Conditional Approval and Approval Under Exceptional Circumstances as Regulatory Instruments for Stimulating Responsible Drug Innovation in Europe

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The need for fast drug innovation and the public demand for risk-free drugs creates a dilemma for regulatory authorities: less restrictive procedures involve uncertainties about benefit/risk profiles of new drugs. The European Union has introduced two instruments that regulate early market access: conditional approvals (CAs) and approvals under exceptional circumstances (ECs). We have studied whether these instruments compromise the safety of new drugs and whether they lead to earlier access to innovative drugs. Our study shows that neither of these regulatory pathways accelerates the approval process for innovative drugs. However, the CA pathway shortens the clinical development period. Approvals under ECs are associated with longer clinical development periods, but this regulatory pathway may open up opportunities for specific drugs to be admitted into the market because less comprehensive data are required. Despite the fact that these advanced approvals are based on limited safety databases, there are no special safety issues associated with using these pathways.

The need for drug innovation and the public demand for risk-free drugs creates a dilemma for regulatory authorities: procedures that are less restrictive may conflict with uncertainty about benefit/risk profiles of new drugs. In the recently published draft "Road Map to 2015," the European Medicines Agency states its objectives as the "promotion and protection of public health … and helping to stimulate innovation."[1] The document acknowledges that the general public has become increasingly risk averse, especially since the withdrawal of Vioxx from the market. At the same time, patients with life-threatening diseases seek early access to new drugs.

In 1993, the European Union introduced an instrument to approve drugs under exceptional circumstances (ECs). Early market access could be granted if an applicant was unable to obtain comprehensive data on safety and efficacy for ethical reasons or because of the rarity of the disease involved.[2] The sponsors, however, were committed to perform further studies to meet "specific obligations" after obtaining marketing approval. Under this regulation, many orphan drugs were initially approved; however, this regulatory pathway has been expanded to include medicines intended for more common indications with a perceived high unmet medical need, such as AIDS.

In the early 2000s, the European Commission wanted to clarify the difference between faster drug approvals for which additional data were required and approvals for which additional data were not expected.[3] They therefore replaced the original EC instrument with two regulatory pathways. First, the approval under ECs, which resembles the original premise of the old EC pathway, is for drugs for which the applicant is unable to provide the European Medicines Agency/Committee for Medicinal Products for Human Use with comprehensive data on efficacy and safety.[4] Second, conditional approvals (CAs) of medicines are authorizations based on less comprehensive data but with demonstrated positive benefit–risk balance and an expectation of more data in the near future.[5] For both pathways, the same postmarketing commitments apply as for standard applications. The new EC pathway attempts to avoid the situation in which drugs have permanent CA status. Drugs can be approved under the CA pathway only if they are intended to fulfill unmet medical needs, i.e., are meant for diseases for which no treatment is currently available

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or if they confer a major therapeutic advantage. The intended use of CA is for (i) seriously debilitating or life-threatening diseases, such as AIDS; (ii) emergency situations; and (iii) medicines designated as orphan drugs. CA is intended to enable early access by the public to promising drugs[6] by abridging the development phase. Speeding up the review process is not a key objective of CA or EC,[7] but a longer review process would contradict the purpose of accelerating access to these drugs. Related to this, an accelerated-assessment procedure was introduced in 2005 that aims at committing both the European Medicines Agency and sponsors to speed the approval process.

Several authors have suggested extending the CA pathway to all new drugs. Ray proposed review and assessment of the viability of the authorization after every step of development.[8] Gale suggests a "provisional registration."[9] The CA concept thereby becomes a continuous dialogue between regulators, developers, medical professionals, and the public that extends to the period after market approval in the form of a continuous benefit/risk assessment. This means that drugs are followed throughout their entire life cycle, making it increasingly possible to fine-tune the labeling ("staggered approval"). It also puts more emphasis on postmarketing research to reveal the real-life performance of drugs.[6]

However, the CA pathway has its critics. Some authors have raised doubts about the quality of this type of approval, especially regarding drug safety, the frequent use of surrogate end points, and difficulties in enforcing compliance with post-authorization commitments.[10]

We studied whether the instruments of CA and approval under ECs compromise the safety of new drugs and whether these instruments do in fact lead to earlier access of innovative drugs to patients. Achieving earlier market access involves shortening the durations of development, approval, and decision

Box 1 Methods

Definitions

- This study focuses on drugs that are granted conditional approval (CA) on the basis of the opinions of the Committee for Medicinal Products for Human Use/European Medicines Agency (CHMP/EMA). Therefore, the drugs that are included in this study are by definition centrally authorized.
- Whether a drug is conditionally approved or approved under exceptional circumstances (ECs) is strictly defined by European Commission regulation and clearly indicated in the European Public Assessment Reports (EPARs).
- The total duration of the approval process is subdivided into: active time (time needed for evaluation by the EMA/CHMP), clock-stop time (time needed for the applicant to answer the questions raised by the EMA/CHMP), and administrative time or EC review time (time between the EMA's final decision and the official decision by the European Commission).

Comparative analysis

- CAs should meet unmet medical needs and therefore, by definition, constitute a therapeutic advance. We therefore compared these drugs with all innovative medicines approved in the same period. In contrast to the US Food and Drug Administration's "priority review" status, the EMA does not have a separate indicator for innovative drugs.
- The indicators that are used to determine whether a drug is innovative are: having priority review status in the United States; being first-in-class according to the Anatomical Therapeutic Chemical Classification System; having obtained CA; having been approved under ECs; having obtained accelerated approval in the United States; and/or being assigned high scores (A or B) in an innovation rating compiled by Motola *et al*. that covers two dimensions: availability of other treatments and therapeutic effect.[16]
- Comparisons are made within several disease areas for which CA and EC have proved to be applicable, such as AIDS and cancer. These comparisons are made because risks and benefits are different for potential life-saving drugs as compared with standard drugs.[17]
- The association between level of innovation (innovative versus noninnovative drugs) and safety-related issues ("Direct Healthcare Professional Communications" and safety withdrawals) is measured using cross-tabulation and Pearson χ^2. From this aspect as well, CA and EC drugs (taken together) were compared with non-CA/EC innovative drugs in general.

Data sources

- Data on brand names, compound names, and status of the drugs (active/withdrawn/refused), along with the names of the market authorization holder and indication area, were obtained from the EPARs, which are accessible from the EMA public website and the European Union Community register of medicinal products for human use. The CHMP press releases were also used to cross-check certain aspects, such as drugs that had been approved under EC or under accelerated assessment.
- Data on active times, clock-stop times, and administrative times were acquired from the EMA annual reports.
- The clinical development duration is calculated as the interval between the start of phase II trials (based on triangulating data taken from company press releases, websites, and annual reports, online clinical trial databases, and scientific literature) and the data of market authorization request (obtained from the EPARs). We chose the start of phase II clinical trials because the CA and EC pathways aim mainly at expediting phases II and III.
- The "Direct Healthcare Professional Communications" were retrieved from the website of the Medicines Evaluation Board in the Netherlands.
- Additional interviews were conducted with experts working in regulatory agencies, companies, and pharmacovigilance centers, and also from patient organizations.

Tools

- Statistical calculations were carried out using Microsoft Excel (descriptive statistics) and SPSS (χ^2-tests).

Exclusions

- Drugs that were filed for approval but were refused approval by the EMA or European Commission were excluded in this study.

making regarding reimbursement. In this article, the focus is on the development and approval processes. The pricing negotiations and reimbursement decisions were not taken into account because they are country specific. We compared drugs authorized by the EC and CA pathways with innovative drugs approved through the normal regulatory procedures (see **Box 1** for details on the methodology). Our analysis provides quantitative and qualitative insights into how these regulatory instruments influence the time needed for development and for approval and the level of drug safety.

RESULTS

Number of registered innovative drugs

In its draft Road Map, the European Medicines Agency states that the CA regulatory pathway has not been used as intended.[6] Thus far, its use has been mainly a process of trial and error by regulators and companies about how to use the CA legislation, leading to a rather low rate of CAs. However, **Figure 1** shows that CA and EC drugs together have become a prominent part of the total number of approvals for innovative drugs (24 of 95 in the period 2006–2009).

Table 1 shows the eight drugs that have obtained CA status. Drugs for seriously debilitating or life-threatening diseases on the list; e.g., nearly all anti-HIV drugs that were approved in the period of study are included (according to European Commission decision 2002/253/EC, AIDS is recognized as an emergency public health threat). However, not all three categories, as defined in the regulation, are included in the list of CA drugs. It remains unclear why orphan drugs and emergency classes are explicitly mentioned as categories, yet most orphan and emergency drugs are classified as having EC instead of CA status. For example, of all drugs approved under the EC pathway since 2006, seven drugs are intended for (pandemic) influenza, and 41% of the EC drugs are orphan drugs.

Duration of development and approval phases of CA and EC drugs

Early market access is an explicit aim of EC and CA regulations. We first compared the duration of the registration process of CAs and ECs with those of innovative drugs that were granted approval through the normal route. We used innovative drugs in our comparison because CA and EC drugs are by definition intended to meet unmet medical needs and are therefore also innovative (**Box 1** illustrates how drugs are designated as innovative). **Figure 2** shows the results. We looked at two time periods and compared

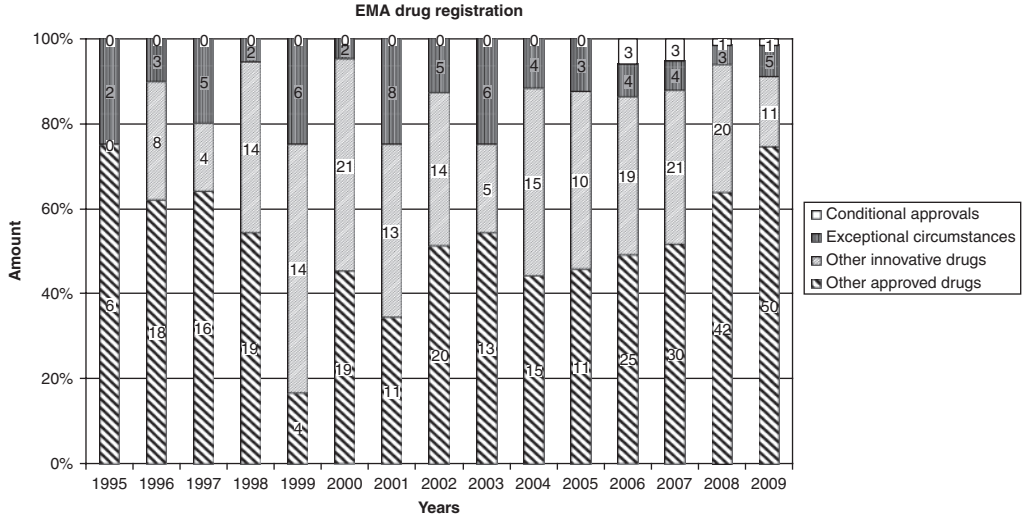

Figure 1 Relative numbers of conditional approval and exceptional circumstance approvals for innovative and other drugs. Absolute amounts are denoted in the bars. EMA, European Medicines Agency.

Table 1 Conditional market authorizations by the European Medicines Agency

Year	Brand name	Compound name	Indication (disease)	Indication extension
2006	Sutent	Sunitinib malate	Cancer	Once
2007	Diacomit	Stiripentol	Severe myoclonic epilepsy in infancy	No
2007	Prezista	Darunavir	HIV	Twice
2007	Vectibix	Panitumumab	Cancer	No
2007	Isentress	Raltegravir	HIV	Once
2008	Tyverb	Lapatinib ditosylate monohydrate	Cancer	No
2008	Intelence	Etravirine	HIV	No
2009	Cayston	Aztreonam	Cystic fibrosis	No

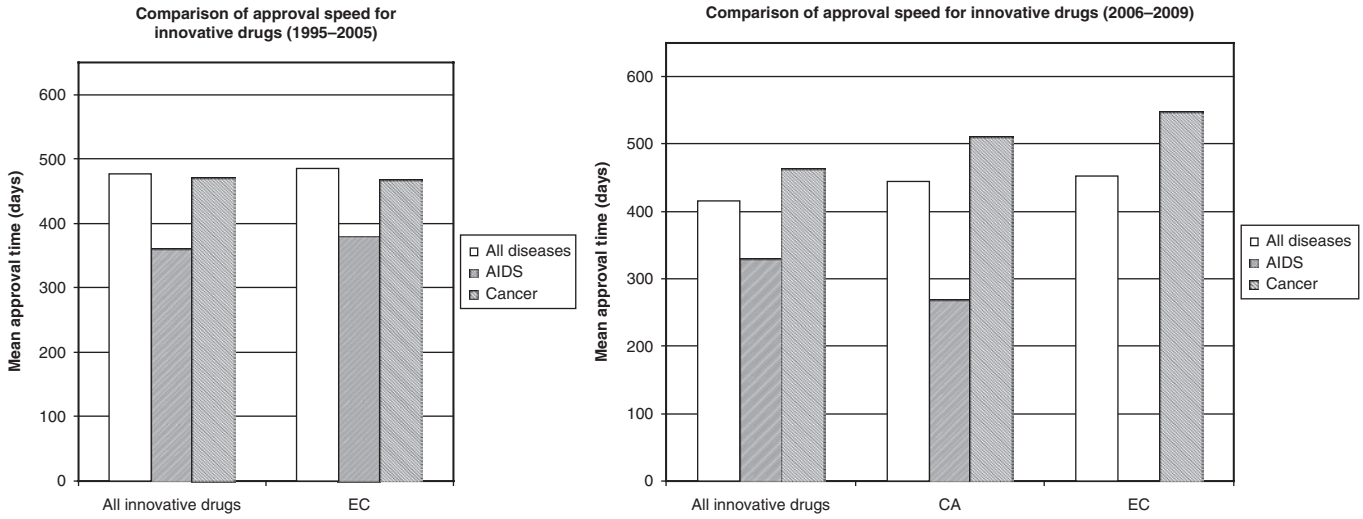

Figure 2 Mean total approval times of all drugs as compared with conditional approval (CA) and exceptional circumstance (EC) drugs (2006-2009) and for EC drugs alone (1995-2005); also differentiated by disease application (all diseases, AIDS, and cancer).

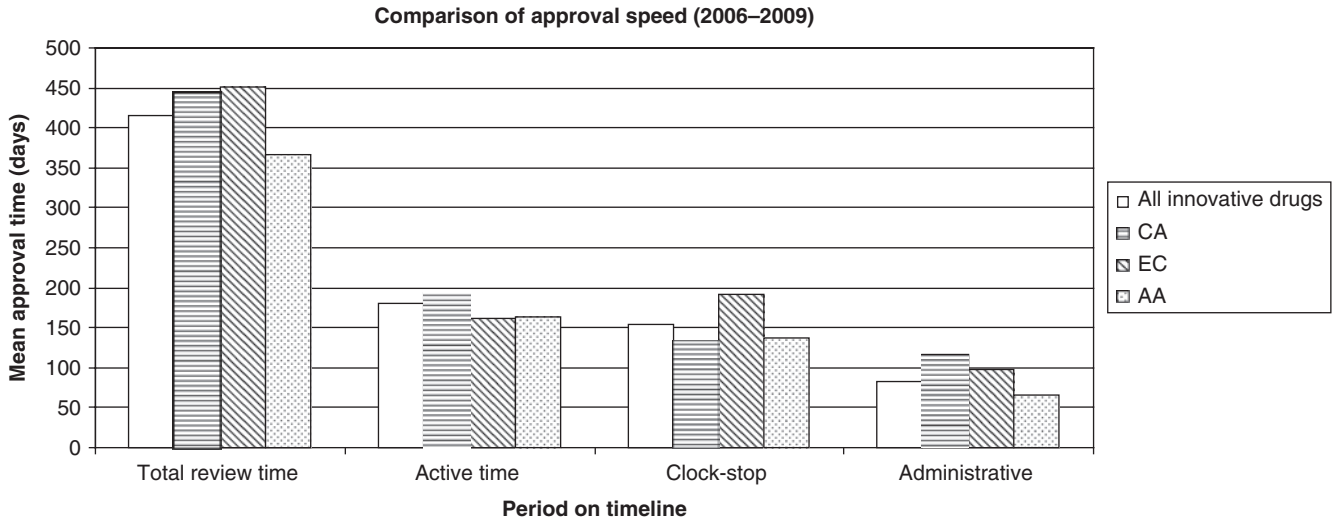

Figure 3 Comparison of durations for different review procedures (all drugs, conditional approval (CA), exceptional circumstance (EC), and accelerated assessment (AA)). European Union regulations stipulate that the active review time is not to exceed 210 days and that the administrative time is not to exceed 90 days.

all CA and CE drugs and those for AIDS and cancer separately because drugs for these two indications were the most numerous among the drugs approved under the CA/EC regulatory pathways. For the period 1995–2005, the mean total approval times for EC drugs for all diseases were comparable to those for all innovative drugs. In the period 2006–2009, the mean total approval times for CA and EC drugs for all diseases were comparable to those for all drugs; this can be explained by the fact that there are no substantial differences in the procedures for approval.

More specifically, the speed of the approval process can be further differentiated by looking at the durations of the various stages of the evaluation (see **Box 1**). This provides more insight into the phases that might be responsible for delays in the review procedure.

The total review times for CA and EC drugs are, on average, a month longer than those for all innovative drugs (see **Figure 3**). For EC drugs, this delay is caused mainly by longer clock-stop periods. This might indicate that the questions posed to the sponsor by the Committee for Medicinal Products for Human Use are more difficult to answer. For CA drugs, the major contributor to longer review times is the administrative period. The drugs approved under the accelerated-assessment procedure show a shorter total review time, indicating the positive influence of the accelerated-assessment procedure on the length of the drug approval period.

Second, we evaluated differences in the time needed for the clinical development phase. **Figure 4** shows that the development phase for innovative HIV and cancer drugs is shorter for the CA regulatory pathway (1,507 days) than for the EC pathway (2,795 days) and for the normal pathway (2,164 days). These findings are consistent with clinical and approval phase durations in the United States in 1990–2006.[11] The figure clearly shows that there is less variation in approval times as compared with the differences in the clinical development phase. These

findings indicate that the CA regulatory pathway accelerates the clinical development period and facilitates earlier access of patients to innovative drugs. Market access through EC is associated with a longer clinical development period. This may be partly attributable to difficulties in recruiting patients and executing clinical trials, which often result in limited clinical data. The EC regulatory pathway is designed mainly to open up opportunities for specific drugs to be admitted into the market on the basis of these confined data sets. For the EC instrument, speeding the process is of secondary importance.

Safety of CA and EC drugs

Does early introduction to the market through EC and CA lead to more safety issues? Olson showed that first-in-class medicines[12] and drugs with faster review[13] are associated with a greater risk of adverse drug reactions. Cancer drugs that obtained accelerated approval by the US Food and Drug Administration did not differ in the number of black-box warnings as compared with cancer drugs approved through the normal regulatory procedure.[14] Giezen and colleagues reported that first-in-class biologicals ran a higher risk of safety-related regulatory action.[15]

Table 2 shows the safety-related issues, expressed in "Direct Healthcare Professional Communications" (DHPCs) and withdrawals, for innovative (including CA and EC drugs) vs. noninnovative drugs.

DHPCs are distributed more often for innovative than for noninnovative drugs ($\chi^2 = 13.3$, $P < 0.001$). Noninnovative drugs are withdrawn from the market more often than innovative drugs are, but this difference is not significant ($\chi^2 = 3.0$, $P = 0.085$). DHPCs are more often written for CA and EC drugs together as compared with innovative drugs in the nonaccelerated approval route ($\chi^2 = 7.6$, $P = 0.006$); however, ICA and EC drugs have fewer withdrawals ($\chi^2 = 4.8$, $P = 0.028$).

One would expect more safety issues with CA and EC drugs because they are allowed on the market with limited clinical data and stricter postmarketing monitoring commitments. However, the number of safety-related withdrawals in these categories is lower than that for other drug categories, and DHPCs are more prevalent. The reasons for this are unclear. One possible explanation is that regulatory authorities are less inclined to withdraw medicines from the market and prefer to send DHPCs for drugs for which there are no alternatives.

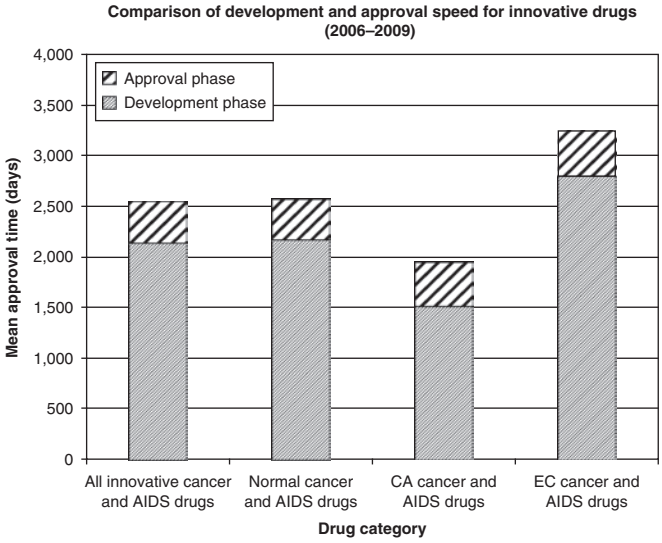

Figure 4 Mean length of development and approval periods for innovative drugs, subdivided into cancer, HIV, conditional approval (CA), and exceptional circumstance (EC) categories for the period 2006–2009.

DISCUSSION

Does early market access compromise the safety of pharmaceutical innovations? This was investigated by focusing on drugs that gained approval under the EC and CA pathways in the European Union. This study shows that 24 of 95 innovative drugs in 2006–2009 were approved as part of the CA or EC procedure. The approval time for the CA and EC categories is not significantly longer (~1 month) than for other innovative drugs. At the same time, the CA procedure abbreviated the clinical development period, thereby leading to earlier market access. The EC pathway prolonged the clinical development period. No special safety issues were demonstrated regarding CA and EC drugs.

This study shows that expedited market access through CAs does not necessarily conflict with the safety of these products. Nevertheless, the application of the CA scheme to a larger spectrum of medicines, as the EMA Road Map has in view, should be carefully considered. First, the process of trial-and-error learning by regulators and companies about how to use the CA legislation has been going on since its introduction. Although experimentation has its advantages, it should not mitigate the intended effects of CA, for instance, by leading to risk-averse behavior or limiting access to drugs. Second, despite the absence of special safety issues for CA drugs, other aspects of the debate remain. For example, the enforcement of compliance with post-authorization commitments is complex because

Table 2 Safety indicators of normal, CA, and EC drugs for 1999–2009

			Approvals for innovative drugs (subdivided)		
	Approvals for noninnovative drugs	Approvals for innovative drugs	Nonaccelerated approvals	CA	EC
Total number of drugs	251	221	163	8	50
DHPCs	14 (5.6%)	35 (15.8%)	23 (14.1%)	1 (12.5%)	11 (22.0%)
Withdrawals	30 (12.0%)	16 (7.2%)	15 (9.2%)	0 (0%)	1 (2.0%)

CA, conditional approval; DHPC, "Direct Healthcare Professional Communication"; EC, exceptional circumstances.

regulatory agencies might be reluctant to withdraw drugs for which no alternatives exist. Instead, these agencies might prefer to distribute DHPCs, and this is supported by our findings. The risk tolerance of society at large and individual patients, medical professionals, and regulators, in the context of serious, life-threatening diseases, is also a factor. Therefore, introducing CA pathways for less serious diseases might demand different ways of risk management and enforcement of compliance. In general, closer examination is needed of risk management as part of the complete life cycle of a drug, including the period that the drug is on the market. This implies governance of postmarketing surveillance systems that act in a dynamic, transparent, and sensitive manner.

METHODS

See **Box 1** for details on the methodology.

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CONFLICT OF INTEREST

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