Regulatory approval options in emergency situations – a comparison between EU and US on the example of the Ebola virus

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2. List of abbreviations

API	Active Pharmaceutical Ingredient
ASPR	Assistant Secretary for Preparedness and Response
AVAREF	African Vaccine Regulatory Forum
BARDA	Biomedical Advanced Research and Development Authority
CBRN	Chemical, biological, radiological, nuclear
CDC	Centers for Disease Control and Prevention
CFDA	China Food and Drug Administration
CHMP	Committee for Medicinal Products for Human Use
CMC	Chemistry, Manufacturing and Controls
CP	Centralised Procedure
CPP	Certificate of Pharmaceutical Product
DoD	Department of Defense
EBOV	Ebola Virus
ECDC	European Centre for Disease Prevention and Control
EMA	European Medicines Agency
EOI	Expression of Interest
EU	European Union
EUA	Emergency Use Authorization
EVD	Ebola Virus Disease
FDA	Food and Drug Administraion, USA
FDASIA	Food and Drug Administration Safety and Innovation Act
FD&C Act	Federal Food, Drug, and Cosmetic Act
FDAMA	Food and Drug Administration Modernization Act
FPP	Finished Pharmaceutical Product
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GOARN	Global Alert and Outbreak Response Network
GSK	Glaxo-SmithKline
HIS	Health Systems and Innovation (WHO)
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

IHR	International Health Regulations
IMI	Innovative Medicines Initiative
IND	Investigational New Drug Application
IRB	Local Institutional Review Board
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MCMs	Medical countermeasures
NDA	New Drug Application
NIH	U.S. department of Health and Human Services – National Institutes of Health
NRA	National Regulatory Authority
OCET	Office of Counterterrorism and Emerging Threats
ODA	Orphan Drug Act
PEPFAR	President´s Emergency Plan for AIDS relief
PMDA	Pharmaceuticals and Medical Devices Agency, Japan
PQP	Prequalification Programme
REMS	Risk Evaluation and Mitigation Strategy
RL	Regulation
SAWP	Scientific Advice Working Party (EMA)
UN	United Nations
UNMEER	United Nations Mission for Ebola Emergency Response
WHO	World Health Organisation

3. Introduction

3.1 Ebola

The Ebola virus causes an acute, serious illness which is fatal if no treatment is applied. The corresponding disease was noticed for the first time in 1976 in outbreaks in Sudan and in the Democratic Republic of Congo. The outbreak in the Congo first started in a village near the Ebola river, from which the disease received its name. The current outbreak starting in December 2013 is the largest since the discovery of the virus and more people have did therein than in all others combined. A total of 27049 cases and 11149 deaths have been reported up to 24th May 2015.[1] It has spread starting from Guinea to Sierra Leone and Liberia and then through travelling to e.g. Nigeria, the U.S., to Senegal and Mali.

The virus family of the Ebola virus includes 3 types:[2] Cuevavirus, Marburgvirus, and Ebolavirus with five identified species: Zaire, Bundibugyo, Sudan, Reston and Taï Forest. The virus causing the (so-called) 2014 Ebola disease outbreak belongs to the Zaire species.

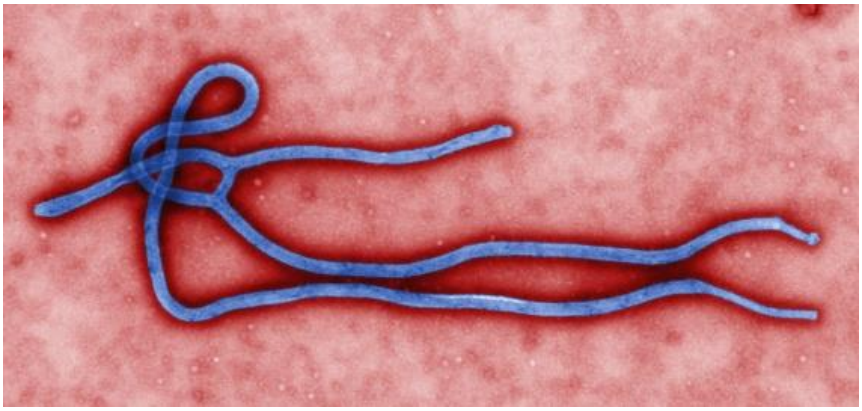

Figure 1: Colorized transmission electron micrograph (TEM) of ebola virus virion from Lit.Ref.[3]

The transmission is thought to have started with fruit bats of the Pteropodidae family as natural hosts of the Ebola virus. Ebola is introduced into the human body via contact with blood, organs, secretions or other body fluids of infected animals (e.g. fruit bats, chimpanzees, forest antelope). Human-to-human transmission then occurs in a similar way or also with contaminated surfaces or materials.

The incubation period is 2 to 21 days and until symptoms develop humans are not infectious. The first symptoms include sudden onset of fever fatigue, muscle pain, headache and sore throat, followed by vomiting, diarrhoea, rash, symptoms of impaired kidney and liver function, and in some cases, both internal and external bleeding.[2] So far, no drug treatments or vaccines are approved, only some

diagnostics are available. The WHO declared Ebola a public health emergency on 8th August 2014 as a result of the first meeting of the IHR Emergency Committee (a committee formed in the context of a possible public health emergency of international concern to advice to the WHO) with consequences and recommendations for the concerned countries, countries with potential cases or borders to case countries and also all other countries (e.g. national emergency declarations in the concerned countries, measures for preparation, surveillance and information to the public for all states etc.).[4]

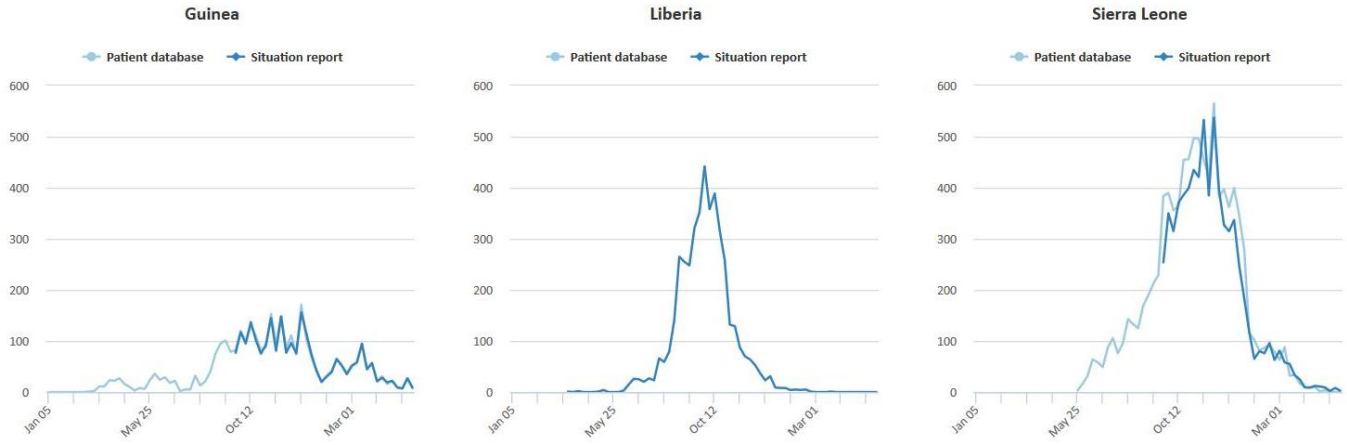

Figure 2: Progression of the Ebola Virus Disease from the beginning of the 2014 outbreak until today (May 2015) in the most concerned countries from Lit.Ref.[5]

Since beginning of 2015, the current Ebola outbreak has decreased remarkably due to a comprehensive supportive care treatment and as there were only 12 confirmed cases of the Ebola virus disease reported in the week of 24th May: 9 from Guinea and 3 from Sierra Leone. A total of 5 districts (3 in Guinea, 2 in Sierra Leone) reported at least one confirmed case, compared with 6 districts the previous week due to the actions taken by the WHO (see chapter 4). Even though the peak of the outbreak is over, at the latest meeting of the IHR Emergency Committee regarding Ebola, the WHO continued to constitute a Public Health Emergency of International Concern for the current EVD outbreak and recommended that all previous temporary recommendations should be extended as there is an issue of inappropriate health measures present in the concerned countries of the outbreak and recent infections of health care workers.[6]

3.2 Emergency declaration and immediate actions of the WHO

The WHO declared Ebola a public health emergency on 8th August 2014 as a result of the first meeting of the IHR Emergency Committee.[7]

On 28th August, the WHO published the "Ebola Response Roadmap"[8] with the main goal to stop the Ebola transmission in the concerned countries within 6-9 months from the publishing date and to prevent an international spread of the disease. As one of the major issues in operationalizing this roadmap is "Research & Product Development: […]to fast-track access to treatment and vaccine options to address Ebola Virus Disease…"[8], the WHO hosted first conferences at the beginning and end of September (4-5th, 29-30th September 2014) on potential Ebola therapies and vaccines and identified several therapeutic and vaccine interventions that should be the focus of priority clinical evaluation as none of these vaccines or therapies had been approved for human use to prevent or treat EVD.[9,10] WHO also initiated the 16th WHO International Conference of Drug Regulatory Authorities (ICDRA)[11] on 3rd September 2014, where drug regulators worldwide committed to enhanced cooperation with the WHO to encourage and support submission of regulatory dossiers and evaluations on potential new drugs, vaccines and diagnostics on Ebola with the aim to accelerate the access to these in the urgent need of the Ebola outbreak - also to ensure that public health authorities in the concerned countries will have safe and efficacious medicines at hand and therefore will be able to strengthen their response with regard to the Ebola outbreak.

Since then, the WHO continuously held numerous meetings throughout the Ebola crisis until today (May 2015) to evaluate and update on possible new Ebola vaccines (e.g. several meetings on Ebola vaccines and their clinical trial designs (latest in March 2015), vaccine access and financing or Safety of possible vaccines))[12], possible new Ebola drugs (WHO meeting on potential Ebola experimental interventions)[13] and Ebola diagnostics (WHO meeting on diagnostics and Ebola control).[14] In addition, several regulatory meetings with health authorities such as EMA, FDA etc. but also from the concerned countries were hosted by the WHO.[11,15,26,27,56]

Also the U.S. officially recognized the status of an emergency situation for the Ebola outbreak as the Secretary of HHS declared pursuant to section 564 of the FD&C Act 21 U.S.C. 360bbb-3[84] "that circumstances exist justifying the authorization of emergency use of *in vitro* diagnostics for detection of Ebola virus"[89] (for further details

see chapter 6.3.2.3). EMA and FDA both also acknowledged the Ebola outbreak as an emergency situation as they agreed on the status and subsequent actions at the 16th WHO International Conference of Drug Regulatory Authorities (ICDRA) on 3rd September 2014[11] after the WHO declaration of a public health emergency on 8th August 2014.[7]

4. WHO and its coordinating role regarding the Ebola disease

The World Health Organisation (WHO) was founded in April 1948 as a global health organization within the United Nations (UN) and today more than 7000 people from more than 150 countries work for it with its headquarters in Geneva, Switzerland. They are directing and coordinating the international health within the UN. Their general tasks are the provision of leadership on critical health matters and where joint action is needed, shaping the research agenda, setting and implementation of international norms and standards, articulating ethical and evidence based policy options, provision of technical support and monitoring the health situation and assessing the health situation and health trends.[16]

Within the Ebola crisis, they fulfill their role as a globally coordinating health organization and work in the following areas regarding the Ebola Virus Disease (EVD):[17]

- **Response**

  The WHO developed a Strategic Response Plan (2015)[18] and an Ebola Response Roadmap in 2014[8] to set the strategic objectives for the WHO:

  - Stop transmission of the Ebola virus in affected countries
  - Prevent new outbreaks of the Ebola virus in new areas and countries
  - Safely reactivate essential health services and increase resilience
  - Fast-track Ebola research and development
  - Coordinate national and international Ebola response

  Due to this Response, more than 950 technical experts are present in the most 3 affected countries in more than 60 field sites. In addition more than 500 trucks, 800 established treatment centers and 1.42 million of personal protective equipments are present in these countries due to the WHO.

- **Preparedness**

  The preparedness activities of the WHO aim to ensure that all countries are ready to effectively and safely detect, investigate and report potential EVD (Ebola Virus Disease) cases and to mount an effective response due to an adequate preparation. Such measures are e.g. international preparedness teams with partners such as Global Outbreak Alert and Response Network, the International Association of National Public Health Institutes and U.S. CDC visiting the corresponding countries to support them in developing readiness for the EVD as good as possible.

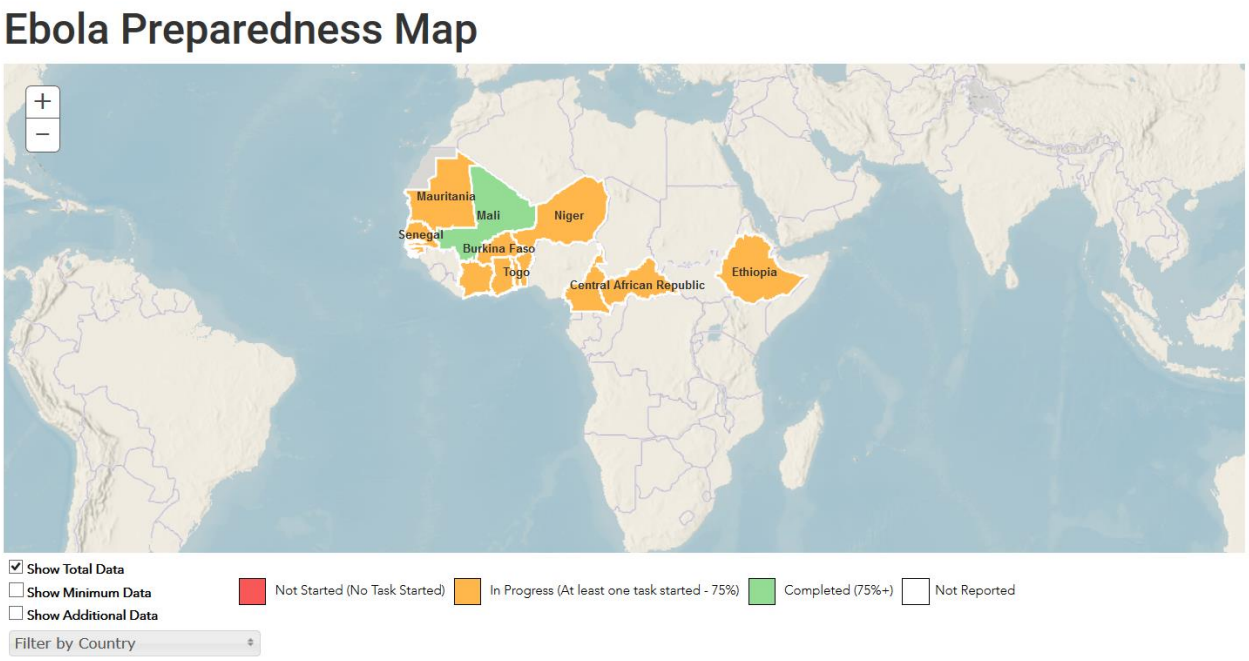

Figure 3: Ebola Preparedness Map from Lit.Ref.[17]

- **Research and Development**

  Research and Development activities are coordinated by the Essential Medicines and Health products, situated within the Cluster of Health Systems and Innovation (HIS). They are responsible to assist countries in increasing the availability of essential medical products, improving quality and safety of products and reduce counterfeit medicines, improving of selection/prescribing/dispensing and use and in implementation of policies. Another responsibility is the Prequalification Programme (PQP) at the WHO.

- **Training**

  The WHO coordinates the Ebola training in cooperation with the United Nations Mission for Ebola Emergency Response (UNMEER) to bring the Ebola Virus disease outbreak under control with the following responsibility:
    - providing scientifically sound advice and guidance to use in training
    - coordinating with and supporting training partners and governments
    - ensuring that trainings are of the required quality to respond to Ebola
    - working with UNMEER and partners to scale up training capacity on the ground
    - designing and delivering pre-deployment training for any personnel going to work in the affected countries

4.1 Prequalification Programme at WHO

The WHO prequalification programme (PQP) is an assessment to guarantee the Quality, Safety and Efficacy of medicinal products being purchased through international procurement agencies such as the UN for billions of US dollars for distribution in resource-limited countries. Originally implemented in 2001, the focus was on medicines for HIV/AIDS, tuberculosis and malaria, which was extended in 2006 to cover medicines for reproductive health and again in 2008 for acute diarrhoea in children. The Prequalification consists of 5 steps: [19]

1. The WHO PQP or other UN agencies issue an invitation to manufacturers to submit an expression of interest (EOI) for product evaluation. Only products listed in an EOI are suitable for prequalification, which is based on one of the following criteria:
    a. Listed in WHO list of essential medicines
    b. Application for the addition to the list of essential medicines has been submitted and is likely to meet criteria for inclusion (public health need, comparative effectiveness, safety and cost-effectiveness)
    c. Recommended for use by a current WHO treatment guideline
2. Dossier submission with a comprehensive set of Quality, Safety and Efficacy data
3. Assessment by a team of assessors including WHO staff and experts from national regulatory authorities worldwide

4. Inspection of manufacturing sites for the finished pharmaceutical product (FPP) and its API – compliance with WHO GMP, clinical studies with GCP and GLP.
5. Decision and listing in the List of Prequalified Medicinal Products, which can take up to 3 months

Prequalification of a medicinal product however does not imply a marketing authorisation approval by the WHO as an MA approval is the sole prerogative of a national health authority.[20] However, after having successfully passed the PQP, manufacturers can sell their product to UN agencies that spend a huge amount of money on these medicines. In addition, the PQP is the only global medicines quality assurance programme with active support from both developed and developing countries.[19]

4.1.1 Exemptions

In addition to the products listed and evaluated by the WHO PQP, also products assessed by other certain regulatory authorities can be listed in the List of Prequalified Medicinal Products.[20] This so-called alternative listing procedure includes generic and innovative products in which the WHO is interested as compounds for treatment of HIV, tuberculosis, malaria, and other diseases or for reproductive health, provided these certain regulatory authorities are willing to share the corresponding information. These certain authorities are EMA, FDA or Health Canada. For FDA regulated products, this can include FDA approved or FDA tentatively approved products (under the President´s Emergency Plan for AIDS relief, PEPFAR), for EMA regulated products these products can be regulated under Article 58 procedure (which is explained in detail in chapter 5.4.2.3). In addition, also medicines that were approved by a Stringent Regulatory Authority (SRA), which either must be member of the ICH, an ICH observer or associated ICH member, can be included in the List of Prequalified Medicinal Products. In this case, the manufacturer must include amongst others a copy of the Marketing Authorisation and a WHO Certificate of Pharmaceutical Product (CPP).[21]
Another exemption exists for missing expression of interests. The current invitations for EOIs are normally published on the PQP website of the WHO. However, in

situation of high public health concern as determined by the WHO, the WHO can directly invite the manufacturers to submit specified product dossiers for evaluation without publication of an invitation for an EOI.[22]

4.1.2 Prequalification Programme for the Ebola Virus Disease

Although for the Ebola Virus Disease there is no expression of interests on the PQP website of the WHO, the WHO declared Ebola a public health emergency on 8th August 2014 as a result of the first meeting of the IHR Emergency Committee.[7] As a result of this declaration, the WHO introduced an emergency procedure under its Prequalification Programme (without publication of an EOI) for rapid assessment of Ebola diagnostics for UN procurement in the countries affected by the Ebola outbreak.[14] A similar procedure can be thought of also for possible approved Ebola vaccines and treatments, if enough data on Safety and Efficacy will have been collected for these products under evaluation (see chapter 7) either by an assessment via the WHO or approval by another suitable health authority such as EMA or FDA (see above, exemptions from the PQP). The PQP would be an excellent tool for possible EMA or FDA approved products to direct them via the WHO/UN to the countries affected with the Ebola outbreak or for Ebola product developing companies to directly approach the WHO for assessment with subsequent approval in the concerned countries.

5. European situation

5.1 Role of EMA – in Europe and internationally

The main focus of the EMA is to accelerate the development and assessment processes of possible treatments and vaccines of Ebola and to share the initial reviews and subsequent updates with the corresponding authorities in those countries being most affected by Ebola.[23,24] Nevertheless on the other hand, the regulatory basis of an evaluation of new medicines has to be kept with a positive Risk-Benefit analysis with scientific evidence for Quality, Safety, Efficacy and value to the public health. To keep both these main aspects currently is a challenge as medicines against the disease are at an early stage of development and no approved option is available (status May 2015)[25].

The Agency agreed on this main goal of acceleration together with many other international agencies (e.g. FDA, CFDA, PMDA etc.) on the 16th WHO International Conference of Drug Regulatory Authorities (ICDRA) held in Rio de Janeiro from 24-29th August 2014. All these agencies also committed to enhanced cooperation with the WHO and between regulatory agencies.[11]

In order to achieve this goal, the EMA implemented several measures in the development and assessment processes for companies developing treatments and vaccines for the Ebola virus like the ad-hoc task force, rapid scientific advice, the encouragement to the parallel orphan designation for EMA and FDA and the rolling review of data, all of which will be explained in detail in chapters 5.3 and 5.4.[25] In addition to the implementations into their own processes at the EMA, the Agency supports the European Commission in their effort for faster information exchange between the European member states and in the coordination of approaches to prevent and prepare Ebola outbreaks.[25]

Internationally, the Agency is working together with other regulatory authorities around the globe to support the WHO in advising "on possible pathways for the development, evaluation and approval of medicines to fight Ebola".[25] The EMA therefore committed on the 16th WHO International Conference on Drug Regulatory Authorities (Rio de Janeiro 24th-29th August 2014) to enhanced cooperation with the WHO and other regulatory agencies to accelerate access to investigational medical products for patients in need and that countries affected by Ebola will in the future have safe and efficacious medicines to respond adequately to such outbreaks.[11] The EMA also participated e.g. at the WHO consultation on potential Ebola therapies and vaccines (Sept 2014) and the WHO consultation on Ebola vaccines (Sept 2014) where the EMA presented their perspective on possible regulatory pathways.[26]

Another example was the EMA participation at the 9th annual meeting of the African Vaccine Regulatory Forum (AVAREF) in Pretoria, South Africa from 3 to 7 November 2014 under the patronage from WHO, where the explicit request was made to the EMA as supporting regulatory authority "to do everything in their power to share data relevant to clinical trials with the NRAs [national regulatory agencies in Africa] of participating countries" and "to provide expertise to support NRAs in the joint reviews when requested".[27]

In addition to the direct EMA actions, there are also further initiatives going on with the European Commission regarding Ebola (see Table 4 below):

The European Commission's Health & Consumers Directorate-General and the European Centre for Disease Prevention and Control (ECDC) have been monitoring events with regard to Ebola and e.g. the ECDC is producing risk assessments, epidemiological updates and other information.[28]

Also on 6 November 2014, the IMI, a partnership between the European Union (represented by the European Commission) and the European pharmaceutical industry, launched Ebola+.[29] In this program on Ebola and related diseases, pharmaceutical companies collaborate with each other, experts from universities, regulators and others in Ebola research.

5.2 Time schedule EMA

In this chapter only the timeline of events with regard to Ebola, which have consequential actions for the EMA, will be discussed; details on these topics will be given in the subsequent chapters.

The Figure below (Figure 4[30]) describes the actions taken by the EMA in 2014 and beginning of 2015 in the upper part of the graphic, whereas in the lower part related World Health Organisation (WHO) or other activities are presented.

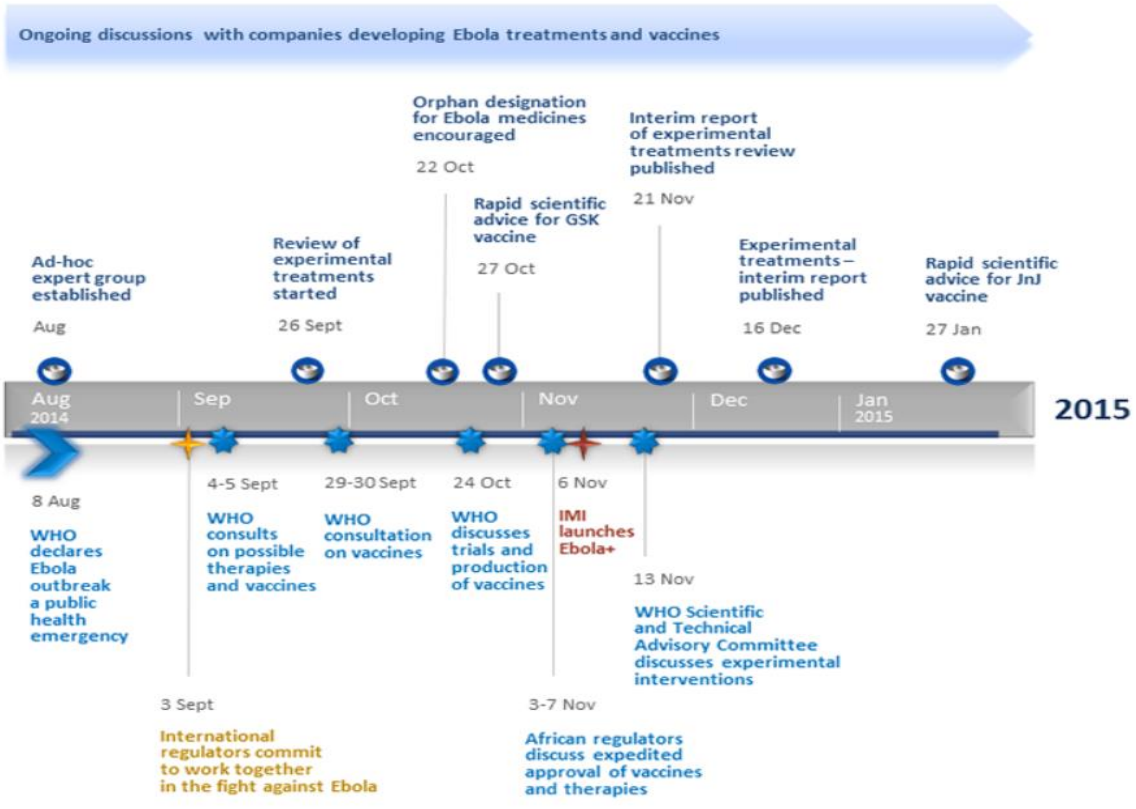

Figure 4: Time schedule EMA actions from Lit.Ref[30]

Immediate EMA actions on the Ebola outbreak started in August 2014 with the establishment of an ad-hoc expert group (detailed information and tasks of the group see chapter 5.3.1.1) directly after the WHO declared Ebola a public health emergency on 8th August 2014 as a result of the first meeting of the IHR Emergency Committee.[7]

As a follow up of the 16th WHO International Conference of Drug Regulatory Authorities (ICDRA)[11] statement (3rd September 2014), the EMA started reviewing potential Ebola therapies (26th September 2014) and their executive director mandated the CHMP "to scrutinize all the available information about experimental treatments and compile everything we know to date about their efficacy, safety and quality."[31] Follow-up interim reports were published by the EMA, the latest in January 2015 (see chapter 5.3.1.4).[32]

The orphan designation for new medical products against Ebola was encouraged from October 2014 onwards and two Rapid Scientific Advices were held for GSK and JnJ vaccines in development so far.

5.3 EMA - New and established measures to accelerate the development for new Ebola treatments and vaccines

5.3.1 New Measures

The EMA implemented different measures and recommends established procedures to achieve their main goal to accelerate the development and assessment processes of possible treatments and vaccines of Ebola and to share the initial reviews and subsequent updates with the corresponding authorities in those countries being most affected by Ebola.[23,24] These measures include the establishment of an ad-hoc Task Force to bring together and concentrate the best expertise regarding Ebola, the facilitation of the development of Ebola medical products via implementing Rapid Scientific Advice and simplifying/encouraging the orphan designation, accelerate the data review by introducing a so-called "Rolling Review" and also to proactively review the available treatments and contact the developers. All of these measures will be discussed more detailed in the next chapters.

5.3.1.1 Ad-hoc Task Force

To bring together the expertise on Ebola and to contribute specifically to the global response against Ebola, the EMA has established a group of European experts.[25]

The group consists of EMA scientific committee and working party members with relevant experience in vaccines, infectious diseases, preclinical and clinical trial design, paediatric aspects and quality of biological medicinal products and is consigned to be responsible for the following tasks: [31,24,26]

- rapid scientific advice
    - on questions from manufacturers on their development plans, endorsed by CHMP
    - to individual developers of Ebola medicines on scientific and regulatory matters
- accelerated assessment of data generated by developers
- proactive contact to developers of potential treatments
- Exploratory review of current investigational products for treatment or prevention of EVD including TCs with developers.
- to identify the most appropriate regulatory pathway to ensure that potential treatments and/or vaccines are approved/made available as swiftly as possible

5.3.1.2 Rapid Scientific Advice

To facilitate and accelerate the development on vaccines and therapies against the Ebola disease, one of the procedures the EMA has established is the so-called "Rapid Scientific Advice". Through this procedure, developers of possible Ebola vaccines/treatments will receive an *accelerated* scientific advice on their questions regarding e.g. clinical trial design, manufacturing related questions (e.g. scaling-up, batch release) and post-authorisation safety monitoring of medicines.[24] The EMA explicitly encourages companies to request this Rapid Scientific Advice for their development plans on Ebola vaccines and treatments to generate the robust data and information needed to assess the developed compounds for efficacy, safety and high quality in an accelerated manner.[33] There are no specific timelines for the Rapid

Rapid Scientific advice

Vollansicht schließen

Von: [redacted]

07.04.2015 um 19:48 Uhr

Dear Florian,

Thank you for your enquiry.

There are no timelines for the rapid Ebola advice. The timelines can be as short as a couple of weeks from the submission of the final request to 40 days or even more depending on the request from the companies, the need to involve additional experts, committees, working parties, the need to coordinate the rapid advice with feedback from WHO, FDA, African authorities or other parties involved in activities related to Ebola crisis.

The information on rapid scientific advice are available in our website, but since advices are confidential we cannot really provide more data.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000624.jsp&mid=WC0b01ac0580841e30

Kind Regards,

[redacted]
Scientific Officer
Scientific Advice Office
Product Development Scientific Support Department

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Figure 5: Email received from the SAWP at EMA on 7th April 2014 regarding timelines of the Rapid Scientific Advice

Scientific Advice. After contacting the Scientific Advice Group at the EMA (as no further information could be found on the EMA websites or guidelines/guidances etc. on Rapid Scientific Advice), the following answer was received: "The timelines can be as short as a couple of weeks from the submission of the final request to 40 days or even more depending on the request from the companies, the need to involve additional experts, committees, working parties, the need to coordinate the rapid advice with feedback from WHO, FDA, African authorities or other parties involved in activities related to Ebola crisis" (Scientific Advice Office, EMA).

The first Rapid Scientific Advice was given to GSK on their possible Ebola vaccine ChAd3-ZEBOV, which is co-developed with NIH, on 29th October 2014.[27,34]

Figure 6: Twitter News on 1st Rapid Scientific Advice by EMA[34]

A further Rapid Scientific Advice was given to Johnson & Johnson by the EMA on their vaccine currently under development on 27th January 2015.[25]

5.3.1.3 Rolling review of data

Another action of the EMA to support their main goal to accelerate the development and assessment processes of possible treatments and vaccines of Ebola and to share the initial reviews and subsequent updates with the corresponding authorities in those countries being most affected by Ebola[23,24] is the Rolling Review of data. This concept was in use in a similar way during the 2009 pandemic influenza to speed up the assessment of influenza vaccines[35] and is used in a different stepwise approach in the adaptive pathway (former adaptive licensing), the latter using only the already implemented regulatory approval options.[36] Rolling Review means that the developers of possible Ebola vaccines and treatments submit the data to the EMA for evaluation as soon as they become available instead of submitting the whole finished package with all data as in a normal application for a centralized procedure. The EMA experts then continuously assess the incoming data as soon as they receive each package and develop increasingly robust scientific opinions based on the additional data that is provided during the process. They will also share each single data review with the healthcare decision-makers in the most affected countries to enable them to take profound decisions on the overall use and timing of use of these Ebola drugs taking into account their specific situation.[33] The former Executive Director of the EMA, Guido Rasi, was convinced that this is one of the right measures in this context: "We are ready and keen to assess data as soon as companies start submitting them. We have put in place regulatory processes that allow the best experts from across Europe to accelerate the assessment of data once we receive them."[24]

5.3.1.4 EMA review

As a proactive measure the EMA has started and is continuing to review[37] the available information on Ebola treatments that are currently under development. This kind of review is possible due to Article 5 (3) of regulation 726/2004, which allows the Executive director or the European Commission to ask the CHMP for an opinion on "any scientific matter" regarding medicinal products for human use:

> "At the request of the Executive Director of the Agency or the Commission representative, the Committee for Medicinal Products for Human Use shall

> also draw up an opinion on any scientific matter concerning the evaluation of medicinal products for human use. […] The opinion of the Committee shall be made publicly accessible." [38]

The former Executive Director of the EMA, Guido Rasi, pointed out the urgent reason for this measure in case of Ebola:[31]

> "Health authorities or practitioners who need to take a decision whether or not to use an experimental Ebola treatment in a patient are currently lacking independent information. I have therefore asked the EMA Committee for Medicinal Products for Human Use, CHMP, to scrutinize all the available information about experimental treatments and compile everything we know to date about their efficacy, safety and quality. This will facilitate evidence-based decision-making."

The review started on 26th September 2014 and focuses only on the treatments under development that are used for people being infected with the virus. Vaccines for protection were excluded from this review. Also, only products under development were taken into account that showed direct antiviral activity against the Ebola virus established e.g. by *in vitro* or *in vivo studies*. As a response to the CHMP request, the data was provided by seven companies fulfilling the corresponding criteria for the following compounds:

BCX4430, Brincidofovir , Favipiravir, TKM-100802, AVI-7537, ZMapp, Anti-Ebola $F(ab´)_2$

The latest updated interim report was published on 22nd January 2015[32] (taking into account all information received until December 2014) and came to the following overall conclusions:

- "The amount of preclinical and human safety data available are highly variable, ranging from no human data to relatively large amounts of data on the treatment of other viral diseases
- While some of these products have been given to a limited number of patients with EBOV infection on a compassionate-use basis, available clinical data are not sufficient for an evaluation of efficacy, safety and pharmacokinetics in the target population at this stage
- The appropriate dosing of all the products reviewed is uncertain."[32]

5.3.2 Established Measures

5.3.2.1 Orphan Designation

A further tool to accelerate the access to possible EVD drugs is the encouragement of the EMA to Ebola treatment and vaccine developing manufacturers to apply for an

orphan designation. According to the EMA, the prerequisites for an orphan designation according to REGULATION (EC) No 141/2000 on orphan medicinal products laid down in §3 (1) are met in the case of Ebola[39,40]:

- intention for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating;
- the prevalence in the EU must not be more than 5 in 10,000 or it must be unlikely that marketing of the medicine would generate sufficient returns
- no satisfactory method of diagnosis, prevention or treatment of the condition concerned has been authorised, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition

The orphan designation also leads to a mandatory scope of the centralized procedure in a subsequent Marketing Authorisation Application. In addition to the possible beneficial incentives for the developers (including reduced fee for scientific advice from EMA, fee reductions for further regulatory activities, access to centralized procedure, EU/Member State grants and 10 years of Market Exclusivity in case of authorisation[41]), the EMA points out that the orphan designation provides the requirements to facilitate and accelerate the dialogue between EMA and manufacturers from the early stage of development on. Also, the EMA encourages the developers of Ebola medicines to submit an application for orphan designation in parallel to the EMA and FDA as this will speed up the development process for these medical products in a global context. In this case, both agencies will then share the information received and also their assessments.[40] Due to a combined application form for EMA and FDA on orphan designation, also the applicant is able to facilitate this process.[42]

5.4 EMA - Fast Regulatory approval and access options in the emergency situation of the Ebola Virus Disease

Members of the EMA committed together with many other international agencies on the 16th WHO International Conference of Drug Regulatory Authorities (ICDRA) held in Rio de Janeiro from 24-29 August 2014 to enhanced cooperation with the WHO and between regulatory agencies with regard to the EVD.[11] The aim of this commitment was to accelerate the development and assessment processes of possible treatments and vaccines of Ebola and to share the initial reviews and subsequent updates with the corresponding authorities in those countries being most

affected by Ebola.[24] The implementation of this commitment was executed by several measures like the Ad-hoc Task Force, the Rapid Scientific Advice, Encouragement of the Orphan Designation for possible Ebola drugs and vaccines, the Rolling Review of Data and the proactive EMA review on present compounds (all of which were discussed in detail in chapter 5.3). All of these methods were established to accelerate the development of new compounds: the Ad-hoc expert group to bring together the necessary expertise for quick and profound decisions, the Rapid Scientific Advice to give direct and fast answers to questions by the developing companies, the encouragement to apply for an orphan designation to facilitate the dialogue between EMA and manufacturers from the early stage of development on and to work closely with the FDA, the Rolling Review to assess the development Safety and Efficacy data of new compounds without delay in real-time and the proactive Review to begin as soon as possible with the assessment of newly developed compounds.

However, no new Marketing Authorisation procedures for human medicinal products in the EU were established to accelerate the development and assessment of possible treatments and vaccines of the EVD in the current situation. According to an EMA presentation held on the WHO consultation: "What could be the clinical and regulatory pathway for Ebola vaccines" in Geneva on the 29th September 2014[26], the following two options can be considered for a fast Marketing Authorisation procedure at the EMA:

- Standard EU approval
- Article 58 procedure

taking into account early approval pathways (like conditional approval and accelerated assessment) and early access options (e.g. compassionate use programs).

Even though presented only for possible Ebola vaccines due to the consultation topic at the WHO, these options also count for possible Ebola treatments.[24]

5.4.1 Early Access options in the EU before CHMP approval

5.4.1.1 Compassionate Use Program and treatment on "named-patient basis"

An early access option for patients to medicinal products before EMA/CHMP approval in the European Union is the Compassionate Use, which makes a promising

medicine, that has not been authorized yet, available to patients with an unmet medical need.

Article 83 (1) of Regulation (EC) No 726/2004 provides the basis for compassionate use compounds that are eligible to be authorized via the Centralised Procedure, stating that

> "by way of exemption from Article 6 of Directive 2001/83/EC, MS may make a medicinal product for human use belonging to the categories referred to in Article 3(1) and 3(2) of Regulation (EC) No 726/2004 available for compassionate use"[38]

However, the implementation of Compassionate use remains the competence of a Member State of the European Union and the role of the CHMP remains to provide recommendations to the member states on administration, distribution and use of medicines and its recommendations aim to standardize the compassionate use program throughout the European Union.[43]

A compassionate use program can only be set up for a group of patients with a chronically or seriously debilitating or life-threatening disease and who cannot be treated satisfactorily by an authorized medicinal product (RL 726/2004 Art. 83 (2))[38]. In general, toxicology studies for the product have been completed and analysed and first studies in humans also have been completed and patients cannot enroll in an ongoing clinical trial.[44]

The possibility of a Compassionate Use Program in general represents a good and reasonable option for new EVD vaccines and treatments, as this route provides patients with a great unmet medical need early access to unauthorized new treatment possibilities. Several compounds in development for the EVD have already been used on a compassionate use basis according to the WHO[45]; however, as most of the programmes probably will not take place in the countries of the European Union due to the geographically focused spread of the disease, this probably will not be a commonly used access possibility in the EU. In single cases of occurrence of the disease, doctors also have the possibility to obtain promising medicines for their patients by directly requesting it from the manufacturer under their direct responsibility without a central register of these treatment cases. These cases are often referred to as treatments on a "named-patient basis".[44]

5.4.2 Fast Regulatory approval options in the EU

5.4.2.1 Conditional approval

As the options for a faster EU Marketing Authorization with an incomplete dataset of the medicinal products are well known and established procedures also in non-emergency situations, these procedures will only be discussed briefly.

For a regular marketing authorization in the EU, the applicant has to prove clinical Safety and Efficacy with a full development dataset of preclinical and clinical trial results, a description of the Risk-Management system and a positive benefit-risk ratio. However, according to Regulation 726/2004 Art. 14 (7)[38] and 507/2006 Art. 2[46] in the special cases of

- Medicinal products for seriously debilitating or life-threatening diseases
- Medicinal products to be used in emergency situations (recognized by WHO or EC)
- Medicinal Products designated as orphan medicinal products

a Conditional Marketing Authorization may be granted where only the clinical part of the dossier is less complete than normal and is filed afterwards. The only exemption from this definition is that "incomplete pre-clinical or pharmaceutical data should be accepted only in the case of a product to be used in emergency situation, in response to public health threats."[46] The following requirements have to be fulfilled (Art. 4 (1) RL 507/2006[46]):

- the risk-benefit balance of the medicinal product, as defined in Article 1(28a) of Directive 2001/83/EC, is positive
- it is likely that the applicant will be in a position to provide the comprehensive clinical data
- unmet medical needs will be fulfilled
- the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required

If the applicant can show that "he is unable to provide comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use" (RL 726/2004 Art. 14 (8))[38], an approval under exceptional circumstances can be granted.

In addition, specific obligations are bound to the conditional approval by e.g. completing ongoing studies or conduct new studies in a clearly defined timeframe to

confirm the positive benefit-risk ratio and the Renewal of the Marketing Authorisation takes place anually (Art. 5 and 6, RL 507/2006[46]). A transformation after fulfillment of these obligations in a full MA however is possible.
Therefore, the Conditional Marketing Authorisation represents a good option for possible EVD vaccines and treatments to achieve faster market access compared to the regular MA procedure as the current situation fulfills the necessary general requirements as the WHO recognized it as an emergency situation.[7] Further requirements according to Art. 4 (1) RL 507/2006[46] depend on the product. In addition, due to the emergency situation of Ebola, a newly developed EVD vaccine or treatment could also be approved via the conditional MA with incomplete pre-clinical or pharmaceutical data.
In combination with the above explained conditional approval, an orphan status for the medicinal product (which was already explained in detail and is encouraged by the EMA for Ebola drug developing companies, see chapter 5.3.2.1) would combine the earlier market access from the conditional approval with several incentives from the orphan designation (e.g. several fee reductions and Market Exclusivity) and therefore would represent a very attractive possibility for the developers of new EVD drugs and vaccines to gain a Marketing Authorisation in the EU.

5.4.2.2 Accelerated assessment

An accelerated assessment (RL 726/2004 Art. 14 (9))[38] can be requested from the EMA only in the case that the application for the medicinal product for human use is of *major interest*

- from the point of view of **public health**
- in particular from the viewpoint of **therapeutic innovation**

If requested, the application for accelerated assessment however has to be thoroughly substantiated. If successful, the review time of the CHMP can be reduced from 210 to 150 days.
An accelerated assessment procedure could therefore also be considered to speed up the two MA procedures of a conditional approval and the Article 58 procedure; however due to the measures already being implemented in case of EVD (e.g. rolling review etc., see chapter 5.3.1.3), already more effective options seem to be established in accelerating the assessment of the CHMP.

5.4.2.3 Article 58 procedure

According to Article 58 of RL 726/2004[38] the EMA is enabled to give a scientific opinion in cooperation with the WHO for the evaluation of certain medicinal products for human use intended exclusively outside the European Union to prevent or treat diseases of major public health interest (which does not exclude a future application for a MA within the EU). Therefore, no Marketing Authorisation within the EU normally is achieved following this procedure. Article 58 was intended to respond to the need to protect public health and to give scientific assistance to non-EU countries in cooperation with the WHO to allow rapid access of drugs in these countries.[47] A new product may be eligible for Article 58 under the following pre-conditions:

- vaccines that are or could be used in the WHO Expanded Program on Immunization
- vaccines for protection against a WHO 'public health priority disease'
- vaccines that are part of a WHO-managed stockpile for emergency response
- medicinal products for WHO target diseases such as human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), malaria, tuberculosis, lymphatic filariasis (elephantiasis), trachoma, leishmaniasis, schistosomiasis, African trypanosomiasis (sleeping sickness), onchocerciasis (river blindness), dengue fever, Chagas disease, leprosy and intestinal helminths.

However, vaccines or medicinal products for further diseases also may qualify for an Article 58 procedure, clarification then will be provided by the EMA.

For the scientific evaluation according to Article 58 by the CHMP, the same standard applies as for the assessment of EU medicines (e.g. on Quality, Safety, Efficacy, Benefit/Risk etc.) as it will be performed according to EU/ICH guidelines. Furthermore, the same data requirements and evaluation standards will be adhered (with possible adjustments if appropriate like e.g. stability).[47] In general, the evaluation also follows the same requirements (e.g. on type of application, documentation, format etc.) and procedures (e.g. 210 days until opinion from CHMP) as laid down in Article 58 of RL 726/2004[38]:

> "For this purpose, an application shall be submitted to the Agency in accordance with the provisions of Article 6. The Committee for Medicinal Products for Human Use may, after consulting the World Health Organisation, draw up a scientific opinion in accordance with Articles 6 to 9."

Also the principles of a “conditional marketing authorisation”-opinion or a “marketing authorisation under exceptional circumstances”-opinion are possible within the Article 58 procedure as it refers to the applicability of Article 9 of RL 726/2004[38], which in turn refers to Article 14(7) and (8) of the same regulation.

However, there are some major differences in comparison to the standard Centralised Procedure, which are listed in the following table:[47,48]

	Article 58[47,48]	**Standard CP**[38,49]
PRE-SUBMISSION		
Scientific Advice	• Yes, in cooperation with WHO	• Yes
eligibility request	• 6 months prior application • WHO consultation	• 7 months prior application
SUBMISSION		
CHMP opinion / Scientific evaluation	• CHMP • Input from WHO experts • Observers from developing countries	• CHMP
Paediatric legislation and PIP	• No • Encouraged by EMA	• Yes
Invented Name	• No	• Yes
Product Information, Mock-ups, Specimens	• Only Product Information • English only	• Yes • Multi-lingual
Data or market exclusivity	• No	• Yes (possible)
Pharmacovigilance System, RMP	• Yes, exceptions only in accordance with EMA	• Yes
Environmental risk assessment	• No	• Yes
Orphan status	• Not possible	• Possible
POST-OPINION		
European decision making process after CHMP opinion	• No (EPAR: yes)	• Yes
Marketing Authorisation in EU	• No	• Yes
• **PSURs** • **Variations**	• Yes • In cooperation with WHO	• Yes • Yes

Sunset clause	• No	• Yes

Table 1: Major differences between Article 58 and Centralised Procedure

So far, 7 positive opinions have been granted by the CHMP, in co-operation with the WHO, on medicines for human use that are intended exclusively for markets outside of the European Union.[50] The application for 1 compound was withdrawn at Day 120 of the procedure (Globorix©, a compound planned to be used to vaccinate infants under one year of age against diphtheria, tetanus, pertussis, hepatitis B and invasive diseases plus serving as a booster for already vaccinated children) as it was not possible in this case to establish the shelf life, too few children from the concerned area were involved in the studies and there was insufficient information on the use of the vaccine as a booster.

5.4.2.4 Article 58 procedure vs EU Marketing Authorisation

The major advantage of the Article 58 procedure lies within the close and early regulatory interaction and alignment of the EMA with the WHO as *the* directing and coordinating authority on international health within the United Nations' system and therefore being the major player in global health crises. Within the Article 58 procedure, the WHO is included from the beginning in the major steps such as the eligibility of the product for the Article 58 procedure, Scientific Advices of the developing company, the scientific evaluation leading to the CHMP opinion and also in post-opinion activities. This makes sure, that the WHO is deeply involved in the actual status/evaluation of a possible new compound and can plan, react and evaluate quickly with this information in possible emergency situations. Also, if a new compound has been granted a positive opinion in the Article 58 procedure, it makes it much faster and easier to gain approval through the WHO prequalification programme (which could be a possibility also for new EVD drugs and vaccines, see chapter 4.1) as seen by the experience with the compound Pyramax.[51] Additionally, also regulators from the concerned countries outside the EU are already involved in the assessment following the Article 58 procedure.

The major disadvantages of the Article 58 procedure are the lacking incentives (no orphan status possible) for the developing companies offered. No automatic fee reductions or exemptions are available; these can only be granted on case-by-case decisions and if requested. In addition, no Marketing Authorisation within the EU is achieved. Also the pharmacovigilance obligations after the opinion may be difficult to

meet depending on the infrastructure of the country where the medicinal product will be used.

The other possibility for a newly developed EVD drug in the EU would be the "normal" centralized EU procedure, especially the combination of a conditional approval with an orphan status. Even though a conditional approval is also possible for the Article 58 procedure and further obligations are added in comparison to Article 58 (e.g. PIP, see Table 1), the orphan status is not possible for Article 58 and provides several automatic incentives for the pharmaceutical company. If granted an orphan designation in the development status, Scientific Advices may be offered partially or totally free. Furthermore, several various regulatory fee reductions (e.g. application fee, inspection fees) are granted as well as Marketing Exclusivity and Data Exclusivity. However, it has to be ensured in the latter case that the product is available on the European market within 3 years as otherwise the Marketing Authorisation ceases to exist.

Both procedures nevertheless represent valuable tools in facilitating the authorization of possible Ebola vaccines and treatments, both providing their advantages and disadvantages and therefore the regulatory route taken depends on the strategy of the applicant. In the end, the presence of each Ebola vaccine or treatment in West Africa ultimately depends on regulatory authorization in each of the affected countries. However, the regulatory evaluations by a regulatory authority such as the EMA, the FDA, or any other with high quality standards and the corresponding capacities will facilitate and expedite regulatory processes at the WHO, in West Africa or any other country affected by the spread of the Ebola disease.

5.5 Initiatives in the EU

There are several funding initiatives worldwide to quickly support and boost new development due to the lack of vaccines and treatments against the Ebola Virus Disease in the current situation[53]; the most important by the European Commission are the following: The Emergency procedure under Horizon 2020 focuses on pre-clinical and clinical aspects, the European Developing Countries Clinical Trials Partnership (EDCTP) is an already established funding programme to accelerate development of new drugs, vaccines and diagnostics against poverty-related

diseases (where Ebola was included in September 2014). The most funded programme in the EU however is Ebola+.[53]

5.5.1 Ebola+

The Ebola+ funding programme was set up to enhance collaboration between pharmaceutical companies and experts from universities, small biotech companies, regulators and others to approach the challenges in Ebola research.[29] This programme was created by the Innovative Medicines Initative (IMI2), which is a partnership between the European Union and the European pharmaceutical Industry, the latter being represented by the European Federation of Pharmaceutical Industries and Associations (EFPIA). The first call for Ebola+ was launched on 6th November 2014 with a funding budget of 215 million Euros, about half of which comes from the EU and the other half from the pharmaceutical industry. The main focus on the 1st call was on five major funding topics that are vaccine development, manufacturing capability, stability of vaccines during transport and storage, deployment and compliance of vaccination regimens and rapid diagnostic tests.[52] The first 8 projects were selected in January 2015 addressing development and manufacturing of vaccines (VSV-EBOVAC (€3.9 million), EBOVAC1 (€91 million), EBOVAC2 (€37.9 million), EBOMAN (€48.6 million)), ensuring compliance with vaccine regimens (EBODAC (€25.7 million)), and the development of rapid diagnostic tests (MOFINA (€1 million), FILODIAG (€2.3 million), EbolaMoDRAD (€4.3 million)). The first projects have started working as of 1 January 2015.[53]

5.5.2 European Centre for Disease Prevention and Control

Another important role concerning the EVD plays the European Centre for Disease Prevention and Control (ECDC). This EU agency was established in 2005 and is aimed at strengthening Europe´s defences against infectious diseases. The ECDC´s task is to identify, assess and communicate current and emerging threats to human health posed by infectious diseases with the following mission:[54]

(a) search for, collect, collate, evaluate and disseminate relevant scientific and technical data;

(b) provide scientific opinions and scientific and technical assistance including training;

(c) provide timely information to the Commission, the Member States, Community agencies and international organisations active within the field of public health;

(d) coordinate the European networking of bodies operating in the fields within the Centres mission, including networks arising from public health activities supported by the Commission and operating the dedicated surveillance networks;

(e) exchange information, expertise and best practices, and facilitate the development and implementation of joint actions.

In case of the Ebola Virus Disease, the ECDC provides several important tasks to overview the disease as e.g. it tracks the actual epidemiological situation of the disease (e.g. actual number of cases, in which countries etc.), provides an actual risk assessment of the current situation of the disease or gives information and an algorithm on how to execute a patient and case management.

6. U.S. situation

6.1 Role of FDA in the US and internationally

The FDA (Food and Drug Administration) in the current Ebola situation pursuits a similar main goal as the EMA "to help expedite the development and availability of medical products – such as treatments, vaccines, diagnostic tests, and personal protective equipment – with the potential to help bring the epidemic under control as quickly as possible" as the former Commissioner of the Food and Drug Administration Margaret A. Hamburg stated on the FDA's official blog "FDA Voice"[55] and is paying a lot of attention and effort into the EVD situation: "FDA has been fully engaged in response activities and is using its authorities to the fullest extent possible to continue its mission to protect and promote the public health, both domestically and abroad. Our staff is fully committed to responding in the most proactive, thoughtful, and flexible manner to the Ebola epidemic in West Africa." The FDA agreed - as the EMA did also - on this main goal of acceleration of access to medical products against Ebola together with many other international agencies on the 16th WHO International Conference of Drug Regulatory Authorities (ICDRA) held in Rio de Janeiro from 24-29 August 2014. All these agencies also committed to enhanced cooperation with the WHO and between regulatory agencies.[11] Together with the EMA, the FDA also participated at the WHO consultation on Ebola vaccines

(Sept 2014) where the FDA presented their perspective on possible regulatory pathways[56] and at the 9th annual meeting of the African Vaccine Regulatory Forum (AVAREF) in Pretoria, South Africa from 3rd to 7th November 2014 under the patronage from WHO, where the same request was made to the FDA (as to EMA) "to do everything in their power to share data relevant to clinical trials with the NRAs [national regulatory agencies in Africa] of participating countries" and "to provide expertise to support NRAs in the joint reviews when requested".[27]

6.2 FDA - New and established measures to accelerate the development for new Ebola treatments and vaccines

6.2.1 New Measures

6.2.1.1 Ebola Task Force

Similar to the Task Force established by the EMA (see chapter 5.3.1.1), also the FDA established an "Ebola Task Force" as one of the immediate response measures to the Ebola outbreak in West Africa. This Ebola Task Force includes members from all across the FDA with the assignment to coordinate the activities of the FDA regarding Ebola and cooperation on this matter with other federal US institutions, the medical and scientific community, industry and international organizations and regulators with the main goal "to help expedite the development and availability of medical products - such as treatments, vaccines, diagnostic tests, and personal protective equipment"[55]

6.2.1.2 Advices and Cooperation

The FDA seems to be in a constant contact to those pharmaceutical companies developing medical products against Ebola to clarify regulatory and data requirements necessary to enhance the development of these compounds, to provide input on manufacturing and pre-clinical and clinical trial designs, and expedite the regulatory review of data as it is received. According to the FDA, they "remain in contact with more than 20 sponsors that have possible products in pipeline".[57]

In addition, the FDA works together with several U.S. government institutions that fund medical product development e.g. participates in an interagency working group led by the Assistant Secretary for Preparedness and Response (ASPR) / Biomedical Advanced Research and Development Authority (BARDA) to facilitate and accelerate development of potential investigation treatments for Ebola or provides scientific and regulatory advice to development supporting U.S. government agencies, including

the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the Department of Defense (DoD).

6.2.1.3 Deployment of FDA employees

Also a direct practical contribution was conducted as 12 FDA employees were being deployed to West Africa as part of the Public Health Service's team to help with medical care.[58]

6.2.2 Established Measures

6.2.2.1 Orphan Designation

For the acceleration on development of new vaccines and treatments against Ebola, similar to the EMA (see chapter 5.3.2.1) the FDA explicitly encourages to use the orphan designation, also for a parallel orphan designation for EMA and FDA:

"The FDA has been actively using orphan designation and other drug development programs to encourage the development of treatments for Ebola. This designation, coupled with other FDA programs used to expedite product development, review and approval, provides incentives to encourage companies to invest and develop treatments for rare diseases like Ebola, with the ultimate goal of getting safe and effective products to U.S. patients as quickly as possible. The FDA has granted orphan designation to products being developed to treat Ebola virus infection. […] FDA has been collaborating very closely with the European Medicines Agency (EMA) on orphan designation over many years. Developers of Ebola medicines are encouraged to submit applications for orphan designation to FDA and EMA in parallel to help speed the development process for these products globally. Both agencies will be sharing information on the applications received and their assessment to facilitate an understanding of data requirements for the relevant applications."[59]

The principle of orphan designation was introduced much earlier in the U.S. in 1983 with the Orphan Drug Act (ODA)[60], whereas the EMA introduced the principle of orphan designation in 2000.[39]

Although the background and principles are similar for orphan designations in the U.S. and EU, there are differences regarding prerequisites and incentives. In the U.S., the conditions for an orphan designation as stated in section 526 (a) of the ODA:

- Drug is intended for a rare disease or condition

- "the term "rare disease or condition" means any disease or condition which
  (A) affects less than 200,000 persons in the United States, or
  (B) affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will recovered from sales in the United States of such drug."

The obtained Orphan designation goes along with various development incentives, including clinical testing of the medicinal product. When obtained a marketing authorisation for a prescription drug with orphan designation, this product is not subject to a prescription drug user fee (PDUFA) unless the application includes an indication for other than the rare disease or condition for which the drug was designated[61] and an orphan-drug exclusive approval for 7 years is obtained (FDA normally then will not approve another sponsor's marketing application for the same drug for the same use or indication).[62]

6.2.2.2 Expedited Programs for serious conditions

There are several possibilities for the expedition of drug development programs for serious conditions at the FDA that can be obtained via the following designations: **Fast Track, Breakthrough Therapy and Priority Review**. A comparison table between these different designations is provided in Table 2 where the qualifying criteria for each of the designations are listed. For all of these 3 designations a prerequisite is the development of a drug for a serious condition, which is defined as "a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. […] Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one."[69]

	Fast Track[63,64,65]	**Breakthrough Therapy**[66,67]	**Priority Review**[68]
Qualifying criteria	• A drug that is intended to treat a **serious condition AND** nonclinical or clinical data demonstrate the potential to address **unmet medical need OR**	• A drug that is intended to treat a **serious condition AND** preliminary clinical evidence indicates that the drug **may demonstrate substantial improvement** on a	• An application (original or efficacy supplement) for a drug that treats a **serious condition AND,** if approved, would provide a **significant improvement in safety** or effectiveness **OR** • Any supplement that proposes a **labeling change pursuant to a report on a pediatric study OR**

	• A drug that has been designated as a **qualified infectious disease product**	clinically significant endpoint(s) **over available therapies**	• An application for a drug that has been designated as a **qualified infectious disease** product **OR** • Any application or supplement for a drug submitted **with a priority review voucher**
Submission of request	•With IND or after • Ideally, no later than the pre-BLA or pre-NDA meeting	•With IND or after • Ideally, no later than the end-of-phase 2 meeting	•With original BLA, NDA, or efficacy supplement
Features	• Actions to expedite development and review • Rolling review	• Intensive guidance on efficient drug development • Organizational commitment • Rolling review • Other actions to expedite review	• Shorter clock for review of marketing application (6 months compared with the 10-month standard review)
Additional considerations	• Designation may be rescinded if it no longer meets the qualifying criteria for fast track	• Designation may be rescinded if it no longer meets the qualifying criteria for breakthrough therapy	• Designation will be assigned at the time of original BLA, NDA, or efficacy supplement filing

Table 2: Comparison Table of FDA designations for Expedited Programs for serious conditions, excerpt from Table in Lit.Ref.[69]

For possible Ebola medical products, all listed designations may be a possibility as discussed by the FDA at the 2015 Public Health Preparedness Summit meeting, depending also on their status of development (see “submission of request” in Table 2)[70]. Remarkable are the features of these designations as e.g. for the Fast Track and Breakthrough Therapy designation, expediting measures such as a Rolling Review are already implemented compared to the measures taken at the EMA, where the Rolling Review was implemented especially for the Ebola Virus Disease. Even though the FDA claims to be in constant contact with the 20+ developers of Ebola medical products (see chapter 6.2.1.2) and therefore will get a regular update of the status of these compounds, the Expedited Programs for serious conditions

designations include several actions to expedite the development in addition (e.g. Rolling Review, intensive guidance or a shorter review of the marketing application) and are established an well-known procedures, whereas these measures are not existent at the EMA.

6.3 FDA - Fast Regulatory approval and access options in the emergency situation of the Ebola Virus Disease

6.3.1 Early Access options before FDA approval

6.3.1.1 Emergency Investigational New Drug (EIND) application and Expanded Access Program

A possibility for an early access before FDA approval is the expanded access program in the U.S., used in a similar way to the Compassionate Use in the EU: "The aim of this subpart is to facilitate the availability of such drugs to patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patient's disease or condition."[71] The term "serious" follows the same definition as described in chapter 6.2.2.2 for Expedited Programs for serious conditions. The prerequisites according to 21 CFR 312 Subpart I for an expanded access program are:

> "(1) The patient or patients to be treated have a **serious or immediately life-threatening disease or condition**, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;
>
> (2) The **potential patient benefit justifies the potential risks** of the treatment use and those potential risks are not unreasonable in the context of the disease or condition to be treated; and
>
> (3) Providing the investigational drug for the requested use **will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval** of the expanded access use or otherwise compromise the potential development of the expanded access use."

In addition to the expanded access program, for the EIND, the following additional prerequisites have to be fulfilled:

> "(1) The physician must determine that the probable risk to the person from the investigational drug is not greater than the probable risk from the disease or condition; and
>
> (2) FDA must determine that the patient cannot obtain the drug under

another IND or protocol."

Under an EIND application it is possible under certain circumstances that an individual patient can obtain investigational products outside of a clinical trial. In this case, a request must be submitted to and authorized by the FDA. This procedure is encouraged via the FDA website on Ebola for patients who are in "dire need of treatment to enable access to an experimental product where appropriate".[57]
In an EIND application the responsibility therefore lies with the prescribing doctor in contrast to normal expanded access program and is therefore similar to the "named patient" option in the EU (see chapter 5.4.1.1). In an emergency situation it is also possible to obtain an EIND application by phone from the FDA.
Similar to the EU, as there will probably not exist an expanded access program in the U.S. due to the spread mainly in African countries so far, probably only the EIND application represents a helpful tool for unapproved Ebola compounds in single cases occurring in the U.S.

6.3.2 Fast Regulatory approval options in the U.S.

The traditional drug approval process at the FDA follows the steps layed down in the Code of Federal Regulations (21 CFR 310-314).[72] The main steps for newly developed active substances are:[73]

- After drug development and animal testing, the sponsor submits an **Investigational New Drug (IND) application** to the FDA, where preclinical testing must be shown and the human testing program must be proposed. The FDA decides whether it is safe to start testing the new compound in humans.
- After IND and IRB (local institutional review board) review, the Clinical Trial program in humans can be started (normally Phase I-III); at the end of Phase II, FDA and the sponsor agree on the Phase III Study-Design (End of Phase II meeting)
- Before filing the application, a pre-NDA (New Drug Application) meeting takes place between FDA and drug sponsor, which is followed by the NDA (including all CMC, preclinical and clinical data

- The FDA decides within 60 days whether to accept the application or not and normally reviews all information, labeling and executes facility inspections within 10 months (~6 months for priority drugs)
- FDA approves the application or issues a complete response letter

However, the application via this traditional drug approval process at the FDA must include all information on CMC, preclinical and clinical data. The demonstration of efficacy has to be based on one or more clinical disease endpoint(s) (or e.g. for vaccines an accepted correlate of protection like antibody response data). As for the Ebola Virus Disease there is no accepted correlate, the demonstration of efficacy on one or more clinical disease endpoint(s) would therefore be required for all new Ebola vaccines or treatments when the traditional route would be followed.[74] To accelerate therefore the approval processes of possible new Ebola medical products and also due to the significant decline in Ebola cases and infection rates within the last months (see chapter 3) - other FDA approval options should be followed in case of the 2014 Ebola crisis as there are faster possibilities at the FDA which do not require the full data package or do not rely on clinical disease endpoints.

6.3.2.1 Accelerated Approval

The conditions for an accelerated approval can be found in the Code of Federal Regulations (21 CFR 314, subpart H, 21 CFR 601, subpart E)[72,75] and in section 506(c) of the FD&C Act (amended by section 901 of FDASIA).[65]

To obtain an accelerated approval, the following conditions have to be fulfilled:

- drug that treats a **serious condition (definition see Chapter 6.2.2.2)**
- generally provides a meaningful **advantage over available therapies**
- demonstrates an **effect on a surrogate endpoint** that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical endpoint)

An Accelerated Approval requires that the applicant will study the drug to be developed further after approval and verifies and describes its clinical benefit, usually in adequate and well-controlled Postmarketing studies.[69]

In contrast to the accelerated assessment at the EMA (see chapter 5.4.2.2), it is not the approval time, but the “effect on a surrogate endpoint” or intermediate endpoint

that represents the major difference between U.S. and EU and advantage for acceleration.

As stated by the FDA Vaccines and Related Biological Products Advisory Committee in May 2015[74] and before at the WHO meeting in September 2014[56], the Accelerated Approval signifies a good option for possible new Ebola Virus Disease treatments and vaccines. As Ebola would qualify as a serious condition and as no vaccines or treatments are available, an Accelerated approval would be based on adequate and well-controlled clinical trials showing an effect on a surrogate/intermediate endpoint that is reasonably likely to predict clinical benefit . This surrogate endpoint could derive from the clinical human studies (e.g. for Ebola vaccines under development according to the FDA "immune responses in vaccinated individuals participating in currently planned or ongoing Phase 2 and 3 studies and/or from a comparison of antibody responses in protected vaccinees to those of vaccinees who contract EVD.") This condition of a surrogate endpoint that is only reasonably likely to predict clinical benefit or an intermediate endpoint would ease the clinical development of possible Ebola vaccines and treatments and make an earlier approval possible as these new medical products could be approved with fewer, smaller, or shorter clinical trials than via the traditional approval. Also due to the significant decline in Ebola cases and infection rates within the last months (see chapter 3) - it would probably not be possible to determine the safety and efficacy for new Ebola vaccines and treatments via the traditional approval pathway including clinical trials with standard clinical endpoints. Therefore, the Accelerated Approval could be a good approval way at the FDA for acceleration of possible new medical products against Ebola.

6.3.2.2 The Animal Rule

The Animal Rule was mostly used so far in the scope of Medical countermeasures (MCMs) at the FDA. MCMs are FDA-regulated products (biologics, drugs, devices) that may be used in the event of a potential public health emergency stemming from a terrorist attack with a biological, chemical, or radiological/nuclear material, a naturally occurring emerging disease, or a natural disaster.[76] The leading Office at the FDA for these MCMs is the Office of Counterterrorism and Emerging Threats (OCET), which coordinates Medical Countermeasures Initiatives (MCMi) at the FDA "to facilitate the development of safe and effective MCMs against chemical, biological, radiological, and nuclear agents and emerging threats[…]"[77] and uses

legal and regulatory mechanisms to facilitate the development and availability of save and effective MCMs.[70]

Figure 7: Medical Countermeasures Initiatives (MCMi) graphic[78]

The MCM-related counterterrorism legislation has been enacted to strengthen the preparedness in the U.S. for responding to public health emergencies involving chemical, biological, radiological, nuclear as well as emerging infectious disease threats since September 11, 2001.[79]

The regulatory pathway of the Animal Rule was discussed by the FDA at the WHO meeting in September 2014 for possible new Ebola compounds[56] and is laid down in 21 CFR 314.600[80] for drugs and 21 CFR 601.90 for biologics.[81] It is foreseen "only to those new drug products for which: Definitive **human efficacy studies cannot be conducted** because it would be **unethical** to deliberately expose healthy human volunteers to a lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substance; and field trials to study the product's effectiveness after an accidental or hostile exposure have not been feasible."[80] In this case, the FDA is able to grant a marketing approval

- if the Human Safety of the product has been established
- based on animal efficacy studies when the results of those studies establish reasonably likely to produce clinical benefit in humans

The animal studies also have to fulfill the following conditions:[80]

"(1) There is a **reasonably well-understood pathophysiological mechanism of the toxicity** of the substance and its prevention or substantial reduction by the product;

(2) The **effect is demonstrated in more than one animal species expected to react with a response predictive for humans**, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans;

(3) The **animal study endpoint is clearly related to the desired benefit in humans**, generally the enhancement of survival or prevention of major morbidity; and

(4) The **data** or information on the kinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, **allows selection of an effective dose in humans**."

In addition, the approval will only be granted with requirements of:

- Postmarketing Studies
- Approval with restrictions to ensure safe use (e.g. certain facilities, specified procedures, recordkeeping etc.)
- Information to be provided to patient recipients

The FDA will determine finally whether the previously noted criteria have been met and the Animal Rule can be used.
In a recently published draft guidance the FDA stated that the Animal Rule is not only limited to chemical, biological, radiological or nuclear threat agents, but also possible for other drugs in development to prevent serious or life-threatening conditions (e.g., emerging virus, snake venom, industrial chemicals) when unethical to conduct human studies.[82] This regulatory pathway was discussed for new Ebola vaccines by the FDA at the WHO meeting in September 2014, but not favorised at that time.[56]
For a rapid response during an international public health emergency such as Ebola and the fast access to new drugs and vaccines in case of an approval via the Animal Rule, the benefit has to be clearly weighed against the potential risks that are highly unknown at that stage of development. The Animal Rule therefore would not be applicable if an approval could take place via the traditional or accelerated approval pathway, which is stated in 21 CFR 314.600.[80] So far, since establishment in 2002, only 8 drugs have been approved under the Animal Rule (including extensions).[83]
However, if the efficacy for possible new Ebola medical products cannot be determined via clinical trials in West Africa, the Animal rule provides an alternative regulatory pathway to gain approval very early in development and therefore fast access to these compounds as only animal studies would be sufficient after having proven the human Safety of the new compound. This concept was taken up in the

Vaccines and related Biological Products Advisory Committee Meeting at May 12th 2015 regarding Ebola and the Animal Rule was discussed as a realistic option (in contrast to September 2014, see above) due to the significant decline in Ebola infection rates recently [May 2015], which might not permit direct assessment of efficacy in currently ongoing clinical trials in West Africa.[74]

6.3.2.3 Emergency Use Authorisation

A further option discussed by the FDA Vaccines and Related Biological Products Advisory Committee in May 2015[74] for new medical products under development for the Ebola Virus Disease is the possibility of the Emergency Use Authorisation (EUA), which is implemented via the FD&C Act §564[84] and amended by the Project BioShield Act of 2004[85] and Pandemic and All-Hazards Preparedness Reauthorisation Act of 2013 (PAHPRA)[86].

Similar to the Animal Rule, the Emergency Use Authorization was mostly used so far as a regulatory mechanism to strengthen the U.S. health protection against CBRN (Chemical, biological, radiological, nuclear) threats and threats against infectious diseases to make Medical Countermeasures (MCMs) available in public health emergencies through the Office of Counterterrorism and Emerging Threats (OCET) at the FDA as coordinating Office.

As an EUA, the FDA can authorize either:

- The use of an unapproved product
- unapproved use of an approved product

An EUA however can issued only if one of the following determinations are issued as otherwise a violation of the FD&C Act would occur:

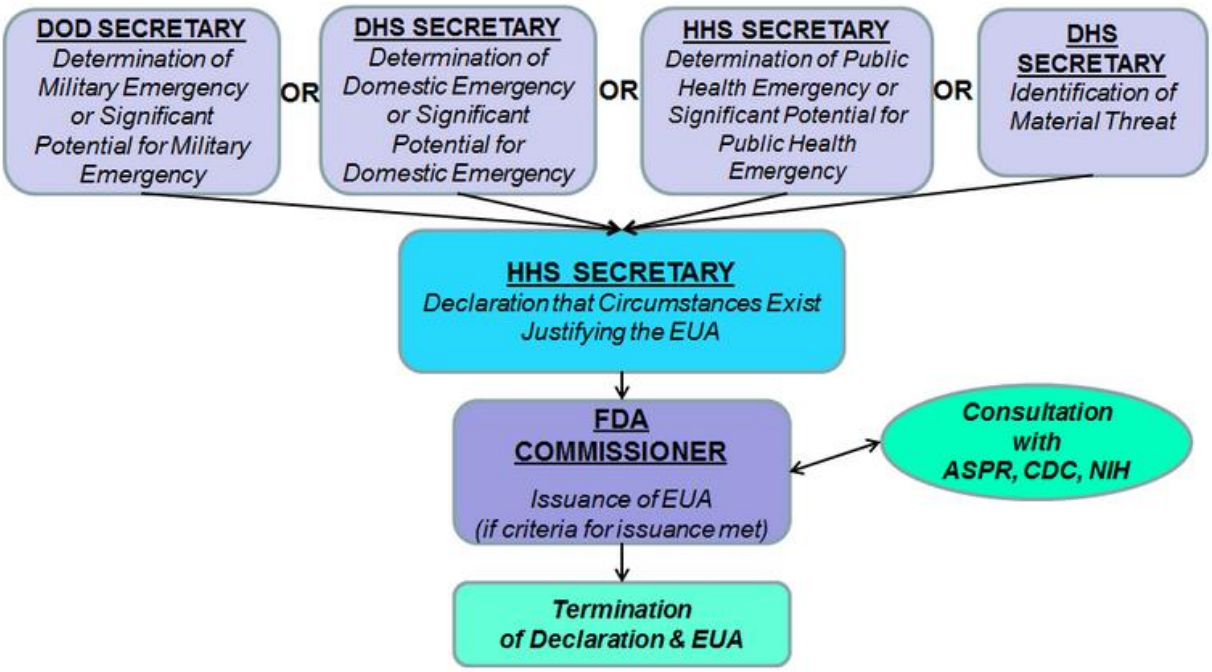

Figure 8: Summary of the process for Emergency Use Authorization Issuance[87]

First, one of the emergency determinations must be issued as either a military, domestic, public health emergency or a material threat determination from the corresponding U.S. departments DoD (Department of Defense), DHS (Department of Homeland Security) or HHS (Department of Health and Human Services). After such a declaration, the HHS Secretary can issue a declaration that the circumstances exist justifying to issue an EUA. After that and in consultation with the ASPR (HHS Assistant Secretary for Preparedness and Response), the NIH (National Institutes of Health) and CDC (Centers for Disease Control and Prevention) (to the extent feasible and appropriate), the FDA Commissioner then may authorize the emergency use of a particular product if the criteria are met.[88]

The criteria the product has to meet to gain an EUA are the following:

- the agent specified in the declaration of emergency can cause a **serious or life-threatening disease or condition**

- **based on the totality of scientific evidence available**, if available, **it is reasonable to believe that the product may be effective** in diagnosing, treating, or preventing
  - (a) the serious or life-threatening disease or condition referred to in paragraph (1) or
  - (b) a serious or life-threatening disease or condition caused by a product authorized

- that the known and potential benefits outweigh the known and potential risks

- no adequate alternative to the product is available

The possibilities of EUA products range from drugs over biological products (e.g., vaccine, blood products, and biological therapeutics) to devices (e.g., *in vitro* diagnostics).
For an EUA there are no mandatory specific requirements regarding the Safety and Efficacy of the possible product as this is depending on the clinical condition, alternative therapies (if any) and specific circumstances of the emergency situation, but there are recommendations by the FDA (see following chapters).

6.3.2.3.1 Safety Data

Regarding the Safety data recommended by the FDA, this depends also on whether the product under evaluation is unapproved or if an approved product is used in an unapproved way. In addition, the FDA strongly recommends to discuss the nature and type of Safety data that might be appropriate.[88]

Recommendations for previously approved products	Recommendations for unapproved products
• new indication **with similar dose, duration, administration, and/or patient population as approved product indication** → reference to approved application	• **inclusion of available preclinical testing data** such as *in vitro* and animal tox. data
• **if new use with different risk to patient population (e.g. increased toxicity)** → reference from relevant *in vitro* studies, animal tox. studies, (and if available human clinical data)	• strong recommendation to **include safety information from human clinical trials and individual patient experience** if available
	• data to link likely/proposed patient exposure to any relevant existing preclinical data
	• any further information on Safety associated with use in humans of this or related compounds/devices

Table 3: Recommendations by FDA for Safety Data of EUAs[88]

6.3.2.3.2 Effectiveness Data

In general, the FDA states that they are aware that comprehensive effectiveness data are unlikely to be available for each possible EUA compound and that this will depend on the circumstances (e.g. kind of emergency, available Safety Profile). The FDA therefore decides on the sufficiency of effectiveness data and benefit-risk profile on a case-by-case basis. The FDA recommends to submit any available relevant scientific evidence regarding effectiveness:[88]

- mechanism(s) of the product's action
- **preclinical testing data**, such as ***in vitro*** evidence of effect of the product in preventing or reducing the toxicity of the specified agent
- for drugs, **demonstration of effectiveness in at least one animal species** expected to react with a response predictive for humans (study endpoint clearly related to the desired benefit in humans)
- **evidence of effect in humans** (e.g., in published case reports, uncontrolled trials, controlled trials, if available, and any other relevant human use experience)
- for drugs, **data to support the proposed dosage** for the intended use
- for devices, clinical testing data to support the proposed intended use, as necessary and appropriate

However, submission of these data is not mandatory, only if these are available as it will be decided on a case-by-case basis.

6.3.2.3.3 Other data considerations

If available and appropriate, the FDA recommends to submit also the following data with an EUA request:

- Final or interim study reports of available Safety and Effectiveness data
- Any relevant statistical analyses
- Source data for clinical, non-clinical and animal studies demonstrating effectiveness (e.g. Case Report Forms etc.)
- Statements whether non-clinical laboratory studies were executed in compliance with GLP
- Submission of data updates that may change FDA´s evaluation of the product´s Safety or Effectiveness available during the review period of the EUA as soon as available

- Discussion of Risks and Benefits

6.3.2.3.4 Timelines and conditions of approval

The timelines for the FDA review of an EUA will depend on the product´s profile, nature of emergency and other relevant factors. However, in an emergency situation occurring or believed to be imminent, a request for an EUA will be acted upon in a matter of hours or days.[88]

With a granted EUA, the following conditions occur, divided in conditions for unapproved products and unapproved use of an approved product:

CONDITION OF AUTHORIZATION	UNAPPROVED PRODUCT	UNAPPROVED USE OF AN APPROVED PRODUCT
Information for Health Care Providers and Authorized Dispensers	Mandatory for manufacturers and others*	Mandatory for manufacturers
Information for Recipients	Mandatory for manufacturers and others*	Mandatory for manufacturers
Adverse Event Monitoring/Reporting	Mandatory for manufacturers and others*	Discretionary for manufacturers
Recordkeeping/Access	Mandatory for manufacturers; discretionary for others*	Discretionary for manufacturers
Compliance with GMPs	Discretionary for manufacturers and others*	Discretionary for manufacturers and others*
Advertising	Discretionary for manufacturers and others*	Discretionary for manufacturers and others*
Restricted Distribution	Discretionary for manufacturers and others*	Discretionary for manufacturers and others*
Restricted Administration	Discretionary for manufacturers and others*	Discretionary for manufacturers and others*
Data Collection/Analysis	Discretionary for manufacturers and others*	
* Others may include, for example, the U.S. government		

Table 4: Authorization conditions for EUAs of an unapproved product and an unapproved use of an approved product from Lit.Ref.[88]

There are more mandatory conditions for an EUA with an unapproved product such as passing relevant information to Health Care providers/dispensers and recipients, AE Monitoring/Reporting, recordkeeping of relevant manufacturing details, whereas only the first two are mandatory for an unapproved use of an approved product with an EUA. Interestingly other requirements essential to traditionally approved drugs as e.g. compliance to GMP, restricted distribution and administration are only conditions on a discretionary basis as waivers can be granted by the FDA on a case-by-case basis and therefore products are able to reach the market much faster as the FDA can authorize these products without time-consuming regulatory burdens as e.g. ensuring that GMP requirements are met.

Due to the Pandemic and All-Hazards Preparedness Reauthorisation Act of 2013 (PAHPRA)[86], the automatic expiration for an EUA after 1 year was eliminated and the EUA now is valid for the duration of emergency declaration unless the EUA is revoked as the criteria are no longer met. In addition, the PAHPRA also allows issuance of an EUA without declaring that an "emergency" exists but the EUA determination can be based on a "significant potential" for a public health emergency or a material threat or even some parts of approved MCMs can be used without EUA issuance (e.g. emergency dispensing orders, emergency use instructions, expiring dating extensions, cGMP waivers, REMS waivers)[86]

6.3.2.3.5 Ebola and EUA

Already on September 22nd, 2006, the DHS Secretary determined that the Ebola virus represents a material threat against the U.S. population sufficient to affect national security. Based on this determination, the Secretary of HHS declared pursuant to section 564 of the FD&C Act 21 U.S.C. 360bbb-3[84] "that circumstances exist justifying the authorization of emergency use of *in vitro* diagnostics for detection of Ebola virus".[89]

Based on this declaration, 9 *in vitro* diagnostics for detection of the Ebola virus have been issued an EUA by the FDA (May 2015):

Year	MCM	Requester	Status
	Ebola Virus		
2014 (reissued in 2014)	DoD EZ1 Real-time RT-PCR Assay	DoD	Current
2014 (reissued in 2015)	CDC Ebola VP40 rRT-PCR Assay	CDC	Current
2014 (reissued in 2015)	CDC Ebola NP rRT-PCR Assay	CDC	Current
2014 (reissued in 2015)	BioFire Defense FilmArray NGDS BT-E Assay	BioFire Defense	Current
2014	BioFire Defense FilmArray Biothreat-E test	BioFire Defense	Current
2014 (reissued in 2014)	RealStar® Ebolavirus RT-PCR Kit 1.0	altona Diagnostics GmbH	Current
2014	LightMix® Ebola Zaire rRT-PCR Test	Roche Molecular Systems, Inc.	Current
2015 (reissued in 2015)	ReEBOV™ Antigen Rapid Test	Corgenix	Current
2015	Xpert® Ebola Assay	Cepheid	Current

Figure 9: Summary of EUAs issued under the current declaration by HHS in August 2014 from Lit.Ref[70]

Even though these 9 EUAs were issued for *in vitro* diagnostics, no EUAs have been issued for potential vaccines or drugs in development where data from animal studies are available. While drug treatments are within the very early stages of development and some researchers are of the opinion that the EUA will speed up Ebola drug approval with only preclinical instead of also clinical data from 5-10 years to 1-2 years from now (as soon as these are available)[90], the FDA was of the opinion that for possible new Ebola drugs and even more for possible vaccines, reliable Safety and Efficacy data in humans should be generated only through randomized clinical trials.[91,92] Especially the decline in Ebola cases in West Africa during the last months due to a comprehensive supportive care treatment (see chapter 3) would make the clinical trials necessary: “fluid replacement, electrolytes, support with blood products when that’s possible – seems to be very effective, effective enough to make it hard to tell whether it’s the drug or the supportive care that is helping” said Edward Cox, director of the FDA’s Office of Microbial Products in an interview with Forbes in December 2014.[92] “With vaccines, the need to have a control group is even greater”, Luciana Borio, the Food and Drug Administration’s Assistant Commissioner for Counterterrorism Policy said in the same interview. “In Liberia, the number of Ebola cases is going down. If vaccines had been widely distributed a few months ago without employing a control group, we’d be attributing that decrease to those

vaccines."[92] However, as discussed during the Vaccines and related Biological Products Advisory Committee Meeting at May 12th 2015 regarding Ebola, it was stated that due to the significant decline in Ebola infection rates recently [May 2015], which might not permit direct assessment of efficacy in currently ongoing clinical trials in West Africa, new possibilities of assessment and approval procedures (as e.g. the Animal Rule) have to be considered.[74] Also Dr Anne Schuchat, director of the National Center for Immunization and Respiratory Diseases at the CDC, came to a similar conclusion.[93]

7. Current development status of vaccines, treatments and diagnostics against the Ebola Virus Disease

7.1 Vaccines

Until today (May 2015) there are several vaccines currently in development against Ebola in North America, Europe, Russia and China with 4 main vaccines candidates in different human trial stages. These main vaccines are:[12]

- rVSV-ZEBOV (NewLink Genetics and Merck Vaccines USA)
- ChAd3-ZEBOV (GSK and Public Health Agency of Canada (PHAC))
- Prime-boost regimen of Ad26- and MVA-EBOV (Johnson & Johnson, Bavarian Nordic)
- Recombinant particle particle of EBOV glycoprotein produced in tobacco plants (Novavax)

The two most 2 advanced vaccines regarding clinical testing of these 4 are rVSV-ZEBOV and ChAd3-ZEBOV. ChAd3-ZEBOV uses a chimpanzee adenovirus that does not grow, which contains the gene for the surface protein of Ebola. One single dose of ChAd3-ZEBOV given a month in advance protected all of 16 animals from a lethal dose of Ebola. The vaccine rVSV-ZEBOV aims to induce EVD-specific immune responses. Similar to ChAd3-ZEBOV, one single dose of ChAd3-ZEBOV given a month in advance protected all of 16 animals from a lethal dose of Ebola; in addition, weakened animals were not harmed.[94]

For these two most advanced vaccines rVSV-ZEBOV and ChAd3-ZEBOV human clinical trials were initiated in September 2014. Safety and Immunogenicity profiles from Phase I trials for both were available in December 2014/January 2015. This very fast timelines could be executed due to the WHO, who coordinated and identified

several trial sponsors in Canada, the U.S., EU and Africa. The vaccines rVSV-ZEBOV and ChAd3-ZEBOV are currently in Phase III trials in the 3 affected countries (overview of the clinical trial programme of the 4 main candidates see Figure 10). Further vaccines in development are a recombinant influenza candidate in development by the Russian Ministry of Health, planned to start Phase I trials in Q2 2015, an oral adenovirus platform (Vaxart), an alternative recombinant protein (Protein Sciences), an alternative vesicular stomatitis virus candidate (Profectus Biosciences), a DNA vaccine (Inovia) and a recombinant rabies vaccine (Jefferson University). Also China is testing a vaccine candidate clinically where further information is not known yet.[96]

The steep decline due to a comprehensive supportive care treatment in the number of Ebola cases in West Africa in the recent months (since beginning of 2015, the current Ebola outbreak has decreased remarkably and as there were only 12 confirmed cases of Ebola virus disease reported in the week to 24th May: 9 from Guinea and 3 from Sierra Leone[5]) could mean a challenge for the further Phase III clinical trial research. While the rapid decline in Ebola cases means a significant advance in the fight against Ebola, it is difficult for the finding of a safe and effective vaccine as Dr Aylard, assistant director-general at the WHO, acknowledged and he stated that “the biggest concern would be the risk of not being able to get a definitve answer as to the clinical efficacy of these vaccines to prevent the disease.”[95] Also the NIH reported that it would be difficult to find the planned 27,000 volunteers for the Phase III PREVAIL trial for ChAd3-ZEBOV and rVSV-ZEBOV as there were no new cases reported in Liberia and a move to the other two remaining affected countries is not possible as there are also the WHO initiated “ring trail” for rVSV-ZEBOV with a planned number of 10,000 volunteers in Guinea and the rVSV-ZEBOV trial of the CDC in Sierra Leone with a planned number of 6,000 volunteers running. But even if Phase III studies were not able to meet these enrollment numbers, Dr Aylard was optimistic that the animal studies and already obtained Safety and Immunogenicity data may be sufficient.[95]

Product / Company	Phase	Trial Location	Dates
ChAd3-ZEBOV GlaxoSmithKline and PHAC	Phase I	By VRC at NIH, USA	September 2014
		By Oxford University in the UK	
		By CVD in Mali	October 2014
		At the University of Lausanne, Lausanne, Switzerland	
rVSV-ZEBOV NewLink Genetics and Merck Vaccines USA	Phase I	By WRAIR in the US	October 2014
		By NIAID in the US	
		By CTC North GmbH in Hamburg, Germany	November 2014
		At Albert Schweitzer Hospital in Lambarene, Gabon	
		At the University of Geneva, Geneva, Switzerland	
		By KEMRI Wellcome Trust in Kilifi, Kenya	December 2014
		At the IWK Health Center, Halifax, Canada	
Ad26-EBOV and MVA-EBOV Johnson & Johnson and Bavarian Nordic	Phase I	By Jenssen Institute in the UK	January 2015
		TBD, US	
		TBD, Ghana	1Q2015
		TBD, Kenya	
		TBD, Uganda	
		TBD, United Republic of Tanzania	
Recombinant protein Ebola vaccine candidate Novavax	Phase I	Australia	February 2015
ChAd3-ZEBOV GlaxoSmithKline and PHAC	Phase II	TBD, Cameroon	1Q2015
		TBD, Ghana	
		TBD, Mali	
		TBD, Nigeria	
		TBD, Senegal	
rVSV-ZEBOV NewLink Genetics and Merck Vaccines USA	Phase III	By WHO and MOH Guinea in Conakry, Guinea	March 2015 – Ring vaccination trial design
ChAd3-ZEBOV GlaxoSmithKline and PHAC	Phase III	By US NIH and MOH Liberia in Monrovia, Liberia	March 2015 – Randomized control trial design
rVSV-ZEBOV NewLink Genetics and Merck Vaccines USA	Phase III	By US CDC and MOH Sierra Leone in Freetown, Sierra Leone	March 2015 – Stepped wedge trial design

Figure 10: Table of current vaccine clinical trials from Lit.Ref.[96]

7.2 Treatments

7.2.1 Medicines

Early in the response to the Ebola outbreak, already approved drugs in other indications were considered as some of them had shown efficacy against the virus *in*

vitro due to their availability. In this context, a clinical trial was started for the drug favipiravir in Guinea in late 2014 and for another re-purposed drug, amiodarone, used to treat patients in Sierra Leone outside of a clinical trial setting. Other new products especially for Ebola are still in early stages of development including the monoclonal antibody cocktail ZMapp (Leafbio, USA) and small inhibitory RNA (Tekmira, USA, Canada), having been tested in small Phase I clinical trials and are now being tested in Sierra Leone.[13] In addition, compounds where clinical studies have been stopped, clinical trials are planned or those already being used on a compassionate use basis are shown in Table 5. Also a wide range of other drugs is currently tested in non-human primates, which are prioritized (in addition to those in clinical trials) by the WHO.[97]

Product / Company	Phase	Trial Location	Description
Favipiravir Fujifilm/Toyama, Japan	Phase II	By INSERM in Guinea: Conakry, Guéckedou, Macenta, Nzérékoré	Used to treat influenza. Clinical trials began in December 2014. Preliminary data presented in February 2015 does not permit a firm conclusion regarding efficacy and more data is required; trial continues.
Brincidofovir Chimerix, USA	Phase II	By Oxford University at the ELWA 3 Clinic, Monrovia, Liberia	An antiviral used to treat CMV. Clinical trial halted and abandoned; the drug has been deprioritized for use in Ebola treatment.
ZMapp MappBio USA	Phase II	By NIAID in Monrovia, Liberia	Cocktail of three monoclonal antibodies with excellent activity against Ebola virus in animal models. Phase I trials completed and Phase II efficacy trial was initiated in early February 2015.
TKM-100802 (siRNA) Tekmira, Canada	Phase II	By Oxford University in Kerry Town, Sierra Leone	siRNA Clinical trial expected to start in the coming weeks.
BCX-4430 Biocryst, USA	Phase I	By Quotient Clinic in the UK	Broad-spectrum direct-acting nucleoside analogue. Phase I safety trial is underway. No efficacy trial is planned until safety data have been analysed.
Interferons		By Guinea MOH in Coyah, Guinea	Approved for treatment of HepB and C and multiple sclerosis. Guinean authorities, in collaboration with Canadian scientists, are launching a clinical study of an interferon in Ebola-infected patients. Details of this study are not yet available.
Amiodarone		At the Lakka & Goderich ETU in Sierra Leone	Used to treat cardiac dysrhythmia. Has been used compassionately in patients in Sierra Leone and reportedly

			reduced case fatality ratio when compared with local historical norms. The statistical significance of this result is not known at this stage.
Atorvostatin + Irbesartan +/- Clomiphene		Sierra Leone	Approved for cholesterol control / hypertension / infertility, respectively. Used alone or in combination to treat some patients in Sierra Leone. No clinical data are available and therefore no conclusion on efficacy is possible.
FX06			Peptide for use in treating vascular leakage. Administered compassionately to two patients. No conclusions can be drawn yet.
Zmab			Non-GMP experimental monoclonal antibody product with no plans for GMP production. Also administered on a compassionate basis.

Table 5: Table of drug clinical trials (March 2015) taken from Lit.Ref.[96]

7.2.2 Blood and blood products

Since late 2014, convalescent blood donated by patients recovered from Ebola has been administered in Sierra Leone in a trial sponsored by the government. Trials with covalescent plasma have started in Liberia (with U.S. government and Bill & Melinda Gates Foundation support) and Guinea (partnership with Belgium, UK, France) at the same time.

The Phase II/III trial of convalescent blood are currently on hold in Sierra Leone to accommodate a corresponding Phase II/III trial with covalescent plasma.

Product	Phase	Trial Location	Dates
convalescent blood	Phase II/III	Sierra Leone	On hold
covalescent plasma	Phase II/III	Liberia, Guinea	ongoing
covalescent plasma	Phase II/III	Sierra Leone	To be started

Table 6: Table of convalescent blood and plasma trials (May 2015)

7.3 Diagnostics

The WHO introduced an emergency procedure under its Prequalification Programme for rapid assessment of Ebola diagnostics for UN procurement in the concerned countries in September 2014.[14] The WHO called on manufacturers to develop rapid and easily usable diagnostics and the first diagnostic regarding Ebola was accepted in November 2014. The WHO also held a consultation on accelerated development,

production and deployment of adapted and rapid Ebola tests on 12th December 2014.[14]

Four diagnostics have been approved under this emergency procedure by the WHO:

Product	Company	Listing Date
RealStar Filovirus Screen RT-PCR Kit 1.0	Altona Diagnostics GmbH	November 2014
Antigen Rapid Test Kit, ReEBOV™	Corgenix	February 2015
Liferiver™ Ebola Virus (EBOV) Real Time RT-PCR Kit	Shanghai ZJ BioTech Co., Ltd.	April 2015
Xpert Ebola Test	Cepheid AB - Solna, Sweden	May 2015

Table 7: Ebola diagnostics approved under the emergency procedure under PQP (May 2015)

8. Perception of the concerned African countries

The first Ebola cases were registered in March 2014 when the Ministry of Health in Guinea reported a “mysterious disease” to the main office of medicines sans frontiers (Ärzte ohne Grenzen, MSF) in Geneva, which immediately set up three MSF emergency teams to deal with the situation. Laboratory confirmation of the disease being Ebola came through on 22nd March and the Guinean Ministry of Health therefore officially declared the outbreak as Ebola.[98] In June 2014 the situation started to get out of control: the Ebola virus was actively transmitting in more than 60 locations in Sierra Leone, Guinea and Liberia. Although Liberia´s Ministry of Health urgently expressed their desperate need of help also via MSF at the WHO´s Global Alert and Outbreak Response Network (GOARN, a gremium to pool and coordinate technical and human resources in response to disease outbreaks)) meeting end of June 2014[99], no further actions other than meetings were taken by the WHO or any health authority other than those in the concerned countries. MSF accused the WHO of “a clear lack of leadership […]: decisions on setting priorities, attributing roles and responsibilities, ensuring accountability for the quality of activities, and mobilizing the resources necessary were not taken on the necessary scale”.[98] International actions were not taken until the WHO declared Ebola a public health emergency on 8th August 2014[7] and the MSF and the concerned African countries accused the WHO of acting far too late and maybe only after the 1st case was reported outside Africa in

the U.S.[98,100] Until then the concerned African countries and MSF had to cope with the situation by themselves lacking enough resources and infrastructure. Also 14 people of the MSF died during their mission in Africa. The WHO just admitted (one year after the outbreak) that they made severe mistakes, should have worked differently, acted too slow and inefficient at the beginning of the crisis, coordinated inefficient and did not alarm the disease soon enough.[101] Due to this reaction, restructuring of the WHO currently is underway.[106]

After the beginning of the Ebola crisis and the declaration as public health emergency by the WHO in August, the 9th annual meeting of the African Vaccine Regulatory Forum (AVAREF) was held in November 2014 in light of the Ebola spread in Africa where also the regulatory authorities and ethics committees of the concerned African member states took part. Recommendations to the WHO, the supporting authorities such as EMA and FDA but also to manufacturers/research organisations were given by the concerned African countries as they were not satisfied on the response to the Ebola crisis and their involvement.[27] The following main recommendations were **made to the WHO**:

- Request Heads of Regulatory Agencies to:
    - Identify and name senior regulator staff as the agency entry focal points for Ebola
    - Designate named reviewer(s) to participate in a joint review process with the mandate to take regulatory/ethics decisions
- To involve the NRAs [National Regulatory Authorities] of the Ebola affected countries in the joint review process
- To proactively play the needed broker role in facilitating the interaction between manufacturers and countries
- Engage with heads of Institutions and research institutions and provide necessary support to countries to develop procedures for accelerated review of Ebola related research.

Further recommendations were **made to the manufacturers:**

- To hold pre-submission meetings with each participating NRA, EC and to attend
- To immediately release the planned timeline for submission of clinical trial applications indicating specific trial sites
- Manufacturers to attend the joint review sessions with their appropriate staff;

- To include in their submissions all pertinent data that is available at the time of submission
- To respond swiftly to any query from NRAs or EC/IRB

To the **EMA and FDA the following recommendations** were made:

- In collaboration with WHO, do everything in their power to share data relevant to clinical trials with the NRAs of participating countries
- To provide expertise to support NRAs in the joint reviews when requested

In general, the health authorities of the concerned countries of the EVD spread criticized that they were not sufficiently involved in the processes between WHO, supporting health authorities such as EMA and FDA and manufacturers, were not content with the processes set up by these participants and requested a better lead and coordination by the WHO. Even though raised during a vaccine forum, these requests and critics are mostly general and therefore can also be seen to be valid for the other medical products.

Although the above critics were made throughout and especially at the beginning of the Ebola crisis, on the conference "Ebola from Emergency to Recovery" held by the EU in Brussels on March 3rd 2015 where presidents of Sierra Leone, Guinea and Liberia took part, the president of Sierra Leone on behalf of all these 3 countries thanked the EU and its member states for their great commitment to supporting them to help fight the epidemic.[102] The Liberian president thanked all international partners for their great help and also urged members of the international partners to support the countries for the reopening and strengthening of healthcare systems to minimize the risk of recurrence of the virus.[103] A similar claim was made at the meeting of the World Bank on April 17th 2015 in Washington, where next to the Secretary General of the UN Ban Ki-Moon also the presidents of Liberia, Guinea and Sierra Leone took part.[104] Therefore, even though there were critics of the concerned African countries at the beginning of the crisis about inefficient set-up and leadership of regulatory processes of WHO, EMA, FDA and manufacturers and lack of involvement of Liberia, Guinea and Sierra Leone into these processes, the concerned African countries in total acknowledge the activities made by the WHO and the supporting health authorities and claim to continue this support to fight Ebola to the last case.

9. Comparison of regulatory options in emergency situations between the EU and U.S.

There are several possibilities in an emergency situation in case of the Ebola Virus Disease for the European Health Authority EMA and the U.S. Health Authority FDA to encourage and expedite the development and the approval of new medical products with already established and specifically new implemented measures, early access options and fast regulatory approval options.

In case of the Ebola spread in West-Africa, emergency actions of both agencies started with the WHO declaration of Ebola as a public health emergency on 8th August 2014[7] and the commitment on the 16th WHO International Conference of Drug Regulatory Authorities (ICDRA)[11] statement (3rd September 2014), where both regulatory agencies committed to accelerate the development and assessment processes of possible treatments and vaccines of Ebola and to share the initial reviews and subsequent updates with the corresponding authorities in those countries being most affected by Ebola.[23,24]

9.1 Comparison of new measures to accelerate the development and assessment processes of possible Ebola treatments and vaccines

Both agencies established several new measures in case of the Ebola Virus Disease, an overview of which is given in the following Table 8:

New Measure	EMA	FDA
Ebola Task Force	Ad-hoc Task Force: • rapid scientific advice • accelerated assessment of data • proactive contact to developers of potential treatments • Exploratory review of current investigational products • identify the most appropriate regulatory pathway	Ebola Task Force: • coordinate the activities of FDA and cooperation with other federal US institutions, the medical and scientific community, industry and international organizations and regulators • main goal: expedite the development and availability of medical products
Scientific Advice	Rapid Scientific Advice: • accelerated scientific advice on questions regarding e.g. clinical trial design, manufacturing related questions, post-authorisation safety	Advices and Cooperation: • clarify regulatory and data requirements necessary to enhance the development, to provide input on manufacturing

	monitoring • explicit encouragement for Ebola compound developing companies to request	and pre-clinical and clinical trial designs • expedite the regulatory review of data as it is received • contact to those pharmaceutical companies developing medicinal products against Ebola
Review of medicines under development	<u>EMA review:</u> • proactive review of the available information on Ebola treatments under development (due to Article 5 (3) of regulation 726/2004)	
Assessment of new data	<u>Rolling review of data:</u> • Submission data by developing companies to the EMA for evaluation as soon as available • concept used in 2009 pandemic influenza	*see established measures (expedited programs for serious conditions)
Deployment of employees	-	• Deployment of FDA employees

Table 8: Comparison of new development measures of EMA and FDA due to the 2004 Ebola crisis

EMA and FDA established mostly similar new measures with regard to the 2004 Ebola crisis. Both agencies established an Ebola Task force, which took over the responsibility to coordinate the Ebola related activities in and outside the authority with the goal to expedite the development and availability of medical products against Ebola. Both agencies also established special Scientific Advices: the EMA installed the possibility of the Rapid Scientific Advice to Ebola, which gives manufacturers a faster possibility to ask questions on their compound development, whereas the FDA claims to be in constant contact with the companies developing new Ebola vaccines and treatments following a more proactive approach. This proactivity however is also shown by the EMA with their proactive review (even though only on new Ebola drugs, not on vaccines) in compiling actual information on the Ebola treatment development – an official request by the European Commission possible due to Article 5 (3) of RL 726/2004. With the last two measures of Table 8, EMA and FDA differ from each other: the EMA has established a Rolling Review of data specifically in case of the Ebola crisis - where the available data is assessed by the agency as soon as it becomes available - in a similar way as used before for the 2009 pandemic influenza. This concept of the Rolling Review however is not a concept only temporarily available in the U.S., but an established process in the designations of FDA´s Expedited Programs for compounds of serious conditions such as Fast Track and Breakthrough Therapy designations in addition to other expediting measures within

these designations. Therefore, the Rolling Review is a concept, the manufacturers as well as the FDA are accustomed with and which is integrated within known procedures. The EMA in contrast will have to familiarize with this concept and its inclusion into the process of expediting the development of new Ebola medicines. The last new measure only implemented by the FDA is the deployment of FDA employees to West Africa, which is however done only for a small number of FDA staff, but might give more insight into practical implications.

9.2 Comparison of established measures to accelerate the development and assessment processes of possible Ebola treatments and vaccines

Established Measure	EMA (RL 141/2000)	FDA (Orphan Drug Act)
Orphan Designation	• reduced fee for scientific advice from EMA + fee reductions for further regulatory activities • access to centralized procedure • EU/Member State grants and 10 years of Market Exclusivity in case of authorization • orphan designation provides facilitated and accelerated dialogue between EMA and manufacturers • parallel orphan designation with FDA	• various regulatory development incentives (e.g. clinical testing) • not subject to PDUFA (unless + other non-orphan indication) • exclusive approval for 7 years • expedited product development, review and approval • parallel orphan designation with EMA
Expedited Programs for serious conditions (designations)	*see accelerated assessment (fast regulatory approval options)	<u>Fast Track (FD&C Act, 506(b)):</u> • Actions to expedite development and review • Rolling review <u>Breakthrough Therapy (FD&C Act, 506(a)):</u> • Intensive guidance on efficient drug development • Organizational commitment • Rolling review • Other actions to expedite review <u>Priority Review (PDUFA 1992):</u> • Shorter clock for review of marketing application (6 months compared with the 10-month standard review)

Table 9: Comparison of already established development measures of EMA and FDA due to the 2004 Ebola crisis

In Table 9, the already established EMA and FDA measures for acceleration of development of new possible Ebola medical products can be seen; EMA and FDA both recommended the use of the Orphan Designation as a tool to expedite the development and the review at their Health Authorities and also have already tagged some of the Ebola compounds in development with this status. With the parallel orphan designation at EMA and FDA, an additional incentive is provided for a company as also an acceleration of review at the agencies can be achieved globally due to the exchange of information between these agencies. A definitive advantage over the EMA for an expedition of development of new medical products is provided by the FDA with the Expedited Programmes for serious conditions (Fast Track, Breakthrough Therapy or Priority Review): for possible Ebola vaccines and treatments, all listed designations are a possibility as discussed by the FDA at the 2015 Public Health Preparedness Summit meeting[70], which include several actions to expedite the development (e.g. Rolling Review, intensive guidance or a shorter review of the marketing application) and are established an well-known procedures. Compared to these Expedited Programmes for serious conditions at the FDA, the EMA only newly established a Rolling Review specifically for the Ebola crisis. In addition, the shorter assessment time of the MAA in the accelerated assessment (discussed with the fast regulatory approval options) is the only established comparable measure to the Priority Review as one of these.

9.3 Comparison of early access options for possible Ebola treatments and vaccines

Early access options before approval	**EMA (RL 726/2004 Art. 83 (2))**	**FDA (21 CFR 312 Subpart I)**
Compassionate Use	Compassionate Use: • for a group of patients with a chronically or seriously debilitating or life-threatening disease and who cannot be treated satisfactorily by an authorized medicinal product	Expanded Access: • serious or immediately life-threatening disease or condition • no comparable or satisfactory alternative therapy • potential patient benefit justifies the potential risks • use will not interfere with the clinical investigations that could support marketing approval
Single prescriptions	Named Patient Basis: • In single cases of occurrence of the disease, doctors have the possibility to obtain promising	EIND: • physician must determine that the probable risk to the person drug is not greater than the probable risk

	medicines for their patients by directly requesting it from the manufacturer under their direct responsibility without a central register of these treatment cases	from disease • FDA must determine that the patient cannot obtain the drug under another IND or protocol • Can be obtained even by phone from the FDA in case of emergency

Table 10: Comparison of Early access options for new Ebola medicines before regulatory approval between EMA and FDA

Both agencies, EMA and FDA, offer the same options for patients to access new drugs in development before these have been approved by a Health Authority. Only in case that there are patients with a chronically or serious debilitating or life-threatening disease (EMA) vs. a serious or immediately life-threatening disease or condition (FDA), a Compassionate Use or Expanded Access program can be applied for. Several compounds in development for the EVD have already been used on a compassionate use basis according to the WHO, however, as most of the programs probably will not take place in the countries of the European Union due to the geographically focused spread of the disease, this probably will not be a commonly used access possibility in the EU or US. In single cases of occurrence in the EU or U.S., single prescriptions can be done in emergency cases, which lie in the responsibility of the treating physician (named patient basis vs. EIND).

9.4 Comparison of fast regulatory approval options for possible new Ebola treatments and vaccines

EMA	FDA
Accelerated Assessment (RL 726/2004 Art. 14 (9)): • medicinal product for human use is of major interest: - from the point of view of public health - in particular from the viewpoint of therapeutic innovation • review time of CHMP reduced from 210 to 150 days	**Accelerated Approval (21 CFR 314, subpart H, 21 CFR 601, subpart E, section 506(c) of the FD&C Act):** • drug that treats a serious condition • provides a meaningful advantage over available therapies • demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit **or** on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM)
Conditional approval (RL 726/2004 Art. 14 (7) and RL507/2006 Art. 2): • Medicinal products for seriously debilitating **or** life-threatening diseases **or** to be used in emergency situations (recognized by WHO or EC) **or** designated as orphan medicinal	**The Animal Rule (21 CFR 314.600 for drugs and 21 CFR 601.90 for biologics):** • human efficacy studies cannot be conducted because it would be unethical • field trials to study the product's effectiveness

products • only the clinical part of the dossier is less complete than normal and is filed afterwards • incomplete pre-clinical or pharmaceutical data should be accepted only in the case of a product to be used in emergency situation, in response to public health threats (WHO or EC) • requirements have to be fulfilled: - the risk-benefit balance of the medicinal product is positive - applicant likely to provide the comprehensive clinical data - unmet medical need - the benefit to public health of the immediate availability on the market outweighs the risk	have not been feasible • Safety of the product has been established • based on animal efficacy studies when the results of those studies establish reasonably likely to produce clinical benefit in humans (animal studies have to fulfill specific conditions) • FDA will determine finally whether the previously noted criteria have been met and the Animal Rule can be used • not be applicable if an approval can take place via the traditional or accelerated approval pathway
Article 58 procedure (RL 726/2004 Art. 58): • Scientific opinion by CHMP in direct cooperation with the WHO for the evaluation of certain medicinal products for human use intended exclusively outside the European Union • prevent or treat diseases of major public health interest • intended to respond to the need to protect public health and to give scientific assistance to non-EU countries in cooperation with the WHO to allow rapid access of drugs in these countries • faster approval in PQP at WHO • same standard applies as for the assessment of EU medicines	**Emergency Use Authorisation (FD&C Act section 564):** • emergency declaration by DoD, DHS or HHS • serious or life-threatening disease or condition • based on the totality of scientific evidence available, if available, it is reasonable to believe that the product may be effective • known and potential benefits outweigh the known and potential risks • no adequate alternative to the product is available • **Safety Data**: inclusion of available preclinical testing data such as *in vitro* and animal tox. data, strong recommendation to include safety information from human clinical trials and individual patient experience if available • **Effectiveness Data**: on case-by-case basis

Table 11: Fast regulatory approval options for new Ebola medical products for EMA and FDA

In terms of the European procedures at the EMA, 3 possibilities for a faster regulatory approval have been identified that can be used in an emergency situation such as the 2014 Ebola crisis: the accelerated assessment, the conditional approval and the Article 58 procedure.

The key feature of the accelerated assessment at the EMA is the reduction of the approval procedure timeframe from 210 to 150 days in case the compound is of major interest in terms of public health or innovation. This is comparable to a Priority Review designation at the FDA, where the timetable is shortened from about 10 to 6-8 months.

The major advantage of the Article 58 procedure lies within the close and early regulatory interaction and alignment of the EMA with the WHO and therefore will

make it easier to gain approval through the WHO (like e.g. in the above mentioned prequalification programme). This can be an essential advantage of accelerating the access to a drug like in the Ebola spread for the concerned countries even though there are no automatic fee reductions, no Marketing Authorisation within the EU is achieved and pharmacovigilance obligations after the opinion may be difficult to meet depending on the infrastructure of the country where the medicinal product will be used. There is not a comparable procedure at the FDA. However, due to the very close contact between FDA and EMA with the WHO in the 2014 Ebola crisis, continuous update meetings and using of WHO emergency procedures (e.g. in case of the emergency prequalification programme for Ebola diagnostics), this close contact between Health authorities is established in a similar way during such an emergency situation.

The conditional approval seems to be the best possibility in the EU for acceleration of market access in an emergency situation as Ebola (as seen by the EMA[26]); also because one of the possible prerequisites is a WHO emergency situation and as an approval can be obtained with an incomplete regulatory dossier as the key step for a faster approval compared to the traditional centralized procedure. The incomplete data usually belongs to the clinical part, whereas comprehensive non-clinical and pharmaceutical data should be available. Incomplete non-clinical or pharmaceutical data should only be accepted in emergency situations.[105] This process on conditional approvals with incomplete non-clinical or pharmaceutical data, however, does not seem to be established and no guidelines are provided on clearer definitions to which amount pre-clinical or pharmaceutical data should be included in emergency situations and which should not.

The FDA provides much more options for faster regulatory approval: from the Accelerated Approval over the Animal Rule to the Emergency Use Authorisation, a decrease in the requirements of data can be seen correlating to the increase of the emergency. With the Accelerated Approval, the compound´s application must still include data from well-controlled clinical trials but with an effect on a surrogate endpoint highly likely to predict clinical benefit; this eases the clinical development of possible Ebola vaccines and treatments and makes an earlier approval possible as these new compounds could be approved with fewer, smaller, or shorter clinical trials than via the traditional approval. However, if the efficacy for possible new Ebola drugs and vaccines cannot be determined via clinical trials in West Africa, the Animal

Rule provides an alternative regulatory pathway to gain approval very early in development and therefore fast access to these compounds as only animal studies would be sufficient after having proven the Safety in humans of the new compound (animal efficacy studies are sufficient when the results of those studies establish reasonably likely to produce clinical benefit in humans). In a declared emergency (by the DoD, DHS or HHS), the emergency use authorization can be applied by the FDA, which can be based even only on animal Safety Data (inclusion of available preclinical testing data such as *in vitro* and animal tox. data, strong recommendation to include Safety information from human clinical trials and individual patient experience if available) and Effectiveness Data on case-by-case basis.
The FDA therefore offers many more possibilities for a faster regulatory approval in emergency situations than the EMA; due to FDA´s variety of possible emergency approval options (Accelerated Approval, Animal Rule, Emergency Use Authorisation) and their corresponding requirements, each situation can be responded on more appropriately, dependent on the grade of emergency. In addition, the emergency procedures with incomplete regulatory data sets at the FDA are more established and with clearer definitions on their specifications compared to EMA´s conditional approval with an incomplete pre-clinical or pharmaceutical data set.

10. Conclusion and Outlook

Soon after the WHO declared Ebola as a public health emergency on 8th August 2014[7], the EMA and the FDA commited themselves on the 16th WHO International Conference of Drug Regulatory Authorities (ICDRA)[11] on 3rd September 2014 to accelerate the development and the assessment processes of possible medical products against Ebola and to share the initial reviews and subsequent updates with the corresponding authorities in those countries being most affected by Ebola.[23,24]
Both agencies established several *new measures* for acceleration of the development of new compounds in case of the declared emergency situation of the Ebola Virus Disease, which were mostly similar (e.g. Ebola Task Force, special types of Scientific Advices), but also use several *established measures* (e.g. Orphan designation). The FDA in the latter case has more methods at hand to accelerate the development of new medical products with their Expedited Programs for serious conditions. The Priority Review designation is similar to its counterpart of the

approval procedure Accelerated Assessment at the EMA. However, Fast Track or Breakthrough Therapy designation are well established and known by applicants and the FDA, and include many tools for acceleration as Rolling Review or other accelerating actions. The EMA instead installed only the Rolling Review of data specifically and temporarily in case of the Ebola crisis, in a similar way as used before for in the 2009 pandemic influenza. The EMA therefore will have to familiarize with this concept in the Ebola spread and its inclusion into the process of expediting the development of new Ebola medicines.

In case of *Early Access options* in an emergency situation such as the 2014 Ebola crisis, both agencies offer the same possibilities and refer to Compassionate Use/Expanded Access and Named Patient Basis/EIND programs.

In case of *fast regulatory approval options*, the FDA provides many more possibilities for an emergency situation than the EMA. The EMA has the options of Article 58 procedure and the conditional approval at hand, which show much more limitations for faster approval options as approvals with incomplete non-clinical or pharmaceutical data do not seem to be established and no guidelines are provided on clearer definitions, only for approvals with limited clinical data. Due to FDA´s variety of possible emergency approvals options (Accelerated Approval, Animal Rule, Emergency Use Authorisation) and their corresponding requirements, each situation can be responded on more appropriately, dependent on the grade of emergency and an approval can therefore be achieved with incomplete data sets either of human clinical surrogate endpoints (Accelerated Approval), Human Safety and Animal Efficacy (Animal Rule) or only animal Safety Data (efficacy on case-by-case basis). In addition, the emergency procedures with incomplete regulatory data sets at the FDA seem to be more established and with clearer definitions on their specifications compared to EMA´s conditional approval with an incomplete pre-clinical or pharmaceutical data set. Therefore, especially in case of the approval options in emergency situations such as the 2014 Ebola spread, the FDA has many more and much more flexible tools at hand.

Especially with a change in the emergency situation like the decline in Ebola cases in West Africa during the last months due to a comprehensive supportive care treatment (see chapter 3), the flexibility of FDA´s emergency approval options for new medical products is needed: whereas in December 2014, the FDA was of the opinion that new medical products should only be approved with efficacy proof via the currently

running clinical trials in West Africa[92], a few months later - due to the significant decline in Ebola infection rates recently [May 2015], which might not permit direct assessment of efficacy in currently ongoing clinical trials in West Africa - new possibilities of assessment and approval procedures (as e.g. the Animal Rule) have to be considered[74] according to the FDA´s Vaccines and related Biological Products Advisory Committee Meeting at May 12th 2015 regarding Ebola and Dr Anne Schuchat, director of the National Center for Immunization and Respiratory Diseases at the CDC.[95]

Also for other acute public health emergencies than Ebola, especially the approval procedures Accelerated Approval, Animal Rule and Emergency Use Authorisation at the FDA offer fast and flexible approval options. The concerned national authorities and also the EMA therefore should - in collaboration with the WHO – evaluate and also harmonize emergency approval options taking into account these valuable options of the FDA (e.g. in the PQP programme). Especially FDA´s Emergency Use Authorisation may be unique among regulatory options for emergency access to medicines, although mitigating of potential risks should be evaluated.

In addition, inefficient set-up and leadership of regulatory processes of WHO, EMA, FDA and manufacturers and lack of involvement of Liberia, Guinea and Sierra Leone into these processes were criticized by these African countries (as the most concerned by the Ebola disease) at the beginning of the crisis although in total they acknowledged the activities made by the WHO and the supporting health authorities and claim to continue this support to fight Ebola to the last case. The health authorities of the concerned countries of corresponding emergencies therefore must not be neglected – even if they do not have such reliable processes as the EMA or FDA – and have to be involved and informed thoroughly as they know the situation best and have to include all measures into their local processes.

In this context, the WHO therefore should think about establishing a permanent international forum for coordination, expediting and harmonizing the regulatory review processes in emergency situations in collaboration with as many concerned national health authorities as possible in addition to supporting health authorities as the EMA and FDA. This could enable streamlined and harmonized regulatory pathways in public health emergencies of international significance with the insight of the concerned local health authorities. A first step in this direction is already done as the WHO currently undertakes “structural reforms so it can prepare for and respond

rapidly, flexibly and effectively to emergencies and disease outbreaks"[106] as a result to the Ebolay Virus Disease outbreak in 2014.

11. Summary

The Ebola virus causes an acute, serious illness which is fatal if no treatment is applied. The corresponding disease was noticed for the first time in 1976 in outbreaks in Sudan and in the Democratic Republic of Congo. The current outbreak starting in December 2013 is the largest since the discovery of the virus and more people have did therein than in all others combined. A total of 27049 cases and 11149 deaths have been reported up to 24th May 2015. There are no approved drugs or vaccines against Ebola so far (May 2015). The WHO declared Ebola a public health emergency on 8th August 2014 as a result of the first meeting of the IHR Emergency Committee. The EMA and the FDA commited themselves on the 16th WHO International Conference of Drug Regulatory Authorities (ICDRA) on 3rd September 2014 to accelerate the development and assessment processes of possible new Ebola medical products. Both agencies offer several new, but also established measures for acceleration of the development of new compounds in case of the declared emergency situation of the Ebola Virus Disease. The EMA established an Ad-hoc Task Force, Rapid Scientific Advice, a proactive review of currently available treatments of Ebola (due to Article 5 (3) of regulation 726/2004), a Rolling Review of data and encourage the use of the orphan designation for possible new compounds against Ebola. In a similar way, FDA installed an Ebola Task Force, advices and cooperation, can rely also on already established measures as the orphan designation but in addition to many more options than the EMA with FDA´s designations for Expedited Programs for serious conditions.
Regarding early access options of possible new Ebola medicines, both agencies offer similar options as Compassionate Use/Expanded Access and a named-patient basis-access/EIND.
As regulatory approval options in emergency situations such as the current Ebola outbreak, the EMA has the possibility of the Article 58 procedure or a conditional approval (with also accelerated assessment), whereas the FDA has the possibilities of the Accelerated Approval, the Animal Rule or the Emergency Use Authorisation.

In general, the FDA has better, faster and more flexible options for an emergency case such as the 2014 Ebola crisis - with regard to the tools of accelerating the development but even more so in case of the regulatory emergency approval options as these show very fast and flexible characteristics compared to the EMA. Other national regulatory health authorities including the EMA therefore should think about taking over these options, particularly the regulatory approval options from the FDA. It should also be considered to take these possibilities into account in the currently undergoing structural reforms at the WHO (e.g. into the PQP programme) regarding emergencies and disease oubreaks - initiated due to the current Ebola outbreak – to achieve streamlined and harmonized regulatory pathways in public health emergencies of international significance. The health authorities of the concerned countries of the emergencies also must not be neglected in such processes as they know the situation best and have to include all measures into their local processes.

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Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.