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Classification of Donated Drugs

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Introduction

Reports of "useless" or "inappropriate" drug donations prompted the development of the WHO *Guidelines for Drug Donation.*[1] The second of the WHO *Guidelines* targets the kind of drugs to donate and states that "[a]ll donated drugs or their generic equivalents should be approved for use in the recipient country and appear on its national list of essential drugs or, if a national list is not available, on the WHO Model List of Essential Drugs, unless specifically requested otherwise by the recipient." Guideline No. 2 "is intended to ensure that drug donations comply with national drug policies and essential drugs programs. It aims at maximizing the positive impact of the donation, and prevents the donation of drugs which are unnecessary and/or unknown in the recipient country."[1]

Guideline No. 2 is complex. It contains potentially contradictory recommendations, namely (1) that donated drugs should be listed on the national essential drugs list (EDL) [part I] or the WHO Model List of Essential Drugs (WHO-ML) [part II], however, (2) if specifically requested [part III], then non-EDL and non-WHO-ML drugs may be donated. Guideline No. 2 also raises questions: How is the "positive impact" of a donated drug measured? Under which circumstances does a drug that is not listed on the national EDL have a "positive impact"? Can a drug that is listed on the national EDL lack a "positive impact" and if so, under which circumstances? Who is the recipient who may request drugs, and on what basis should she or he request drugs for donation? The WHO *Guidelines* do not address these questions, nor do they explain the assumption of Guideline No. 2 that donated drugs listed on the national EDL "maximize the positive impact of donations."

In this component of our assessment of pharmaceutical donations, we pursue five objectives related to the three parts of Guideline No. 2. First, we explore the purported rationale underlying the first part of Guideline No. 2 and discuss why donated drugs on a national EDL may have the highest likelihood of a "positive impact." Second, we discuss which donated non-EDL drugs may have a "positive impact." Third, we propose a method to assess the potential "positive impact" of donated drugs and apply the method to drugs donated to the three field study countries. Fourth, we discuss the role of the recipient in the drug donation process. And, fifth, we formulate recommendations for different participants involved in the drug donation process to aid in the selection of drugs for donation.

The premises of our discussion are as follows: As stated in WHO Guideline No. 2, a donated drug should have a "positive impact." However, the WHO *Guidelines* do not define a "positive impact" or indicate how it should be measured. We understand a donated drug's "positive impact" to be the improvements in functioning and well-being of individuals and groups of people that result from the drug's curative, preventive, or symptom and disease ameliorating effects. Functioning and well-being effects of donated drugs are difficult to measure. In the absence of data that directly demonstrate the effects of donated drugs on patients' functioning and well-being, for the purposes of this discussion we assess the therapeutic efficacy of a donated drug as one of multiple intermediate factors that contribute to the drug's potential for a "positive impact." We refer to a potential "positive impact," in quotation marks, to remind ourselves and our readers that we do not know the actual impact of donated drugs on patients' functioning and well-being. We define the recipients of donated drugs as including the clinicians prescribing, dispensing, and possibly administering the drugs.

National EDL Drugs

In this section, we describe the development of the WHO-ML and country-specific EDLs. We then discuss the relationship between a drug's potential for "positive impact" and its EDL status.

Essential drugs lists

The concept of essential drugs originated in the 1970s, amid increasing attention to more equitable distribution of healthcare resources. This concept has since been endorsed unanimously by the World Health As-

sembly.[2,3] *Essential drugs* are "[…] those that satisfy the healthcare needs of the majority of the population; […and that] should therefore be available at all times in adequate amounts and in appropriate dosage forms."[4] WHO provides six criteria for countries selecting essential drugs for their country-specific EDLs.[4] An essential drug should be: (1) used to treat prevalent diseases that can be diagnosed and treated in the local setting; (2) clinically proven to be safe and effective; (3) available in a high-quality form that is stable under the local conditions; (4) the less expensive and available, when two drugs are equal in efficacy, safety, and quality; (5) able to provide a favorable cost/benefit ratio when taking into account a number of factors, including pharmacokinetic properties and storage conditions; and (6) a single compound, unless a combination product has proven advantages over the single compound.

In 1977 WHO published the first version of the WHO-ML to guide individual countries in the development of their essential drugs programs. The list recommended specific drugs for inclusion into a country's national EDL. Since 1977 the Model List has been updated biennially. The current (1995) Model List organizes 304 drugs into 27 therapeutic sections.[4]

Beginning in 1983, WHO designated certain drugs on the Model List as being representative of a set of drugs within a specific therapeutic group. This change in format signified a change in policy. The change acknowledged that several drugs within one pharmacological group might meet the criteria underlying the selection of an essential drug. The WHO-ML does not clearly define the criteria for deciding which drugs within a therapeutic group are acceptable alternatives and does not list acceptable alternatives within each therapeutic group. However, the WHO Expert Committee illustrates,[4] with five examples, that acceptable alternatives are drugs that, while of different chemical structures, are of the same pharmacological group and usually can be expected to have similar therapeutic effect and adverse reaction profiles when administered to patients in therapeutically equivalent doses. For example, several beta-adrenergic blocking agents can be used to treat high blood pressure. The current version of the WHO-ML indicates that atenolol represents a *therapeutic group* of drugs (that is, beta-adrenergic blocking agents) within the antihypertensive drugs of Section 12 (Cardiovascular Drugs). Under the current WHO-ML scheme, any orally administered, beta-adrenergic blocking agent used for the management of hypertension can be considered an acceptable *therapeutic alternative* to atenolol and, therefore, an "essential

drug." Today, eleven such "alternative" beta-adrenergic blocking agents are available in the United States.

As a reflection of the increasing number of therapeutic groups that contain more than one "alternative" drug, revisions of the WHO-ML over the past 15 years have contained increasing numbers of drugs designated as representative of a therapeutic group.[5] The current 1995 version lists 108 distinct drugs as representing a therapeutic group (Appendix 3) and 196 drugs that are considered not subject to acceptable substitution. According to WHO, a country's choice of a specific drug from among all drugs within a therapeutic group "is influenced by the comparative cost and availability of equivalent products."[4]

To date, more than 110 countries have developed EDLs[6] as one component of a national essential drugs program. Among the purposes of such programs are to make essential drugs available, at reasonable cost, to the majority of people in the country and to foster the rational use of drugs. The current study focused on the EDL status of drugs donated to three countries: Armenia, Haiti, and Tanzania.

The Potential for a "Positive Impact"

Much like formulary systems utilized in many hospitals and clinics in the US,[7,8] drug selection guidelines used to create national formularies based on the WHO-ML are intended to take into account the factors that contribute to a "positive impact" of a drug. These include the existing pattern of diseases, characteristics of the treatment facility in which the drug is used, the training and expertise of the health care personnel, genetic and demographic factors of the patients, the drug's pharmacodynamic and pharmacokinetic properties, and the drug's quality, affordability, and continued availability. Ideally, health workers who can represent practicing clinicians collaborate with policymakers to establish and regularly and frequently update a national formulary. The national formulary should list the most effective, safe, and cost-effective medications for the treatment of the majority of the national health problems.

A drug formulary, such as a country's EDL, has many potential advantages for clinicians and patients.[9] A formulary ensures that the therapeutic needs of most people in a specific population are met. The selection of drugs to be included in a formulary is based on objective evaluation of their relative therapeutic merits, safety, and cost. Restricting the number of available drugs makes it easier to educate health workers and the lay public about the use of the medications. Prescribers are more likely to

remember the pharmacodynamic and pharmacokinetic properties of the drugs on the EDL and can prescribe these medications in a safer way than would be possible when faced with a broad, constantly changing drug supply. Health workers and patients can come to recognize the therapeutic and toxic effects of the limited number of drugs on the list. Restriction of available antibiotics, if combined with a surveillance program, may reduce the development of antibiotic resistance. Formularies also help in the continuous procurement and, potentially, the competitive pricing of listed drugs, thus making essential drugs more available and affordable.[10] These factors should improve the potential of positive health outcomes for patients. Of course, a thoughtfully managed national formulary is just one component of a medication system

By definition, drugs listed on a national EDL meet the country's drug selection criteria that take into account the multiple factors listed above. Consequently, donated drugs that are on a country's EDL are expected to have a high probability of having a "positive impact" for a large number of patients.

Those concerned that a formulary may negatively impact the quality of care stress that, to ensure high-quality care, qualified medical staff, pharmacists, and other professionals must be involved in designing and maintaining formularies.[10] They also emphasize that a mechanism be created to allow the prescriber to obtain products outside the formulary system for individual patients, when the prescriber's decision is based on "sound scientific evidence or expert medical judgment."[11]

When donated non-EDL drugs may have a "positive impact"

In this section, we discuss the potential "positive impact" of non-EDL drugs. The country EDLs of Armenia, Haiti, and Tanzania are based on the WHO-ML. Many of the 108 therapeutic groups for which alternatives are considered acceptable in the WHO-ML are represented on the EDLs of these countries (see Appendix 3). However, country EDLs also reflect decisions about cost and availability of individual drugs. For example, a government or healthcare facility may negotiate a lower purchase price with a pharmaceutical seller when agreeing to routinely order large quantities of a single beta-adrenergic blocking agent, instead of purchasing smaller quantities of different such drugs. Therefore, country EDLs usually do not provide for acceptable substitution of a listed drug by an alternative drug.

While important for the negotiation of prices in the procurement of drugs, selection of only one of a group of therapeutically equivalent drugs

may not be necessary from a bargaining perspective for donated drugs. On the other hand, a national policy that denies therapeutic alternatives may significantly decrease the number of donated drugs that are considered having a potential "positive impact" if the country EDL is used as the exclusive list of acceptable donated drugs.

Not being listed on the country EDL does not necessarily mean that a drug does not have a potential to have a "positive impact" in the local setting. For example, the anti-emetic drug promethazine is listed on the EDL for Tanzania. What if prochlorperazine (a therapeutic alternative for promethazine as defined by the WHO-ML) is donated to Tanzania? Restricting donations to only products that appear on the country's EDL would prevent potentially useful therapeutically equivalent drugs from reaching patients in Tanzania at times when the EDL drug is not available. Or, individuals or groups of patients may suffer from less common diseases for which there are no drugs on the country's EDL. The EDL may be out of date, so that patients and clinicians may not have access to more recently developed compounds with improved benefit/risk ratios.

As described by interviewees in Haiti,[11] medications deemed "necessary" by healthcare workers may not be listed on the national EDL. If such drugs are requested and used by clinicians that are familiar with these medications, then the potential risks of donations of non-EDL drugs unknown to clinicians are diminished. Not all non-EDL drugs, however, have a potential "positive impact" in a country. For example, the antimalaria drug chloroquine (listed on the WHO-ML) would be of little use in a country where malaria does not exist. Combination products that are considered of doubtful efficacy in one country are also likely to be of doubtful efficacy elsewhere. Thus, the question arises, "Under what circumstances are donated drugs that are not on a country's EDL likely to have a 'positive impact' in this country?"

A Classification System of Donated Drugs

In this section, we propose and illustrate a classification system for donated drugs based on therapeutic efficacy and apply the system to drugs donated to the three study countries. The resultant categorization of drugs donated to each of the three study countries is used to identify a potential effect of Guideline No. 2 in terms of the number of drug products that would have been donated if the first part of Guideline No. 2 were narrowly applied, restricting drug donations only to EDL drugs. Using the criteria implicit in Guideline No. 2 and the concept of thera-

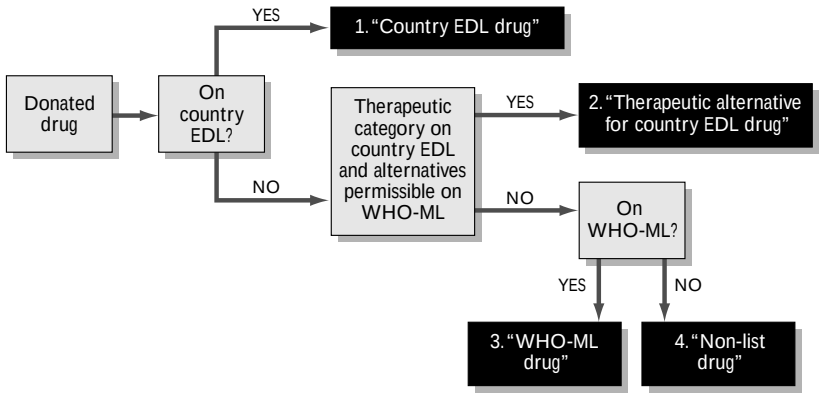
peutic alternatives expressed in the WHO-ML, we propose to arrange donated drugs into the following four descriptive categories (Figure 2.1):

1. *Country EDL drug:* A donated drug that is listed on the recipient country's national EDL.
2. *Therapeutic alternative for country EDL drug:* A donated drug that is not listed on the recipient country's EDL *but* belongs to the same therapeutic group as a drug listed on the national EDL *and* belongs to a therapeutic group for which the WHO-ML allows the use of alternatives.
3. *WHO-ML drug:* A donated drug that is neither listed on the recipient country's EDL nor is a therapeutic alternative for a drug on the country's EDL, but is listed on the WHO-ML.
4. *Non-List drug:* A donated drug that is neither listed on the recipient country's EDL nor is a therapeutic alternative for a drug on the country's EDL, and is NOT listed on the WHO-ML.

The following examples illustrate the four categories.

Example 1. Cimetidine, a histamine$_2$ receptor antagonist, is listed on Haiti's EDL. When cimetidine is donated to Haiti, it is classified as a "Haiti EDL drug."

FIGURE 2.1
Classification of Donated Drugs—I



Example 2. Famotidine, a histamine$_2$ receptor antagonist, was donated to Haiti. Cimetidine is listed on Haiti's EDL *and* cimetidine is listed on the WHO-ML as an example of a therapeutic group (that is, histamine receptor antagonists) for which other drugs of the same group can be substituted. Thus, applying the substitution principle of the WHO-ML to Haiti's EDL, famotidine would be classified as a "therapeutic alternative" for cimetidine.

Example 3. Enalapril, an angiotensin-converting enzyme (ACE) inhibitor for treatment of hypertension, was donated to Haiti. The Haiti EDL does not list any ACE inhibitors. Thus, enalapril is neither a Haiti EDL drug nor a therapeutic alternative for a Haiti EDL drug. However, the ACE inhibitor captopril is listed on the WHO-ML as an example of a therapeutic group for which drugs can be substituted. Therefore, enalapril would be classified as a "WHO-ML drug."

Example 4. Cefixime, an orally administered third-generation cephalosporin, was donated to Haiti. No third-generation cephalosporin is listed on the Haiti EDL; thus, cefixime is neither an EDL drug nor a therapeutic alternative in Haiti. The WHO-ML lists two intravenously administered third-generation cephalosporins for restricted indications but does not indicate that therapeutic alternatives for these drugs are allowed. In addition, cefixime is not available for intravenous administration. Cefixime would therefore be classified as a "non-list drug."

Following the criteria implied in Guideline No. 2, drugs in the four categories differ in the potential of a "positive impact" for patients. *Category 1:* As implied in Guideline No. 2 and discussed above, donated drugs listed on the country EDL have a high probability of having a "positive impact" for patients. *Category 2:* In the absence of EDL drugs, drugs that are considered therapeutically similar to EDL drugs (that is, therapeutic alternatives) are also likely to have a "positive impact" for patients in the country. However, more than the drug is needed when a therapeutic alternative is donated. Clinician and patient education materials need to accompany the therapeutic alternative to realize the potential for a "positive impact," because practitioners may be less familiar with the drug's specific characteristics. *Category 3:* Drugs that are neither listed on the country's EDL nor therapeutically similar to a listed drug, but have met WHO's drug selection criteria and are thus listed on the WHO-ML, may have a "positive impact" in the local setting. *Category 4:* Drugs that have not been evaluated by WHO or those that do not meet all

criteria for inclusion in the WHO-ML also may have a "positive impact." For Categories 3 and 4, contrary to the first two categories, questions about their applicability to local disease patterns and diagnostic and therapeutic capabilities of the recipient clinicians and facility have to be answered before they can be presumed to exert a "positive impact." For Category 4 (non-list drugs), questions about efficacy need to be answered, and for both Categories 3 and 4, education of clinicians and patients about the drugs' use needs to accompany the donation if providers are not familiar with the donated WHO-ML and non-list drugs.

Application of the classification system

We used the above categories to classify donated drugs sent through two private voluntary organizations (PVOs) to the three study countries. Figure 2.2 illustrates the classification results of donations through one PVO to one country, and Table 2.1 summarizes the results for both PVOs and the three countries. Donated drugs are counted as unique drug products. Unique drug products are those that differ in active ingredient, dosage form, and/or strength; drug products that differ in package size, but contain the same ingredient, in the same dosage form and strength, are counted as one unique drug product. Donated drug products are considered listed on the country EDL or WHO-ML if a drug with the same active ingredient, in the same dosage form is listed, regardless of the strength of the drug product. Thus, donated atenolol tablets containing

FIGURE 2.2

Classification of Unique Drug Products Donated Through One PVO

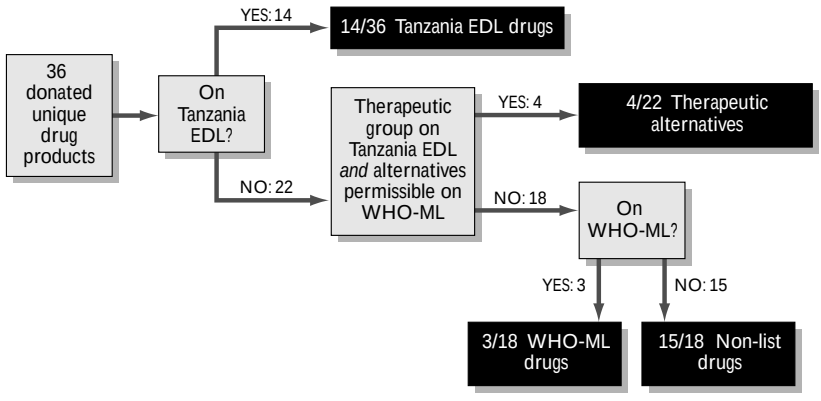


TABLE 2.1

Total Number of Unique Drug Products, and Percentage of Unique Drug Products in Each Category, Shipped to Armenia, Tanzania, and Haiti by Two PVOs

	Armenia		Tanzania		Haiti	
	PVO A	PVO B	PVO A	PVO B	PVO A	PVO B
Unique drug products shipped, *n*	164	20	31	36	230	13
Classification category:						
(1) Country EDL drugs, (%)	46	65	39	39	37	46
(2) Therapeutic alternatives, (%)	28	15	23	11	15	23
(3) WHO-ML drugs, (%)	1	10	6	8	11	15
(4) Non-list drugs, (%)	25	10	32	42	37	15

50 mg of atenolol each would be considered a Tanzania EDL drug, although only the 25 mg and 100 mg atenolol tablets are listed on the Tanzania EDL. Although the numbers of unique drug products in each category are small, percentages of all donated products through the PVO to a country in each category are presented in Table 2.1 to facilitate comparison across countries. (Because the 1995 Armenia EDL does not specify dosage form or strength of listed drug products, drugs in any dosage form or strength were classified as on the Armenia EDL if the active ingredient of the donated drug was listed and the donated drug was indicated for use in the therapeutic category in which the ingredient was listed.)

The proportion of donated drugs on country EDLs (Category 1) ranged from 37 percent (drugs sent by PVO A to Haiti) to 65 percent (drugs sent by PVO B to Armenia). In addition, between 11 and 28 percent of the donated unique drug products were considered therapeutic alternatives for drugs on the respective country EDLs, as described above (Category 2). From 20 percent (drugs sent by PVO B to Armenia) to 50 percent (drugs shipped by PVO B to Tanzania) of donated unique drug products were not listed on the recipient countries' EDLs or therapeutic alternatives (Categories 3 and 4). Most of those drugs were not listed on the WHO-ML (Category 4). In Tanzania, almost half of the non-list (Category 4) drugs (7/10 and 8/15 for PVO A and PVO B, respectively) were either cough and cold preparations or combination vitamin and mineral preparations. In Haiti, one third (26/84, or 31 percent) of the non-list drugs shipped by PVO A were cough and cold preparations.

Any conclusions drawn from these results of the classification of the drug products sent through only two PVOs to three countries, during a limited time period, require great caution, for a number of reasons. First, neither the PVOs, nor the countries, nor the time frames of shipments were randomly chosen from the worldwide donation processes; thus, extrapolation of these results to other PVOs or other countries is not possible. Second, the volume of each unique drug product donated is not considered in this assessment, nor is the time to expiration. For example, a PVO may have shipped a year's supply of EDL drugs to a country and a small amount of non-list drugs, or vice versa. Or, the therapeutic alternatives sent may have had an expiration date on arrival of several years, while EDL drugs had short expiration dates.

These limitations notwithstanding, the results indicate that, if the first part of Guideline No. 2 were followed narrowly, so that only drugs on the country EDL are donated, then between 63 percent (drugs sent by PVO A to Haiti) and 35 percent (drugs sent by PVO B to Armenia) of the two PVOs' unique drug products would not have been shipped to the three countries. In Tanzania, for example, these products included a calcium channel-blocking agent, sulfonamides, and topical steroids, for which similar products are listed on the Tanzania EDL. If therapeutic alternatives for country EDL drugs were considered acceptable within a country-specific adaptation of the first part of WHO Guideline No. 2, then a smaller percentage—between 50 percent (drugs sent by PVO B to Tanzania) and 20 percent (drugs sent by PVO B to Armenia)—would not have been shipped, and the number of donated drug products in accordance with the country-specific adaptation of the first part of Guideline No. 2 would increase to range from 50 to 80 percent. It is important, however, to note that we do not know which of the donated drugs in either category were requested by the "recipients," as provided for in part three of Guideline No. 2.

The role of the recipient

The third part of Guideline No. 2, like hospital formularies in the United States, provides for recipients of donated drugs to override the EDL requirement for a donated drug. We now turn to the potential for a "positive impact" from the recipient's perspective, including the recipient clinician.

While not specified by the WHO *Guidelines*, the "recipient" of donated drugs may be the local PVO, the Ministry of Health, the clinician providing care, or the patient receiving the donated drug. These recipients may differ in their assessment of the potential (and actual, in the case

of the patient) "positive impact" of the donated drug. For example, a Ministry of Health attempting to guarantee continued availability of EDL drugs as part of the development of a long-term essential drugs program may want to restrict drug use to EDL drugs only. Practicing clinicians, on the other hand, who are concerned about individual patients, may want to use a newer non-EDL drug or a therapeutic alternative to treat their patients. Others may perceive the donation of EDL drugs as a threat to the local industry's production of EDL drugs. For financial or public health reasons, authorities may want to restrict the use of certain antibiotics, while clinicians or patients may deem them valuable treatments. The third part of Guideline No. 2 honors recipients' requests. However, because different recipients often have different priorities, the third part of Guideline No. 2 requires interpretation of who is the "recipient" if this part of the guideline is to be implemented.

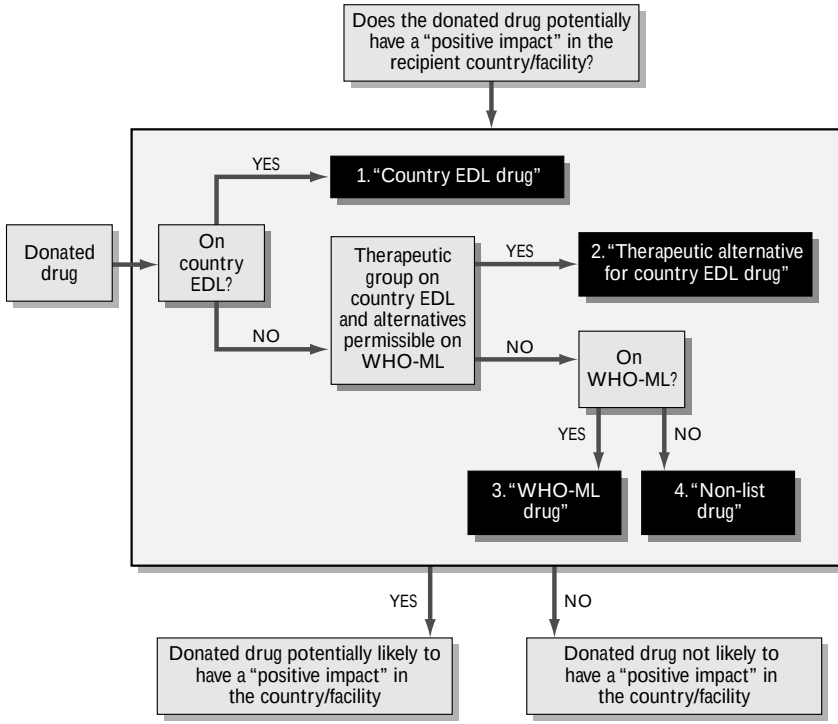
We believe that recipient clinicians must be included in the decisions about the potential "positive impact" of a particular donated drug. From their perspective, EDL and non-EDL drugs may have a potential "positive impact" (as shown in the bottom part of Figure 2.3).

Availability, as well as the safety and efficacy, of a drug for an individual patient are crucial factors in the clinician's decision-making process. Other important factors include expiration date, patient preferences, ease of administration for the patient, dosing frequency, continued supply for the duration of treatment, availability of concomitant medications, if necessary, need for and availability of patient education, and storage requirements.

For the reasons mentioned above, we hypothesize that recipient clinicians will find drugs that are on the national EDL more likely to have a "positive impact" than drugs that are not listed on the national EDL, but this assumption may not always hold true. For example, if country EDL drugs are readily available in sufficient amounts, but non-EDL drugs considered important to treat patients with less common disorders are not available, then recipients may find donated drugs not listed on the national EDL more likely to have a "positive impact" than EDL drugs. For example, captopril (an ACE inhibitor) may be requested by clinicians to treat patients with heart failure, even though an ACE inhibitor is not on the country EDL. In this situation, clinicians may view the potential of a "positive impact" of donated captopril greater than that of available EDL drugs.

The potential "positive impact" of donated therapeutic alternatives is also situation-dependent. For example, cimetidine and famotidine are

FIGURE 2.3
Classification of Donated Drugs—II



therapeutic alternatives for the treatment of duodenal ulcer. However, although they are therapeutic alternatives, different dosages need to be prescribed. Thus, the healthcare worker needs to know the differences between two therapeutic alternatives, which may offset one of the advantages of adherence to a country's EDL—that is, familiarity of clinicians and patients with the listed drugs. Taking into consideration available resources, recipients may decide that the risks of a donated drug outweigh its benefits, and may consider the therapeutic alternative not beneficial in their setting. On the other hand, recipients may decide that use of a therapeutic alternative, with the necessary adjustments, is preferable to having no histamine antagonist available. In this case, recipients may consider donation of the therapeutic alternative famotidine likely to have a positive impact.

Thus, as implied in the third part of Guideline No. 2, the recipient (including the recipient clinician) needs to assess the potential "positive impact" of a donated drug. The classification of donated drugs into four categories may assist this assessment and thereby may assist decisions about the selection and use of donated drugs. Importantly, donated drugs in the four categories require different additional assessments (for example, applicability to local disease patterns for Category 3 and 4 drugs) and provisions (for example, drug information materials for Category 2, 3, and 4 drugs) to facilitate realization of a "positive impact."

Conclusions and Recommendations

As long as drug shortages exist and pharmaceutical companies donate drugs, decisions have to be made about which drugs are donated to whom. Even considering only one criterion, the therapeutic profile of donated drugs, as a proxy for the potential of a "positive impact," the decision about which drugs have the highest potential to achieve a "positive impact" for patients is complex.

We suggest that making explicit the assumptions of Guideline No. 2 and including therapeutic alternatives of EDL drugs as one of the four categories can aid WHO, pharmaceutical companies, PVOs, ministries of health, and local clinicians in the selection of donated drugs in the following ways:

- *Ministries of health* and *clinician*s in recipient countries, with support from *WHO*, could adapt Guideline No. 2 to the specific circumstances of drug utilization in their country and national priorities in drug provision. For example, in a country such as Armenia, where well trained clinicians are available, the country-specific adaptation of Guideline No. 2 may provide for the donation of therapeutic alternatives for national EDL drugs. Adaptations of Guideline No. 2 may also be facility-specific, so that clinicians in a tertiary care facility may include the provision of therapeutic alternatives for certain EDL drugs as well as specified non-EDL drugs in their adaptation. In this case, clinicians could add the requirement for provision of drug information to accompany donation of non-EDL drugs. In a country where most pharmaceutical care is provided by nonmedical caregivers, the ministry of health may decide to exclude therapeutic alternatives and non-EDL drugs from donation.

- As increasingly more alternative drugs within particular therapeutic groups are developed and manufactured, and increasingly more data on the effectiveness of alternative therapies are available, *WHO*, donor *pharmaceutical companies*, and *PVOs* could maintain continuously updated lists of drugs that qualify as therapeutic alternatives for drugs listed on national EDLs.
- *Recipient clinicians* and *ministries of health* could specify the therapeutic groups of drugs for which donated drugs are most needed and could include a description of the level of knowledge and the technical, organizational, and managerial resources present. Via their country- (and maybe facility-) specific adaptation of the WHO *Guidelines*, they need to communicate to *pharmaceutical companies* and *PVOs* for which drugs therapeutic alternatives could be accepted and for which that is not the case. *Pharmaceutical companies* and *PVOs* need to collect from recipients their country- (and maybe facility-) specific adaptations of the Guideline No. 2. This communication process could direct donated drugs to countries (and facilities) where clinicians can best use them.
- *Pharmaceutical companies* need to accompany donated non-EDL drugs (therapeutic alternatives and others) with the necessary clinician and patient education materials to facilitate the drugs' safe and effective use.
- *PVOs* could develop computerized systems that incorporate country EDLs and country-specific guideline adaptations to facilitate management of drug donations according to different requirements for different countries and changing drug availability.
- Because the donation of drugs is not simply a commodity transfer, *ministries of health*, *pharmaceutical companies*, *PVOs*, and *clinicians* need to share in the education of all involved parties about the appropriate use of donated drugs, particularly those that are not listed on a country's EDL.

These recommendations recognize the importance of considering all three parts of Guideline No. 2, and stress the potential negative effects of restricting donations to the first part of Guideline No. 2, especially in situations where recipients can use and rely on the donation of non-EDL drugs. The recommendations emphasize the importance of increased communication about selection of donated drugs, which is expected to increase the likelihood of the (therapeutically) right drug reaching the

right patient at the right time in the right dose and formulation with the right information.

Our recommendations for the selection of donated drugs are based on clinical considerations only. The selection of donated drugs also raises political and ethical questions that we have not addressed. The donation of drugs potentially impacts local industry. How does a country-specific adaptation of Guideline No. 2 affect the local manufacturing of EDL drugs and the long-term provision of EDL drugs in the country independently from donations? Should recipients base the requests for donation of particular drugs on the drug's expected "positive impact" on individual patients or the expected impact on the majority of patients? Further studies should address the impact of drug donations on the local economy and the long-term development of national drug programs, and, importantly, the resulting impact on patients' functioning and well-being.

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