse or recklessness. Moreover, in addition to already available safety data, safety reporting obligations in CU would further inform the risk and benefit profile of a therapy in a particular patient population for the indication in scope. However, it should be considered to prioritize the reporting of only key safety information in CU to reduce the burden of exhaustive reporting on treating physicians.

While the current pluralistic approach allows for local flexibility, the lack of a globally standardized framework detailing essential factors was observed to impact patient access even in countries with CU regulations. While our proposed 8-factor framework is by no means prescriptive, we would encourage local policy makers to assess their existing regulations against these factors for opportunities to strengthen the regulations in certain areas to better address patient needs. For countries without CU regulations, our framework provides a starting template for the development of their local CU policies, which can then be tailored according to local needs.

In addition to the factors in the Table, the scope of regulations should provide clarity on when and how CU can be provided, ie, access principles and criteria, and consider possible access scenarios (eg, off-label use, emergency use, or pandemic or outbreak use), duration, and access options (eg, individual patient provision or cohort program for a group of patients). Furthermore, comprehensive CU regulations in a country must be made transparently available to the medical community, patients, and HCPs, so that seriously ill patients can more easily access treatment options via this pathway.

### Table. The 8-Factor Framework for CU Regulations

<table>
<thead>
<tr>
<th>Regulatory robustness factor</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>1. Roles of involved stakeholders</td>
<td>To eliminate unnecessary delays in patient access, robust CU regulations will define the roles of the various stakeholders involved (ie, HAs, EC/IRB, HCPs, pharmaceutical companies) throughout the life cycle of a CU request.</td>
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<tr>
<td>2. CU request process</td>
<td>A well-defined and publicly available application process can reduce uncertainties and enable HCPs to easily request CU. Scope and scenarios covered by the regulations, CU access criteria, pathways (ie, individual and cohort access) and duration of access should be outlined.</td>
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<td>3. Involvement of HA in request evaluation</td>
<td>HA involvement in the evaluation of a CU request supports legitimation. HAs can act as facilitators of the process to enable patient access.</td>
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<tr>
<td>4. EC/IRB review</td>
<td>Approval by an EC/IRB should be a requirement for treatments via CU as it ensures that ethical and medical standards are being met and promotes consistent oversight.</td>
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<tr>
<td>5. Informed consent requirements</td>
<td>Obtaining patient informed consent prior to treatment via CU is the treating physician’s responsibility. Informed consent ensures that patients understand all known risks and benefits.</td>
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<tr>
<td>6. Documentation requirements</td>
<td>The outline of the documentation required can help to eliminate delays and enable consistency in processing requests.</td>
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<tr>
<td>7. Drug importation/shipment process</td>
<td>Both geopolitical and logistical considerations play important roles during import and shipment. Well-defined, simplified, and pragmatic processes and requirements would prevent substantial delays and enable speedy product delivery to the patient.</td>
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<tr>
<td>8. AEs/safety reporting requirements</td>
<td>The reporting of AEs and other safety reporting responsibilities for HCPs and pharmaceutical companies is an important factor to be outlined in the regulatory framework. However, this factor should be limited to the reporting of key safety information only to reduce the burden on HCPs.</td>
</tr>
</tbody>
</table>

Abbreviations: AE, adverse event; CU, compassionate use; EC, ethics committee; HA, health authority; HCP, health care professionals; IRB, institutional review board.
We believe that the identified 8 factors could contribute to the enhancement of the development of local CU regulations and strengthen existing ones, to facilitate provision of CU in a safe, responsible, and enabling environment.

**REFERENCES**


