MEDICINAL PRODUCT EARLY ACCESS PROGRAMS: EXPERIENCE OF THE BRICS GROUP, EUROPEAN UNION, AND UNITED STATES OF AMERICA

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Timely accessibility of effective and safe medicinal products is one of the main tasks of healthcare. The goal of the present review is to assess various approaches that provide an early access to medicinal products within the BRICS group (list of participants as of 01.10.2023), European Union and United States of America. The stage of the life cycle of medicinal products is closely associated with their further movement in the market, patient access rate, and partially with the issues of their financing and reimbursement, which directly influence their affordability for population. The article contains data about the specifics of expanded access to unregistered medicinal products used on a compassionate basis and presenting therapy under early access programs financed by pharmaceutical companies; it also describes approaches to accelerated registration and registration of medicinal products in case of limited clinical data. Experience of the reviewed countries in early access programs is described.

Key words: regulatory approval of drugs, compassionate use, expanded access, expedited access, accelerated expertise, conditional registration, scientific advice, breakthrough therapy, technology transfer

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ПРОГРАММЫ РАННЕГО ДОСТУПА ЛЕКАРСТВЕННЫХ ПРЕПАРАТОВ: ОПЫТ БРИКС, ЕВРОПЕЙСКОГО СОЮЗА, СОЕДИНЕННЫХ ШТАТОВ АМЕРИКИ

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Одной из основных задач здравоохранения является обеспечение своевременной доступности эффективных и безопасных лекарственных препаратов населению. Цель настоящего обзора заключается в оценке различных подходов, обеспечивающих ранний доступ к лекарственным препаратам в странах БРИКС (список участников по состоянию на 01.10.2023), а также в Европейском Союзе и Соединенных Штатах Америки. Данный этап жизненного цикла лекарственных препаратов тесно связан с дальнейшей траекторией их движения на рынке и скоростью доступа пациентам, а также отчасти и с вопросами финансирования и возмещения, которые напрямую определяют их доступность населению. В статье приведена информация об особенностях расширенного доступа для незарегистрированных лекарственных препаратов в рамках сострадательного использования и предоставления терапии в рамках программ раннего доступа, финансируемым фармацевтическими компаниями, а также отображены подходы ускоренной регистрации и регистрации лекарственных препаратов при ограниченных клинических данных. Описаны практики рассматриваемых стран по программам раннего доступа.

Ключевые слова: регистрация лекарственных препаратов, сострадательное использование, расширенный доступ, ускоренный доступ, ускоренная экспертиза, условная регистрация, научное консультирование, прорывная терапия, трансфер технологий

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Population health is a priority of state policy around the globe. Timely provision medicines is a key task of healthcare [1]. Development and launching original medicines to the market is associated with enormous labor, time and resource expenditures. It may take 10–15 years to register a new molecule after its discovery, whereas the costs may vary from 160 million US dollars to 4.56 billion US dollars depending on the therapeutic use and specifics of medicines manufacture [2]. So, many years of medicinal product development and launching will pass before patients are able to use it.

In the global practice, there exist different methods of accelerated access to innovative and specifics of medicines manufacture [2] within the most important nosologies under early access programs. The following directions can be identified here:

1. **Making medicines accessible prior to commercial circulation (expanded access/compassionate use) [3].**
2. **Accelerated access during registration procedures:**
   a. Scientific counseling at different pre-marketing stages of medicines life cycle;
   b. Shorter term of registration procedures;
   c. Mechanisms of registration based on limited clinical data.

The goal of these programs is to provide the necessary therapy to patients, on the one hand, and make the therapy safe and effective, on the other hand. It should be noted that medicines become accessible to population to the necessary extent only following approval for public funding. Today, the issue of access to novel medicines at the national level is mainly raised during post-marketing period. They can also be reviewed to ensure subsequently accelerated implementation of access into clinical practice. The early access measures reviewed in the article constitute the first stage of provision of patients with required medicines.

Within the review, various practices providing a faster access of medicines to the market of Russia and BRICS (Brazil, Russia, India, China, South Africa; an international unity of five countries such as Brazil, Russia, India, China, South Africa), European Union (EU) and United States of America (USA) will be provided.

EXPANDED ACCESS PROGRAMS (COMPASSIONATE USE):

Expanded access, which is also called ‘compassionate use’, makes it possible to use the medicines at different stages of its life cycle. The expanded use programs can provide patients with medicines utilized during clinical studies (CS) or medicines that were assessed as effective and safe during the CS but with pending requests for registration or medicines with pending permission for authorization after the registration was approved. Thus, these programs allow patients to use unregistered medicines, medicines registered prior to approval for commercial circulation and, in some countries, prior to approval for remuneration. Compassionate use programs can be used only in relation to those medicines that can help patients with life-threatening, long-term or severely disabling diseases with no current therapy available or with an unsatisfied medical need [3, 4, 5].

It should be noted that expanded use programs differ from CS mainly by the goal of providing a patient with the required therapy taking into account the unmet medical need. The goal does not involve collection of information related to therapy effectiveness as it is done during a CS. Therapy-related adverse effects should be recorded within the rules of pharmacovigilance, and, in some cases, while providing access medicines under the expanded use programs sponsored by pharmaceutical companies; data related to effectiveness and safety of medicines are additionally collected to ensure its further market promotion [6]. A doctor deals with the primary appointment of medicines to a patient based on a clinical situation, whereas a regulatory body in every country delivers a resolution regarding the possible import of an unregistered drug and its use by a patient. The expanded access program can be initiated by a doctor or a group of doctors or an authorized national regulatory body [3, 4]. Meanwhile, an ethical committee can be involved into taking a decision about the necessary medicines provision under the expanded access program in some countries only (USA, Spain and Italy) [7].

Various expanded access programs depend on the country where they are used and are divided as follows:

- allow the use of unregistered medicines within a certain cohort/group of patients (USA, Germany);
- allow the use among individual patients (BRICS, many countries within the EU, USA).

It should be noted that the expanded access programs are presented within all analyzed countries [3, 8, 9, 10, 11]. For instance, import of unregistered medicines to Russia for patients or a group of patients is possible in the presence of a decision issued by a medical commission and import permit issued by an authorized federal executive agency based on the corresponding application [12]. In India, import of unregistered medicines to treat patients is possible based on the personal application from a patient or a hospital. For instance, the mechanism was implemented to provided patients with resistant tuberculosis with bedaquiline and delamanid [13]. In Brazil, an additional early access program for innovative drugs was introduced. This made it possible to continue previous therapy after CS completion but prior to medicines registration in the country [14, 15, 16].

EXPANDED PROGRAMS

No similar regulatory systems exist for today. However, in the examined countries the expanded procedures often overlap both terminologically (in the name), and by the approaches used. It should be noted that though some names overlap, the programs do not have a semantic identity (fig).

SCIENTIFIC COUNSELING AT DIFFERENT PRE-MARKETING STAGES OF MEDICINES LIFE CYCLE;

As Russian is a member of the Eurasian Economic Union (EEU), scientific and pre-marketing consultations by authorized bodies or expert organizations of member states are set by article 26 of Decision No. 78 as requested by the applicant. Consultations are provided prior to submission of marketing authorization for medicines regarding the issues related to analytical studies, preclinical and clinical studies, aspects of registration procedures, etc. A center of medical technology transfer was created in Russia while implementing the project entitled Human-Oriented Medical Science. Its goal is to assist developers of drug and methods of health protection [17].

Scientific counselling is practiced in Brazil, South Africa, and China by the main authority regulating drug circulation. The goal of consultation with the respective authority is to review and agree upon the application format and discuss technical matters of dossier submission and registration approaches [18, 19, 20].

The USA and EU have the longest review experience in scientific counselling. Scientific counselling is done by the FDA (USA) since 2009 and by EMA (EU) since 1995. Moreover,

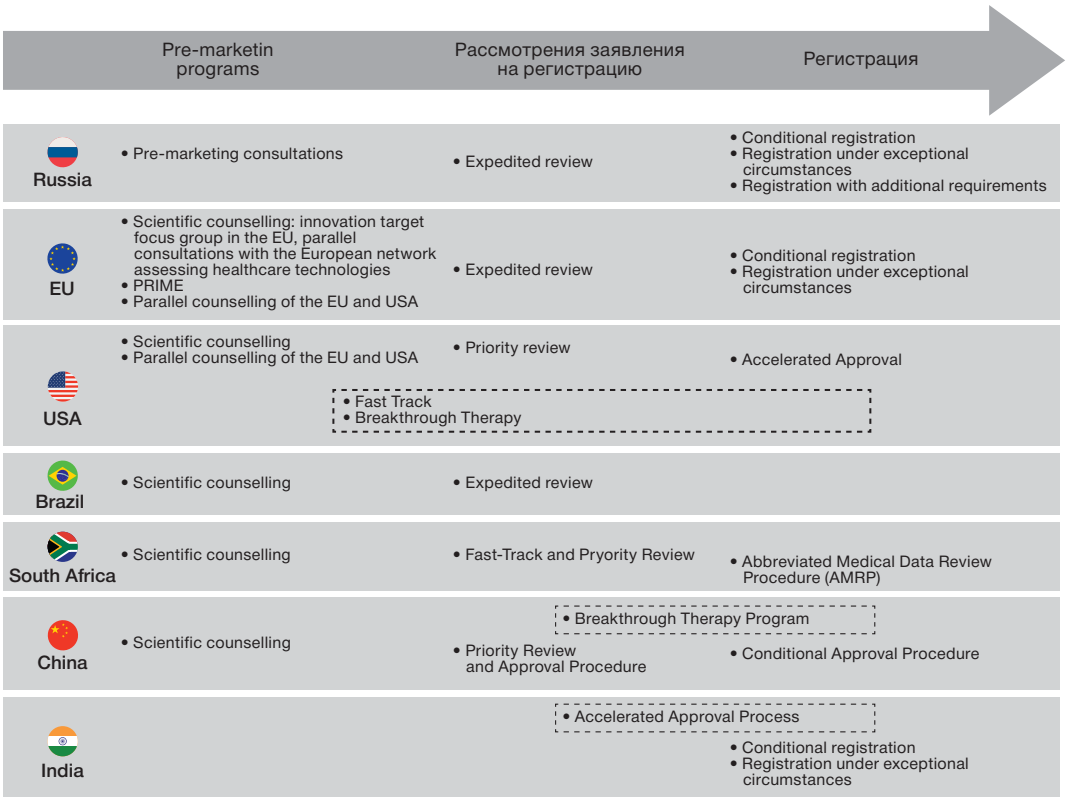

Fig. Accelerated access programs in the BRICS group, European Union (EU), United States of America (USA) (programs combining several approaches are shown with dashed lines)

parallel counselling with two agencies (EMA and FDA) is available since 2006 [21].

FDA practices four types of counselling with certain issues to be discussed during each of it [22].

The Innovation Task Force (ITF) makes it possible to have an informal early dialogue with applicants [23].

Since 2016, the *PRIME* program has been used to support the development of drugs intended for therapy of diseases with no current therapeutic options available. The program allows for extended interaction and early dialogue with developers of perspective drugs to optimize the plans of development and accelerate assessment during registration [24]. The results show that successful conditional registration of 8 drugs under the PRIME program was possible 3.75 years earlier as compared to standard registration [25].

It should also be noted that parallel counselling of EMA and European Network for Health Technology Assessment, (EUnetHTA) have been possible since July 2017. The procedure replaces the scientific counselling by EMA and EUnetHTA when developers of drugs had to refer to European Agencies for Health Technology Assessment on the individual basis. The counselling results are used later to inform of reimbursement of treatment expenses and of price of the approved drug at the national level [26].

PROGRAMS WITH REDUCED INTERVALS OF REGISTRATION PROCEDURES.

Direct reduction of registration intervals is one of the most obvious options that accelerate access of patients to medicines.

In the USA, the option is used in the priority review program *when* the application is reviewed (accelerated check by the FDA of how the application for a new drug is filled in) during 6 months as compared with 10 months while performing a standard examination.

The program, if it is participated, can be completed with the *Fast Track*. The goal of this program is to develop and accelerate the process of registration of drugs to treat serious diseases and intended for use within the area of unsatisfied medical needs.

As soon as the drug is assigned Fast Track, it is possible to use the program preferences such as

1) consultations with the regulating authority (FDA);
2) participation in the program of **accelerated approval** (presented below);
3) reduced interval of registration procedures due to the consistent review and possible participation in the priority review program [27].

In the EU, the program is accessible when the programs of drug registration based on limited data are combined with an accelerated review of drugs during the registration. EMA suggests that very essential drugs should undergo through the accelerated review (150 days). A standard centralized procedure can last for up to 210 days (not taking into account the time intended for submitting additional data by the applicant) [28].

In the BRICS group, the programs of accelerated access are of different types. In Russia, the situation reminds of EU-based approaches. The program is accessible when the drug accelerated review is combined with the programs of drug registration based on limited data. According to Decision No. 78, since 2022 an accelerated expertise can be used during the registration of orphan, pediatric medicines and medicines, which are especially important for the health of the population, with registration in a reference state for no more than 100 working days, which is 40 working days less than in case when standard registration procedures are applied [29].

In Brazil, medicines undergo through the procedure of accelerated approval regulated by resolution RDC 204/2017 for common nosologies (the selection criterion is hard-to-treat

diseases, conditions that occur in the result of urgent situations, neglected tropical diseases, etc.) and resolution RDC 205/2017 for orphan diseases. The period of CS registration can be reduced to 60 days [30, 31].

In India, it's called **an Accelerated Approval Process.** Under the program, medicines have reduced terms of registration and it's possible to use clinically sound surrogate endpoints. The type of data required by the Central Drug Standard Control Organization (CDSCO) to take a decision depends on the stage of medicines development. When the pandemic occurred, several COVID-19 vaccines were registered in the country under the program [32, 33].

In China, they used the **Priority Review and Approval Procedure to accelerate the registration process.** Shorter terms of review allow to reduce the waiting period while filing an application for marketing authorization. The National Medical Products Administration (NMPA) and Center for Drug Evaluation (CDE) [34] belong to the regulating authorities. Medicinal preparations for emergency care, innovative and many other medicines indicated by NMPA can participate in the program [35].

Two similar early access programs (Expedited review process, Fast-Track) and Priority Review are available in South Africa. Their goal is to accelerate the registration of some medicines with an important therapeutic effect. They have to be urgently acquired to solve the basic healthcare problems. Fast-Track is regulated by the Medicines Control Council (MCC). The procedure is valid for the medicines included into Essential Drugs List (EDL) and novel chemical compounds which are essential for national healthcare but are not on the List. Priority Review is regulated by the South African Health Product Regulatory Authority (SAHPRA). It applies to the medicines which replenish a non-satisfied medical need, show a significant therapeutic advantage related to safety and effectiveness as compared to the existing therapy options; medicines to treat conditions and orphan diseases which are life-threatening or cause serious complications; medicines used in case of emergencies in public healthcare and animal health; medicines that constitute a national priority determined by the National Healthcare Ministry.

The target time for consideration of applications issued under the program is 250 calendar days [36, 37]. It should be noted that the average time for consideration of expedited applications approved in 2015, 2016 and 2017 amounted to 1218, 921 and 609 calendar days respectively [36].

Another expedited access program occurring in the USA and China is represented by **Breakthrough Therapy** *in the USA* **and Breakthrough Therapy Drug Procedure (BTD)** *in China*. It accelerates development and review of innovative drugs aimed at the prevention and treatment of serious diseases dangerous for life or diseases significantly influencing the quality of life when no effective options of prevention and therapy are available.

In the USA, both pharmaceutical companies, and the FDA can initiate the program. Under the program, the preliminary clinical data should inform that medicines has significant advantages as compared to the affordable therapy in relation to the clinically significant endpoint (endpoints) [38].

Spesolimab (SPEVIGO) is an example of the drug registered in 2022 under the program. It is used to treat exacerbated generalized pustular psoriasis in adults. It is the first medicines approved for treatment of the nosology [39].

In China, it is required to obtain recommendations from CDE (NMPA) during a CS via a special interaction channel (it reduces possible risks and allows for better understanding of the expectations of a regulating authority); the right of the studied medicines for priority review while filing an application for marketing authorization (significantly reduces the review period reduces the time spent on clinical development and approval of a marketing authorization [35].

Thus, all the countries mentioned herein provide for a shorter registration period under the individual or combined programs for certain groups of medicines.

THE REGISTRATION PROGRAMS BASED ON LIMITED CLINICAL DATA

The next group of programs accelerating access of patients to medicines is aimed at the possible use during registration of somehow limited clinical data on effectiveness and/or safety, and when it is impossible to present them at all (in case of orphan diseases) or due to unfinished CS.

In the USA, the option is provided under the program of **accelerated approval**. The goal is to ensure access of medicines to the market based on surrogate outcomes, which are considered justified regarding the probable benefit for a patient. It makes it possible to accelerate the CS by allowing to complete the trials before severe clinical outcomes occurred. In 2022, the program was used to register adagrasib to treat adult patients with progressing or metastatic non-small cell lung carcinoma in the presence of KRAS G12C mutation. Indication for this medicines was approved based on such outcome-related results as tumour response rate and duration of response. Whether the medicines will be subsequently used depends on the outcomes that confirm the studies [40].

In the EMA, there exist two related programs depending on the possibility to present complete data after medicines registration, — **conditional registration and registration under exceptional circumstances**. The first one is applied when the total volume of data are planned to be presented following registration (for instance, following completion of a CS). The following medicines can be registered [41]:

- medicines intended for treatment, prevention or medical diagnostics of severe debilitating diseases or life-threatening diseases;
- medicines intended to be used in emergency situations that threaten the public health;
- orphan medicines.

Over the 10-year period of the program (2006–2016), 30 marketing authorizations were registered under the conditional registration; 11 of them were standard, 2 were withdrawn for commercial reasons, whereas 17 remained conditional [41].

Just as in case with any medicines, if according to new data the drug benefit outweighs the risk, the EMA can accept the regulatory measures and, for instance, stop or withdraw sale permit[41]. Registration can be terminated based on an applicant's decision (following commercial reasons). Thus, betibeglogene autotemcel (ZYNTEGLO) to treat beta-thalassemia was conditionally registered in 2019. The initial duration of action for conditional registration was 1 year. Later the registration was prolonged for 1 more year in 2020 and 2021. However, in 2022, Bluebird Bio BV notified the European Commission that the permit for its sale is terminated permanently due to commercial reasons [42].

Registration under exceptional circumstances is possible in the following cases:

- Prevalence of therapeutic indication is so low that it is impossible to expect exhaustive data from the applicant;
- no exhaustive data can be presented taking into account the current condition of scientific knowledge;

– collection of data contradicts the general principles of medical ethics.

Thus, registration under exceptional circumstances differs from conditional registration because conditional registration means addition of data as soon as the CS is over and in case of subsequent replacement of conditional registration with standard one, whereas registration under exceptional circumstances doesn't require addition of data [28].

Defibrotide (DEFITELIO) is a medicinal preparation registered under exceptional circumstances and used to treat severe vein occlusion among patients who underwent haematopoietic stem cell transplantation. Though a comparative placebo-controlled study can't be carried out, a company compared it with the historical control when effectiveness of the assumed preparation was proved taking general survival into account [5].

In Russia, supranational law contains the following programs of a similar type:

1) registration of medicines with establishment of additional requirements;
2) registration of medicines under exceptional circumstances;
3) conditional registration of medicines.

Thus, a possible **additional requirement** can include post-marketing studies of drug safety and, if required, a study of various aspects of drug effectiveness, which can't be examined prior to drug marketing.

In Russia, approaches to drug registration **under exceptional circumstances** (applicant as an initiator) and **conditional registration** (applicant or an authorized body (expert company) of a reference state as an initiator) are similar to the principles used in the EU. Health-related benefit associated with immediate registration of all mentioned medicines should outweigh the risks related to the delay of the additional data [29].

Tisagenlecleucel (Kymriah) was the first high-tech medicinal product registered under the program of conditional registration for CAR-T-cell therapy in oncology [43].

In India, **conditional registration** is done under the initiative of the sponsor or applicant. It is also applied to those medicines, which are used with a significant decrease in the rate of adverse reactions that restrict treatment and with an increase of patient compliance, which, as it was expected, could lead to an accelerated achievement of clinically important outcomes. However, orphan drugs should undergo through an accelerated expertise; it is allowed that the results obtained during some (not all) phases of CS can be presented. Further presentation of results of post-marketing studies is an obligatory condition. CDSCO assesses the presented information just like in case with other programs of accelerated registration [32, 44].

Analogous program of medicines registration **under exceptional circumstances** is available in India. It applies to medicines, which are developed to be used under exceptional circumstances. The program is used at the request of a sponsor or an applicant when preclinical data confirm that the preparation is effective, when it is impossible to conduct a CSCT and when there exists a common therapeutic strategy. The approval can be used only once. It can be prolonged only when a detailed report about effectiveness of this intervention was prepared [32].

In China, **the Conditional Approval Procedure** allows to have more frequent meetings with regulatory bodies, reduce the length of submission and obtain approval based on surrogate endpoints or non-comparative studies until the confirmatory testing is completed[45, 46]. medicines can be approved if the studies are completed after medicines entrance to the market if the medicines effectiveness will be shown at early stages [47].

In South Africa, medicines can be registered based on incomplete clinical data when the abbreviated medicine review process is applied. A program limiting the time required to assess the pharmaceutical products registered in the countries with SAHPRA-recognised registering authorities (RAA), for instance, USA (FDA), Canada (Ministry of Health) and other bodies provided that the medicines assessment report is easily available [37].

Thus, the idea of using incomplete clinical data somehow presents in all registration systems and allows to significantly accelerate the process of development of and access to various groups of medicines.

ADDITIONAL PROCEDURES

The procedures developed and used by the states in different emergency situations can be considered as additional activities.

In Russia, these are governmental regulations related to the circulation of medicines, which significantly reduced the period required for medicines to get an access to the market (GR No. 441 and 593). It was necessary to adopt these regulations in connection with the WHO coronavirus pandemic (2020) and introduction of restrictive economic measures against the Russian Federation (2022). The abovementioned regulations make registration, which is carried out by the Ministry of Health of Russia, possible within a term not exceeding 20 working days and 60 working days [48, 49].

In China, **they use the Special Review and Approval Procedure as an additional program**. In case of any public health emergencies, a special review and approval of respective therapeutic and preventive medicinal preparations are carried out based on the NMPA decision. The use of medicines included into a special procedure can be limited in a timely manner taking into account certain requirements for the prevention of and struggle with diseases [35].

In Brazil, when COVID-19 vaccines were launched to the market, the process of the clinical trial application review was reduced from 180 days to 72 hours; the marketing authorization file for the vaccine was reviewed during 60 days instead of 120–360 days [50].

CONCLUSION

Improved and accelerated access to drug-induced therapy plays an important role in treatment of patients with life-threatening diseases and/or diseases that significantly reduce the quality of life. Unregistered medicines can be provided in all countries on the compassionate use basis irrespective of any existing limitations in the development of legal documents. Mechanisms supporting medicines development and registration using the shorter application term and registration based on a limited number of data make it possible to reduce the time prior to approval significantly. Meanwhile, the regulatory bodies use various additional measures to control effectiveness and safety of these medicines. Expedited and/or conditional registration is possible in all the mentioned countries. However, their number, variety and additional requirements for medicines by regulators are mainly determined by the social and economic context of the analyzed countries. The current practice shows that early scientific counseling is essential. It should be implemented both by the regulatory authorities issuing recommendations about the registration of medicines and agencies assessing healthcare technologies for their subsequent implementation into the clinical practice and taking decisions regarding state financing and getting a real access to medicines for patients.

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