Federal Institute
for Drugs
and Medical Devices

New Antiinfectives: EU Regulations and DZIF-BfArM Cooperation

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New antiinfectives

In the last years there were authorised <u>amongst others:</u>

<u>New antibacterials:</u>

- **Telavancin** (Vibativ®, 2011)
- **Fidaxomicin** (Dificlir®, 2011)
- **Ceftaroline** (Zinforo®, 2012)
- **Ceftobiprole** (Zevtera®, 2014)
- **Oritavancin** (Orbactiv®, 2015)
- **Tedizolid** (Sivextro®, 2015)
- **Dalbavancin** (Xydalba®, 2015)
- **Ceftazidime + avibactam** (Zavicefta®, 2016)

New antiinfectives

New drugs as part of multi-drug-resistant *Mycobacterium tuberculosis* combination therapy :

- **Bedaquiline** (Sirturo®, 2014)
- **Delamanid** (Deltyba®, 2014)

New HCV drugs:

- **Sofosbuvir** (Sovaldi®, 01/2014)
- **Simeprevir** (Olysio®, 05/2014)
- **Daclatasvir** (Daklinza®, 08/2014)
- **Dasabuvir** (Exviera®, 01/2015)

New antiinfectives

New HIV drugs, amongst others:

- **Elvitegravir/Cobicistat/Emtricitabine/Tenofovir** (Stribild®, 2013)
- **Dolutegravir** (Tivicay®, =1/2014)
- **Darunavir + Cobicistat** (Rezolsta®, 11/2014)

New antimalarial drugs:

- **Piperaquine / Dihydroartemisine** (Eurartesim®, 10/2011)
- **Pyronaridine / Artesunate** (Pyramax®, 11/2015, for use outside the EU)

New antifungal drugs:

- **Isavuconazole** (Cresemba®, 10/2015)

New antiinfectives „in the pipeline“

vfa: Research-Based Pharmaceutical companies:

- **Antibiotics:** Phase III: Eravacycline (a Fluorocycline, against Gram-neg.!) …, see:

https://www.vfa.de/de/arzneimittel-forschung/woran-wir-forschen/neue-antibiotika-den-vorsprung-wahren.html

- **HCV:** Phase III: Tegobuvir, Beclabuvir, Vaniprevir, …, see:

https://www.vfa.de/de/arzneimittel-forschung/woran-wir-forschen/hepatitis-c-heilung-neue-medikamente-verbessern-chancen.html

- **Tuberculosis:** https://www.vfa.de/print/de/arzneimittel-forschung/woran-wir-forschen/tuberkulose-neue-medikamente-gegen-die-infektionskrankheit.html : „**TB Alliance**“ is a not-for-profit organization dedicated to the discovery and development of better, faster-acting, and affordable tuberculosis drugs that are available to those who need them (https://www.tballiance.org/portfolio)
- **Malaria:** Phase III: Artemether spray, Tafenoquine … , see:

https://www.vfa.de/de/arzneimittel-forschung/woran-wir-forschen/malaria-tb-ntd

New antiinfectives

- All the marketing authorisations listed above based on a EC decision following the opinion of the CHMP (Committee for Medicinal Products for Human Use) as result of the assessment in centralised procedures by the EMA (European Medicines Agency).

- All details on each drug / procedure (including EPAR + product information + post-authorisation procedures) see:

  http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124

- Antiinfectives: The centralised procedure is (only) obligatory for all antivirals with a new active substance (Regulation (EC) No 726/2004).

EU Regulations

- In general, the marketing authorisation based on the justification of quality, safety and efficacy
  - with the proposed application (dosage form)
  - in the proposed indication
  - in the intended population
  - in the proposed dosing regimen.
- Basis: required quality, non-clinical and clinical data, tests and studies

EU Regulations: EMA

1. **Pre-authorisation regulatory and procedural guidance**

   European Medicines Agency pre-authorisation procedural advice for users of the centralised procedure (14. Nov. 2016, EMA/339324/2007): Q & A

2. **Scientific advice and protocol assistance**: CHMP on recommendation of the Scientific Advice Working Party (SAWP): helps the company to make sure that it performs the appropriate tests and studies, so that no major objections regarding the design of the tests are likely to be raised during evaluation of the marketing-authorisation application. Such major objections can significantly delay the marketing of a product, and, in certain cases, may result in refusal of the marketing authorisation. Following the Agency's advice increases the probability of a positive outcome.

3. **Scientific Guidelines:** Guidelines reflect a harmonised approach of the EU Member States and the Agency on how to interpret and apply the **requirements for the demonstration of quality, safety and efficacy set out in the Community directives (for all EU and national MA applications)**.

EU Regulations: EMA

Scientific Guidelines:

- **Quality:** active substance, drug product, pharmaceutical development, manufacturing, impurities, specifications, analytic, excipients, packaging, stability, specific types of products, Q&A
- **Non-clinical:** pharmacology and safety pharmacology, pharmacokinetics and toxicokinetics, toxicology, non-clinical development and environmental risk assessment
- **Clinical efficacy and safety guidelines: antiinfectives for systemic use**
  for treatment of bacterial infections, HIV infections, fungal disease, HCV, HBV …

The Agencies strongly encourage applicants and marketing authorisation holders to follow these guidelines. Applicants need to justify **deviations from guidelines** fully in their applications at the time of submission. Before that, they should seek **scientific advice**, to discuss any proposed deviations during medicine development.

(http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000043.jsp&mid=WC0b01ac05800240cb)

EU Regulations: a new regulatory way

until now: accelerated assessment procedure

new: PRIME (PRIORITY **ME**DICINES**):** a scheme launched by the EMA (02/2016) to enhance support for the development of medicines that target an unmet medical need (enhanced interaction and early dialogue with developers of promising medicines, to optimise development plans and speed up evaluation so these medicines can reach patients earlier with the following key benefits for applicants:

- appointed **rapporteur** will provide continuous support and **help to build knowledge ahead of a marketing-authorisation application;**
- **guidance on the overall development plan and regulatory strategy;**
- **scientific advice at key development milestones**, involving additional stakeholders such as health-technology-assessment bodies, to facilitate quicker access for patients to the new medicine;
- **potential for accelerated assessment** confirmed at the time of an application for marketing authorisation.

(See: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000660.jsp&mid=WC0b01ac05809f8439)

EU Regulations: the new EMA Innovation Task Force (ITF)

- In order to provide support to medicines innovation in EU, the EMA established an internal EMA horizontal cross-sectorial group, the ITF, to focus in particular on ***Emerging Therapies and Technologies*.**
- ITF brings together competences from the areas of Quality, Safety, Efficacy, Pharmacovigilance, Scientific Advice, Orphan Drugs and good practices compliance, legal and regulatory affairs.
- **Some objectives of ITF**

– establish a discussion platform for early dialogue with applicants, in particular micro, small and medium-size enterprises (SMEs) to proactively identify scientific, legal and regulatory issues of emerging therapies and technologies

– address with relevant EMA Committees + their Working Parties impact of emerging therapies and technologies on current scientific, legal and regulatory requirements

– identify early the need for specialised expertise

DZIF-BfArM cooperation

7. DZIF Member Meeting 06.05.2015: New members:

- Friedrich-Loeffler-Institut (FLI)
- Robert Koch-Institut (RKI)
- **Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)** →Partner Site: Bonn-Köln

→ **Translational Infrastructure: Product Development Unit (DZIF-PDU):**

Coordinator: Klaus Cichutek, Paul Ehrlich Institute (PEI)

DZIF Office for Scientific and Regulatory Advice (DZIF-OSRA):

Christoph Conrad (PEI) and Sibylle Matz + Miriam Wilmes (BfArM)

DZIF Translational Project Management Office (DZIF-TPMO):

Thomas Hesterkamp + Lisa Heitmann

DZIF-BfArM cooperation: the new partner BfArM

The new partner BfArM:

- **Independent federal authority within the portfolio of the Federal Ministry of Health: Roughly 1,000 employees are involved in**
- **Task of licensing, improving the safety of medicinal products on market, detecting and evaluating the risks of medicinal devices, and monitoring the legal traffic in narcotic drugs and precursors**

Note: Certification of medical devices occurs by a notified body.

AND: The PEI is the Federal Institute for Vaccines and Biomedicines.

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DZIF-BfArM cooperation: the new partner BfArM

BfArM as national competent authority is involved in the European and national drug regulation for antiinfectives (and other drugs):

- Pre-authorisation: Scientific Advice (written procedures or discussion meetings)
- Authorisation procedures
- Post-authorisation:
    - Variations: such as extension of indication (new indications)
    - Renewals: evaluation of the current benefit risk ratio (drug resistance?)

and by collaboration within EU

- as member in the Infectious Diseases Working Party (IDWP), Quality Working Party (QWP), Saftey Working Party (SWP), Pharmacokinetics Working Party (PWP) and others
- by drafting / updating of European Regulatory and Scientific Guidelines for Antiinfectives

DZIF-BfArM cooperation: the new partner BfArM

… and by collaboration within Germany:

BfArM is collaborating with other Institutes in the portfolio of the Federal Ministry of Health (BMG) in national projects, **within the German Antibiotic Resistance Strategy: DART 2020** e.g.:

- **ART** (Commission Anti-Infectives, Resistance and Therapy), at Robert Koch Institute
- **ARS** project (Antibiotic Resistance Surveillance), Robert Koch Institute
- **NAK** (National Antibiotics Committee of EUCAST)
- Cooperation with our collegues for resistance monitoring in the veterinary sector in Germany (**BVL** = Federal Office of Consumer Protection and Food Safety)
- national „**Z.A.R.S Project**“

DZIF-BfArM cooperation: the new partner BfArM

The national „Z.A.R.S. – Project“

- Startet in 2005, initiated by BfArM together with Marketing Authorisation Holders for antibiotic drugs
- Based on data of several national surveillance projects + resistance studies
- Yearly update of the German resistance situation for about 60 systemic antibiotics → in section 5.1 of the product information
- Also used for approval of generic antibiotics
- **Result/aim should be: prudent use of antibiotics (provided: physicians read the product information!)**

DZIF-BfArM cooperation:

Cooperation of BfArM with German Center for Infection Research (DZIF):

Scientific advice already during the translational phase of drug development:

- Answers to quality, non-clinical, clinical and regulatory aspects
- Also as „Kick-off Meeting“ (brain storming discussion) at a very early stage of development
- Benefit: scientists can consider the requirements for quality testing, non-clinical and clinical studies already very early → target-oriented research and development
- In some cases / projects together with Paul Ehrlich Institute (PEI)

DZIF-BfArM cooperation:

- **Use of the regulatory and scientific expertise of quality, non-clinical and clinical assessors of the BfArM's**
  - **unit 61 „Clinical trials“**
  - **unit 32 „Antiinfectives**/Antiallergics/Dermatology/ENT“

    and
  - **unit 63 „Scientific Advice, Expert Panels”** (I/2017: plus “Innovation Office”, connected with EMA Innovation Task Force; and also involvement of the Federal Joint Committee (GBA = Gemeinsamer Bundesausschuss) in Scientific Advice)

DZIF-BfArM cooperation:

Until now Kick-off Meetings/Scientific Advice Meetings for the Thematic Translational Units (TTUs):

- HIV
- Malaria
- Tuberculosis
- Gastrointestinal Infections

As result of our (DZIF, PEI and BfArM) experiences:

The procedures for the Kick-off Meetings and Scientific Advice Meetings will be definded in detail.

DZIF-BfArM cooperation:

Kick-off Meeting:

- Informal project presentation
- Without application and precise list of question
- Short presentation of project idea by the applicant
  - Identification of regulatory relevant questions
  - Feedback to missing data and reference to relevant guidance documents
  - Preparation of a scientific advice meeting
- Meeting structure: “unstructured”; open scientific discussion
- Short Minutes of the results
- Fees (AMGKostV): No

DZIF-BfArM cooperation:

Scientific Advice Meeting:

- Scientific Advice Meeting adhering to federal agency‘s formal standards on structure and content
- Answers to regulatory and scientific questions
- Submission: cover letter, application, detailed briefing document, presentation
- Meeting structure: structured, answers to precise list of questions
- Summary Meeting Minutes
- Fees (AMGKostV): Yes

Details see also:
http://www.bfarm.de/DE/Service/Beratungsverfahren/_node.html;jsessionid=9F47C1416D6B9928EBD8798264320305.1_cid340

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DZIF-BfArM cooperation:

The

- **information on Kick-off and Scientific Advice Meetings**

and

- **overviews on relevant quality, non-clinical and clinical Scientific Giudelines**

will be available in detail on the DZIF homepage in the next days.

AND in May 2017 BfArM-PEI-DZIF-Workshop:

- **the new Clinical Trial Regulation** (see: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000629.jsp)
- **and first in human clinical trials**

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Thank you very much for your attention!

Contact

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