jections for back and joint pain, a procedure that lacks high-quality evidence of efficacy.[4,5] These problems cannot be laid entirely at the feet of compounders when clinicians persist in clinical practices despite weak evidence of efficacy.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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This article was published on November 7, 2012, at NEJM.org.

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DOI: 10.1056/NEJMp1212667

Drug Policy for an Aging Population — The European Medicines Agency's Geriatric Medicines Strategy

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In almost every country, the proportion of people over 60 years of age is growing faster than any other age group, as a result of longer life expectancy and declining fertility rates. In Europe, the median age is already the highest in the world, and in 2050 there are projected to be 88.5 million Americans 65 years old or older — more than double the 40.3 million in the 2010 census.

Although population aging is a mark of the success of public health policies, it also challenges the established way of implementing such policies. In the case of the European Medicines Agency (EMA), it has prompted an analysis of whether the regulatory system is adapted to taking the needs of older people into account in the development, approval, and use of medications.

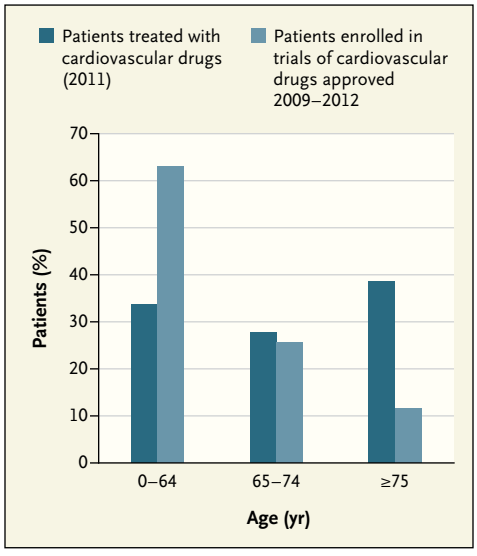
The process started in 2006, when the EMA provided an opinion on the adequacy of guidance on the elderly regarding medicinal products. In 2011, the agency's Committee for Human Medicinal Products adopted the EMA geriatric medicines strategy,[1] marking its commitment to improving our understanding of how best to evaluate the benefit–risk ratio for a medication in older patients.

First, the strategy recognizes that older people are the main users of medications — not a minority or special population (a fundamental difference between the geriatric and pediatric populations). Therefore, legislative and regulatory frameworks must be designed to ensure that the use of newly approved medicines in the intended population is supported by relevant data on the benefit–risk balance. The strategy's second aim is to improve the availability of information to patients and prescribers, to support safer use of medications.

Analysis of the data submitted in support of recent applications for marketing authorization shows that the current regulatory environment has ensured reasonable representation of "younger old" patients, but drug-usage patterns reveal a high prevalence of use in "older old" patients (see graph). Patients who are 75 years old or older often present a complex picture involving coexisting conditions and frailty: they are the fastest-growing demographic group but are largely underrepresented in clinical trials given their disproportionately high actual use of drugs. This imbalance will make it increasingly difficult and potentially inappropriate to extrapolate data to these patients.[2] Though trials are less likely to set unjustified age limits than they were a few decades ago, this improvement must be considered in the context of a rapidly aging population and the continued widespread use of exclusion criteria based on coexisting conditions. Corrective efforts must be maintained to ensure that a representative population of patients covering the entire age range is studied in the preauthorization phase, in accordance with international guidelines.[3]

Chronologic age alone is inadequate for characterizing the population enrolled in a clinical trial. Frailty is a predictor of clinical outcomes,[4] and the reduction of frailty has benefits for individuals and society. The EMA is exploring the possibility of reaching a consensus on an operational definition of frailty and tools for evaluating it that could be used for clinical research and to guide therapeutic decisions.

Medications commonly prescribed to treat other conditions



The Example of Cardiovascular Drugs: Percentages of All Patients in a Given Age Group Treated with Cardiovascular Drugs (Italy) versus Percentages in Each Age Group Included in Cardiovascular Drug Trials (Globally).

Data on all patients treated are for 2011 and come from the Italian census and the Italian ministry of health; data on patients in clinical trials are for drugs approved between 2009 and 2012 and come from the drug-registration dossiers submitted to the EMA during that period.

that occur frequently in patients with the condition under study should be allowed to be used during clinical trials,[5] either in the pivotal phase 3 trials or — if better recruitment results would be expected — in a separate trial. Excessive "confounder cleansing" may result in the study of nonrepresentative populations.

Even when inclusion and exclusion criteria are set adequately, clinicians and ethics review boards often act as gatekeepers in the recruitment process, creating a selection bias by allowing enrollment of only some of the eligible patients. They are particularly likely to exclude the "older old" and patients with coexisting conditions. Again, every effort should be made to gather evidence in these patients during the premarketing period of drug development. Regulatory guidance for these patients is often lacking, and more work is needed to strengthen the guidance on expectations concerning such patients when guidelines are drafted or revised.

The acquisition of relevant data to elucidate the benefit–risk ratio in the target population requires more than merely balancing the absolute numbers of patients. Depending on the drug's profile and the target population, investigators will face a learning curve with regard to acquiring data and modulating risk for patients who might be more susceptible to adverse outcomes, such as frail patients or those taking multiple medications. In designing a strategic plan for drug development, it will be important to engage in a dialogue with regulators to ensure that the needs and requirements of older patients are considered. Investigation of population pharmacokinetics or a specific pharmacokinetic study including the very elderly should be performed and will help inform prescribing. Modeling and simulation can offer powerful tools for quantitatively evaluating differences in pharmacokinetics and pharmacodynamics, recommending dosing regimens, and identifying patients at risk. Some of the lessons learned from the experience in pediatric clinical trials can be applied to the older population; heterogeneity can, in some measure, be allowed and analyzed in clinical-trial design both before and after market authorization.

Depending on patients' frailty and disability status, the desirable outcome and treatment choices might vary: different patients place different values on benefits and risks. Certain adverse events, such as dizziness leading to falls, may be of greater importance in the geriatric population. The design of a clinical trial should consider age-appropriate end points; for older people, functional outcomes may be most important, and an emphasis on such outcomes could lead to reduced costs for health care systems.

Inappropriate formulations and packaging may contribute to low adherence, medication errors, and safety and efficacy problems. Additional considerations for a largely elderly population will include the need for easy administration, possible dose reduction, the effects of visual and motor impairment, and the likelihood of polypharmacy. If appropriate, protocols should be designed for evaluating patients' ability to manage their own medications. Regulators should also look favorably on nondrug technologies such as information and communication technology systems for monitoring adherence or clinical signs.

It's important to provide adequate information to patients and prescribers. That's impossible if there are no good data, but sometimes data included in a drug-development dossier are not adequately reflected in the approval documents. There must be greater focus on the package insert, the regulatory document most widely referred to by the public, which must do a better job of explaining how to take the medication, whether dosage adjustments are advised for older patients, and what is known about use with concomitant medications.

Although we expect the age distribution of patients to be representative in studies presented for marketing authorization, postmarketing studies might also be required to consolidate knowledge regarding higher-risk subpopulations. Regulators should make better use of pharmacovigilance tools

to strengthen the planning of the postauthorization phase and reduce preventable harm.

Once a product is on the market, new safety signals may emerge. Spontaneous reports of adverse reactions can be used to identify patterns of drug–drug and drug–disease interactions that were not apparent before authorization. Collection of data from all possible sources should be optimized, since adverse reactions in elderly populations are generally underreported. The risk-management plan for a drug — based on its risk profile — should be designed to fill knowledge gaps, and targeted measures should be used to minimize risk.

Regulators must ensure that the development and evaluation of drugs take into account global demographic changes, so that safe and effective drugs reach the patients who ultimately use them.

The views expressed in this article are those of the authors and do not necessarily reflect those of the European Medicines Agency or its committees or working parties.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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DOI: 10.1056/NEJMp1209034

Intensive Care in Low-Income Countries — A Critical Need

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Mbarara is a small town in the rural southwest of Uganda, one of the poorest countries in the world. The per capita income in this equatorial East African nation is less than $4 a day, and one third of the population lives below the poverty line.[1] When the Ugandan government and foreign donors recently committed to upgrading Mbarara Hospital's aging infrastructure, the hospital steering committee identified the expansion of the intensive care unit (ICU) as a critical objective.

At first glance, the provision of critical care may not appear to be a rational or cost-effective priority in a country where the annual health care expenditure is just over $100 per person.[1] However, the inadequate basic medical infrastructure, the spectrum of diseases, and the demographic characteristics of Uganda, combined with the broader, less tangible benefits of an ICU, make critical care an essential component of improved health care delivery in such a low-income setting.

The lack of access to early treatment means that many Ugandan patients present in critical condition, with late stages of disease. There is roughly one doctor for every 8500 people in Uganda, as compared with approximately one doctor for every 375 Americans.[1] In Mbarara's catchment area, this scarcity is exacerbated by the rural–urban maldistribution of health care professionals that is common to many countries around the globe. The paucity of community-based general surgeons, for example, has contributed to a situation in which approximately half the surgical operations performed at Mbarara Hospital are urgent or emergency procedures. By comparison, at Massachusetts General Hospital, an acute care referral hospital in Boston, less than 5% of surgical procedures are scheduled on a nonelective basis.

Although diseases faced by Ugandans are usually advanced by the time patients are seen by a clinician, many of these diseases are acute, isolated problems that are possible to cure. The leading causes of premature death in low-income countries include obstetrical complications, traffic accidents, pneumonia, and malaria.[2] By contrast, in wealthier countries, people tend to die of acute exacerbations of chronic conditions such as vascular disease, cancer, or dementia — problems that are less amenable to cure.

Most of the patients admitted to Mbarara Hospital are young — in part because of the high population growth and young age distribution typical of sub-Saharan African populations. Almost half the surgical admissions, for example, are for patients under 30 years of age. Of these young patients, more than one third are children less than 10 years old.

The patient demographic characteristics and patterns of use in Mbarara's two-bed ICU reflect