

## CHAPTER 3

---

### Current issues in drug regulation

Marcus Müllner<sup>1</sup> and Hans-Georg Eichler<sup>2</sup>

<sup>1</sup>AGES PharmMed/Austrian Medicines and Medical Devices Agency, Vienna, Austria

<sup>2</sup>EMA – European Medicines Agency, London, UK

---

The role of drug regulatory agencies is to protect and promote public health. In everyday practice, this broad mandate translates into two distinct objectives: first, into an obligation to protect patients against ineffective or harmful drugs, and second, to protect patients against the consequences of untreated disease. The first objective results in a gatekeeper function and obliges regulators to apply stringent standards of assessment and to deny marketing authorization where deemed necessary. By contrast, the second objective requires regulators to support and enable drug development – with a view to ensuring that patients have access as early as possible to safe and effective drugs.

This chapter summarizes the processes put in place in the European Union (EU) to ensure that regulators can meet these objectives, and briefly describes some of the challenges surrounding drug approval. The technical term in the EU for drugs is “medicinal product” and we will use that term throughout the text.

#### 1 The drug regulators’ decision-making

When approving new medicinal products, regulatory authorities need to be convinced that the (pharmaceutical) *quality* of the product fulfils predefined standards and that *safety* and *efficacy* are in a favourable balance; this is sometimes referred to as “Q–S–E”, or the first three hurdles a new drug has to pass on its route to market. While the issues around adequate product quality appear manageable in most instances, this is often not the case when it comes to large and complex molecules, such as biologicals [1, 2].

---

**Keywords:** European Union, market authorization, human medicinal products, regulatory affairs, centralized procedure, Mutual Recognition Procedure, Decentralized Procedure, risk–benefit assessment, relative effectiveness, pharmacovigilance, signal detection

**Table 1** The regulators dilemma: “Regulators are confronted with a growing number of external needs, stakeholders, and their interests and concerns. All of these factors influence, or seek to influence, the timing of marketing authorization, which determines the time at which patients gain access to new drugs. The conundrum results from the fact that some of these external forces, although often legitimate in their own right, are pointed in different directions and become irreconcilable. HTA health technology assessment.” [3]

Request for shorter timelines with higher level of uncertainty	Need for more or larger studies with delayed market access
<i>Industry</i> Require favourable conditions for innovation <i>Patients and carers</i> Demand early access to potentially lifesaving drugs  <i>Unmet medical needs (examples):</i> Ageing popultions, epidemiology of obesity, diabetes	<i>Payers, prescribers and HTA assessors</i> Request comparative efficacy and effectiveness data <i>Media and the scientific community</i> Demand more thorough safety assessment after repeated market withdrawals  <i>Excess medicalization</i> Obesity, metabolic syndrome, mood disorders

Assessment of safety and efficacy is even more challenging [3]. Considering that no drug is devoid of potential safety issues, the benefits expected from drug treatment have to be weighed against potential harm; this is often referred to as the “benefit-risk balance”. The definition of an acceptable trade-off between safety and efficacy is not straightforward and invariably requires value judgements. Moreover, the balance is a dynamic process and benefit-risk may change as more information about a new medicinal product emerges when it is used in a large population and under everyday conditions (as opposed to clinical trial conditions).

Regulators are therefore finding themselves in a mounting dilemma: the need to balance early market access with the need for comprehensive benefit-risk data (Table 1). Setting the regulatory evidence requirements very high might not only stifle innovation but could also delay or inhibit patients’ access to effective treatment. Pharmaceutical industry and some patient advocacy groups strongly emphasize the point that these are undesirable consequences, particularly in therapeutic areas characterized by a high degree of unmet medical need. On the other hand, lowering the regulatory entry barrier might lead to insufficient knowledge about the benefits and risks of newly authorized medicinal products and thus harm patients. Detrimental consequences could result from unidentified risks or lack of efficacy in real life settings. It is widely assumed that the benefits from a range of medicinal products authorized in developed countries are debatable. It is difficult to predict how the regulators’ dilemma will play itself out in the years ahead.

2 Authorizing a medicinal product in the EU

We have described that quality, safety and efficacy are the main pillars for assessing a medicinal product. Depending on the type of product, each pillar may carry different