

**A comparative study of the different approaches for approval of new
HIV drugs to guidelines of the U.S. Food and Drug Administration
(FDA) and the European Medicines Agency (EMA) including possible
implications on future drug development**

Scientific examination paper

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Abbreviations

ACT	Adaptive Clinical Trial
AIDS	Acquired Immune Deficiency Syndrome
ARV	Antiretroviral drug
ART	Antiretroviral Therapy
CMA	Conditional Marketing Authorization
CT	Clinical Trial
CTA	Clinical Trial Application
EC	European Commission
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FDC	Fixed Dose Combination
GTE	General Treatment Experienced patients
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HTA	Health Technology Assessment
HTE	Heavily Treatment Experienced patients
IND	Investigational New Drug
MAA	Marketing Authorization Application
PAES	Post Authorization Efficacy Study
PASS	Post Authorization Safety Study
PDUFA	Prescription Drug User Fee Act
RCT	Randomized Clinical Trial
SmPC	Summary of Product Characteristics
STR	Single Tablet Regimen
TPP	Target Product Profile
U.S., USA	United States of America
w	week
WHO	World Health Organization

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1 Introduction

The discovery and development of any pharmaceutical drug is both very costly and time-consuming. To the time required for the development of the drug itself and the realization of the required clinical trials must be added the time necessary for approval by the responsible authorities. In general, it takes on average 10 to 15 years from discovery to launching a drug on the market (Paul *et al.* 2014).

The pharmaceutical industry is one of the most regulated in the world. The purpose is to ensure that the developed drugs satisfy patients' needs and are likewise safe for use without unintended side-effects such as those that led to the Thalidomide (Contergan) tragedy of the 1960s. Since then more structured drug regulations have been continuously developed by the authorities, in particular by the United States Food and Drug Administration (U.S. FDA, or FDA below) and in Europe by the respective national authorities. To facilitate coordination among the twenty-eight (as of October 2015) member states of the European Union (EU), each with their own somewhat different procedures, the European Medicines Agency (EMA) was founded in 1995 as an organizational bureau.

Nowadays a company must provide proof of quality, efficacy, and safety of any new drug proposed for commercial release. Companies often describe these three requirements as "the three hurdles". Approval will only be given by the authorities if the benefit-risk balance is positive, i.e. the expected benefits outweigh the possible risks for patients.

In recent years, the European Health Technology Assessment (HTA) bodies have implemented an additional requirement for drug approval: companies must now also supply evidence that the drug developed for a particular disease that was until now treated according to a 'Standard of Care', must also have a so-called 'added benefit'. Germany, in 2011, was one of the last countries to introduce this measure with the Arzneimittelmarktneuordnungsgesetz (Bundesgesetzblatt 2010). The criteria defining the 'additional benefit' does not differ substantially among the European countries. With this approach, the authorities intended to reduce the ever increasing cost pressure and

financial burden on their social security systems. Unfortunately, the consequences of this are further delays to market launch and, hence, later access to drugs for patients.

Launching drugs on the European market is more challenging than on the U.S. market for several reasons. First, the additional benefit must be proved and, additionally, as required by the EMA, the EU member states must come to an agreement for approval, a procedure that is very time-consuming given that it requires communication between the 28 respective responsible national authorities. In contrast, the total U.S. market is supervised only by one authority, the FDA. Since drug approval policies differ fundamentally between the FDA and EMA, market launch is considerably faster in the USA. Hence, the lack of harmonization of legislation between these two important markets contributes to a distortion of competition. It is therefore obvious, that manufacturers face a huge challenge in placing a drug on both markets simultaneously. Not least for this reason, Japan, Europe and the USA launched an initiative in 1992 (the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, ICH) with the main long-term objective of harmonizing the standard drug development and approval process worldwide (ICH 2015).

The conditions influencing the European and American pharmaceutical markets described above force companies to seek new efficient ways for drug development and subsequent approval by simultaneously keeping in mind the needs of patients and their own economic ones. The involved authorities face a similar dilemma: they must ensure the quality, efficacy and safety of a drug in relation to the patient's need while not wishing to retard or even impede the development of new drugs required for patient care. For both parties – pharmaceutical companies and regulatory authorities – this situation is particularly difficult when dealing with chronic and life-threatening diseases such as cancer, Hepatitis B and C (HBV, HCV), Human Immunodeficiency Virus I (HIV) and others. The EMA and FDA have established guidelines for these diseases (European Medicines Agency 2006a [HBV], 2011 [HCV], 2012 [cancer], 2013a [HIV]; Food and Drug Administration 1998 [cancer], 2006 [HBV], 2013a [HCV], 2013b [HIV]), but the conflicts between patients' needs (safety, timely access, affordable price) and the companies' needs (incentives for development and approval) are becoming more intense and tight. Solutions to improve this situation are urgently needed. HIV is a particularly appropriate example of such conflicts since, untreated the virus is usually fatal but also

displays a high rate of resistance to current treatment agents, and some drug combinations may produce fatal adverse events (Wittcop *et al.* 2011). Therefore, urgent medical needs of novel treatment options exist which, to date are not satisfied.

Objective of this thesis

This thesis compares the currently used guidelines of the EMA and FDA (as of 2013) for the development of new HIV drugs. The different underlying policies and the corresponding rules and standards of the EMA and FDA and their impact on drug development are analyzed. The changes for drug approval already in force in the USA and the new adaptive approaches currently being tested by EMA are presented. Their potential to improve the situation for both, patients and companies is discussed.

The most current status of the EMA and FDA guidelines and updates of respective documents considered in this thesis is to July 2015.

2 Different policies for drug development and approval in the European Union and the United States of America

The approaches for drug development and approval differ fundamentally between the EU and the USA. For a better understanding of the detailed analysis in the subsequent chapters, first a short overview of the different policies is given. In Figure 1 the time flow, all parties involved, and their responsibilities and competences regarding drug development, drug approval, and commercialization are visualized.

The FDA controls almost all steps from the very beginning of drug development until the final granting of a claim for marketing which is valid for the entire USA (highlighted in dark green in Figure 1): one country, one authority. The EU actually consists of 28 member states. This implies: 28 national authorities, one coordinator (EMA) and one decision maker, the European Commission (EC). For approval and authorization of clinical trials the National Competent Authorities (NCAs) are responsible (highlighted in light green in Figure 1). This reflects the fragmentation of the EU and the lack of an inner-European harmonization. The EMA becomes involved later when manufacturers submit the documents of the registration package. This must also contain a dossier with the evaluation of quality, safety and efficacy of the drug by the company itself. The subsequent scientific evaluation of the application is done by the Committee for Medicinal Products for Human Use (CHMP, see red text, Figure 1). If the CHMP comes to a positive opinion, the proposal is sent first to the European Commission which grants the marketing authorization for Europe as a whole. Afterwards the launch for individual national markets must be applied to the corresponding national authorities (highlighted in light green in Figure 1). In contrast to Europe, the FDA involves the scientist of the Center of Drug Evaluation and Research (CDER, see red text, Figure 1) from the very first. CDER is accompanying and evaluating the entire developmental procedure until granting of the claim for marketing by FDA. The manufacturer must not supply an own scientific evaluation of the drug. Both, CDER and CHMP are also involved in the evaluation of the post approval studies.

Figure 1 illustrates that the entire procedure takes less time in the USA than in Europe. This is not only due to the fact that less authorities are involved, but also because the

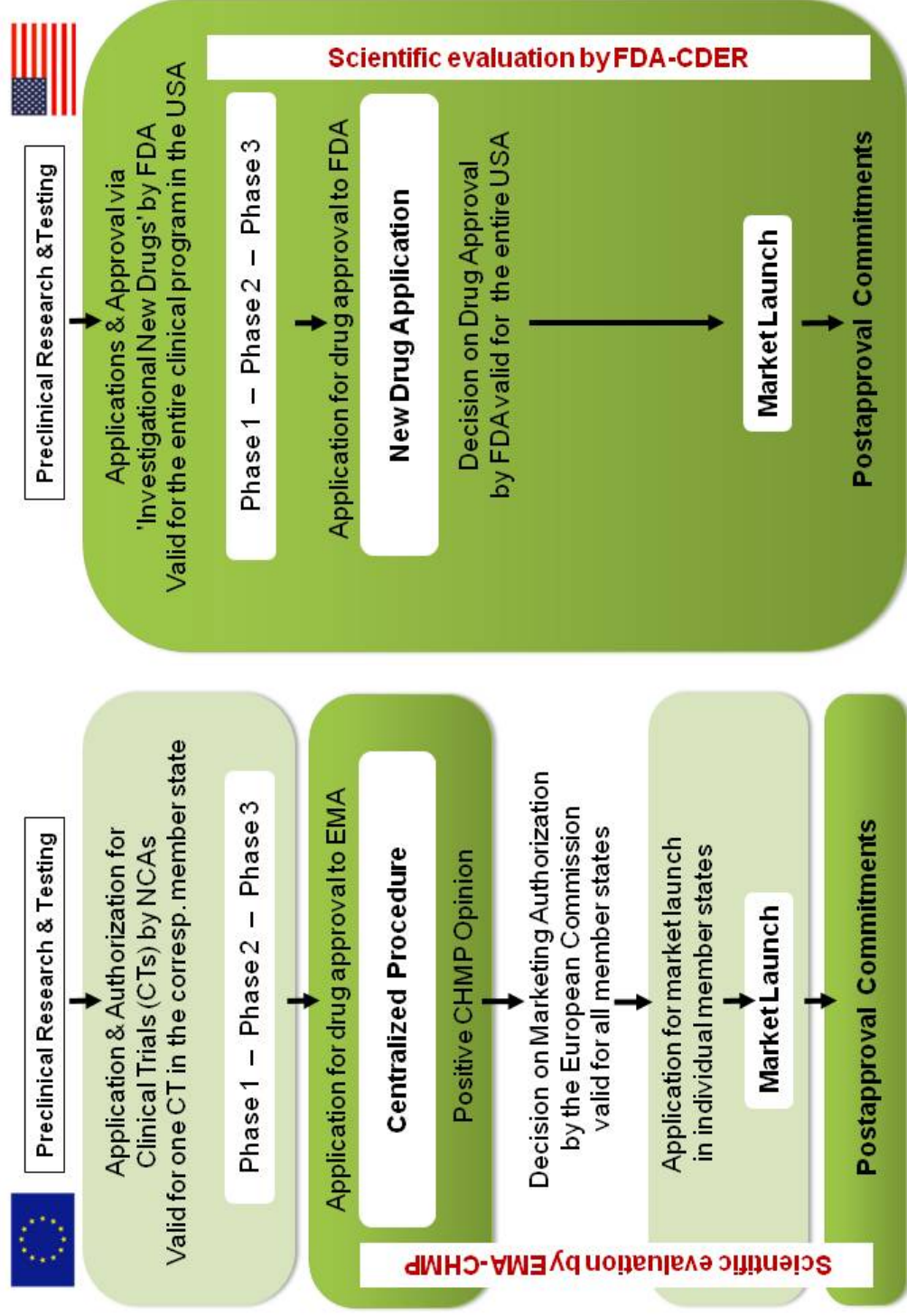


Figure 1: Comparative schematic overview of the drug development, approval and market access procedures in Europe and the USA. Dark green areas: Processes under control of FDA resp. EMA, Light green areas: Under control of national authorities. For details compare text. (EMA = European Medicines Agency, FDA = Federal Drug Administration, NCA = National Competent Authority, CHMP = Committee for Medicinal Products for Human Use, CDER = Center of Drug Evaluation and Research)

management by the FDA is supported by the so-called Target Product Profile (TPP), a document which offers a lot of flexibility for the entire procedure. In contrast, the EMA uses a predefined and rigid tool, the Summary of Product Characteristics (SmPC) which forms part of the registration package and may not be modified without permission of the EC. Both, TPP and SmPC are legal documents serving as guidance to achieve marketing authorization (EU) respective assignation of a market claim (USA). Both tools are analyzed below in more detail.

Summary of Product Characteristics

In September 2009 the European Commission provided "A Guideline on a SmPC" (European Commission 2009) in which the legal character and aims of this tool are specified:

"Article 8(3)(j) of Directive 2001/83/EC and Article 6(1) of Regulation (EC) 726/2004 require that, in order to obtain a marketing authorization, a Summary of Product Characteristics (SmPC) [...] must be included in the application¹. In accordance with Directive 2001/83/EC, when the marketing authorization is issued, the Marketing Authorization Holder shall be informed, by the competent authorities of the Member States concerned, of the SmPC as approved by it. For decisions concerning centralized marketing authorizations, according to Article 10 of Regulation (EC) No 726/2004, the final Commission decision with the SmPC is addressed and notified to the Marketing Authorization Holder. Thus, the SmPC forms an intrinsic and integral part of the marketing authorization.

The SmPC sets out the agreed position of the medicinal product as distilled during the course of the assessment process. As such the content cannot be changed except with the approval of the originating competent authority."

(Source: European Commission 2009, p. 2)

Considering the topic of this thesis it is important to keep in mind, that the SmPC is an obligatory integral part of the marketing authorization procedure and can only be changed with approval of the originating authority. It is a legal contract between the European Commission (EC) and the pharmaceutical company. To accomplish legal changes within this contract is challenging and time-consuming because before the EC

can approve a revision, all corresponding national authorities must be consulted and an agreement must be reached.

Target Product Profile

The TPP is the tool equivalent to SmPC used by the FDA for development and strategic management of new or modified drugs. A template included in the guidance defines the objectives and utilization in detail:

"A TPP is a format for a summary of a drug development program described in terms of labeling concepts. A TPP can be prepared by a sponsor and then shared with the appropriate FDA review staff to facilitate communication regarding a particular drug development program. Submission of a TPP is voluntary.

The purpose of a TPP is to provide a format for discussions between a sponsor and the FDA that can be used throughout the drug development process, from pre-investigational new drug application (pre-IND) or investigational new drug application (IND) phases of drug development through post marketing programs to pursue new indications or other substantial changes in labeling. The TPP embodies the notion of beginning with the goal in mind. That is, the sponsor specifies the labeling concepts that are the goals of the drug development program, documents the specific studies intended to support the labeling concepts, and then uses the TPP to assist in a constructive dialogue with the FDA. The ideal version of what the sponsor would like to claim in labeling guides the design, conduct, and analysis of clinical trials to maximize the efficiency of the development program. Ideally, the final version of the TPP will be similar to the annotated draft labeling submitted with a new drug application (NDA) or biologics license application (BLA)."

(Source: Center for Drug Evaluation and Research 2007a)

With regard to the workflow for the collaboration of the manufacturer and the FDA, Retzios (undated) summed up the most relevant key features more concisely:

"A Target Product Profile (TPP) is a summary of the drug development program described in terms of labeling concepts. It is prepared by the all

departments of the company involved in the development of the therapeutic or diagnostic agents. Its submission to the FDA is voluntary but has specific benefits. The TPP is a "living document" evolving and maturing with increasing knowledge and experience." (Source: Retzios undated.)

The above given definitions of SmPC and TPP reveal that SmPC is a document with predefined requirements focusing on the proof of quality, effectiveness, and safety (risk-benefit profile); it cannot be changed legally fast and easily due to its full integration into the established drug approval procedure of the EU. Therefore, it is an inflexible tool which does not support a fast and target-orientated drug development and approval. This situation is in particular disadvantageous and harmful for patients with high unmet medical needs as is the case for chronic diseases such as HIV.

In contrast, TPP can be considered as a target-orientated format as a base for discussions between all parties, departments, and authorities involved in drug development and approval. It is not legally binding and can be changed and adapted to new knowledge and data emerging during the drug development process; it reflects the complete life cycle of a drug but is not part of the registrational package and must not be approved by the FDA. Because of this feature it is a very flexible tool which can be considered rather as a workflow or business plan than an obligatory and fixed *modus operandi* which must be strictly followed. Figure 2 illustrates at which step of drug development and subsequent approval SmPC and TPP are embedded into the workflow.

The profound differences between the SmPC and the TPP have crucial impacts on the approach for drug development and the regulatory approval process for novel HIV agents. They will be elucidated in detail in Chapter 3 which addresses the medical, economical and regulatory aspects with special emphasis on the development of new HIV drugs.

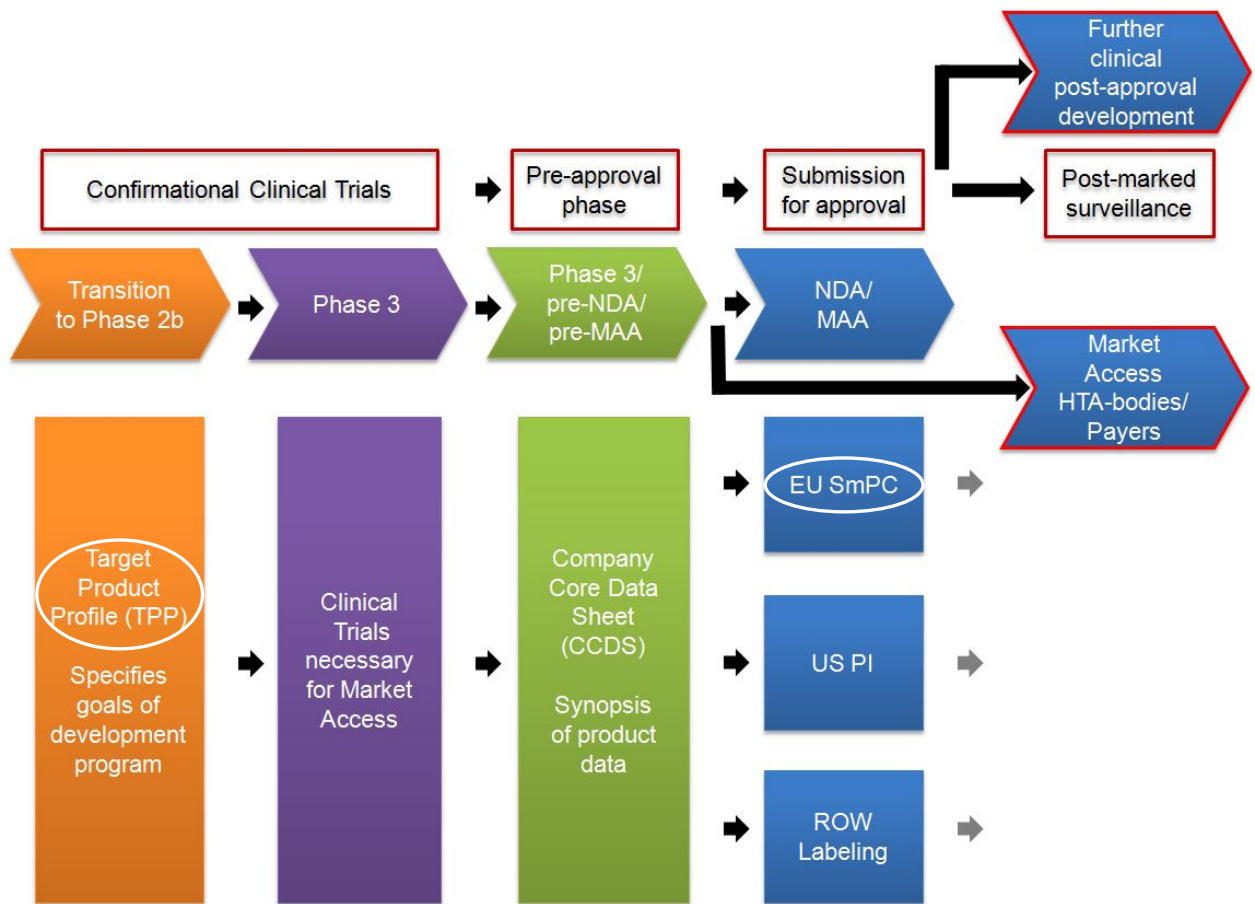


Figure 2: Comparison of drug development according to the TPP (USA) and the SmPC EU (modified acc. to Jennings 2015).

(NDA = New Drug Application, MAA = Marketing Authorization Application, EU SmPC = European Union Summary of Product Characteristics, US PI = United States Product information, ROW Labeling = Rest Of World Labeling; HTA = Health Technology Assessment)

3 Challenges and hurdles for development of new HIV drugs

3.1 Medical aspects

The human immunodeficiency virus (HIV) is a retrovirus that infects cells of the immune system, destroying or impairing their function. The number of cells carrying the CD4 (cluster of differentiation 4) receptor is a measure for the progression of the disease (U.S. Department of Health & Human Services 2015a). Infected individuals gradually become immunodeficient and more susceptible to opportunistic infections (Center for Disease Control and Prevention 2015). For more medical information the Factsheet No. 360 of WHO can be consulted (WHO 2015). The most advanced stage of HIV infection is the acquired immunodeficiency syndrome (AIDS), which was first described in 1981 as a clinical entity. It can take 10 to 15 years for a HIV-infected person to develop AIDS (Hoffmann 2014, Page 7, Figure 1).

Prevalence of HIV infections

Since the beginning of the epidemic, almost 78 million people have been infected with HIV and about 39 million people have died. Globally, at the end of 2013 approx. 35 million people were living with HIV, thereof more than 1.4 million in the USA and approx. 900.000 in Western Europe. Sub-Saharan Africa remains the most severely affected, with almost 1 of 20 adults infected and accounting for approx. 71 % of all HIV-carriers. Worldwide an estimated 0.8 % of adults (15 – 49 years) are infected (WHO 2013; compare Figure 3). The anticipated prevalence will continue to grow at a slow, steady rate (UNAIDS 2015).

Necessity for new antiretroviral drugs and therapies

At the end of 2014 approx. 14.9 million – thereof 823.000 children – of the infected persons received antiretroviral therapy (ART; WHO 2015). With introduction of ART the AIDS mortality declined markedly (Palella *et al.* 1998). As a consequence the number of carriers surviving has increased worldwide, and HIV infection is now considered a chronic disease requiring life-long therapy (Deeks *et al.* 2013).

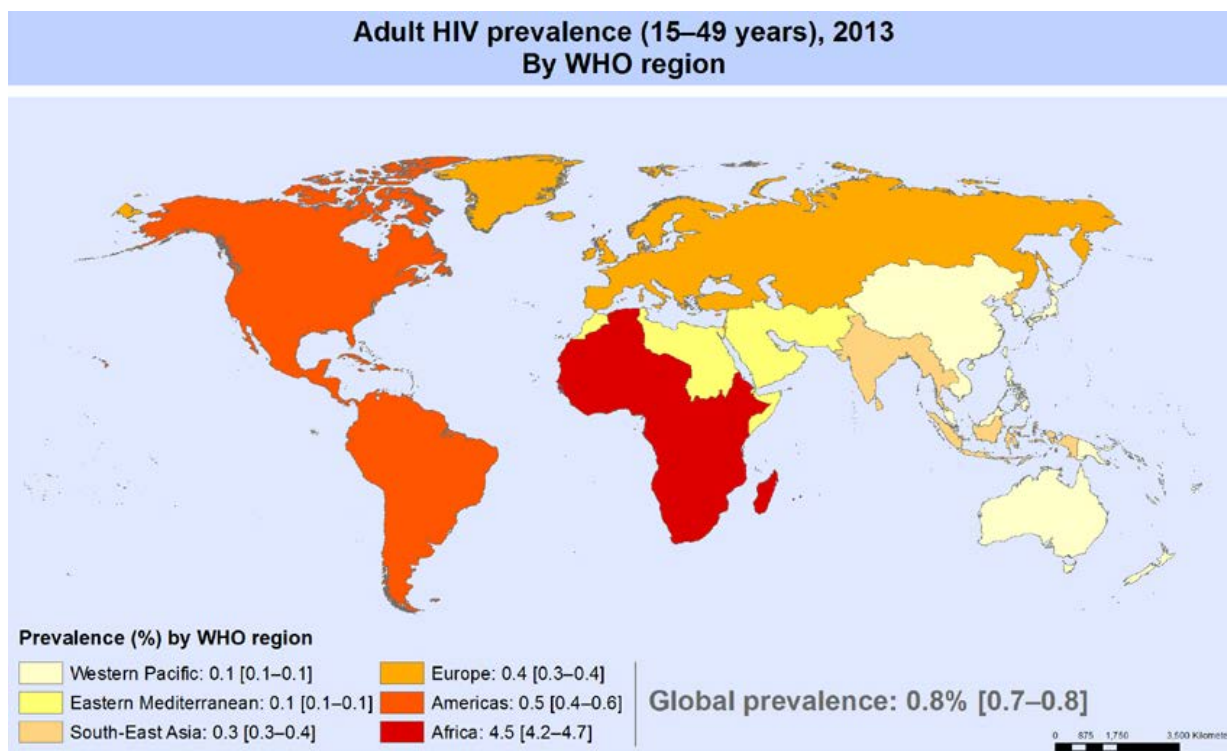
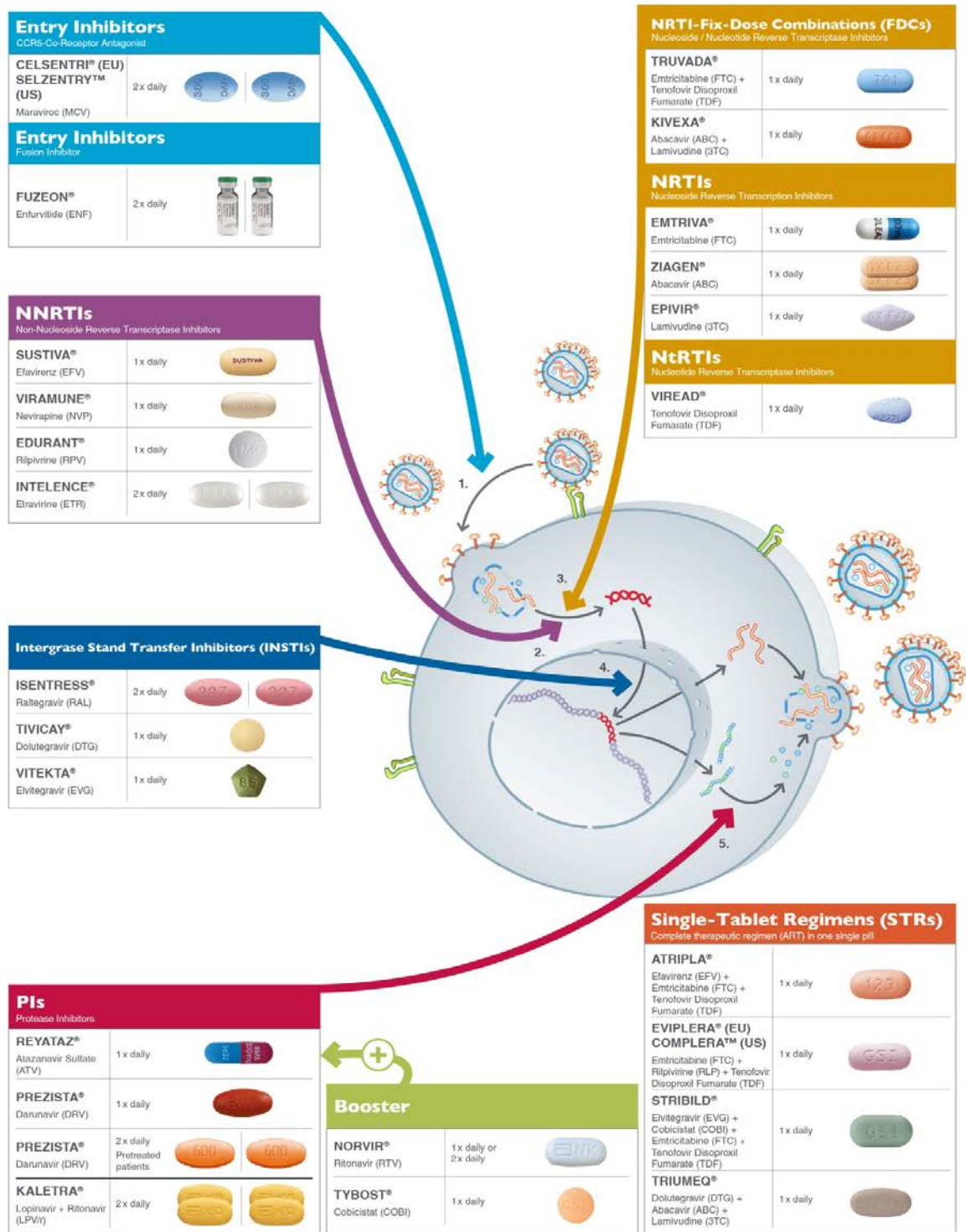


Figure 3: HIV prevalence amongst adults (15 - 49 years) in 2013 by WHO region.
(Source: WHO 2013)

The classification system of the substance classes used may differ slightly. According to the National Institute of Allergy and Infectious Diseases (2013) five classes of antiretroviral substances are currently used:

- Reverse Transcriptase Inhibitors
 - a) Nucleoside (Nucleotide) Reverse Transcriptase Inhibitors (N(t)RTIs)
 - b) Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs),
- Protease Inhibitors (PIs), usually used with boosters (e.g. RTV, COBI)
- Integrase Inhibitors,
- Entry Inhibitors, and
- Fusion inhibitors.

Figure 4 illustrates the point of attacks of the different substance classes within the virus's life-cycle and the brand names of the most commonly used drugs. More than 27 drugs and additional Fixed Dose Combinations (FDCs) and Single Tablet Regimens (STRs) are licensed currently in the USA (U.S. Department of Health and Human Services 2015b). All antiretroviral drugs licensed in the EU can be seen on the EMA website (European Medicines Agency 2015a). They provide a variety of treatment options with current standard combinations that include at least 3 active agents to



For more information please refer to the appendix. Only selected HIV treatment options are displayed. For more information about the products please refer to the summary of product characteristics (SmPC) at <http://www.ema.europa.eu/ema>

Figure 4: The poster shows the current substance classes, the point of attacks within the virus's life-cycle, the treatment regimens, and the brand names of the most commonly used HIV drugs.

control viraemia to undetectable levels (≤ 20 -50 virus copies/ml blood; U.S. Department of Health & Human Services 2015c). Transmission of antiretroviral drug-resistant viruses to as yet not infected persons has been documented with a prevalence of 5 % to 25 % in for the first time diagnosed patients (James *et al.* 2009, Simen *et al.* 2009, Little *et al.* 2005). Furthermore, it has been estimated that despite therapy, viraemia persists in approx. 63 % of patients receiving combination therapy: they displayed viral loads > 500 virus copies/mL (Oette *et al.* 2006) because of viral heterogeneity, drug resistance, drug-associated toxicity, poor adherence, secondary side effects, and complicated drug regimens. Hence, despite the number of agents currently available and different regimens applied, a high necessity exists for new classes of antiretroviral drugs to satisfy unmet medical needs, such as improving tolerability, treatment, adherence, addressing and preventing comorbidities, and long-term safety issues. For patients for whom previous drug classes failed, novel mechanisms of action for use in highly active antiretroviral therapy are desirable (Montaner 2003, Jain *et al.* 2006). The last new "first in class" entry (i.e. first type of drug of its kind) was the integrase inhibitor Raltegravir in 2008 (European Medicines Agency 2015a). Since then, only additional "second in class" entries (e.g. Tivicay), Fixed Dose Combinations (FDCs) and Single Tablet Regimens (STRs) have been developed. Manufacturers are trying to optimize the drug formulations to reduce toxicity and intolerance as well as to improve the bioavailability of active agents.

3.2 Economical aspects

Costs of drug discovery and development are extremely high and in order to stay competitive a company must develop a drug as time- and cost-efficiently as possible. Additionally, for chronic and life-threatening diseases the newly developed drug must compete with already available ones on the market. Cost estimations for research and development and subsequent registration range from approx. \$ 500 million to \$ 2 billion USD (Adams *et al.* 2006). This is more than fivefold of the costs in the 1970s and twice as much as in the 1980s. The increase is mostly due to the gradually increasing costs of clinical testing, which grew fivefold faster than the preclinical testing costs. The highest costs are generated in the late clinical development phases with focus on confirmatory

Phases 2b and 3. Figure 5 elucidates the relationship between the cost of research and development and the number of compounds investigated. From originally 5,000 to 10,000 sometimes even up to 30.000 active substances under investigation only one active ingredient will be approved. A traditional clinical development plan is paved by high drop-out rates of potential new agents (see Figure 6). Only 18 % of potential new substances under investigation make it to the end of preclinical development and only 14 % from these will obtain authorization. The highest losses of new agents take place in Phase 2 and 3. The most expensive part for development are the clinical trials with 57,6 %, thereof Phase 3 accounts for 36,7 % of the budget (see Figure 7). Because of this economical importance it is understandably that manufacturers pay special attention to Phase 2 and 3.

Analysis of the HIV market

The EMA and FDA guidelines use different criteria and terms to distinguish between patient populations with different medical needs and the corresponding clinical drug development options. Therefore, companies elaborated a proprietary classification system based on market analysis and suggestions of advisory boards for the disease in question. The terms used as description for the characteristics of patient populations in this thesis and explicit in Figure 8 are an example for widely used criteria.

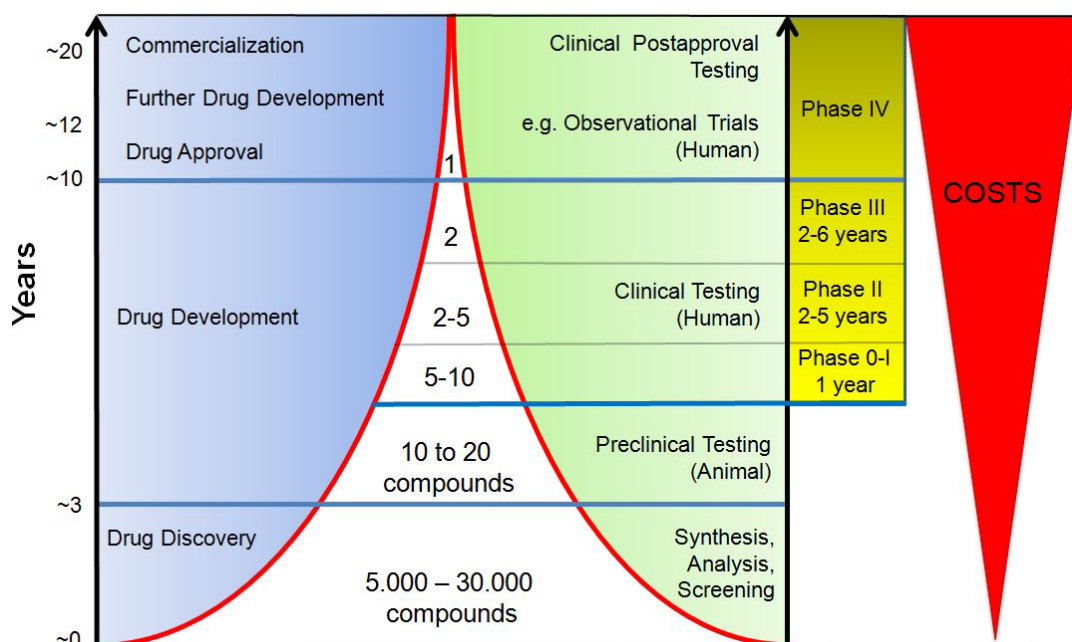


Figure 5: Schematic overview of the relationship between the numbers of compounds screened and costs; numerical data taken from Paul *et al.* 2010).

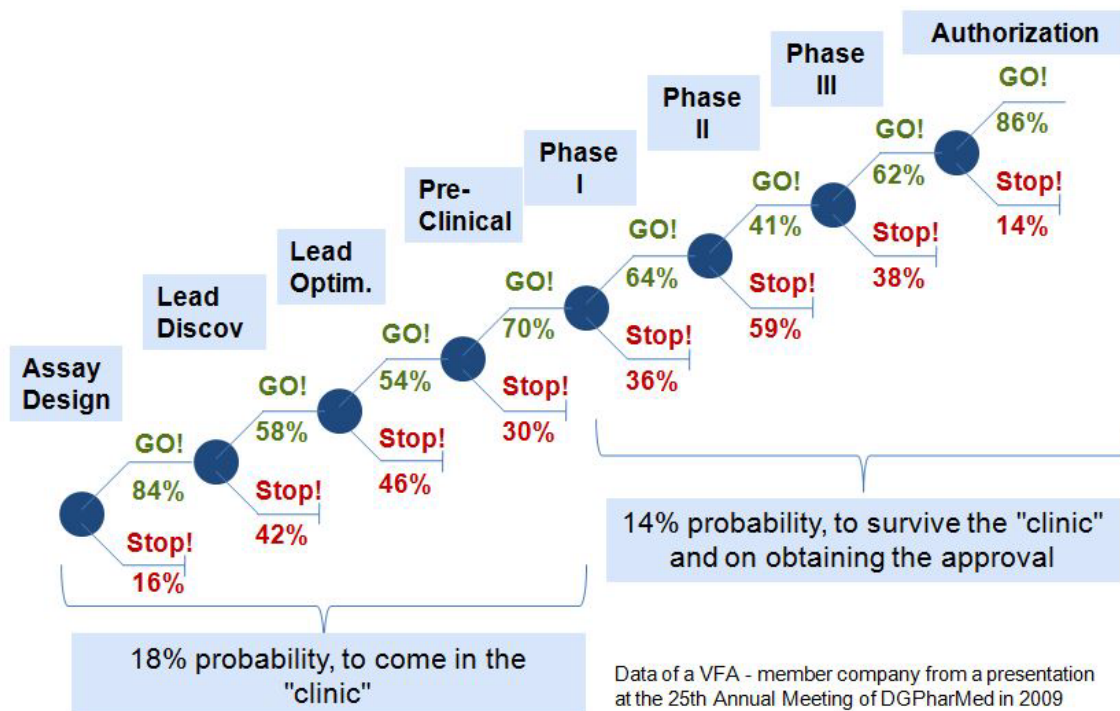
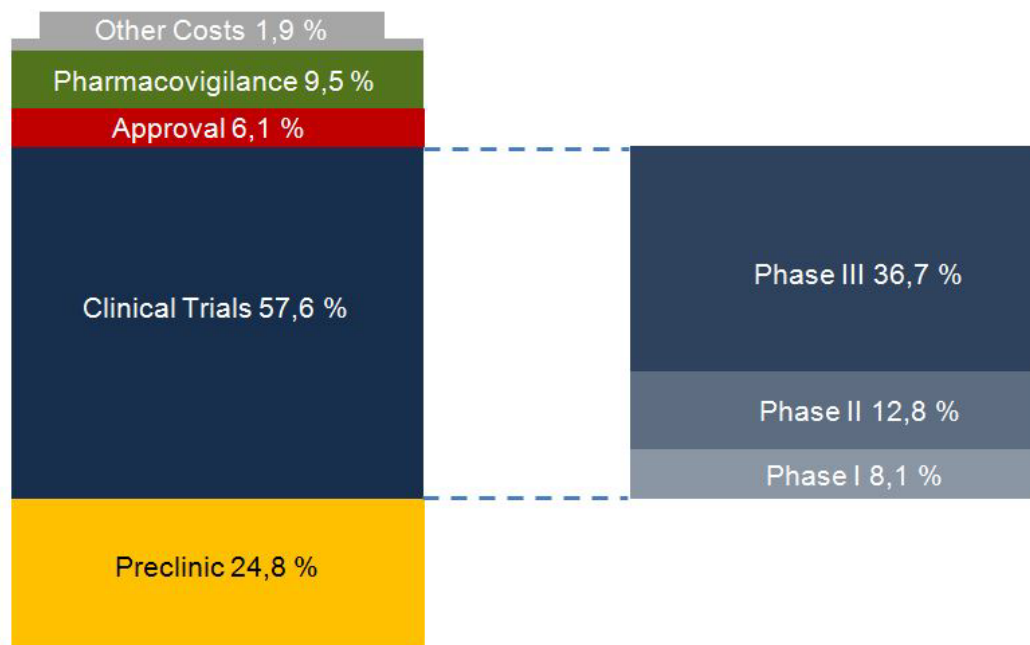


Figure 6: Drop-out-rates of substances entering the traditional multistep drug development process. (Source: VFA member company, presentation at the 25th Annual Meeting of DGPharMed, 2015)



Source: EFPIA, The Pharmaceutical Industry in Figures Key Data 2012

Figure 7: Costs of drug discovery and clinical development (Source: VFA member company, presentation at the 25th Annual Meeting of DGPharMed, 2015)

The so far depicted medical (Chapter 3.1) and economical key factors have a great impact for the decision of any pharmaceutical company on

- the target population in question: patients naive for ARV or with general treatment experienced (GTE) or with heavily treatment experienced (HTE)
- development of a new “first-in-class” drug and/or “second-in-class” drug,
- the market(s) and the date(s) it should be launched on
- the type of utilized development and approval procedure.

The Figure 8 exemplifies the interdependencies between the type of populations and prospects for market access and pricing. The Naive and GTE patients of the 2nd line are designated in the relevant literature also as “early line of therapy”.

From an economic point of view the Naive group is not attractive for oral, direct acting suppressive therapies in the future because many FDCs (3 active ARVs form a complete regimen) and STRs (with 2 active ARVs) even with updated formulations are

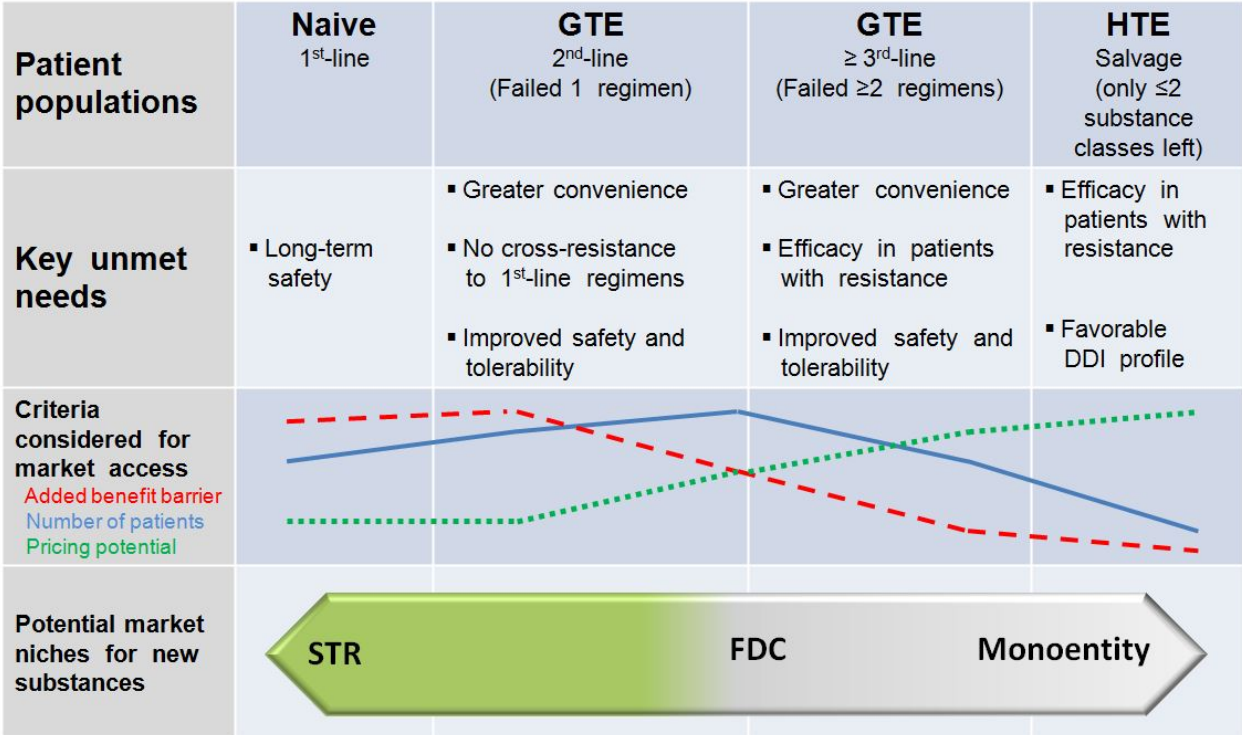


Figure 8: Current market situation for new HIV drugs according to the different patient populations. For further details see text.
 (GTE = General Treatment Experienced, HTE = Heavily Treatment Experienced, DDI = Drug-Drug-Interaction, STR = Single Tablet Regimen, FDC = Fixed Dose Combination).

available for naive patients. Additionally, the approval hurdle for any new substance for this segment is very high, because the added benefit must be proven for both markets. To make matters worse, generics for STRs and FDCs, e.g. from the company HEXAL AG and others, will enter the market soon because corresponding patents are expiring. Therefore, the pricing potential is low despite the quite high numbers of patients in need of long-term safety and innovative therapeutic approaches.

The GTE 2nd line group (i.e. one regimen has failed already) is currently dominated by the use of boosted protease inhibitors and recycling of NRTIs. STRs are still not approved. This segment is commercially attractive in the future for oral direct acting viral suppressive therapies which fulfill unmet needs as long as payers are willing to reimburse for innovation. This is the segment with most patients and still good pricing opportunities due to the fact that generics (e.g. STRs, FDCs) are not, until now, available. New agents should be developable as monoentities but also for FDCs and STRs because these will have good sales opportunities.

The GTE patients of the $\geq 3^{\text{rd}}$ line segment as well as HTE patients are designated in the relevant literature also as "later lines of therapy". The GTE $\geq 3^{\text{rd}}$ line segment consists of general treatment experienced patients for whom two or more regimens have failed. The regimens applied are dominated by third agent polytherapy and up to date no STR (complete ART) and no FDC (with 2 active ARVs) are approved.

In comparison to the GTE 2nd line group the number of potential patients' decreases, but the barrier for proving the added benefit over existing treatment to form a viable regimen is lower and the pricing potential increases furthermore.

The HTE segment has the highest medical need for new effective drugs to form an efficacious new regimen and to avoid clinical progression. This group has the lowest number of patients but a very low market access barrier. The latter aspect facilitates the market launch. As the pricing flexibility is high and competition limited, this group is still commercially attractive. A development for new agents as a monoentity would be sufficient for this segment. But their characteristics do not fulfill the requirements for GTE 2nd line and naive patients and therefore a further development is not economically attractive. Such further development would only be feasible when a coformulation within an existing STR or FDC is possible. Drugs and injectables for weekly and quarterly administration are in development.

3.3 Impact of the EMA and FDA guidelines on cost and time for clinical development of new HIV drugs

Unfortunately, the situation for a prioritized drug development for people with multiclass-resistant HIV is alarming due to the lack of incentives to manufacturer by authorities and appropriate guidance for the manufacturers. Naive and treatment experienced patients still have many treatment options available, but new class agents are urgently needed for people with multiclass-resistances to design a suppressive antiretroviral therapy in order to impede the disease progression. Although about 44 new medicines (incl. combinations, vaccines, cell therapies) are listed in current HIV development pipelines (Pharmaceutical Research and Manufacturers of America 2014), only few new active substances of two new antiretroviral classes are under evaluation in ongoing clinical trials (Clayden *et al.* 2014). Below the impact of the FDA and EMA approaches for the standards for development of new HIV drugs are discussed based on the currently valid guideline (term used by the EMA) resp. guidance (term used by FDA).

The EMA and FDA HIV Drug Development Guidances support applicants in fulfilling the requirements for approval of new HIV substances (European Medicines Agency 2013, U.S. Department of Health and Human Services Food and Drug Administration 2013), but both approaches differ considerably and have therefore significant, but different impacts for manufacturers which want to develop and launch new HIV drugs on the American resp. European market.

Both guidelines were published in 2013 based on the same scientific and medical knowledge and background and face common challenges in respect of developing new agents for ART. The most important characteristics and differences will be depicted in the following sections, firstly for the FDA and subsequently for the EMA.

3.3.1 The FDA guideline of 2013 for development of new HIV agents

The changes of this guideline in comparison to the previous are:

- "(1) More details on nonclinical development of antiretroviral drugs;*
 - (2) A greater emphasis on recommended trial designs for HIV-1-infected heavily treatment-experienced patients, those with multiple-drug resistant virus and few remaining therapeutic options);*
 - (3) Use of a primary endpoint evaluating early virologic changes for studies in heavily treatment experienced patients; and*
 - (4) Use of the traditional approval pathway for initial approval of all anti-retrovirals with primary analysis time points dependent on the indication sought instead of an accelerated approval pathway followed by traditional approval."*
- (Source: U.S. Food and Drug Administration 2013, lines 35 - 42)

The guideline of 2013 focuses on speeding up drug development and the drug approval procedure:

"All drugs that received accelerated approval, either before 1997 or since that time, subsequently received traditional approval. [...] Given that HIV-RNA is a validated surrogate for predicting efficacy of anti-retrovirals, a paradigm of accelerated approval (based on viral load changes at 24 weeks) followed by traditional approval (based on viral load changes at 48 weeks) is no longer needed for the development of anti-retrovirals. Instead traditional approval can be the initial approval for all antiretroviral drugs, with the duration of viral load assessments dependent on the population studied, as will be described in this guidance." (Source: U.S. Food and Drug Administration 2013, lines 159 - 160 and 170 - 175)

Different options for drug development are available which speed up the approval:

"HIV treatment development plans may be eligible for consideration under 21 CFR part 312, subpart E, Drugs Intended to Treat Life-Threatening and Severely-Debilitating Illnesses, fast track, breakthrough therapy

designation, 10, 11 or priority review if the specifics of the development plan justify such an approach.” (Source: U.S. Food and Drug Administration 2013, lines 466 - 469)

For the clinical development program the guidance focuses on patient populations and their unmet medical needs rather than drug characteristics:

"We encourage the evaluation of anti-retroviral drugs in a wide range of patients including treatment-naïve (naive) and treatment-experienced patients (general treatment experienced and heavily treatment experienced, as appropriate. [...]

We encourages the study of antiretrovirals in patients having the greatest need for new drugs, such as patients who cannot tolerate other antiretrovirals or have developed resistance to multiple antiretrovirals. We realize that trials in heavily treatment-experienced patients may need to be supported by preliminary data from trials in healthy volunteers and in HIV-infected populations with less or no prior antiretroviral therapy to define preliminary activity, safety, and pharmacokinetics (e.g., drug-drug interaction trials)."

(Source: U.S. Food and Drug Administration 2013, lines 350 – 351 and 366-372)

A claim can be given for a single patient segment, but approval for other indications is also possible according to the characteristics of the particular new agents under investigation.

3.3.2 The EMA guideline of 2013 for development of new HIV agents

In comparison to the previous guideline, the EMA guideline of 2013 changed its approach also fundamentally and

"defines trial populations according to documented viral resistance rather than treatment histories" (Source: European Medicines Agency 2013a, line 55 – 56).

This change influences substantially the future clinical development programs for HIV drugs. Safety was and still is a serious concern for European health systems. Therefore it is not surprising, that also the guideline of 2013 focuses on safety as well as on high-level study design and the recruitment of many patients for evaluation.

Whenever possible, safety, efficacy and quality must be evaluated in treatment-naive, treatment experienced and heavily pretreated patients, including those with multiclass failure who have no chance to form a suppressive regimen.

“[...] the size of the safety database that would be required before initial approval of an antiretroviral agent or before approval of additional indications and alternative dose regimens must always take into account the demonstrated and anticipated benefits and risks. Generally safety data on 500-1000 patients treated for 48 weeks with the relevant dosing regimen have been available at the time of initial approval for use in treatment naïve populations. If a new agent has not been studied in the treatment naïve but appears to have benefit in patients with limited treatment options then a smaller safety database and a shorter duration of exposure may be acceptable, subject to the actual data that are available. [...] In these situations there is a need to consider whether the potential safety issues associated with the alternative, higher dose-intensity regimen are of sufficient concern that sound data are required pre-licensure or whether data could be collected during a targeted post-licensure PASS. It is recommended that sponsors discuss with EU regulators on the extent of pre-licensure safety data are deemed to be necessary and how to generate the information. (Source: EMA 2013, lines 598 - 605 and 610 - 615)

The guideline encourages long-term post marketing and pharmaco-epidemiological studies (EMA 2013, line 554).

For analyzing the characteristics and scope of application for new drugs the guideline proposes a development program. All studies for any kind of “first-in-class” and “second-in-class” agents have to be performed with treatment naive patients whose recruitment is known to be difficult:

“For a new agent of a new class randomised controlled double-blind studies in patients with fully drug susceptible HIV (referred to as treatment-naïve patients for the purposes of the following text, although it is acknowledged that drug-resistant virus may be acquired through transmission) might suffice to support use in HIV-infected subjects regardless of prior treatment history and presence of RAMs relevant for agents of other classes.

For a new agent of an existing class it is also proposed that randomised controlled double-blind studies are conducted in treatment naïve patients to provide the basic evidence that the selected dose regimen is suitably efficacious and has an acceptable safety profile when compared with appropriate widely-recommended regimens. This could suffice if a claim is to be made only for use in class-naïve patients. However, an endorsement for use in patients infected with virus that is resistant to some or all of the other agents that are in the same class as the new agent would require additional clinical evidence of efficacy. [...]

Finally, it is possible that a drug of an existing or new class might be developed only for patients with extensively drug resistant virus (e.g. this could apply for agents that would not be suitable for use in other patient populations due to an injectable route of administration or need for a complex dosing regimen, or perhaps due to safety considerations). Specific recommendations for development of such agents are not included below and it is recommended that each case is discussed with EU Regulators to identify suitable development strategies.” (Source: European Medicines Agency 2013a, lines 239 – 250 and 253 – 258; underlines added by the author)

The most important conditions hindering the development of new drugs for patients in Phase 3 are summarized in Figure 9. It is evident, that the FDA approach is more flexible and therefore more advantageous for the manufacturers as well as for patients. The EMA guideline of 2013, however, favors even a broad indication (the so-called blockbuster strategy) for the development of new HIV agents, although such approach is not suitable for this chronic disease because for treatment experienced patient subgroups multiple treatment options are not available.

A study program for approval according to the EMA consists of the following steps:

1. Short-term monotherapy in ART-naive patients to explore activity and dose effects.

It is suggested that patients with CD4 counts ≥ 200 c/ μ L are included in such studies.

2. Combination regimen studies in relatively small numbers of ART-naive patients using a background regimen which probably allows the detection of dose effects. The primary endpoint (i.e. with a viral load below the detection level) for regimen selection purposes must be determined within weeks 16 - 24.

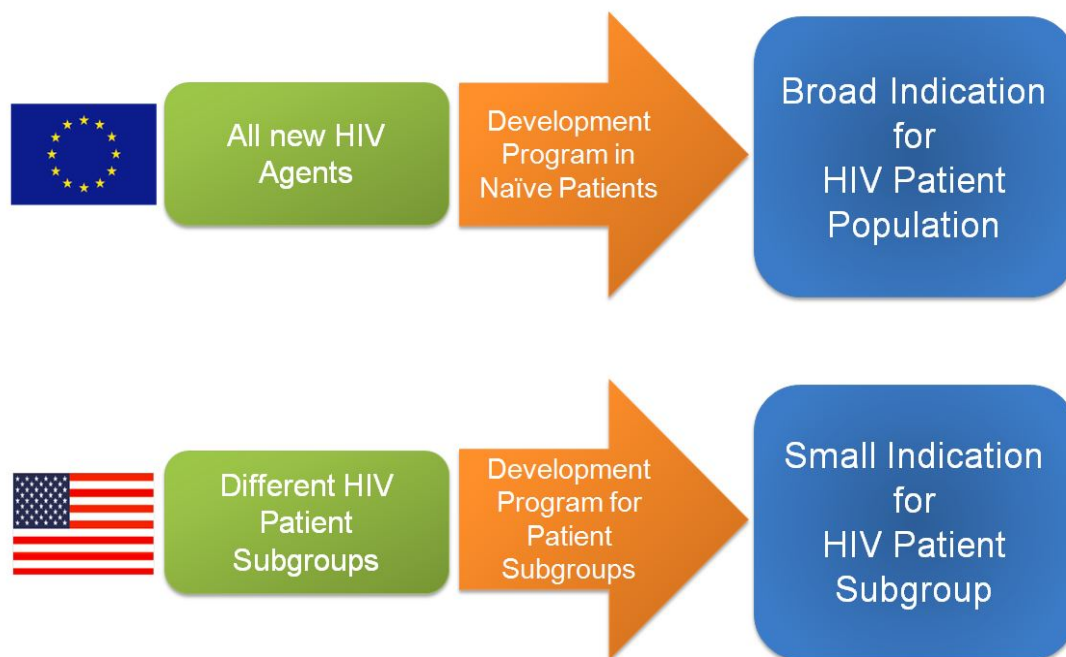


Figure 9: Schematic overview of the fundamentally different approaches for development of new HIV agents according to the EMA guideline (European Medicines Agency 2013a) and the FDA guidance (U.S. Food and Drug Administration 2013).

3. Confirmatory randomized clinical trials (RCTs) in ART-naive patients in order to prove non-inferiority vs. an appropriate active control regimen with a primary endpoint (i.e. with a viral load below the detection level) at week 48.

Only when the third requirement is fulfilled, is an approval granted for the treatment of any HIV patient population regardless of their treatment history and presence of resistance towards agents of other classes. In contrast, the FDA guidance suggests the following clinical trial design for Phase 3 and the HTE group (compare U.S. Food and Drug Administration 2013, Figure 1):

"The primary efficacy analysis is the short duration (e.g., 2 weeks) comparison to placebo. At 24 weeks, the comparison is no longer controlled unless a dose response is being evaluated. Given that doses chosen for study in HIV trials usually are on the plateau portion of a dose-response curve, demonstration of a dose response is considered unlikely. [...] Evaluation for both safety and efficacy beyond 24 weeks is recommended and could be accomplished during the postmarketing period." (Source: U.S. Food and Drug Administration 2013, Lines 617 – 621 and 626 - 627)

Candidates for Phase 3 trials are the first drugs of a new class or second generation drugs of an existing class which are effective against drug-resistant virus strains.

Mani *et al.* (2012) suggested already before the guidelines have been published that concerned stakeholders including the FDA, EMA, industry, clinical sciences, community advocacy, and regulatory sciences should discuss how safety and efficacy of new agents could be proved in such novel clinical trial designs, this proposal was already considered by the FDA for the guideline 2013 but not by the EMA.

In spite of suggesting this novel study design for HTE patients, the FDA itself expressed some concerns:

"Criticism of this approach primarily related to the uncontrolled design of the study beyond the primary 2-week comparison and the concern that it doesn't allow for an adequate assessment of virological durability or safety. However, the unmet medical need in this population and the potential to decrease further development of resistance in the background regimen of trials patients outweigh any modes loss of certainty in the interpretation of results from this type of trial." (Source: U.S. Food and Drug Administration 2013, Lines 642 – 667)

In Table 1 the consequences of the striking differences between the FDA and EMA guidelines for the realization of clinical trials are summarized. The FDA and EMA use different criteria for categorizing the patients (U.S. Food and Drug Administration 2013, lines 501 - 503, European Medicines Agency 2013a, lines 57 – 63).

Table 1: Differences between clinical trials realized acc. the FDA and EMA guidelines as of 2013.

EMA	FDA
New agents must be developed for all patients regardless of prior treatment.	Different requirements for different target populations.
Randomized controlled confirmatory clinical trials have to be conducted in treatment naïve patients.	Confirmatory trials in target populations.
Primary endpoint at 48 w; population size must allow subgroup analyses; control population with same treatment background.	Comparison with controlled regimens at 24 – 48 w for naïve patients. Placebo-controlled at 2 w followed by an uncontrolled 24-w-evaluation against an optimized background for HTE.
For safety reasons a population size of 500 – 1000 patients/48 weeks is required.	Population size range from > 500 patients (48 w) to 300 patients (24 w).
Short term (2 w) functional monotherapy design with uncontrolled continuation is reserved for populations with viral resistance to agents of the same class.	Design for HTE patients accepted by FDA and insurance companies

Summary of chapter

The EMA and the FDA current draft guidelines take divergent approaches and raise hurdles for parallel development of new HIV drugs.

The EMA guideline requires a broad indication which must be proven by double blind controlled RCTs and focuses less on needs of special patient segments. The FDA guidance sets priority on medical needs, targeted indication and regulatory standards tailored for special study populations. More flexible study designs are possible for development of new HIV substances for different subpopulations, irrespective of the characteristics of the substance. This flexibility is automatically an ethical approach: GTE or naïve patients must not be unnecessarily exposed to risk. Broader indications are possible if wanted by stakeholders.

Overall it can be stated, that the FDA guideline deals better with the unmet medical needs of HIV patients and provides incentives for manufacturers to develop drugs for this special clientele; costs can be reduced and the time saved allows a timely access to the drug for the patients.

3.4 Regulatory aspects for accelerated approval in the European Union and the United States of America

The EMA and FDA have already established several pathways and procedures (named 'designations' by the FDA) and special review options to accelerate the development processes for drugs for chronic and life-threatening diseases. The expedited pathways are controlled and influenced by 5 stakeholder groups:

- pharmaceutical industry
- regulators
- HTA bodies
- payers and insurers
- patients advocacy groups (and other third-party entities)

While the industry develops the drug, the regulators are responsible for evaluating the safety, efficacy, and quality of the drug and to decide on the market launch. The HTA bodies are responsible for the scientific assessment (e.g. relative-effectiveness) and negotiate with payers about reimbursements. Cooperation between the EMA and the HTA-bodies has existed since 2008. In this respect, the HTAs can be considered as the "final gatekeeper" for market access.

Basically there are two possibilities for accelerating the entire approval procedure:

1. Shortening the preclinical and clinical development to enable assessment by the authorities as soon as possible.
2. Speeding up the evaluation by the authorities by shortening the review period.

Below the different possibilities for accelerated approval are presented, first for the American and subsequently for the European market.

The FDA offers several possibilities for accelerated approvals which are listed comprehensively in the 'Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics' (U.S. Food and Drug Administration 2014e):

1. Accelerated Approval (since 1990)

This pathway has been the most frequently used for HIV drugs.

"These regulations allowed drugs for serious conditions that filled an unmet medical need to be approved based on a surrogate endpoint."

(Source: U.S. Food and Drug Administration 2014a)

The use of a surrogate marker (reduction of viral load) instead of the conventional clinical endpoint (morbidity/mortality) can substantially accelerate development and approval because it can be combined with a 'Priority Review' and with the 'Fast Track Designation' and the 'Breakthrough Therapy Designation' (see below). During the last decades surrogate markers proved to be valid endpoints. Nevertheless, the manufacturer must agree on post-approval studies in order to prove safety and efficacy for reduction of uncertainty:

"Post market commitments: trial to evaluate effects on clinical outcomes, and submission and review of promotional materials. Approval subjects to expedited withdrawal if commitments are not met. Congress encouraged broader use of Accelerated Approval in 2012 as part of FDASIA."

(Source: Baird *et al.* 2014; FDASIA = Food and Drug Administration Safety and Innovation Act)

2. Priority review (since 1992)

"A Priority Review designation means FDA's goal is to take action on an application within 6 months." (Source: U.S. Food and Drug Administration 2014b)

This option reduces the regular review time of 10 to 6 months. It is eligible if the new drug provides a significant improvement in safety or efficacy when compared with existing therapies. Priority review can only be combined with the 'Accelerated Approval' or in combination with 'Fast Track' or 'Breakthrough Therapy Designation' (see below).

3. Fast Track Designation (since 1997)

"Fast track is a process designed to facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need."

(Source: U.S. Food and Drug Administration 2014c)

The assessment is based on clinical outcome or a full valid surrogate end point. The acceleration is achieved by more frequent meetings and exchange of documents (e.g.

the 'Design of CTs') between the manufacturer and the FDA with possible staggered submission and sequential review of marketing applications ('Rolling Review') with the FDA. This designation is eligible in combination with 'Accelerated Approval' and 'Priority Review' or alternatively with a 'Rolling Review'. The manufacturer must agree on post-approval studies in order to prove safety and efficacy.

4. Breakthrough Therapy Designation (since 2012)

"A process designed to expedite the development and review of drugs which may demonstrate substantial improvement over available therapy."

(Source: U.S. Food and Drug Administration 2014d)

In contrast to the 'Fast Track Designation' this designation requires a *"substantial improvement over existing therapies"* (U.S. Food and Drug Administration 2014d). It is the newest and fastest procedure to get approval. It shortens the clinical development time due to intensive interaction between the FDA and the manufacturers. In addition the administrative transactions are pushed further ahead by consultation of the FDA's senior staff and advisory committees. The required proof of substantial improvement over existing therapies is based on promising results resp. clinical significant endpoints or valid surrogate marker during early drug development.

Breakthrough Therapy Designation allows a staggered approval for subpopulations and was used in the past frequently for development and approval of cancer treatments: Meanwhile it is also used for a first HIV agent (e.g. for the new class of attachment inhibitors) based on surrogate markers and for HTE patients (Bristol Myers Squibb 2015). This designation owns all features of the 'Fast Track Designation' and can be combined with 'Accelerated Approval' and 'Priority Review' or alternatively with a 'Rolling Review'. Post-approval safety studies are significantly enlarged according to the 'Prescription Drug User Fee Act' (U.S. Food and Drug Administration 2007b) and the 'Food and Drug Administration Safety and Innovation Act' (U.S. Food and Drug Administration 2012).

5. Rolling (New Drug Application) Review

This review procedure takes place in real time and enables a staggered submission and a stepwise approval of marketing applications (U.S. Food and Drug Administration

2014e). The procedure is also applicable for Fast Track and Breakthrough Therapy Designations. This shortens the review time even more.

Summarizing, it can be stated that so far the Breakthrough Therapy Designation is the most effective pathway in place for medicines of highest medical need. The required safety and efficacy is assured by post-approval studies.

For the European markets the EMA offers the below described possibilities for expedited pathways.

1. Approval under exceptional circumstances (since 1993)

This option shortens the drug development time, but is restricted to drugs with insufficient non-clinical and clinical data (orphan drugs) or to cases of emergency for public health (e.g. outbreaks of epidemics). Post-approval data is used for annual reassessments of the benefit-risk ratio (European Medicines Agency 2005).

2. Conditional Marketing Authorization (CMA; since 2005)

The CMA (European Medicines Agency 2005, 2006b) resembles the FDA's 'Accelerated Approval'. Since just recently – with the update in July 2015 (European Medicines Agency 2015b) – the EMA now places emphasis on therapeutic innovation and requires substantial improvement of new drugs compared to previous standard therapies. The clinical development time - mainly of Phase 3 - is shortened by early submission and evaluation of clinical data. If data quality is high, a conditional approval for one year can be granted even before completion of clinical trials. The acceleration is achieved by an intensive and permanent dialogue between the EMA and the manufacturer and focused joint scientific advice with the HTA bodies. Every six months submission of a safety update report is required. After a certain time the conditional approval can be converted into a regular one.

3. Accelerated Assessment (since 2005)

This assessment (European Medicine Agency 2006c) accelerates approval of substances developed according to the CMA. The review time is reduced from 210 days to 150 days; this feature resembles the FDA's 'Priority Review'. According to the update of July 2015 (European Medicines Agency 2015b) communication will be intensive and

permanent in order to ensure that only clinical data of the required high quality is submitted before completion of the clinical trials. This was not always the case in the past. In this way an early assessment and subsequent approval is possible. This feature is similar to the 'Rolling Review' procedure of the FDA. An Accelerated Assessment can be combined with the Conditional Marketing Authorization. Both pathways are not mandatory and can be converted into standard procedures.

4. Pilot project for adaptive licensing resp. adaptive pathways

These procedures are emerging and still not approved by the European Commission (European Medicine Agency 2014). The overall objective is to convert the conventional 'all-or nothing' marketing authorization into a stepwise one (see Chapter 4 for more details) using pre-established pathways.

Additionally to all the efforts in view of the aspired harmonization, the EMA and FDA established a legally non binding 'Mutual Scientific Advice' (European Medicines Agency and U.S. Food and Drug Administration 2009). The objective of this convention is, to come to an agreed development plan that is, to seek harmonization for drug development between Europe and the USA. A manufacturer can apply for this scientific advice in order to reduce the complexity and diversity of the development plan.

The importance and urgency of an implementation of the adaptive pathways can be recognized by the fact that after the last approval of a 'first-in-class' substance in 2008 only co-formulations have been developed. From the co-formulations approved for the EU three are not listed in the Lauer-Taxe database for Germany because they have not yet been commercialized: Evotaz, Resolsta and Dutrebis. For commercialization the proof of an added benefit would be necessary to get reimbursement. But to do so would even be counter-productive for the marketing authorization holder, because the single substances of these co-formulations were already marketed already with fixed prices. For this reason these three approved medicines have never been marketed.

4 Adaptive approaches

Although the introduction of expedited pathways on the part of the EMA was already an improvement when compared to the situation before 2000, more flexibility of the regulatory pathways is needed to favor a prompt adaptation to the ongoing changes of the health care environment. The tools developed for this purposes (presented in Chapter 3.4) are designated frequently as adaptive approaches (adaptive licensing, adaptive pathways, adaptive approval). In the below sections the mode of application of these tools and their impact on clinical trials is analyzed.

4.1 Adaptive Pathways resp. Adaptive Licensing

In around 2006 the pharmaceutical industry underwent a decline in productivity and rise in product failure. It was the consequence of the then current paradigm: developing drugs for a broad indication – the ‘blockbuster strategy’. According to Ukwu (2011) this crisis might lead to increased regulatory requirements (compare Figure 10, the there used term “Perfect storm” refers to the crisis). The low productivity of R & D has undermined the ability of the industry to address the growing needs for healthcare worldwide (Eichler *et al.* 2015, Hay *et al.* 2014). Traditional treatments have a high rate of non-response in the general patient population. Treatments are evolving from ‘one size fits all’ to patient-focused treatments (Eichler *et al.* 2015). In this context the personalized medicine with its fast growing knowledge will become important in the future. This new reality must be reflected in the amount of reimbursements and regulatory pathways should keep pace with the scientific progress (Stoeckert I 2015).

The FDA tried to overcome the crisis in 2012 among other measures with the implementation of the ‘Breakthrough Therapy Designation’ (described in Chapter 3.4). This was not really new as already in 1997 the ‘Fast Track Designation’ as well as ‘Accelerated Approval’, ‘Priority Review’ and ‘Rolling Review’ were introduced in order to accelerate regulatory review for important medicines. All these tools have been designed to allow faster review of drugs especially for serious or life-threatening diseases.

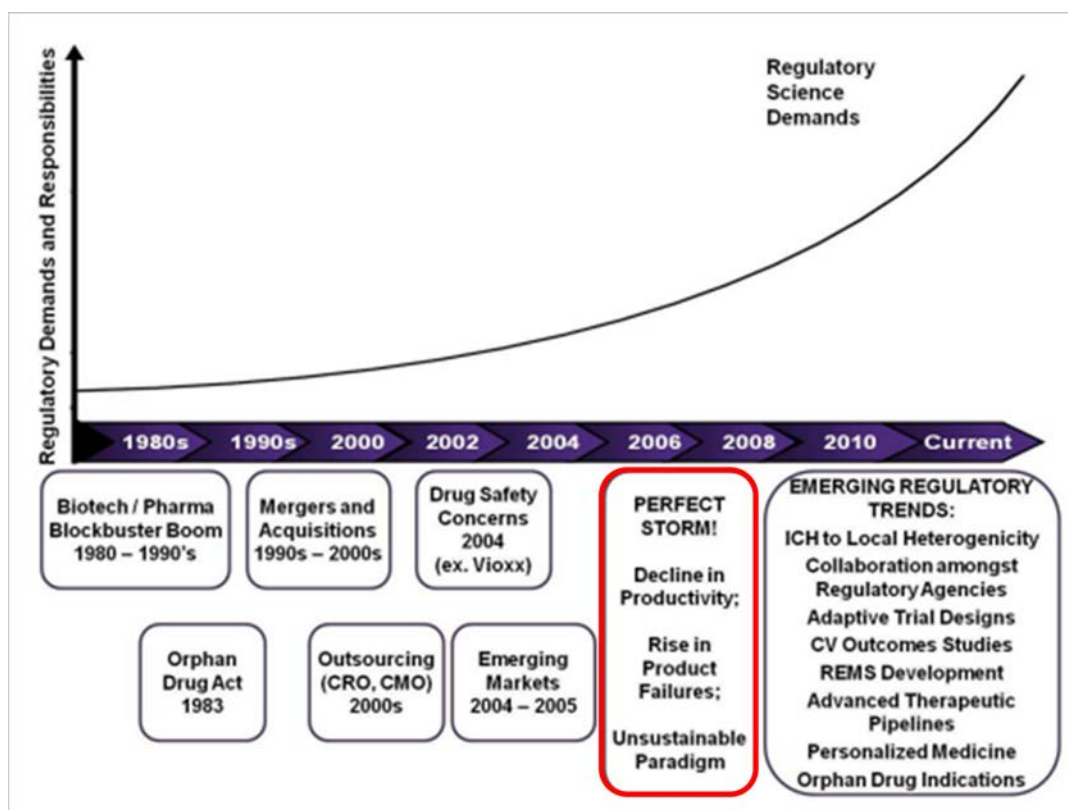


Figure 10: Changes in the pharmaceutical market and their relationship to scientific progress and regulatory demands. (Source: Ukwu 2011; red coloring of one frame added by the author).

The Breakthrough Therapy Designation requires evidence of substantial improvement in comparison to existing therapies by using validated surrogate(s), enable drug development for small subpopulations; FDA senior staff is involved too, to support a fast approval. In contrast, the Fast Track Designation is only allowed to address unmet medical needs and senior FDA staff is not involved. In other respects, both designations are identical.

According to the FDA guideline, designs of clinical trials can be adapted to the drug and patients characteristics, but of course keeping safety and efficacy in mind. The CT design suggested by the FDA for the HTE patient segment was elaborated and proposed by an independent 'Scientific HIV forum' (Mani *et al.* 2012). Post-approval safety commitments are required to ensure true safety and efficacy to reduce uncertainty.

The Breakthrough Therapy Designation can be combined with a 'Rolling Review' (see Chapter 3.4) which enables a staggered submission and a stepwise approval of marketing applications for patient subpopulations. A new HIV drug with potential for substantial

improvement over existing therapies – e.g. for earlier lines of treatments such as GTE patients – could be developed in a staggered way for getting first an initial approval for HTE patients, followed by a second approval expanded for populations in earlier lines of treatment ($\geq 3^{\text{rd}}$ line and 2^{nd} line GTE). The expansion of the approval is based on the constant accumulation of safety data to foster development and treatment for this patient segment.

So far, many products passed via the Breakthrough Therapy Designation, some of which already have been authorized in spite of the concerns that the earlier market introduction is based only on a smaller and therefore eventually more uncertain data base.

The FDA controls all – from the very early to the latest – stages of drug development (compare Figure 1) by keeping in close contact and permanent communication with the companies. An investigational new drug (IND) application has to be filed prior to the first clinical trials in humans followed by the submission of a new drug application (NDA) for granting marketing approval. Post market commitments and commercialization issues are also under control of the FDA. (Figure 1 left side)

This comprehensive flexibility is easily feasible thanks to the dynamic character of the TPP which enables steady and constant adjustments to the development and review processes.

Unfortunately, regulatory pathways in Europe have not kept the pace with scientific innovation (Stoeckert I 2015). In spite of the revised guidelines for Accelerated Approval and Conditional Marketing Authorization one problem has not been resolved: the adaptive pathways are still not authorized legally by the European Commission. Therefore, the informal advice given by the HTA bodies in an early stage of development are not legally binding. This situation is unsatisfactory because a fast commercialization is not assured even if a new drug is recommended by the EMA to EC for approval. As long as the reimbursement problem is not solved this 'Efficacy-Effectiveness-Gap' will persist (compare Figure 11). The updates of the guidelines for Accelerated Approval and Conditional Marketing Authorization (European Medicines Agency 2015d) emphasize the necessity of an early and active - not only optional - interaction with the EMA, in particular in the context of the joint scientific advices with the HTA bodies. The new legislation for pharmacovigilance (Directive 2010/84/EU, Regulation (EU) No 1235/2010)

effective since July 2012 has amended the previous one contained in the Directive 2001/83/EC and Regulation (EC) No. 726/2004 supp. post approval studies.

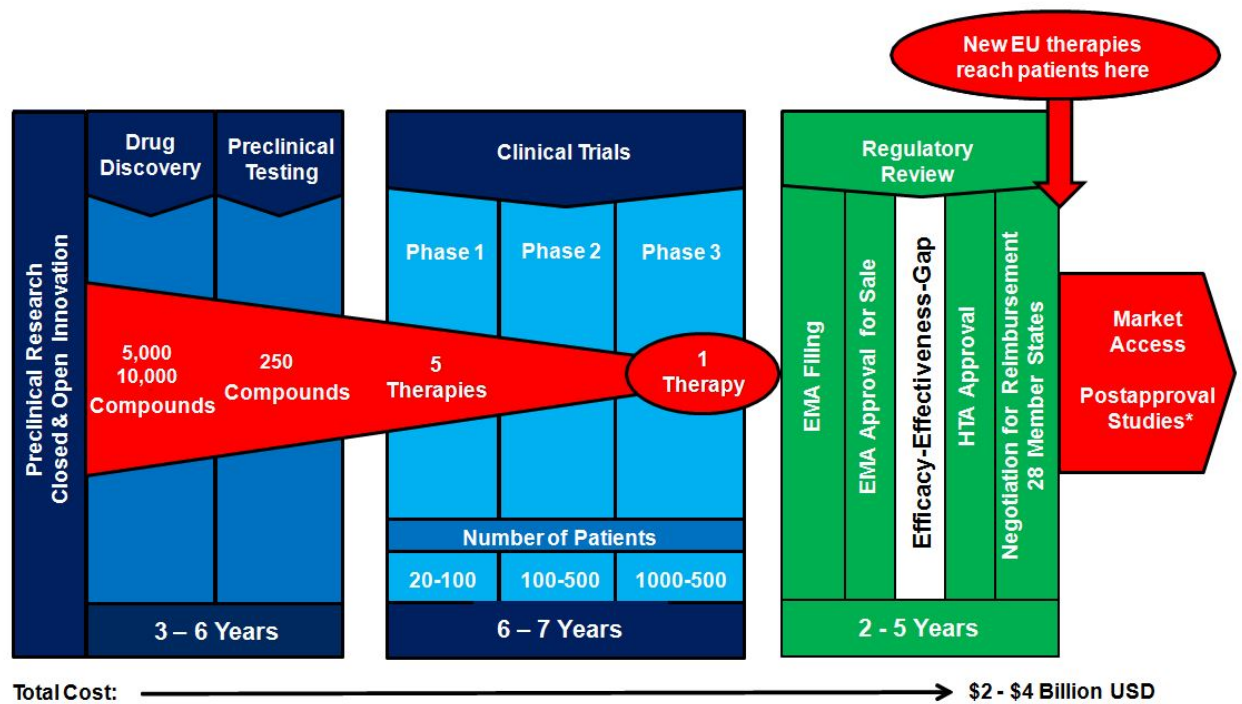


Figure 11: Overview of the current pathways for approval and market access in Europe.

*: Post-approval studies refer likewise to post authorization Efficacy Studies (PAES) and post authorization Safety Studies (PASS) according to the new Pharmacovigilance legislation (Directive 2010/84/EU, Regulation (EU) No 1235/2010). (Modified acc. to Stoeckert I 2015)

As the FDA, the EMA in Europe has already implemented some expedited pathways since 1992 and recently even caught up with the FDA due to the latest updates, the upgrading of Accelerated Approvals and the CMA even for therapeutic innovations, and not just for substantial improvements. The CMA of the EMA is similar to the Accelerated Approval of the FDA. The Accelerated Assessment of the EMA is similar to the Priority Review of the FDA. With the last update of July 2015 it even approximates to the Fast Track Designation and the Breakthrough Therapy Designation. But unfortunately, only the legalization of this revision and the adaptive pathways themselves are still missing. As a consequence the EMA still sticks to the CMA and Accelerated Assessment and to the predefined and mandatory SmPC for getting marketing authorization. Furthermore, the EMA cannot directly influence the clinical trial applications

(CTAs) because this is responsibility of the member states. Only the Marketing Authorization Application (MAA) is controlled by the EMA.

In comparison to the FDA, the EMA started with the introduction of the adaptive approvals relatively late. This could have been due to several cumbersome factors (partly depicted in Figure 1) which cannot be altered quickly and not by the EMA itself:

- a) The EMA is only a coordinating agency which first must come to an agreement with all member states of the EU.
- b) The EMA has no full control over all stages of the drug development process.
- c) Drug regulatory approval requirements are very complex and predefined with very limited options for flexibility (e.g. the SmPC predefines requirements as part of the registration package).
- d) The EC has to grant marketing authorization additionally and after the positive opinion of the Committee for Medicinal Products for Human Use (CHMP) of the EMA.
- e) In addition to quality, safety, and efficacy a new drug must have an added benefit to get the market commercialization. The reimbursement issue is assessed by the national HTA bodies and debated with the relevant national payers.

The last aspect is the most important one. The FDA grants marketing authorization and the payers (e.g. insurers, hospitals, social insurances, and others) have to decide on an individual basis, whether or not they pay for the treatment. In contrast, in the EU granting marketing authorization is only the first step of assessment (proof of quality, safety, and efficacy). In the next step the national HTA bodies evaluate whether an added benefit is given and prepare a proposal about the amount of reimbursement which will be negotiated with the respective national payers, but because up to 28 different HTA bodies with their own national assessment criteria are involved, the market commercialization may be greatly delayed.

In summary, it can be stated, that the EMA and the EC are finally taking a stand for more flexibility, but the reimbursement question is still a crucial problem.

The term used in general for the new innovative possibilities for drug approval has been 'Adaptive licensing'. Recently, the EMA introduced and officially using the 'Adaptive pathways' for the same topic. The subsequent remarks follow this usage.

Pilot project for adaptive pathways in the EU

As defined by the EMA, adaptive pathways is a designation for existing pathways which will be coordinated and harmonized among each other. The concept of Adaptive Pathways will allow patients timely access to new medicines addressing unmet medical needs. The EMA started a pilot project in March 2014, the aim is to complement the traditional authorization process – which only consisted in ‘approved or not approved’ for all types of patient populations’ – with a step by step approval for patient subpopulations.

According to the EMA

“the adaptive pathways approach builds on regulatory processes already in place within the existing EU’s legal framework. These include:

- *Scientific advice*
- *Compassionate use*
- *Conditional approval mechanism (for medicines addressing life-threatening conditions)*
- *Patient registries and pharmacovigilance tools that allow collection of real-life data and development of the risk-management plan for each medicine.”*

(Source: European Medicines Agency 2015e)

The Centralized Procedure, the Exceptional Circumstance Mechanism and the Accelerated Assessment also form part of the established regulatory processes.

Development plans will be reviewed at an early stage by the EMA and other medicine regulators and potential stakeholders (e.g. the HTA bodies, patient and consumer organizations, pharmaceutical industry, organizations issuing clinical treatment guidelines, healthcare professionals, researchers). In particular for common chronic indications the conventional development and licensing pathways are economically inefficient (Stoeckert I 2015). For example, manufactures of HIV drugs are forced to lock themselves into large long-term outcome RCTs in sequential multistage development programs with unknown results and success (Hay *et al.* 2014). The EC definitively supports the aims of the adaptive pathways:

“As the project progresses, the European Commission will examine the legal and policy aspects related to adaptive licensing, in collaboration with the EU

Member States and in consultation with relevant stakeholders as necessary.”

(Source: European Medicines Agency 2015e).

Two scenarios of approval are proposed in the EMA guideline (European Medicines Agency 2014) for Adaptive Licensing:

- An initial approval is granted for a well-defined, high medical need subgroup, and subsequently the indication is widened to a larger patient population
- An early regulatory approval (e.g. the Conditional Marketing Authorization) which is prospectively planned (e.g. based on surrogate endpoints) and complemented by post approval studies (PAES and PASS). In this way the original marketing authorization can be converted into a ‘full’ approval.

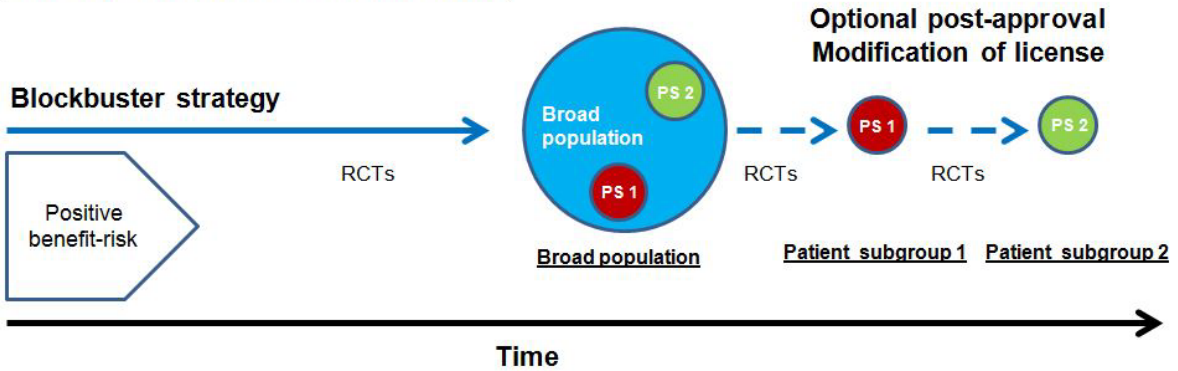
Figure 12 summarizes and illustrates the main features and differences between the traditional and the adaptive pathways as well as the corresponding clinical trial designs. The in the figure 12 mentioned ‘blockbuster strategy’ causes several dilemmas.

Recruitment of populations with naive patients for development of a new drug is difficult because these patients are not willing to participate because there are a lot of treatment options already available for them. Additionally, the costs for development of new drugs for any patients will be very high, development times too long and the reimbursement problem must be solved for the resp. health systems, therefore, new pathways are urgently needed. It has been postulated by Eichler *et al.* (2015) that

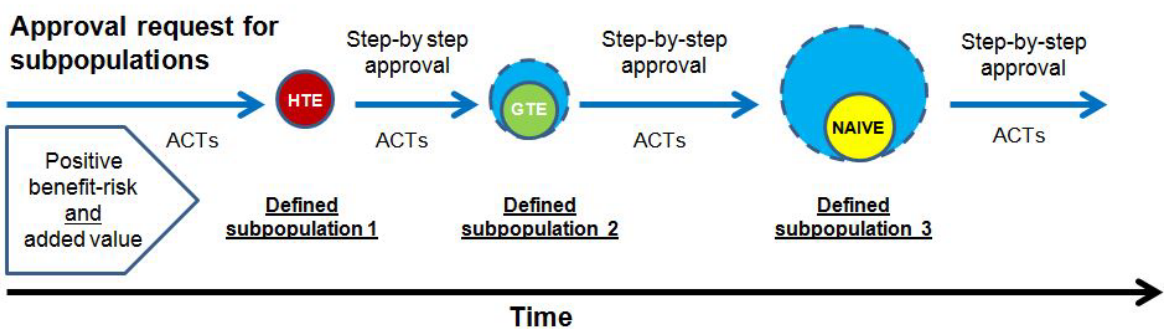
“redesigning clinical trials to include fewer patients, providing conditional approval of drugs, and requiring post marketing surveillance could have a profound effect” on overall development costs. This [...] *paradigm shift would lower the threshold for financing a drug’s development so that more drugs would be brought forward.”*

As mentioned the national healthcare system of the member states of the EU and the USA differ considerably. In the USA decisions on access to and payment of drugs are not centrally managed while in Europe manufacturers, regulators, HTA bodies, and payers collaborate and try to find an agreement. Hence, solving the reimbursement question will be more challenging in the USA (Gaydos *et al.* 2012, Eichler *et al.* 2013).

Traditional pathway approach



Adaptive pathways approach



(Naive = Patients are treatment naive to antiretroviral therapy, GTE= General Treatment Experienced (>2 therapies failed), HTE = Heavily Treatment Experienced (only 1 or 2 treatment options left), ACT = Adaptive Clinical Trial, RCT = Randomized Clinical Trial)

Figure 12: Comparison between the characteristic of traditional pathway approach and the new adaptive pathways approach exemplarily adapted for HIV patient populations (Source: modified according Eichler *et al.* 2015)

Summarized, the advantages of the adaptive pathways are the stepwise approval and the stepwise widening of the indication for different subpopulation. Additionally, this approach allows the prospectively planned reduction of uncertainty post-approval due to the smaller subpopulations used. Altogether, the adaptive pathways and adaptive clinical trials offer a lot more flexibility than the traditional approach.

The pilot project for adaptive pathways will finish soon. One can only hope that this promising concept will quickly become legal and manufacturers as well as patients can benefit from its seminal improvements regarding fast approval of new drugs for specific subpopulations. It must be emphasized that the concept even considers innovative therapies which show considerable improvement compared to the previous regulations.

4.2 Adaptive Clinical Trial

Another starting point to achieve flexibilization and acceleration of drug development is shortening and increasing the effectiveness of the clinical program. An adaptive clinical trial (ACT) design is defined as

“a multistage study design that uses accumulating data to decide how to modify aspects of the study without undermining the validity and integrity of the trial.” (Dragalin 2006)

Maintaining study validity requires correct statistical assumption and minimal operational bias. Maintaining study integrity means providing convincing results, preplanning, and maintaining blinded interim analysis results (Cheng *et al.* 2005). Such ACT approach facilitates switching from the traditional multistep approach (blockbuster) to adaptive pathways which on its part enable a flexible and cost-efficient development and investigation of drug efficacy and effectiveness (Maca *et al.* 2014). In other words, the ‘Efficacy-Effectiveness-Gap’ (see Figure 11) can be closed due to prepone the HTA-bodies requirements into pre-approval drug development.

There are 3 major types of adaptation for clinical trials:

1. Typical adaptations include but are not limited to adaptive randomization. According to Maca *et al.* (2014) adaptive group sequential designs are commonly used; they permit:
 - stopping a trial early due to safety concerns,
 - assessing efficacy at an early stage,
 - discarding unsuitable data
 - changing type and size of populations based on interim analyses (population enrichment designs).
2. Concurrent adaptation (or *ad hoc*) includes modifications of inclusion/exclusion criteria, evaluation criteria, dose or regimen, treatment duration.
3. Retrospective adaptations are possible by modifications of statistical analysis prior to database locks or unblinding.

Adaptive clinical trials have several benefits:

1. Patient subgroups can be used for the trials, thus exposing fewer patients to ineffective or toxic drugs.
2. Increasing cost-effectiveness
3. The use of adequate information technologies and corresponding software allows complex simulations to elaborate eventual adaptations of the trial design.
4. Trials can be executed in a seamless way, which increases their speed without compromising quality.

Seamless designs are especially suited to reduce the total time for clinical trials because the different trial phases are fused and hence, there is no idle time between the different phases. According to Eichler *et al.* (2015)

“Adaptive trials offer an opportunity to assess accumulating results at given time points with the possibility of modifying the trial design: for example, by changing the trial population to focus on patient subsets that are responding better to the experimental therapy [...]”

An additional advantage of a seamless design is the reduction of the drop-out rate (see Figure 6) and hence, also a cost-reduction for Phase 3 (see Figure 7).

The corresponding documents of the EMA and FDA for the adaptive clinical trials (European Medicines Agency 2007, U.S. Food and Drug Administration 2010) have been reviewed in detail in Gaydos *et al.* (2012). Regulators want to ensure that the applied adaptations have no impact on the validity and integrity of the trial data.

Additionally, an intensive and constant communication between the authorities and the manufacturers is implemented in the adaptive licensing concept (Elsässer *et al.* 2014).

The EMA document about the adaptive clinical trials is still not an integral part of the current HIV-guideline, but it is legal and applied.

In summary, it can be stated that both current regulation for adaptive clinical trials share the same major principles, this makes it easier when setting up an ACT and request for a step-by-step approval for both markets simultaneously.

Unfortunately, drug development according to adaptive approaches will increase the regulatory and administrative burden because of the additional post approval commitments (e.g. real-life-data) and the complex methodology for setting up an adequate

design for the trials. It is obvious, that this fact is especially critical and time-consuming for the EU, because the EMA as an organizational agency needs approval of all involved member states, whereas the FDA is the sole executive authority.

4.3 Solving the ‘Blockbuster Dilemma’

The current guideline for the EU and up until a few years ago also the U.S. demands also a broad indication for development of new HIV drugs, this is generally disadvantageous, in Europe an additional obstacle aggravates the situation: For final commercialization manufacturers must develop a substance with an added benefit in comparison to existing standard therapies. It is extremely difficult to prove this for a blockbuster drug with its broad indication. The evaluation criteria for assessment of an added benefit of drugs for the GTE and HTE segments differ between the EMA and the individual member states of the EU. This bedevils the situation for the companies, if the ‘Adaptive Pathways’ are put into force by the European Commission, the negotiations for reimbursement will be easier because drugs are only developed for a special patient segment with high medical needs and the requirements of payers and HTAs are considered at an early stage before approval.

If the adaptive pathways become legal in Europe the previous situation (see Figure 9, Chapter 3.3) will mutate into a patient-friendly environment for European patients, whereas in the USA the situation for all patients with low income remains very disappointing because of the unsolved reimbursement problem (see Figure 13).

The new EMA approach finally covers all stages of a drug: from the preclinical stage to its use as an affordable medication. This will be not the case for American patients as long as the structure of the U.S. health care system remains the same without a socially acceptable solution of the reimbursement problem.

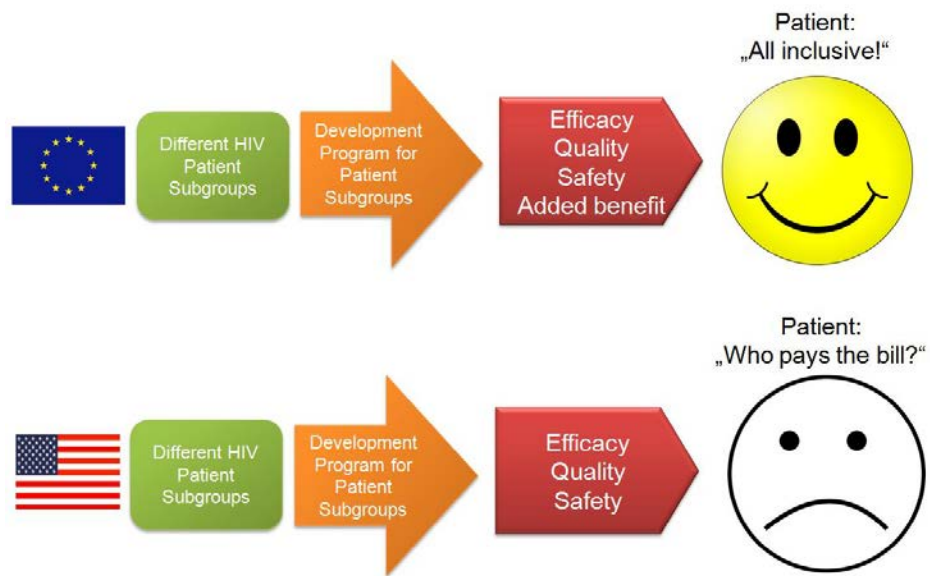


Figure 13: Status of the patients' situation in Europe and USA after implementation the adaptive pathways in Europe.

5 Conclusions and outlook

Since the beginning of the AIDS epidemic in the 1980s the life expectancy of HIV patients has increased steadily until today it approaches that of the general population, thanks to a variety of effective drugs and the optimized treatment schemes available. However, the long-term therapies required, together with the limited variety of substances available has triggered the emergence of resistant virus strains and development of intolerances of the patients towards the agents. As a result, only few or even no therapeutic options are left for patients with the highest medical needs. The pharmaceutical industry has not been able to satisfy these needs because in the 1990s the requirements of the legal guidelines at that time in Europe and the USA neither supported the fast and targeted drug development for these patients, nor a rapid review and approval. This unsatisfactory situation started to change thanks to the engagement and public actions of HIV patient advocacy groups. Because of this the FDA felt obliged to introduce the Accelerated Approval and Priority Review in 1993. Nevertheless, in spite of established faster approval and special review procedures, the time-consuming clinical endpoint was still used as a marker for assessment of the drug's efficacy. A faster method is the use of surrogate markers, which the FDA duly introduced for HIV drugs in 1997. Since the beginning of this century, for an accelerated approval, the evaluation of efficacy (primary endpoint) could be done with surrogate markers after 24 weeks instead of the previously used 48 weeks (U.S. Food and Drug Administration 2013b).

In Europe in 2005, the EMA introduced the Conditional Marketing Authorization process which corresponds to the FDA's Accelerated Approval process. However, the frame conditions established by these pathways were still not a true incentive for pharmaceutical companies to develop blockbuster drugs because complex and laborious randomized clinical trials were still required even for smaller subpopulations with high medical needs. These frame conditions provoked a crisis around 2006 when it was found that very few substances were in the development pipeline. Additionally, since 2012, patents on existing drugs have started to expire. Thus, the end for blockbusters was preprogrammed because national Health Technology Assessment bodies and health insurers were demanding even lower prices for new drugs than for existing ones despite the new

drugs having demonstrated their added benefit.

The result of the crisis was a paradigm shift in the approval process for new drugs. While the previous focus of both the FDA and EMA was the treatment history, now they emphasized the patient populations in question (FDA) or the analysis of the pharmacologically active substance (EMA). Both agencies reacted promptly and established in the subsequent years several new but different tools (Chapter 3.3) which became legal with their implementation in the guidelines in 2013 (U.S. Food and Drug Administration 2013b, European Medicines Agency 2013a). However, whereas the FDA enabled the development of all types of agents for all subpopulations (e.g. naive, GTE, HTE), the priority of the EMA was the proof of quality, safety and efficacy of substances for broad indication using double blind RCTs with naive patients (Table 1), a procedure which does not favor a targeted and rapid drug development. This priority can be considered a reflection of the precautionary principle which is more prevalent in European societies than in the USA.

The significant differences in the regulations for drug approval are clearly reflected in the Target Product Profile (TPP, USA) and the Summary of Product Characteristics (SmPC, EU) which were analyzed in Chapter 2. The SmPC is a predefined and static document that is mandatory for approval. The TPP, however, is a target-orientated, flexible and non-mandatory tool which can be adapted like a business plan to new needs and situations by means of constant interaction between the manufacturer and the FDA. Another structural difference is that the FDA is the sole responsible authority and controls all steps of drug development and approval in the USA. The EMA, on the other hand, is an organizational agency and must reach agreement with all involved member states of the EU. This can be very time-consuming. Granting of final marketing authorization is the responsibility of the European Commission, which normally follows the proposal of the EMA. However, the decision concerning the launch of the product on national markets is the responsibility of the respective national authorities after their agreement with the national Health Technology Assessment bodies and the payers (Figure 1).

In 2012 the FDA introduced the Breakthrough Therapy Designation. Implementation of the aims of these procedures was possible due to the constant intensive communi-

cation between the manufacturer and the authorities as well as the application of the existing Rolling Review process. The EMA, however, strengthened the role of pharmacovigilance by means of a revision of the corresponding regulation which was put in force in 2012. Also, the SmPC was updated in view of safety concerns (European Medicines Agency 2013b). This was done in preparation of the necessary upcoming changes for faster drug development and approval to ensure the proof of quality, safety and efficacy.

In order to avoid that these new measures, together with the other known obstacles raised by the guidelines of 2013 will cause an additional administrative and economic burden for manufacturers, the procedures for drug development and subsequent approval must be fundamentally revised, accelerated and harmonized.

In preparation for the future in 2014, the EMA initiated a pilot project for adaptive licensing and adaptive pathways which is applicable for all current approval procedures. The most important features with an appreciable impact on clinical development and approval are:

- drug development for small patient subgroups is possible and accelerates the clinical program and timely access to new drugs for patients;
- applies also for innovative therapeutic approaches;
- safety and efficacy is assured through post approval studies;
- payers and the HTA bodies are involved at an early stage for debating aspects of the clinical program and solving the reimbursement problem;
- communication between the EMA and all stakeholders is intensified;
- in view of future harmonization, joint mutual consultation with the FDA was established.

In addition to this pilot project, the national HTA bodies and payers on their part are making efforts to harmonize their assessment criteria with each other. This will facilitate the future communication and negotiations with the EMA. An overview of the respective existing and emerging reimbursement access pathway is given by Baird *et al.* (2014, Table 2).

Taken together, it can be stated that the EMA is on a good way with its efforts to harmonize and implement procedures that consider the needs of all parties involved, he timely

access of safe and efficacious drugs for patients and the necessity of an attractive market landscape for the drug manufacturers. Nevertheless, it is desirable that the following measures be urgently executed

Mutual scientific advice

To ensure that all HIV patients worldwide have timely access to new and innovative agents, an advanced global harmonization of drug developmental and approval procedures is necessary. To achieve this, the exchange of information and mutual scientific advice on the basis of the commitment between the FDA and the EMA and the involved European national HTA bodies about parallel scientific advice (European Medicines Agency and U.S. Food and Drug Administration 2009) should be intensified.

Legalization and full implementation of adaptive pathways into the EMA guidelines

The first, most important and mandatory measure would be that the European Commission legalizes the adaptive pathways for all member states of the EU. This is a precondition for a revision of the guideline of 2013 by the EMA. Only then can the adaptive approaches be implemented. The revised guideline should also integrate the national Health Technology Assessment bodies and the payers requirements in the Adaptive Pathway procedure. Additionally, the EMA should make the SmPC more flexible. Early consultation and participation would be necessary because HTAs must verify whether the drug in question does indeed produce an added benefit since this is decisive for the negotiation on the amount of reimbursement. It is also crucial in reducing the time to market launch. Looking ahead, the overall objective is to harmonize the criteria for market access amongst all member states and to fix this in the guideline.

The reimbursement problem

The health care system in the USA has no universal regulation in respect of general assessment criteria for the problem of proportional cost sharing for drugs. It is well-known that in the USA, lower income patients have great problems paying for their medical care (medicines and treatments).

"In the words of one patient representative, "the safest drug that no one can afford or that arrives too late is of no benefit to a patient" (HTAi policy forum 2014, Washington, DC)." (Source: Eichler et al. 2015)

Details about current initiatives to solve the reimbursement problem in the USA are given in Baird *et al.* (2014, Table 2). But implementation of such measures is obviously more a political question which cannot be resolved by the FDA and the other stakeholders alone. The Clinton administration failed with its efforts to reform the health care system and Obama was only partially successful with 'Obamacare'. One can only hope that patient organizations as well as manufacturers will use their influence and act together for further improvement of the HIV landscape, they have already done so in the past, as described in Eichler *et al.* (2015):

"In the 1980s, the call for rapid access to new treatments was heard almost exclusively from HIV advocacy groups. [...] More recently, it expanded to advocacy for chronic inflammatory and neurologic conditions, and other chronic diseases. [...] These patients and their advocates emphasize that drug development and market access should not only benefit patients in some distant future state but should also address the unmet needs of the current generation of patients."

If the EMA and the European Commission will realize the above mentioned measures, it will be possible for the first time to develop and administer true therapeutic innovations for HIV such as immunomodulators, which are already used for cancer treatment, and not only concerning ongoing development of drugs for new classes as has been the case until now. This may open the door to functional healing of a HIV infection (Passaes *et al.* 2014) and other chronic viral diseases, and facilitate a timely and patient-friendly utilization of the rapid ongoing scientific progress in this field.

Taken together, it can be stated, that after the revision of the EMA Guideline becomes effective for HIV drug development and approval, approaches in the EU and the USA will be widely harmonized. The unsolved problem is the reimbursement. The USA should seek a more patient-friendly solution and within the EU the partially quite diverging financial power of its member states is a problem for the negotiation about the amount of reimbursement.

6 Summary

The European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) apply different approaches for development and approval of new HIV drugs. The objective of this thesis was to compare their respective guidelines and to discuss the impact of the current pathways on the future of drug development.

Development of new drugs for HIV and other chronic diseases is for different reasons a complicated undertaking for pharmaceutical companies. On the one hand, viral strains with resistance to the active substances emerge and patients no longer respond to therapies based on the original drugs with the consequent urgent need for new regimes. On the other hand, it is not economically profitable for a company to develop drugs tailored for small subpopulations. Apart from this, the greatest challenge is the legislative one: The lack of harmonization of drug approval procedures for these two important markets impedes commercialization and may result in a distortion of competition.

A comparison of the different approaches revealed a significantly higher flexibility in the FDA guidelines than those of the EMA for both the development and the approval procedure. The FDA facilitates development of any kind of drug for any patient group (naive, general and heavily treatment experienced) in any combination. The corresponding clinical trials are adapted to patients' needs and the characteristics of the population. An essential part of the FDA procedures is a continuous intensive communication between the FDA and the manufacturer during all stages of development ('Fast Track Designation' since 2007, 'Breakthrough Therapy Designation' since 2012). In contrast, the EMA allows development of any new agent only on the basis of data for quality, safety and efficacy generated in randomized double-blind clinical trials with first-time patients to get a broad indication. Exceptions for late general and patients with heavy treatment experience are possible on a case-by-case basis.

For the approval of new drugs tailored for subpopulations, the FDA enables a fast-track process by means such as the 'Rolling and Priority Review' and the 'Accelerated Approval' procedure which furthermore can be combined to allow a flexible step-by-step approval. Since 2005, the EMA has facilitated a 'Conditional Marketing Authorization'

(CMA), but only in 2014 did it initiate a pilot project, the 'Adaptive Licencing' (recently renamed Adaptive Pathways) process, for testing measures for faster approval. The used tools for implementation of CMA and Accelerated Assessment were revised in July 2015. The updates now endorse 'innovative medicine' and, hence, allow development of drugs under the same conditions as the Breakthrough Therapy Designation in the USA. An intensive continuous communication between all stakeholders, including the Health Technology Assessment bodies is now also an essential part. As a consequence, for many applications the review time can be reduced from 210 to 150 days. To assure the long-term safety for all patients, post approval studies are required according to the pharmacovigilance regulations in place since 2012.

The difference between the health care systems in the EU and the USA is the additional hurdle faced by companies wishing to enter the European market whereby the National Health Assessment bodies and the manufacturers must agree on the amount of reimbursement to be paid by health insurances. Reimbursement is only possible after manufacturers have proven the so-called additional benefit of a new drug in comparison to standard therapies. Proof of added benefit is a mandatory requirement for achieving market access (Efficacy-Effectiveness-Gap). To overcome this obstacle, the adaptive licensing procedure permits the integration of proving the added benefit already during the pre approval phase in adapted clinical trials. A soon to be introduced and efficient revision of the current EMA guideline should integrate the adaptive clinical trials and pathways, this would be a real incentive for companies to develop innovative new HIV pharmaceuticals. The adaptive approaches have already been used for approval of drugs for some types of cancer and HCV, but the matter of reimbursement is still unsolved for these drugs due the lack of data for Phase 3, i.g. no proof for added benefit, of the registration package.

The legal implementation of the adaptive pathways into the EMA guidelines is a precondition to develop new therapeutic interventions for the HIV disease which provide opportunity for functional healing. Taken together, it can be stated that, after the legalization of the adaptive pathways, the HIV drug development and approval approaches between the EU and USA will be widely harmonized. The unsolved problem is the patients' unfriendly reimbursement in the USA and the different financial power of the member states of the EU.

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Declaration on oath

Herewith I affirm that I have written this thesis myself and have not used any other resources and auxiliary means than those acknowledged.

05.11.2015

Date

Dr. J. Rahman

Signature