Introducing New Strategy on Bioequivalence in Ukraine
December 2018
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### ACRONYMS

<table>
<thead>
<tr>
<th>ACC</th>
<th>American Chamber of Commerce (in Ukraine)</th>
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<tr>
<td>API</td>
<td>Active Pharmaceutical Ingredient</td>
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<tr>
<td>BCS</td>
<td>Biopharmaceutics Classification System (BCS)-based bio waiver system</td>
</tr>
<tr>
<td>CMC</td>
<td>Chemistry, Manufacturing, and Controls</td>
</tr>
<tr>
<td>CMDh</td>
<td>Coordination Group for Mutual Recognition and Decentralized Procedures-CMDh</td>
</tr>
<tr>
<td>CMU</td>
<td>Cabinet of Ministers of Ukraine</td>
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<tr>
<td>CRO</td>
<td>Contract research organization</td>
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<tr>
<td>CTD</td>
<td>Clinical Trial Directive (2001/20/EC); Common Technical Document</td>
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<td>CTR</td>
<td>Clinical Trial Regulation (EU) 536/2014</td>
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<td>DCP</td>
<td>Decentralized Procedure (EU)</td>
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<td>EBA</td>
<td>European Business Association (Kyiv)</td>
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<td>EBRD</td>
<td>European Bank for Reconstruction and Development</td>
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<td>EEAU</td>
<td>Eurasian Economic Union</td>
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<td>EMA</td>
<td>European Medicines Agency</td>
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<td>EU/EEA</td>
<td>European Union/European Economic Area</td>
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<td>FDA</td>
<td>Food and Drug Administration of the United States of America</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>GLP</td>
<td>Good Laboratory Practice</td>
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<td>GMP</td>
<td>Good Manufacturing Practice</td>
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<td>HTA</td>
<td>Health Technology Assessment</td>
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<tr>
<td>ICH</td>
<td>International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use</td>
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<tr>
<td>IMP</td>
<td>Investigational Medicinal Product</td>
</tr>
<tr>
<td>INN</td>
<td>International Non-Proprietary Name</td>
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<tr>
<td>MA</td>
<td>Marketing Authorization</td>
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<td>MAA</td>
<td>Marketing Authorization Application</td>
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<td>MAH</td>
<td>Marketing Authorization Holder</td>
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<td>MOH</td>
<td>Ministry of Health</td>
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<td>MRP</td>
<td>Mutual recognition Procedure</td>
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<td>PAR</td>
<td>Public assessment report</td>
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<tr>
<td>PIC/S</td>
<td>Pharmaceutical Inspection Cooperation Scheme</td>
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<td>PK</td>
<td>Pharmacokinetics</td>
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<td>Q&amp;A</td>
<td>Questions and Answers</td>
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<td>QMS</td>
<td>Quality Management System</td>
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<td>RA</td>
<td>National Drug Regulatory Authority</td>
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<td>RLD</td>
<td>Reference listed Drug (FDA)</td>
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<td>SAUMP</td>
<td>State Administration of Ukraine on Medicinal products</td>
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<td>SBP</td>
<td>Similar Biotherapeutic Product</td>
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<tr>
<td>SEC</td>
<td>State Enterprise “State Expert Centre of the Ministry of Health of Ukraine”</td>
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<tr>
<td>SmPC</td>
<td>Summary of Product Characteristics</td>
</tr>
<tr>
<td>SPC</td>
<td>Supplementary protection certificate for medicinal products</td>
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<tr>
<td>SRA</td>
<td>Stringent Regulatory Authority</td>
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<tr>
<td>USA</td>
<td>United States of America</td>
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<td>USD</td>
<td>US Dollar</td>
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<td>WHO</td>
<td>World Health Organization</td>
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### TERMS

**Acquis Communautaire:** the accumulated legislation, legal acts, and court decisions which constitute the body of European Union law

**Generic medicinal product:** the term generics used in this report comprises both generics + branded generics
ACKNOWLEDGMENTS

Many thanks to the project partners in the Ministry of Health, the State Expert Centre, the Ukrainian Medical Expert Community (UMEC) as well as the interview partners from the ACC, EBA, WHO Office in Kyiv, JSC Farmak, the staff of the Department of Clinical Pharmacology and Clinical Pharmacy and Clinical Diagnostic Center of the National University of Pharmacy in Ukraine, Kharkiv, and the PHARMBIOTEST Clinical and Diagnostics Centre in Rubezhnoe for their willingness to share all necessary information to discuss the presented recommendations, strategy, and roadmap for implementation.

The expert thanks Ms. Inna Sacci, succeeding Mr. Malcolm Clark as Chief-of-Party, Ms. N. Kadyrova, Deputy Project Director, Mr. Ivan Loboda, Senior Technical Advisor in Pharmaceuticals financing, Ms. Maria Miroshnychenko, Translator, and Ms. Larysa Dovgan, Administrator, for many informative discussions and the necessary administrative support.
EXECUTIVE SUMMARY

Generic medicinal products (together with hybrids and biosimilars) contribute significantly to cost savings in the national healthcare systems and facilitate access of the population to effective, safe, and good quality medicinal products due to affordable prices [1-3]. They are copies of innovator (originator, reference, comparator) drugs, which have received marketing authorization based on a “full dossier”, demonstrating efficacy, safety, and quality of the product (pre-clinical data, results from clinical studies, etc.) [4-6].

Generic drugs must fulfil the same requirements concerning quality, safety, and efficacy as the originator’s drug, i.e. both drugs must be equivalent [3,4,7-9]. In order to provide (indirect) evidence that the test product is as safe and efficacious as the originator/reference product, its bioequivalence must be demonstrated [5,10-13]. There are several possibilities to demonstrate bioequivalence: the “gold standard” is to perform a phase I clinical study with pharmacokinetic endpoints and a limited number of participants to proof that rate and extend of the active pharmaceutical ingredient (API) or its (active) metabolite in the body fluid(s) (blood, plasma, serum, urine) is essentially similar (i.e. concentrations are in within pre-defined limits) [5,10-16]. Other ways to demonstrate bioequivalence are to conduct comparative clinical trials and/or comparative pharmacodynamic studies. In defined, justified cases in-vitro dissolution tests, i.e. the application of the Biopharmaceutics Classification System (BCS)-based biowaiver system, may be acceptable [10,13,14,17,18].

Bioequivalence plays a fundamental role in the definitions of a generic medicinal product (multi-source product, as the product is in general marketed by several manufacturers), which must be pharmaceutical equivalent, i.e. have the same qualitative and quantitative composition of its active ingredient(s) and the same pharmaceutical form as the reference product, and it needs to be bioequivalent to the reference product [3-16,19]. Bioequivalent drugs should also be therapeutically equivalent and interchangeable with the reference (comparator) product, as this is absolutely necessary in the daily medical-therapeutic practice to guarantee the proper safe and efficacious treatment of patients [3,12,20-28]. Interchangeability includes not only equivalence of the dosage forms, but also of the indications and instructions for use.

Therapeutical equivalence and interchangeability (“generic substitution”) are not within the scope of the (dossier) assessments within the marketing authorization application (MAA) process at the national regulatory authorities. In EU/EEA these issues are subject to separate, different regulations of the individual member states [3,6,12,20-28].

The critical assessment and comparison of the applicable, relevant legislative/regulatory provisions in Ukraine and EU concerning the investigation of bioequivalence revealed, that many terms and definitions, like “generic medicinal product”, “bioequivalence”, “pharmacetically equivalent”, have different meanings in the respective regulatory provisions. Nevertheless, the regulatory/legislative framework in Ukraine and EU in general, including the rules concerning bioequivalence, is almost completely harmonized. However, significant differences exist:

1. Within the relevant regulations in Ukraine, when e.g. different definitions for the same issue are given in the Law, Decrees, Orders, and Guidelines,
2. Between the provisions in Ukraine and those of the EU/EEA, and
3. Between the provisions from (1) and (2) and those of the WHO and FDA (relevant provisions from WHO and FDA were taken into consideration as supportive material, because they often contain more detailed and specific information than the respective national provisions).
This finding corresponds well with those of a survey on similarities and differences among bioequivalence approaches used by 13 international regulatory authorities/organizations: “there are more similarities than differences…” [15].

Terms and Definitions must be consistent in all regulatory/legislative documents as they are the common basis of understanding for all stakeholders and the fundament of all further discussions and reflections on procurement and reimbursement systems. This holds true for both the provisions in the MAA process and those stipulated in different, separate regulations ruling areas like generic substitution (therapeutically equivalence and interchangeability). However, not all regulations in the pharmaceutical sector in EU are covered by Community law. Therefore, the harmonization/approximation of the legislative/regulatory systems in Ukraine and EU is limited to those regulations ruled by the Common Law in EU. The Association Agreement with EU leaves Ukraine with a lot of freedom to consider national regulations in EU, like those for generic substitution (therapeutically equivalent, interchangeable, etc. [20-28].

The identified key differences, inconsistencies, and non-conformities concerning the Terms and Definitions in Order #460 [14], Directive 2001/83/EC [4], the Ukrainian [10] and EU [13] Guidelines on the investigation of bioequivalence, WHO, and FDA are summarized in Annex C, Table 4 and comprise:

1. **Definition of a generic medicinal product**: The provisions of Order #460, Directive 2001/83/EC, Ukrainian and EU Guidelines on the Investigation of Bioequivalence, WHO and FDA, request “Pharmaceutically equivalent” plus demonstrated bioavailability. However, in addition, Decree #376 and Order #460 request that the products are interchangeable. The FDA expects that the product is (1) pharmaceutically equivalent, (2) bioequivalent, and, consequently, (3) therapeutically equivalent.

2. **Definition of Bioequivalence**: Order #460, WHO and FDA have the same provisions, whereas the Ukrainian and EU Guidelines on the Investigation of Bioequivalence request “Pharmaceutically equivalent or Pharmaceutical alternatives” (i.e. same or different way of administration); Directive 2001/83/EC has no definition of bioequivalence. The EU Guideline [13] defines bioequivalence as: “Two medicinal products containing the same active substance are considered bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailabilities (rate and extent) after administration in the same molar dose lie within acceptable predefined limits. These limits are set to ensure comparable in vivo performance, i.e. similarity in terms of safety and efficacy”.

3. **Definition of pharmaceutically equivalent**: Pharmaceutically equivalent are medicinal products, which contain the same active ingredient(s) (API), in the same strength (concentration) and dosage form, and, in addition, Order #460, WHO and FDA demand the use the same route of administration. The “Guidelines on the Investigation of Bioequivalence” [13] defines: “Medicinal products are pharmaceutically equivalent if they contain the same amount of the same active substance(s) in the same dosage forms that meet the same or comparable standards (quality)”. 

4. **Pharmaceutical alternatives** All five compared provisions request the same active ingredient (API): Order #460 and the FDA request the same amount (strength) of API and dosage form, the WHO and the Ukrainian and EU Guidelines on the Investigation of Bioequivalence allow different dosage forms. Only WHO and FDA demand the “same route of administration”.

5. **Therapeutically equivalent**. Therapeutic equivalence is based on 2 conditions: both products must be (1) pharmaceutically equivalent, and (2) after administration of the same molar dose produce
similar effects for both safety and efficacy (shown by a bioequivalence study); therapeutically equivalent drugs are interchangeable [3,9,12,20-28]. As per definition by the FDA, two medicines that have the same clinical effect and safety profile are considered as therapeutic equivalent. These two drugs have nearly identical properties and thus can be interchanged [16,23].

Therapeutic equivalency is the basis for the ultimate goal of a generic medicine i.e. to be interchangeable with the reference product [3,9,12,20-28]. No such reference is in the Law of Ukraine on Medicines [29], Order #460 [14], or Order #426 [11], but in Decree #376 [19] it is ruled that therapeutic equivalence (interchangeability) must be demonstrated according to the “WHO recommendations” in the MAA process for a generic medicine.

In EU, aspects concerning “generic substitution” are subject to national regulation(s) [13]. Thus, in EU e.g. the Swedish [22] and Irish RA [26] have published on their website a list of therapeutically equivalent and interchangeable medicines, as well as the applicable criteria for considering them to be therapeutically equivalent and interchangeable.

6. **Interchangeability** [3,9,12,20-28,30] Order #460 demands that the generic is pharmaceutically equivalent and that it is interchangeable with the reference product, proofed by “relevant studies”. Decree #376 requests that the test product is therapeutically equivalent and interchangeable according to the provisions of the WHO. WHO and FDA stipulate that the products must be therapeutically equivalent and can be interchanged with the comparator in clinical practice. Like therapeutically equivalence, interchangeability issues are ruled in EU/EEA by the individual Member states.

7. **Selection and definition of the Reference (comparator) product** Directive 2001/83/EC and the EU Guidelines on the Investigation of Bioequivalence define that the reference product (comparator) must be authorized in EU/EEA with a full dossier, whereas the Ukrainian Guideline in addition requests compliance with the provisions in Order #460. Order #460 and WHO request an innovator product with a full dossier, irrespectively of a marketing authorization in EU/EEA. Decree #376 requires that the reference product is therapeutically equivalent (interchangeable) and selected by following “WHO recommendations” [31]. If a comparator product is not available, it should be selected by following WHO recommendations [31] from a “List of International comparator products after public consultation” [32]. Furthermore, it must be interchangeable in clinical practice. According to FDA rules the comparator must be selected from the Reference Listed Drug (RLD) [16,23]. In EU Directive 2001/83/EC there is no reference, neither to therapeutic equivalence, nor to interchangeability, nor to the requirement of the FDA, the WHO, and Order #460 that the same route of administration must be utilized, only the term bioavailability is used. This may cause some uncertainties with the applicants and needs to be clarified.

8. **Different requirements when bioequivalence studies are necessary.** In Annex 18 of Order #460 [14] a list of medicinal products is presented, which need to demonstrate bioequivalence in the registration process. This list is only partly compatible with the respective provisions in the Ukrainian [10] and EU [13] Guidelines for Investigation of Bioequivalence, which are almost completely harmonized. Terms, like “emergency medicine” are only in Annex 18.

9. **Different requirements when bioequivalence studies are NOT necessary.** Like in (8) the list in Annex 18 of Order #460 for medicinal products for which no bioequivalence study is required (for registration), the listed products include those eligible for the “Simplified registration
procedure” and the provisions laid down in Annex 18 of Order #460. Again, the provisions in Order #460 (Annex 18) on one hand and those of the Ukrainian [10] and EU [13] Guidelines on the Investigation of Bioequivalence on the other hand, are significantly different.

10. “Product-specific bioequivalence guidance” documents, “summarizing in a standardized format the relevant study design principle for demonstration of bioequivalence published by the EMA and FDA [33,34] have not yet been published in Ukraine.

In summary, the performed comparison of the legislative/regulatory provisions in Ukraine and EU/EEA concerning bioequivalence as well as the interrelated provisions, like in the MAA application rules, clearly shows that both systems are almost harmonized. However, important differences in the “Terms and Definitions” exist not only between Ukrainian, EU/EEA, WHO, and FDA rules, but also within the Ukrainian regulatory system itself. These differences, inconsistencies and non-conformities within the Ukrainian regulatory system must be eliminated as soon as possible, as they are the common basis of understanding for all stakeholders in Ukraine. Key challenges and possible strategies (scenarios) are in Chapter 4, followed by a SWOT analysis of the proposed strategies in Chapter 5.

The implementation plan in Chapter 7 (Table 1) lists and summarizes all proposed strategies with a detailed description of the required activities. Implementation arrangements are listed in Chapter 8. The presented roadmap for the implementation of the proposed strategies/scenarios comprises a 10-point action plan (Chapter 9.1) and a brief outline for a “Model regulation for generic substitution in Ukraine”, including alternatives from Germany, Ireland, and Sweden (Chapter 9.2). Some of the described activities have already been addressed by the SEC, which has developed Draft amendments to the MOH Order #460 to further harmonize it with Directive 2001/83/EC, and the guidelines on the Investigation of Bioequivalence. Furthermore, product-specific guidance documents (reflecting those published by the EMA and FDA) and recommendations for the proper selecting of reference comparator products in bioequivalence studies are in preparation, as well as a list of recommended reference products [10(b)].
Governance of bioequivalence in Ukraine is not aligned with EU standards, and there are risks Ukrainians may be exposed to sub-standard generic medicines that would not be allowed in EU states and damage the trust of the general population toward the health care system. As part of the objectives of governance improvement and ensuring the availability of quality medicines, SAFEMed provides technical assistance to compare EU standards and best practices with the current state of bioequivalence in Ukraine. The work includes consultation with in-country expertise, evaluation of actual current practices, and in-depth analysis of current and future legislative requirements. As a result, MOH will be provided with a situation analysis and recommendations for changes to align with EU standards, both in legislative terms and taking into account the impact on registration and enforcement processes and the organizational capacity of SEC and the State Service on Drug Control and Narcotic Circulation. Following agreement on the way forward, SAFEMed will provide financial and legal assistance for the drafting of legislation required to enact change.

Development of the proposed bioequivalence strategy for Ukraine started with the review of key relevant, applicable literature and references. Laws, decrees, regulations, rules, and guidelines/guidance, covering the regulatory/legislative framework concerning bioequivalence in both Ukraine and EU were selected to identify possible differences, discrepancies and non-conformities. Documents were reviewed, gaps identified and draft conclusions, followed by draft recommendations and a draft strategy for their implementation (roadmap, action plan), developed. In addition, possible risks and costs borne by the implementation were estimated. In the next step, draft recommendations and strategy were discussed with key stakeholders, namely the State Expert Center (SEC), pharmaceutical industry represented by their business associations, two clinical research organizations (CROs) performing bioequivalence studies in Ukraine, and the WHO. Comments, corrections, proposals, and other additional inputs from the reviewing process were included into the Final Report and presented to key stakeholders and other interested parties in December 2018 at the roundtable.

1.1 Methodology

Objectives: SAFEMed provided technical support to the MOH to develop a strategy on improving regulations on the bioequivalence of generic medicines in line with European Union (EU) practices. In addition, hybrid applications and biosimilars were included into the scope of work for this undertaking.

Team: SAFEMed identified Dr. Werner Gielsdorf, an international recognized expert from Germany, to prepare a state of play, identify feasible options for Ukraine, develop draft strategy and a roadmap for actions in order to assure bioequivalence of generic medicines in Ukraine. Dr. Gielsdorf was supported primarily by Mr. Ivan Loboda, SAFEMed’s Senior Technical Advisor assigned to lead these efforts within SAFEMed, with some guidance from Dr. Ninell Kadyrova, Deputy Director, Mr. Malcolm Clark, interim Chief-of-Party. Other members of the SAFEMed Team included Ms. Maria Miroshnychenko who supported the work as translator, and Ms. Larysa Dovgan as administrator.

Timeline and Methodology: Working on this task started on August 12, 2018 and was completed by December 18, 2018 with the submission of the technical report. As such, it included:

- A series of meetings on September 16-22, 2018 in Kyiv and Kharkiv by Dr. Werner Gielsdorf with the representatives of the Ministry of Health, Department of Clinical Pharmacology and Clinical Pharmacy and Clinical Diagnostic Center of the National University of Pharmacy in Ukraine in Kharkiv, and the CRO PHARMBIOTEST in Rubezhnoe that perform bioequivalence (phase I) studies;
Introducing New Strategy on Bioequivalence in Ukraine

- Development of the draft report with recommendations by Dr. Werner Gielsdorf in English and Ukrainian;
- Feedback on the draft report by key Ukrainian stakeholders: government, academe, and industry;
- Finalization of the report during the second visit by Dr. Werner Gielsdorf to Ukraine on December 10-18, 2018 to further discuss initial findings, draft strategy, and the road map for actions during final face-to-face individual meetings with key stakeholders and a round table discussion that brought everyone together.

The works were conducted in the following steps:

**Step 1:** Collection of the relevant, applicable literature and references, i.e. laws, decrees, regulations, rules, guidelines/guidance, etc. covering the regulatory/legislative framework concerning bioequivalence in both Ukraine and EU. Key Ukrainian documents were translated into English.

**Step 2:** Reviewing the collected documents to identify possible differences, discrepancies and/or non-conformities (initial findings); gap analysis.

**Step 3:** Identifying the driving forces for a successful and feasible strategy in Ukraine.

**Step 4:** Developing draft conclusions, followed by draft recommendations and a draft strategy for their implementation (roadmap).

**Step 5:** Discussing the draft recommendations and strategy with the key stakeholders from the regulatory authority, representatives from the pharmaceutical industry and their business associations, two clinical research organizations (CROs) performing bioequivalence studies in Ukraine, and the WHO.

**Step 6:** Developing recommendations (mutually agreed to be accountable, useful, and goal-orientated to support the Healthcare Reform in Ukraine), taking into account the comments, corrections, proposals, and other additional inputs from the reviewing process.

**Step 7:** Developing a draft strategy for implementing the recommendations (roadmap).

**Step 8:** Presentation of key findings, i.e. recommendations, strategy for implementing them, and a roadmap covering the estimated time horizon, to the key stakeholders and other interested parties.

1.2 Limitations

**Translations:** Not all Laws, Governmental Decrees, and Executive Orders, etc. listed in the references, literature lists, which were retrieved from the Ministry’s and/or Governmental and other websites, offered the texts also in English. Consequently, translations into English were done by translation programmes in the Internet. Thus, the correctness and accuracy of the English versions of the documents could not be verified but considered to be correct.

**Amending the “Law of Ukraine on Medicines”:** The expert has been informed that several revisions, amendments, etc. of the Law of Ukraine on Medicines (from 04 April 1996) [29] are planned. It is unclear which provisions exactly will be affected.

**Approval/Registration of legal documents:** Legal documents like Orders must be registered/approved by the Ministry of Justice to get into power. The expert couldn’t evaluate whether each document/Order has been registered or not by the Ministry of Justice. If not, they might be considered invalid and/or not applicable.
Generics need to be seen in the context with biosimilars: both are “me-too” (copy) products of the originator’s product, but by definition biosimilars cannot be bioequivalent, because they are produced by biotechnical processes and the originator’s cell line cannot not be identical to the one of the originators [37-39]. Thus, different provisions concerning the legislative/regulatory provisions in the marketing authorization application (MAA) process apply [9,14,37-39]. Consequently, the term “bioequivalence” applies only to generics, whose active principle(s) are chemically defined substances. Nevertheless, the key aspects concerning biosimilars have been included into the scope of this project to give a full picture of both generics and biosimilars.

### 2.1 The role of generics and biosimilars in the pharmaceutical markets in the EU, Ukraine, and USA

In almost all pharmaceutical markets generics/branded generics together with biosimilars represent the by far biggest share of medicinal products for humans: in Germany (as an example for an EU market) the market segment for generics in 2017 was at approx. 70% by volume, but only about 29% by value [40]. In addition to this share, biosimilars contribute by 25%. In the US generics account for 88% of prescriptions, but only for 28% of the drug costs [1,2]. In Ukraine, the market share of generics, including traditional products, accounts to about 98% by value and 89% by volume [41]; other data report a market share of 90% for generics (including biosimilars, traditional products, and well-established medical use products. Interestingly the market share of local manufacturers is by volume 68%, but by value only at 32%, in contradiction to foreign suppliers, which take about 67% by value, but just 33% by volume [6].

The market for biopharmaceuticals in general and for biosimilars in particular is the fastest growing in all key pharma markets, in some countries already outperforming (by value) the market share of generics. The pharmaceutical markets in the CIS countries and countries with less developed capabilities for (new) drug development, like China, have an even higher market share for generics: in China the market share of generics is at about 90% (by volume). This is because R&D for developing a new chemical entity (NCE) from starting to identify potential drug candidates till the marketing of a new drug requires very high investments of up to 1.2 billion USD [2], the availability of qualified human resources, and a favorable economic environment. Low and middle-income countries in general don’t have easy access to these necessary resources.

For many governments, generics are an important tool to cap national healthcare spending, as generics in general cost only about 20% of the originator’s price. In 2017 in the USA cost savings due to generics are estimated at 265 billion USD [1]. Therefore, the generics sector receives favorable conditions from the health authorities, e.g. in a faster and less cumbersome registration process. Recently the 500 leading US hospitals joined forces to lower drug prices by creating their own non-profit generic company (CivicaRx) [42]. This revolutionary model might be a model to explore for Ukraine, too.

Generic products (including hybrids and biosimilars) represent the by far biggest share in all pharma markets: consequently, it is therefore of paramount interest that generics, branded generics and hybrid medicinal products on the market are safe, effective, and of good quality.
3.0 CURRENT ENVIRONMENT

All over the world national governments and their health authorities have implemented a series of measures, both for controls and incentives to influence supply of and demand for pharmaceuticals. Even though the national healthcare expenditures for medicinal products are by far outweighed by the expenses for hospitals (in Germany only 7-8 % of the healthcare budget is consumed by medicinal products), governments try to limit costs of reimbursed medicines by controlling their price and level of reimbursement, as well as by limiting their accessibility by imposing e.g. positive and negative lists.

After gaining its independence in 1991, Ukraine implemented in 1993 a new registration system for medicinal products. In 1996 the “Law of Ukraine on Medicines” [29] was introduced, and in 2001 the harmonization/approximation process with the rules governing pharmaceutical products in the EU/EEA started. Rules concerning bioequivalence were established during several legal/regulatory provisions concerning generic interchangeability. The legislative/regulatory framework concerning bioequivalence in Ukraine and the EU/EEA are described in Annex A and B addressing the following issues:

(1) Legislative/regulatory overview
(2) Applicable, relevant legislative/regulatory provisions in the State registration procedures concerning bioequivalence
   2.1 When bioequivalence studies are required and types of studies necessary
   2.2 When bioequivalence studies are not required
(3) Provisions concerning the requirement to demonstrate bioequivalence in the MAA process for generics and hybrid applications.

In addition, the interrelated legislative/regulatory provisions concerning biosimilars in Ukraine and EU/EEA are presented in Annex D. Furthermore, as bioequivalence studies are phase I clinical studies, in Annex E the provisions for conducting clinical trials in Ukraine and EU/EEA are shown. In the light of the ongoing process of the (gradual) approximation/harmonization of the legislative/regulatory systems in Ukraine and EU/EEA within the Association Agreement, the applicable, relevant legislative/regulatory provisions concerning bioequivalence in Ukraine and the EU/EEA were compared and identified differences addressed (Annex C). The comparison/assessment included:

(1) Comparison of the relevant, applicable Guidelines on the investigation of bioequivalence
(2) Evaluation of specific differences concerning bioequivalence
(3) Key differences in the general legislative/regulatory framework
(4) Key differences concerning Terms and Definitions
(5) Summary and discussion of identified differences, non-conformities and discrepancies.

An in-depth report “On conformity of the process of state registration of medicinal products in Ukraine with the EU law and standards” was published by an EBRD-funded project in 2016 [44]. The evaluations, observations and recommendations in the areas of legislation, organization of the registration process, and policy in the report were analyzed in the light of their relevance to the actual project’s topic “bioequivalence”.

The actual assessment of the regulatory/legislative framework with a focus on bioequivalence issues revealed that in general the applicable, relevant provisions in both systems are very similar. However, considerable differences were identified and recommendations, including a strategy, roadmap and action plan for their implementation, developed. The identified differences in the regulatory systems are directly related to the evaluation of bioequivalence and its role in many areas and processes, like marketing authorization, procurement, reimbursement, price regulation, drug safety and efficacy.
4.0 KEY CHALLENGES AND POSSIBLE STRATEGIES

4.1 Key challenges—differences, non-conformities and discrepancies—between the legislative/regulatory framework in Ukraine and EU

A critical comparison/reviewing of the relevant, applicable legislative/regulatory provisions in Ukraine and the EU/EEC concerning the marketing authorization application process in general and those concerning bioequivalence in particular, revealed that both systems are almost completely harmonized. However, significant differences exist:

1. within the relevant regulations in Ukraine, when e.g. different definitions for the same issue are given in the Law, Decrees, Orders, and Guidelines,
2. between the provisions in Ukraine and those of the EU/EEA, and
3. between the provisions from (1) and (2) and those from WHO and FDA (provisions from WHO and FDA were taken into consideration as supportive material, because they often contain more detailed and specific information on specific issues than the respective national provisions.

In Annexes A and B detailed presentations of the legislative/regulatory framework in Ukraine and the EU/EEA are given, followed by a comprehensive analysis of the identified differences in Annex C. Table 4 in Annex B summarizes the relevant Terms and Definitions laid down in the applicable provisions of the Ukrainian legislation [14,19,29], in the Ukrainian and EU Guidelines on the Investigation of bioequivalence [10,13], and in the relevant WHO and FDA guides.

Since 2001 Ukraine continues to harmonize/approximate its legislative/regulatory framework with the regulations in force in EU/EEA. In this context, the SEC has developed Draft amendments [10(b)] to the MOH Order #460 [14] to further harmonize it with Directive 2001/83/EC [4], and the Guidelines on the Investigation of Bioequivalence [10]. The latter has been updated and its 2018 version published [10(c)]. Furthermore, product-specific guidance documents (reflecting those published by the EMA and FDA) [33,34] and recommendations for the proper selecting of reference comparator products in bioequivalence studies are in preparation, including a list of recommended reference products.

Similarities and differences among bioequivalence requirements applied by 13 international drug regulatory authorities are discussed in [15]. The authors conclude that “although there are important differences in bioequivalence approaches throughout the various regulatory agencies investigated in this article, we observed that, in general there are many more similarities”. These findings match those presented in this report.

Terms and Definitions must be consistent in all national regulatory/legislative documents as they are the commonly agreed basis of understanding for all stakeholders and the fundament of all further considerations, strategies, and planning.

These key differences, inconsistencies, and nonconformities are described in detail in Annex C and comprise:

4.1.1 Differences, non-conformities and discrepancies in the Terms and Definitions within the Ukrainian legislative/regulatory system and between the Ukrainian and EU/EEA (Community) rules

Table 4 in Annex C presents the key differences concerning the Terms and Definitions in Order #460 [14], Directive 2001/83/EC [4], the Ukrainian [10] and EU [13] Guidelines on the investigation of
bioequivalence, as well as WHO, and FDA provisions. Several Terms and Definitions are inconsistent within the Ukrainian legislative/regulatory system itself and differ from those in EU and the (supportive) provisions from WHO and FDA.

The following key Terms and Definitions are the fundament of all further discussions and reflections in both the harmonization process and the ongoing healthcare reform in Ukraine, and thus need to be consistent (supportive provisions from WHO and FDA should be taken into consideration, too). This holds true for both the provisions in the MAA process and those stipulated in different, separate regulations ruling areas like generic substitution (therapeutically equivalence and interchangeability).

In particular, the following definitions are affected:

- Generic medicinal product
- Bioequivalence
- Pharmaceutical equivalence
- Pharmaceutical alternatives
- Generic substitution
- Therapeutically equivalent
- Interchangeability
- Original (Innovator) medicinal product
- Selection of the reference medicinal product (comparator).

For example, the definition of a reference product (like in Order #460) [14] is not in compliance with the respective provisions in Directive 2001/83/EC [4]. In Directive 2001/83/EC there is no reference, neither to therapeutic equivalence, nor to interchangeability, nor to the requirement of the FDA, the WHO, and Order #460 that the same route of administration must be utilized, only the term bioavailability is used. This may cause some uncertainties with the applicants and needs to be clarified.

Therapeutic equivalency is the basis for the ultimate goal of a generic medicine i.e. to be interchangeable with the reference product [3,9, 12, 20-28]. No such reference is in the Law of Ukraine on Medicines [29] or Order #426 [11], but in Decree #376 [19] it is ruled that therapeutic equivalence (interchangeability) must be demonstrated according to “WHO recommendations” in the MAA process for a generic medicine, and in Order #460 [14] “interchangeability” is in the Terms and Definitions.

This shows that in the regulatory documents in Ukraine non-regulatory terms, like “generic substitution,” “interchangeability” and “therapeutically equivalency” are mixed with regulatory provisions used in the MAA process, like “bioequivalence”, “generic product”, “pharmaceutically equivalent”. The latter terms apply only to already registered products on the market.

In EU/EEA aspects concerning “generic substitution” are subject to national regulation(s) [5,13]. Thus, in EU e.g. the Swedish and the Irish RA have published on their website a list of therapeutically equivalent and thus interchangeable medicines [22,26].

4.1.2 Differences, non-conformities and discrepancies in the general legislative/regulatory frameworks

(1) Simplified procedure

The so-called “Simplified procedure”, for registration of medicinal products authorized by Regulatory Authorities from selected foreign countries with a Stringent Regulatory Authority (SRA) (WHO, [45]) (U.S.A, Switzerland, Japan, Australia, Canada, EU-centralized procedure only) allows registration in Ukraine of products which have not undergone a scientific assessment in line with the requirements of Directive 2001/83/EC and thus contradict EU
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legislation. It might thus be possible that drugs with a different safety profile, different dosages for the same indication are on the Ukrainian market.

Secondly, medicinal products subject to procurement under agreements between Ukraine and international organizations (WHO, UNDP; UNICEF; UK Crown agents). However, the latter provisions are valid only till 31 March 2020.

(2) In-bulk products, Active pharmaceutical ingredients (API)
The Law of Ukraine on Medicines [29], Order #460 [14], and the Guidelines on Investigation of Bioequivalence [10] have similar, but different definitions of an API, focusing on the possible usage of the API, whereas the definition in Directive 2001/83/EC [4] reflects the action(s) of an API. In Ukraine both in-bulk products and APIs need a marketing authorization, but not in EU/EEA.

(3) Medicinal products
The Law of Ukraine on Medicines [29] and the Guidelines on the Investigation of Bioequivalence [10] define a medicinal product as: an API, “in bulk” products; finished medicinal products (medicinal preparations, drugs, medicaments); homoeopathic agents; agents used to detect and eliminate pathogenic organisms or parasites; cosmetic products and medicinal supplements to food products”. Except for “finished medicinal products” and “homeopathic agents” all other mentioned types of products are not considered as a medicinal product in EU/EEA; they are regulated by separate rules in EU/EEA. Order #460 in its “Terms and Definitions” lacks a definition.

The Ukrainian Guidelines “Investigation of bioequivalence” [10] defines a medicinal product as “any substance or combination of substances (one or more AFIs and excipients), which has the properties and is intended for treatment or prevention of disease in humans, or any substance or combination of substances (one or more AFIs and excipients), which can be designed for prevention of pregnancy, restoration, correction or change of physiological functions in humans by means of pharmacological, immunological or metabolic actions, or for establishing a medical diagnosis. Medicinal products include: AFIs, in bulk products; finished medicinal products (drug products, drugs, medicines); homoeopathic products; products used for identifying causative agents of disease, as well as for combating causative agents of diseases or parasites; medicinal cosmetics and medicinal supplements to foodstuffs”.

Directive 2001/83/EC defines a medicinal product as (a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings, or (b) Any substance or combination of substances which may be used in or administered to human beings either with a view of restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolite action, or to making a medical diagnosis.

(4) Definition of pharmaceutically equivalent
Pharmaceutically equivalent are medicinal products, which contain the same active ingredient (API), in the same strength (concentration) and dosage form, and, in addition, Order #460, WHO and FDA demand the use the same route of administration. Differences in the manufacturing process or excipients may result in a different dissolution profile and thus pharmaceutical equivalence doesn’t necessarily imply therapeutic equivalence or bioequivalence. In both guidelines the definition is identical.
(5) **Pharmaceutical alternatives**
All 5 compared provisions in Table 4, Annex B, request the same active ingredient (API). Order #460 and FDA request the same amount (strength) of API and dosage form, the WHO and the Ukrainian and EU Guidelines on the evaluation of bioequivalence allow different dosage forms. Only WHO and FDA demand a “same route of administration”.

(6) **Definition of Bioequivalence**
Order #460, WHO and FDA have the same provisions, whereas the Ukrainian and EU Guidelines on the Investigation of Bioequivalence request “Pharmacologically equivalent OR Pharmaceutical alternatives” (i.e. same or different of Administration). Directive 2001/83/EC has no definition of bioequivalence.

(7) **Provisions of data protection in the MAA process, data exclusivity, market exculsivity, SPC**
Directive 2001/83/EC in its Article 10, 1, as amended, stipulates that the time period of data exclusivity is 8 years for a product which is or has been authorized in EU/EEA. A generic shall not be placed on the market until 10 years have been elapsed from the initial authorization (requesting a “full dossier”) of the reference product (market exclusivity) (may be extended to 11 years in defined cases).

In Ukraine any use of safety and efficacy data of the reference product in the MAA process for a generic is considered as an “unlawful use of registration information” and thus forbidden for a period of 5 years after registration of the originators (reference) product. These data can only be used if the MAH of the reference product gave his permission (Order #460(36)). Violation of this provision is a reason for the SEC to reject the MAA.

Furthermore, in the course of an MAA, the applicant needs to provide information on the patent situation (protection) of his product. SEC shall refuse State registration in cases of violation of patents. Both provisions, the unlawful use of registration information and possible patent violations are not covered by EU Community law, in the first line Directive 2001/83/EC. Instead, the national provisions of the EU Member states apply. In addition, there is no provision to prolong the patent protection period up to five years in order to compensate the manufacturer for the time elapsed between patent application and marketing authorization approval when he couldn’t generate revenues (so-called Supplementary protection certificate, SPC) [46].

4.1.3 Differences, non-conformities and discrepancies in the regulations on the investigation of bioequivalence of generic drugs/hybrids

The Ukrainian guidelines cover several more points, which are addressed in the EU guidelines by separate provisions: it includes (as Appendix IV) the templates for presenting biopharmaceutical and bioanalytical data in Module 2.7, a Supplement 1 “Recommendations for Determining absolute and relative bioavailability” and “Recommendations for superbioavailable products”.

In the “National Supplement” (for reference) the list of editorial changes and addenda with reference to the applicable terms in the EU rules is presented. “Changes have been made to these Guidelines prompted by legal requirements and harmonized regulatory documents adopted in
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Ukraine”. In addition, several changes (modifications) addressing a specific issue in the actual text are inserted directly into the text (with a different font and marked by an N).

The two major differences are that (1) not only a reference product marketed in EU can be chosen, but also a reference product according to the requirements of Order #460, and (2) that bioequivalence studies with a non-EU reference product might be included into the MAA dossier in Ukraine.

The Ukrainian “Guidelines on Investigation of Bioequivalence” [10] and the corresponding guidelines in EU [13] need to be fully harmonized, i.e. the two main differences concerning the selection of a reference product and that a non-EU reference product is recognized in the MAA process in Ukraine, be eliminated.

Annex 18 in Order #460 needs to be brought in conformity with them and be defined as the only official reference concerning investigating bioequivalence.

The SEC has developed Draft amendments, recommendations and explanatory notes for applicants (1) to the MOH Order #460 to further harmonize it with Directive 2001/83/EC, and (2) the Guidelines on the Investigation of Bioequivalence. Furthermore, (3) product-specific guidance documents (reflecting those published by the EMA and FDA), and (4) recommendations for the proper selecting of reference comparator products in bioequivalence studies are in preparation, as well as a list of recommended reference products [10(b)]. Furthermore, recently the 2018 Edition of the Guideline for Investigation of Bioequivalence has been published [10(c)].

(2) Different requirements when bioequivalence studies are necessary or not
The list of medicinal products in Annex 18 of Order #460, which need to demonstrate bioequivalence and thus a bioequivalence study (or as surrogate the 3 alternatives, comparative pharmacodynamic studies, comparative clinical trials, justified application of the BCS-based biowaiver system) is required or not, is only in parts comparable with the Ukrainian and EU Guideline for Investigation of Bioequivalence. Terms like “emergency medicine” are only in this Annex and the “Simplified registration procedure” contradicts EU legislation. Annex 18 in Order #460 needs to be brought in conformity with the harmonized Ukrainian and EU “Guideline on Investigation of Bioequivalence” [10, 13] and be defined as the only official reference concerning bioequivalence.

(3) “Product-specific bioequivalence guidance” documents, SmPC and PARs
At present, in Ukraine no “Product-specific bioequivalence guidance” documents, published by the EMA and FDA [33,34] “summarizing in a standardized format the relevant study design principle for demonstration of bioequivalence”, has been published; neither had been Summaries of Product characteristics (SmPCs), nor Public Assessment Reports (PARs). However, the SEC has prepared Draft amendments to the MOH Order #460 to further harmonize it with Directive 2001/83/EC, and the guidelines on the Investigation of Bioequivalence [10(b)]. Furthermore, product-specific guidance documents (reflecting those published by the EMA and FDA) and recommendations for the proper selecting of reference (comparator) products in bioequivalence studies are in preparation, as well as a list of recommended reference products. This information material is available to the public and constitute a well-established source of information both to regulators, experts, and scientists, but also to patients and/or other interested parties.
(4) **Adherence to new Clinical Trial Regulation (EC) 536/2014 [35]**

Bioequivalence studies are phase I clinical studies and must be conducted by following ICH-GCP rules, as well as GLP rules concerning the bioanalytical part of the study [10,13]. Preparations for complying with the new Clinical trial regulation (EC) 536/2014 [35] should be started and the actual status of ICH-GCP implementation in Ukraine assessed.

(5) **Recognition of GMP Certificates from other PIC/S member states**

Ukraine is a member of the PIC/S network and thus should introduce a simplified/abbreviated procedure concerning the verification of GMP Certificates issued by the competent bodies in other PIC/S Member states. Actually, except for GMP Certificates for centrally registered products in EU, the SAUMP needs to confirm the validity of this certificate. This may take several weeks.

(6) **Procedure for handling WHO Pre-qualification dossiers in the national MAA process**

Many manufacturers in Ukraine strive to join the WHO pre-qualification scheme. Medicinal products from the “WHO List of pre-qualified products” should receive MA in Ukraine by an “Abbreviated registration” process, as these products fulfil the (Internationally recognized) requirements concerning safety, efficacy, and quality. Furthermore, many of these pre-qualified medicines are for fighting against widespread dangerous diseases endangering national public health systems (HIV/AIDS, Tuberculosis, Influenza). This will also be beneficial for local manufacturers, because they will be able to participate in international tenders and may use the dossier, which needs to be established within the pre-qualification process, also in the national MAA process. The relevant provisions given in Order #460, Chapter V “Basic demands to the registration dossier materials”, Article 10.2, which refers only to WHO pre-qualified TB and HIV/AIDS drugs should be amended to “all pre-qualified products from the respective WHO list” [47].

(7) **Considering supportive documents from WHO and FDA**

Many EU Guidelines provide no or only general information on many topics, leaving much space for interpretation and address some important issues only marginally. It is, therefore, useful to refer to provisions published by the WHO and/or FDA, as these are often much more detailed and can be used as supportive materials/references. They might also be considered in future updated or new regulatory provisions.

(8) **Harmonization/approximation of the regulatory provisions in the Association Agreement between Ukraine and EU**

The provisions concerning bioequivalence and associated topics in the key regulatory documents, i.e. the Guidelines on the Investigation of Bioequivalence” [10], Annex 18 of Order #460 [14], Decree #376 [19], and the Law of Ukraine on Medicines [29], need to be harmonized. Afterwards, they need to be harmonized with the key regulatory bioequivalence-related documents in EU/EEA, i.e. the Guidelines on the Investigation of Bioequivalence” [13], Directive 2001/83/EC [4], and product-specific guidance [33]. This will be a significant step forward towards mutually agreed Terms and Definitions, and it will also provide stakeholders (applicants) with a consistent, reliable frame of applicable, relevant regulatory provisions for investigating bioequivalence.
4.2 Possible scenarios and proposed strategy

Proposed strategy depends on the constant political will of the Ukrainian government to foster compliance of the legislative/regulatory framework (in the pharmaceutical sector) in Ukraine with the EU acquis communautaire, based on the criteria, terms and conditions set by the EU for countries intending to join EU. These criteria are defined in the broad, general provisions of the Association Agreement, which opens Ukraine a number of alternatives for approximation/harmonization with the respective EU rules. Possible alternative options for Ukraine include:

1. approximation with the legislative/regulatory system in the USA,
2. following the provisions in the sector published by the WHO,
3. attempting to harmonize with the EU (an approach obviously followed by a neighboring country).

Alternative options for Ukraine

| Approximation with the legislative/regulatory system in the USA |
| Following the provisions in the sector published by the WHO |
| Harmonize with centralized EU regulations and other international best practices based on the Ukrainian reality |

- Many regulations (the provisions on therapeutically equivalence, generic substitution, reimbursement rules, etc.) in the pharmaceutical sector in EU are ruled by the individual Member states. Therefore, only those legislative/regulatory rules can be harmonized/approximated, which are in the [EU Community law]. This leaves Ukraine with the possibility to choose the best way to fit its national needs/demands.

If Ukraine chooses to follow option 1, harmonization with the system in the USA would create no additional benefits for the country, because the USA, EU, and Japan constitute the ICH region with many harmonized rules, provisions. Option 2, following WHO provisions, has the advantage that WHO recommendations/rules are internationally-recognized. However, in EU dossiers submitted in the marketing authorization application process must be consistent exclusively with EU rules. An example for option 2 might be from a neighboring country: it attempts to fulfill the requirements, legislative/regulatory rules, of both systems. This may lead to a situation when two systems operate in parallel, possibly leading to an unclear or even contradictory patchwork of rules.

Globalization has shown that even large pharma companies cannot be profitable without a worldwide marketing of their products, as national markets are too small for a profitable return-of-investment. This accounts also for local manufacturers, as the restricted market will not be profitable, and exports will be difficult. Therefore, the most feasible option will be to continue the harmonization/approximation process within the frame of the Association Agreement with the EU (option 3) However, it must be taken into account that many regulations in the pharmaceutical sector in EU are ruled by the individual Member states themselves: e.g. the provisions on therapeutically equivalence, generic substitution, reimbursement rules, etc. Therefore, only those legislative/regulatory rules can be harmonized/
approximated, which are in the (EU) Community law. As already said, this leaves Ukraine with the possibility to choose the best way to fit its own national needs/demands.

Since 2001 Ukraine is in the process of gradual harmonization/approximation of its legislative/regulatory framework in the pharmaceutical sector with the regulations valid in EU/EEA. Experience shows that the strategy of a “gradual approximation/harmonization of the regulatory/legislative systems” in many CIS countries with the acquis communautaire has led to many inconsistencies, unclear provisions/rules, as well as discrepancies and unconformities: only defined parts of the regulations were implemented, but other parts not, leading to a patchwork of rules mixing both systems, basic definitions differ, already harmonized rules don’t reflect the actual (updated, amended) status of the rules in EU, etc. Furthermore, a full harmonization would require the removal of all provisions valid only in Ukraine. During their EU-accession process, States like the Czech Republic and Poland, opted for a comparably very fast adaptation of the almost complete acquis communautaire avoiding any time delays caused by long negotiations. However, to avoid chaos, long transition periods must be granted, minimum 5-10 years. Afterwards a fully compliant system will be in place.

A general outline for the proposed strategy is given below, details of the Implementation plan are provided in Chapter 7.

**Proposed Strategy for Ukraine**

Goal: Improve access to quality generic/hybrid medicines and biosimilars in line with EU practices


**4.2.1 Objective 1: Harmonize the “Terms and Definitions”**
- **within the Ukrainian legislative/regulatory system**
- **with applicable, relevant EU provisions,**
- **and take into account supportive provisions from WHO and FDA**

Key terms and definitions need to be made consistent, as these terms and definitions are the fundament of all further discussions and reflections. The “Terms and Definitions” in the Law of Ukraine on Medicines [29], Decree of the Cabinet of Ministers [19], Orders of the MOH [11,14,39], and the Guidelines on the Investigation of Bioequivalence [10] should be the same. For example, the definition of a reference product (like in Order #460) [14] is not in compliance with the respective provisions in Directive 2001/83/EC [4]. The Ukrainian [10] and EU [13] “Guidelines on the Investigation of
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Bioequivalence” have an identical definition of pharmaceutical equivalence but are different from the provisions in Order #460. The “Terms and Definitions” should be approximated with the provisions from the relevant and applicable EU rules, in particular Directive 2001/83/EC [4], Guidelines on the Investigation of Bioequivalence [10], and the guidelines on defined medicinal products, like [48-52]. For example, under the provisions of the actual “Simplified procedure”, it is possible that in Ukraine medicines are on the market with no scientific expert evaluation by the SEC. Last year hundreds of marketing authorizations in EU and elsewhere were repealed because of falsified bioequivalence studies conducted in India; however, these products could still be on the market in Ukraine, posing a threat to the population.

Supportive guidelines from the WHO and FDA, like on interchangeability [23,27,34,], bioequivalence studies [8,16], reference (comparator) products [23,31,32] should be taken as supportive references. They provide much more detailed advice for applicants (regulatory issues, like on bioequivalence), and healthcare managers (generic substitution, therapeutic equivalence, interchangeability, reimbursement). They might be considered in future updated/amended and/or new provisions, like on:


(2) Applicable, relevant provisions of the WHO “Guidance for organizations performing in-vivo bioequivalence studies” (Annex 9, WHO Technical Report Series no. 996, 2016; [8]) should be considered to be reflected in the “Guidelines on Investigating Bioequivalence” [10], because this guidance is one of the few internationally recognized documents covering all aspects for performing bioequivalence studies.

(3) Selected, relevant, applicable provisions from the WHO “Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products” (WHO Technical Report series no. 992, Annex 8) [31] might be taken as supportive references. They might also be considered in future updated or new provisions e.g. of the “Guideline on Investigating Bioequivalence” [10].

The guidance contains a list in order of preference for choosing a reference (comparator) product. The corresponding provision for a reference product in the EU guidelines stipulates that the reference product must have an MA in the EU. However, these products may not always be obtained or may no longer be available on the market. By choosing an alternative comparator product, significant differences may exist between the comparator products used in different countries.

The SEC has developed recommendations for the selection of a suitable reference (comparator) product and a list of recommended reference products. The document has already passed the public consultation process and entered the formal approval process [10(b)]. Until then, the WHO provisions may serve as reference.

4.2.2 Objective 2: Improve the regulations on bioequivalence in the legislative/regulatory system

Rules defining medicinal products, which need to demonstrate (or not) bioequivalence, or are eligible for a BCS-system biowaiver procedure need to be updated. In particular, the provisions concerning the “Simplified procedure” and the provisions of Annex 18 of Order #460, need to be amended, i.e. brought in line with EU rules. The “Guidelines Investigation of Bioequivalence” [10] needs to be harmonized/approximated with the corresponding EU guidelines [13], and afterwards be defined as the only official reference document concerning bioequivalence. This will contribute to more clarity for applicants and contributes to make the regulatory provisions more consistent.
The actual procedure for confirming GMP-compliance by the SAUMP needs to be simplified/abbreviated, because Ukraine as a PIC/S member should recognize (automatically) GMP certificates issued by the competent authorities in other PIC/S Member states. Actually, except for GMP Certificates for centrally registered products in EU, the SAUMP needs to confirm the validity of this certificate, which may take several weeks.

An “Abbreviated procedure” for the acceptance of dossiers for WHO pre-qualified medicines within the national MAA process in Ukraine should be developed by the SEC (in co-operation with the MOH). This will allow a faster market entrance for new products and opens new procurement (export) opportunities for Ukrainian manufacturers by participating in international tenders.

“Product-specific bioequivalence guidance” documents, like those published by the EMA and FDA, support generic manufacturers in choosing the adequate conditions for their product development. New products will enter the market in a shorter time, and possibly unnecessary or inappropriate studies or other evaluations in the development process be avoided. The SEC has prepared such guidance (for the industry) and is in the process of going to publish them after their endorsement/approval [10(b)].

4.2.3 Objective 3: Secure safe, effective and good quality generics

Requirements for medicinal products to be eligible to participate in procurement/reimbursement schemes need to be amended, including the demonstration of the products efficacy, safety and quality. Efficacy and safety will be demonstrated by bioequivalence of both products, quality by a GMP-compliant manufacturing.

The Data protection provisions concerning data exclusivity periods in Ukraine (5 years) and EU (8 years) should be harmonized. Market exclusivity provisions, based on the Bolar exemption, expanded by the “Export waiver”, “Manufacturing waiver” and Stockpiling waiver”, which will be in force in EU in 2019, should be implemented. This will allow manufacturers of generics and biosimilars to place their (new) products in adequate quantities one day after patent expiration (“Day-1-launch”) and will facilitate exports. The provisions in Directive 2001/83/EC, 10(1) [4] should be implemented, and the relevant provisions in Decree #376 [19], Order #426 [11], and Order #460 [14], be amended. The provisions for Supplementary protection certificates (SPCs) on the legal basis of Regulation 469/2009/EC [46], which prolong the patent protection period up to five years in EU, should NOT be implemented, as they prevent a rapid market access of generic drugs.

In-bulk products and Active pharmaceutical ingredients (APIs) should be exempted from the requirement to have a marketing authorization (registration). By this, Ukrainian manufacturers save costs and time in bringing products to the market. In EU/EEA these are not medicinal products regulated by Directive 2001/83/EC [4]. In general, all legislative/regulatory documents which apply only in Ukraine, “In-bulk-products,” APIs”, should be removed in the process of harmonization/approximation.

“Product-specific bioequivalence guidance” documents, published on the MOH and/or SEC website or possibly as Annexes to the “Guidelines on the Investigation of Bioequivalence [10], will support manufacturers in the drug development process: not- or unnecessary evaluations, like specific studies, will be avoided, and the developer can focus on following the provided guidance. This will facilitate the MAA process and will save time and costs for the manufacturers.

Many manufacturers in Ukraine strive to join the WHO pre-qualification scheme. Medicinal products from the “WHO list of pre-qualified products” might receive MA in Ukraine by an “Abbreviated-registration” process, as these products fulfil the (internationally recognized) requirements concerning safety, efficacy, and quality. Furthermore, many of these pre-qualified medicines are for fighting against
widespread dangerous diseases endangering national public health systems (HIV/AIDS, Tuberculosis, Influenza). This will also be beneficial for local manufacturers, because they will be able to participate in international tenders and may use the dossier, which needs to be established within the pre-qualification process, also in the national MAA process. The relevant provisions given in Order #460, Chapter V “Basic demands to the registration dossier materials”, Article 10.2, which refers only to WHO pre-qualified TB and HIV/AIDS drugs should be amended to “all pre-qualified products from the respective WHO list” [47].

For the sake of public safety, Ukrainian competent authorities should be supplied with sufficient evidence documents confirming that the imported product is identical to the product manufactured in the exporting country. If not, it’s safety and efficacy might be different and thus presents a threat to patients in Ukraine, as e.g. galenic differences in the formulation of a product, like different excipients, can significantly alternate the dissolution profile of the product. In doubt, further evidence, like proof for bioequivalence, should be requested.

It must be considered, that testing alone of the finished drug is insufficient for control of product quality [53]: a CMC (Chemistry, Manufacturing, and Controls) review of the dossier should be conducted during the assessments of the MA process. The role of CMC (in connection with GMP) is to ensure the connection in quality between the originator’s drug and the generic drug, as well as drug(s) used in clinical trials and the commercial product.

The existing “old” medicinal products on the Ukrainian pharma market, which were registered in the past without sufficient or even any proof of their safety, efficiency, and often quality, present a possible public health threat. The existing marketing authorization dossiers of these products should be bought in line with European standards within a defined timeframe (possibly 5 years), taking into account the limited capacities of the SEC for the necessary reviewing process and to ensure continuous access to these medicines for the patients.

On 4 October 2018 Article 9 of the Law of Ukraine on Medicines [29] was amended, and from that time it is possible to have public access to data from pre-clinical and clinical studies (similar to the European Public Assessment reports (EPAR). In combination with the proposed update of the already existing 2nd version of the “Medicinal Products Equivalence Reference Book - Ukrainian Orange Book” [6], which will provide a classification of medicinal products in Ukraine together with its related evidence level (score), products with a low score can be easily identified and eventually banned from the market.

For generic/hybrid medicinal products complying with the conditions for procurement/reimbursement a list or website should be prepared showering those products considered be therapeutically equivalent and interchangeable [20-28]. These provisions are regulated in EU/EEA solely on a national level and therefore harmonization on this level is possible, but not with the Community Law.

This list comprising all aspects of generic substitution, procurement/reimbursement/co-payments, etc. must be consolidated in a separate regulation, because terms like therapeutically equivalent, interchangeable, are not within the scope of assessments in the MAA process, they apply only to already registered products on the market. The criteria for interchangeable medicines, like in [26], need to be established (see Action plan in Chapter 9.1), and the preconditions for their enacting prepared jointly by the MOH and the SEC. A further option would be to review/update the already existing 2nd version of the “Medicinal Products Equivalence Reference Book-Ukrainian Orange Book”, which contains marketed (in Ukraine) “equivalent” medicinal product [6]. A general template could be a modified, “adapted to the needs of Ukraine version of the “Orange Book” published by the FDA [23]. However, the FDA Orange
book contains NO herbal drugs, drugs with well-established/well-studied medical use, biosimilars, traditional use medicines. and homeopathic products.

In Chapter 9.2 a Brief outline for a “Model regulation for generic substitution in Ukraine”, including alternatives from Germany, Ireland, and Sweden is presented, taking into account relevant experiences in Ukraine (2nd version of the “Medicinal Products Equivalence Reference Book - Ukrainian Orange Book) and the USA; as examples for EU Member states experiences from Ireland, Sweden, and Germany are described.

In order to fulfill its obligations to safeguard public health by ensuring that only medicinal products are on the market which are safe, efficient, and of good quality, the MOH and SEC together should consider establishing or upgrading 3-4 more Official Medicines Control Laboratories (OMCLs) in various regions of Ukraine. At present only one OMCL (with an Associated EDQM/GEON membership) exists in Ukraine. Possibly some already existing (regional) Quality control laboratories can be upgraded and possibly e.g. ISO 17025:2017 certified. This will significantly contribute to raise public safety.

Bioequivalence studies are clinical phase I studies, which must be conducted in compliance with the good clinical practice guideline (ICH-GCP) [4,7,8,10,13,14,16,27,54]; the bioanalytical part of the clinical study needs to be conducted according to the good laboratory practice (GLP) rules. This is also a requirement stipulated in the paper published by the EMA concerning the acceptance of clinical data from third countries [55]. It is recommended that (like in a project of the framework of the “Partnership for Modernization (P4M) cooperation programme in the field of clinical trials, a comparison of the GCP implementation and compliance in the Russian Federation and the EU”), a pilot-project should be initiated to address possible differences in (ICH)-GCP and possibly GLP-compliance in Ukraine and the EU.

The same holds true for biosimilars: for these more and more important medicinal products a pilot project should be initiated to identify possible differences in the regulation ruling this area in Ukraine and EU/EEA. Compliance with this requirement is a prerequisite for exporting medicinal products into EU.

A policy change concerning generic medicinal products in the course of the planned healthcare reform in Ukraine, taking into account the fundamentally different approach concerning generic and generic substitution in EU/EEA (Directive 2001/83/EC), and the USA (FDA): within the national generic substitution policy in Ukraine first priority should be given to the aspects of generic substitution (therapeutically equivalence and interchangeability) (like in the USA). In EU a product receives marketing authorization when it demonstrates a positive benefit-risk balance: generic substitution issues aren’t in the scope of the MAA process but regulated on a national level of the Member states.

The competent bodies, and all other organizations concerned, like CROs in Ukraine should start in-time preparations to comply with the new Clinical Trial Regulation (EU) No 536/2014 [35] (=CTR) “On Clinical Trials on Medicinal products for Human use, and repealing Directive 2001/20/EC” [36] (=CTD). This new Regulation was adopted on 16 April 2014 and entered into force on 16 June 2014 but will be applied possibly only in late 2019. The date of its first application depends on the availability of the EU-portal and database: The Regulation will be in force six month after the official confirmation of the availability of the dedicated EU-portal and database. Until then the Clinical Trials Directive [36] remains in force and then for three years more, as in the defined transition period.

There are many new provisions included into the new Regulation (e.g. “a duly justified written statement on the suitability of the clinical sites to perform such clinical studies” must be provided), and some explanatory guidelines for the CTD have already been published to facilitate its implementation.
Training and capacity building in the areas of bioequivalence, GCP, biostatistics, quality management (systems), and biosimilars for the staff of the MOH and SEC, but also other stakeholders in the sector, like, CROs, manufacturers, and concerned scientists (like clinical pharmacologists, investigators and other staff conducting clinical studies) needs to be promoted. Training, workshops, seminars, and hands-on practical learning programs for all stakeholders are required to successfully implement the proposed strategies.

In addition, the implementation process requires the availability of sufficient, adequate resources (human, technical, financial, and time), most important will be the availability of suitable, qualified personnel (see Chapter 5.4 Threats). For instance, vocational training in the area of clinical trials and investigation of bioequivalence is highly demanded, especially for those scientists seeking a qualification as a “Clinical Studies Professional” based on the Ukrainian occupational classification (Code 2212.2).

Many international organisations and (Donor) organizations offer such qualification training courses. One of the most successful approaches in this area was the EU-sponsored programme of twinning organizations, i.e. the SEC partners with an RA in EU ensuring a continuous exchange of information, temporary exchange of personnel, joint further and continuous learning in seminars, workshops, and by joint inspections and assessments, etc.

4.2.4 **Objective 4: Assure full compliance with the proposed strategy**

The legislative/regulatory framework is constantly changing, amendments are issued, new rules are published, etc. In order to comply constantly with the actual legal provisions, the competent bodies need to maintain and update their databases. This holds true in particular for new guidelines and other documents on a comparable level of legislation in EU and Ukraine, which mirror recent developments in science, practical experiences, best practices, and upcoming questions.

Therefore, it is necessary that the competent bodies (MOH, SEC) closely monitor the legislative/regulatory changes in the sector both in Ukraine, the EU, and other “Stringent Regulatory Authorities” (SRAs), as defined by WHO [45]. Thus, an organizational unit should be established at the MOH or SEC charged with the monitoring, retrieving, and distribution of information to the concerned bodies.

**Additional recommendations, Comments, received from the interviews**

During the interviews and discussions on September 17-21, 2018, in Kyiv, Kharkov, and Rubezho, participants brought forward the following points of interest, which should be addressed:

1. The mandatory insurance of study participants in clinical studies isn’t in the “List of insurances” in the “Law on Insurances” and thus needs to be included into this Law. Insurance coverage for clinical trial subjects needs to be updated and an (obligatory) insurance, covering the professional liability of the investigator/researcher, be requested.

2. In case of misconduct of SEC staff during the MAA process this is considered a criminal offense. This clause might be and occasionally is abused by applicants to threaten SEC staff and prevent them to properly execute their duties. This clause needs to be repealed and the applicable rules of the Civil law applied.

3. For the actually registered medicinal products on the market in Ukraine different quality standards exist, mainly because these products were registered a long time ago and without
providing sound scientific data on quality, safety, and efficacy. It is required that one common standard must be defined and applied.

(4) MOH Order #711 should be repealed, because it introduces a new type of medicinal products in Ukraine, the so-called “non-comparative biotechnological medicines”, which can be registered without robust data on quality, safety, and efficacy, i.e. it has not been demonstrated to be similar with regards to quality and non-clinical properties, as well as, clinical safety and efficacy in head-to-head comparative studies (WHO Regulatory criteria for Similar Biotherapeutic products, SBPs). This violates both Ukrainian and EU law.

(5) Interview partners suspect that despite ICH-GCP and GLP are officially introduced in Ukraine, there are still areas of non-conformities and differences, which need to be addressed soon.

(6) SmPcs and PARs should be published like in EU: this will ensure more transparency and provides quick access to information for medicinal products.

5.0 SWOT ANALYSIS OF PROPOSED STRATEGIES

5.1 Strength

(1) Harmonization of the “Terms and Definitions” within the legislative/regulatory framework in Ukraine (definitions in the Law of Ukraine on Medicines [29], Decree of the Cabinet of Ministers [19], Orders of the MOH [11,14,39], and the Guidelines on the Investigation of Bioequivalence [10] should be the same, and those from the relevant and applicable EU rules, in particular Directive 2001/83/EC [4], Guidelines on the Investigation of Bioequivalence [13], the guidelines on defined medicinal products, like [48-52], and supportive guidelines from the WHO and FDA, will ensure that Terms and Definitions are consistent in all regulatory/legislative documents as they are the commonly agreed basis of understanding for all stakeholders and the fundament of all further considerations, strategies, and planning.

(2) Moving those Terms and Definitions like “generic substitution”, “interchangeability”, “therapeutically equivalent”, which are NOT legislative/regulatory documents concerning the regulatory provisions in the MAA process to a separate regulation comprising all aspects of generic substitution, procurement/reimbursement/co-payments, etc. These latter terms apply only to already registered products on the market.

(3) Removing all legislative/regulatory documents with provisions which apply only in Ukraine, like “Simplified procedure”, “In-bulk-products”, “APIs”, and the provisions addressing a possibly “unlawful use of registration information” and possible “patent violations”, which are assessed within the assessment of the registration dossier, will be a further step forward in harmonizing both legislative/regulatory systems.

(4) Harmonizing the different requirements when bioequivalence studies are necessary or not, together with the publication of product-specific bioequivalence guidance documents, defines the common operating conditions and regulatory/legislative basis for both the industry and regulators.

(3) Key general, principal differences in the legislative/regulatory framework will be in line with EU rules:
• the actual provisions concerning the simplified procedure, which are not in line with EU rules, will be amended,
• the number of products considered as “Medicinal product” will be edited,
• rules concerning in-bulk products and APIs will be aligned with EU rules,
• the Provisions of data protection, i.e. data exclusivity, market exclusivity, and SPC will be considered and then approximated/harmonized (or not).

5.2 Weaknesses/Risks

Possible weaknesses, which pose possible threats, are as follows:

(1) Implementation completely depends on the political will of the Ukrainian government to continue to harmonize/approximate the legislative/regulatory systems with the EU within the framework of the Association Agreement. Political changes, e.g. changing priorities, or the rules and directions, will endanger the planned activities.

(2) Implementation of the proposed strategies requires the availability of adequate resources over several years. This holds true especially for the allocation of suitable, skilled, experienced, and enough qualified personnel for 1-2 years for the task-/work groups charged with the supervision, co-ordination of the practical work in the implementation process. In addition, financial and administrative support, as well as adequate working conditions (offices, technical equipment) need to be provided and guaranteed over several years.

(3) The legislative/regulatory in all countries changes frequently and often very rapidly. These changes must be carefully observed, investigated, their possible impact on the system(s) in the own country assessed, and strategies developed to cope with possible risks and opportunities.

5.3 Opportunities

Opportunities will by far outweigh possible weaknesses and threats: the results of the implementation of the proposed strategy will be a major step forward towards an almost complete harmonization/approximation of the Ukrainian and EU legislative/regulatory frameworks within Association Agreement. The Association Agreement leaves Ukraine with a broad spectrum of alternatives for approximation and to identify its best way for harmonizing with the EU rules. This allows Ukraine to abstain from potential unfavorable EU-provisions, in particular provisions which might prevent a rapid market entry of (new) generic products in Ukraine, like:

(1) The extension of the patent protection period stipulated in the Supplementary protection certificates (SPC) rules in EU. In both Ukraine and EU data exclusivity rules are in place (8 years in EU, 5 years in Ukraine), but in Ukraine no market exclusivity exists. However, in both Ukraine and EU the so-called Bolar exemption is in force, stipulating that even within the data exclusivity (protection) period, an applicant has the right to develop a medicinal product (but not to put it on the market). For generic manufacturers short patent protection periods are beneficial, because this will allow them to place their product(s) comparably fast on the market. Provisions like the SPC rule would prevent them from an “Day-1-launch”. Consequently, the SPC provisions, as well as the market exclusivity rules, shouldn’t be implemented in Ukraine. Instead, the Export waiver, Manufacturing waiver, and Stockpiling waiver should be implemented, as they will allow Ukrainian manufacturers of generic and biosimilar products to
be on the market the day after patent expiration ("Day-1-launch"). Furthermore, the chances for Ukrainian manufacturers to export their products will be enhanced.

(2) Ukraine may choose the most favorable Terms and Definitions in the legislative/regulatory rules to facilitate the availability of generics and biosimilars on the market with good quality, and proven efficacy and safety. Clear, appropriate, and mutually agreed rules for generic substitution should be developed to avoid the scattered, often unclear situation in EU where generic substitution is regulated on the national level of the 28 (27) Member States.

(3) A modified so-called “Simplified procedure” for the registration of medicines authorized by foreign Drug Regulatory Agencies with a Stringent Regulatory Authority (SRA, as defined by the WHO) will significantly speed-up their registration/MA in Ukraine and thus will faster be available to patients in the Ukraine (“Abbreviated registration”). However, such provision isn’t foreseen in the EU/EEA regulations.

(4) An almost completely harmonized/approximated legislative/regulatory framework in Ukraine and EU/EEA will facilitate business opportunities for partners (manufacturers, CROs), etc. on both sides. This applies not only for export, but also for service providers, like for contract manufacturing and research, joint research taking advantage of synergistic and economy of scale effects. Patients will benefit from better drugs at affordable prices and better availability because more pharma firms will enter the market or expand on a more attractive market.

5.4 Threads

5.4.1 General threats and risks

Implementation of the proposed recommendations includes the possibility of emerging threads and risks, which may hinder, postpone, or even prevent an implementation and the desired effects. Possible threats and risks may be:

(1) Implementation requires the availability of sufficient, adequate resources (human, technical, financial, and time). This includes the availability of qualified personnel for a longer period of time (up to 1-2 years), which has access to modern IT-technology, like communication, and access to relevant databases (refer to 5.4.1(1)).

(2) Important parts of the recommendations can only be implemented by establishing a close cooperation with external experts, pharmaceutical companies and their business organizations/associations (refer to 5.4.1(2)). The proposed establishing of a list of therapeutically equivalent/interchangeable medicinal products following the “Swedish, Irish, or German model” or a review/update of the already existing 2nd version of the “Medicinal Products Equivalence Reference Book - Ukrainian Orange Book”, which contains marketed (in Ukraine) “equivalent” medicinal product [6] cannot be accomplished without a strong support from the key stakeholders. The creation of “Reference Groups” needs a close collaboration with all major stakeholders in the healthcare system, including representatives from the medical and pharmaceutical professions, manufacturers, contract research service providers, health economists, scientific institutions, like Universities, and last not least support from the political representatives in the Parliament and Public health administration.

(3) Registered medicinal products on the market, which were registered without sound scientific proof of its safety, efficacy, and quality should in principle not be marketed anymore. Even after
a (grace) transition period of e.g. 5 years, it can be expected that many products must be withdrawn from the market and thus manufacturers may face financial difficulties. Consequently, there might be political resistance to implement at least parts of the recommendations (4).

The actual report on the role of bioequivalence in the legislative/regulatory framework in Ukraine and the EU/EEA needs to be seen in the broader frame of the strategic goal of Ukraine to approximation its regulations and best practices with those in EU/EEA. It is evident that bioequivalence plays a central role concerning the claims of medicinal products to be therapeutically equivalent and interchangeable, the most important aspect in procurement and reimbursement systems. These aspects of “generic substitution” are regulated in EU on a national level, so harmonization cannot cover the aspects of “Non-Community level” regulations. However, national regulations, like the Swedish or Irish list of therapeutically medicinal products, might be considered and the Association Agreement with the EU leaves Ukraine with a lot of freedom in these aspects.

During the last decade several initiatives, concepts, strategies, roadmaps, etc. have been published by public/governmental organizations, donors, and non-governmental (NGO) groups. Almost ten of them are shortly reviewed in the report of the EBRD-sponsored project in [44]. This report confirms the experiences of the last years that a strategy of a “gradual approximation/harmonization of the regulatory/legislative systems” has led to many inconsistencies, unclear provisions/rules, as well as discrepancies and non-conformities, as only defined parts of the regulations were implemented, but other parts not.

Nevertheless, work on a cohesive, conclusive strategy for the entire pharmaceutical sector in Ukraine is continuing; the SEC for example has developed Draft amendments to the MOH Order #460 to further harmonize it with Directive 2001/83/EC, and the Guidelines on the Investigation of Bioequivalence. Furthermore, product-specific guidance documents (reflecting those published by the EMA and FDA) and recommendations for the proper selecting of reference comparator products in bioequivalence studies are in preparation, as well as a list of recommended reference products [10(b)].

5.4.2 Availability of adequate financial and human resources

Implementing the strategic goals will inevitably require the allocation of adequate financial and human resources. Their timely and adequate availability will be crucial for the project’s success. Most of the recommendations involve changes to the legislative/regulatory system, mainly the Law of Ukraine on Medicines. These regulatory changes are cost-neutral, but additional costs include:

1. Training and capacity-building of MOH and SEC staff, and other stakeholders in the sector, like, CROs, manufacturers, and concerned scientists (like clinical pharmacologists, investigators and other staff conducting clinical studies) needs to be promoted. Notably training is required in biostatistics, good clinical practice (GCP), good laboratory practice (GLP), investigation of bioequivalence/bioavailability, the proper conduct of phase I and III clinical trials, and on Quality management (systems) (ISO 9001:2015, ISO 17025:2017). Costs for training courses (conducted by trainers from abroad) are about 2,000 USD per day, depending on the type of training, number of participants, etc.

2. Preparation of the list of therapeutically equivalent/interchangeable medicinal products or alternatively the updating/upgrading of the 2nd Edition of the “Ukrainian Orange Book with “equivalent” products, “Ukrainian Orange Book” should be managed (preferably a Taskforce/
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working group (“National Scientific Expert Committee on Generic medicines”), as a focal point and network of knowledge, founded, financed, and supervised by the MOH in close co-operation with the Head of the SEC. The daily co-ordination of its operation will be handled by the Head of the Department at the MOH charged with Registrations/Marketing authorizations, and the Head of the corresponding Department of at the SEC (refer to Chapter 9 Action plan). Members of the Committee should be the key stakeholders in the area of clinical research, with a strong focus on the evaluation of bioequivalence, and the regulators. External representatives/experts from the key stakeholders should be invited to ensure scientific/technical/business-related input to pave the way for decisions to be taken by on the regulatory/political level. External experts, e.g. from the Clinical Pharmacology Department of the National University of Pharmacy, Business Associations (like ACC, EBA), manufacturers, and clinical research organizations (CROs) should be invited to participate and to share their experiences and specific technical and scientific knowledge with the regulators.

The additional costs for one, or better two suitably trained pharmacists working on behalf of the Committee, including the necessary resources (office, communication equipment, etc.), should be taken into account. The main part of the expected additional costs for (2) and (3) will be for the necessary equipment and personnel expenses.

(3) For the new organizational unit at MOH charged with the monitoring, retrieving, and distribution of information from international sources in the pharmaceutical area to the concerned bodies, i.e. the MOH and SEC, also 2-3 trained staff (pharmacist, IT-specialist), plus the necessary equipment/resources are needed. Furthermore, as additional responsibilities will be charged to the SEC in the implementation process (preparing the necessary documents for the planned changes in the legislation, possible re-assessment of the registration dossiers from “old” MAs), additional considerable resources will be needed or alternatively work might be outsourced. However, it will be difficult, if not impossible, to identify well-trained, suitable experts for this (very specific) work.

(4) The proposed establishing of 3-4 more, or (preferably) upgrading of already existing local quality control laboratories, to receive an Associate Member status of the EDQM/GEON network of OMCLs (Official Medicines Control Laboratories) requires significant investments into the qualification of staff and technical equipment. The existing OMCL in Kyiv could serve as a crystallization point in this respect. In several CIS countries OMCLs were established in the framework of various EU-funded projects, so it can be reasonably expected that most costs might be covered by such programs. Before starting any preparations, a fact-finding mission should evaluate the exact needs of these laboratories and the incurred costs be calculated.

(5) On the Ukrainian pharma market there are many medicinal products which were registered in the past without sufficient or even any proof of their safety, efficiency, and often quality. The existing marketing authorization dossiers of these products should be bought in line with European standards within a defined timeframe (possibly 5 years), taking into account the limited capacities of the SEC for the reviewing process and to ensure continuous access to these medicines for the patients.

Consequently, a number of products will be forced to leave the market and the manufacturers might face economic difficulties, but also the public organization (SEC) will lose registration/renewal fees. In essence, the expected costs for implementing the recommendations will be for the “soft-costs”:
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1) training/capacity building (6 training courses, 5 days, for 10 participants, each) = 80,000 USD, for both the MOH and the SEC;

(2) new staff at the MOH and SEC for the review/update of the already existing 2nd version of the “Medicinal Products Equivalence Reference Book - Ukrainian Orange Book”, and/or for preparing of the list of therapeutically equivalent, interchangeable products, plus staff for the “Information Center” = (4 people, yearly salary of 8,000 USD) 32,000 USD, and for the “hardware”;

(3) office equipment, including IT (PC, Fax, etc.), depends on what is already available – estimated at 30,000 USD;

(4) laboratory equipment for the OMCLs, which needs to be recognized by EDQM, and depending on the already available equipment will be at several million USD.

Most of the presented estimated costs are related to issues concerning the establishing and maintaining of a solid, highly practice-orientated and mutually agreed framework around “generic substitution”. This includes significant changes in the existing legislative/regulatory framework, so, except of the inevitable administrative costs, no significant additional costs can be expected. However, costs for training of MOH and SEC staff, the hiring of new staff for the MOH and SEC (capacity building), and possibly payments to external experts must be accepted. However, these measures are necessary for the proper functioning of the system, defining bioequivalence as the fundament of generic substitution and the to harmonize/approximate the legislative/regulatory systems in Ukraine and EU/EEA within the framework of the Association Agreement.

6.0 PROPOSED STRATEGY TIMELINE
7.0 IMPLEMENTATION PLAN

In Chapter 4 possible strategies (scenarios) are presented, including three alternatives to the actual harmonization/approximation process within the frame of the Association Agreement with the EU. Eventually, the presumably most successful strategy will be to continue the ongoing harmonization/approximation process, under the mandatory prerequisite of a constant political will of the Ukrainian government to continue its way to achieve compliance of the legislative/regulatory frameworks (in the pharmaceutical sector) both in Ukraine and EU’s acquis communautaire.

7.1 Objective 1: Harmonization/approximation of the legislative/regulatory framework within Ukraine and those provisions defined in the EU Community law

Activity 7.1.1 Align the Terms and Definitions within the Ukrainian legislative/regulatory system

The provisions, in particular the “Terms and Definitions” in Order #426 [11], Order #460 [14], and its Annex 18, and the Guidelines “Medicinal products. Investigation of Bioequivalence” [10] should be harmonized/approximated and made consistent, as these terms and definitions are the fundament of all further discussions and reflections. Supportive provisions from WHO and FDA could be taken into consideration, too. These terms and definitions include, but not are limited to:

- Bioequivalence
- Generic medicinal products
- Pharmaceutical equivalence
- Pharmaceutical alternatives
- (Therapeutically equivalent)
- (Interchangeability)
- Original (Innovator) medicinal product
- Reference medicinal product (comparator).

In addition, all Definitions and Terms which are not regulatory terms, like interchangeability and therapeutically equivalent, should be eliminated from the regulatory documents (Decree(s) of the Cabinet of Ministers, MOH Orders, etc.), and moved to a separate regulation comprising all aspects of generic substitution, procurement/reimbursement/co-payments, etc. These terms apply only to already registered products on the market.

Activity 7.1.2 Align the Terms and Definitions between Ukraine and EU/EEA Community legislation to get them comparable:

- Relocate those products in the Ukrainian definition of “medicinal products”, like APIs, “in bulk” products, homoeopathic preparations, cosmetics, and medicinal supplements to food products, which are NOT medicinal products in EU and thus regulated by separate legislations. They should be moved to their according position in the relevant legislative/regulatory framework, or, in case this will not be possible, because e.g. no applicable, relevant provision(s) exist, consider amending the existing regulation(s).

- In-bulk products and APIs should be exempted from the requirement to have a marketing authorization. By executing the previous activity, for in-bulk products and APIs different regulatory provisions will be relevant and this issue be resolved. In general, all legislative/regulatory documents with provisions which apply only in Ukraine, like “In-bulk-products and “APIs”, should be removed at all in order to get compliant with EU/EEA regulations. However,
the relevant, very broad and general provisions in the Association Agreement would allow Ukraine to keep such rules.

- Provisions concerning the “Simplified procedure” should be amended in order to get compliant with EU/EEA regulations. However, the relevant, very broad and general provisions in the Association Agreement would allow Ukraine to keep such rules. Recognition of products registered in non-EU countries is incompatible with EU law (for drug safety reasons). If Ukraine decides to keep this provision, the simplified procedure should be applied only for products with an MA in the ICH regions (EU, USA, Japan), countries with a stringent regulatory authority (as defined by WHO; [45]), and products on the WHO List of pre-qualified products (actually 508) [47]. Actually, such procedure will shorten the time for the market entry for manufacturers and thus will have a beneficial effect for patients in Ukraine.

- Amend the rules concerning data protection: the data exclusivity periods in Ukraine (5 years) and EU (8 years) should be harmonized. Market exclusivity provisions, based on the Bolar exemption, expanded by the “Export waiver”, “Manufacturing waiver” and Stockpiling waiver”, which will be in force in EU in 2019, should be implemented, as these will allow Ukrainian manufacturers of generic and biosimilar products to be on the market the day after patent expiration (“Day-1-launch”). This will also enhance the chances for Ukrainian manufacturers to export their products. The provisions for Supplementary protection certificates (SPCs) on the legal basis of Regulation 469/2009/EC [46], which prolong the patent protection period up to five years in EU, should NOT be implemented, as they prevent a rapid market access of generic drugs. The provisions concerning the “unlawful use of registration information” and possible patent violations in Order #460 [14], Order #426 [11], and Decree #376 [19] need to be removed or amended accordingly.

- Annex 18 in Order #460 needs to be brought in conformity with both the Ukrainian and the EU “Guidelines on Investigation of Bioequivalence” [10,13] and be defined as the only official reference concerning bioequivalence. The provisions of Directive 2001/83/EC [4] should be included in to this harmonization process. This will contribute to more clarity for applicants and contributes to make the regulatory more consistent. In general, Terms and Definitions in Order #460, the Guidelines on investigation of Bioequivalence, and Directive 2001/83/EC, as amended, should be the same.

### 7.2 Objective 2: Necessary changes in the Ukrainian legislative/regulatory system to improve the regulations on bioequivalence of generic medicines and hybrid applications

#### Activity 7.2.1

Define those medicinal products for which bioequivalence studies are required (EU/EEA rules) (additional Ukrainian regulations are in italics and might be included):

- Tablets, capsules, oral suspensions
- Oral immediate release forms with systemic action
- Non-oral immediate release dosage forms with systemic action
- Modified release forms with systemic action
- Medicinal products with different dosage forms
- Medicinal products with several strengths
- Fixed combinations
• Hybrid medicinal products
• Extensions
• Variations
• Oral, immediate release medicines with systemic action used as an emergency medicine; with a narrow spectrum of therapeutic action/window; published data show bioavailability problems of a specific drug; difficult physicochemical properties; problems in in-vitro dissolution tests
• Non-systemic medicines which are not solutions (oral, nasal, ophthalmic, dermatological, rectal, vaginal use without systemic action)

**Activity 7.2.2**

Define the medicinal products for which bioequivalence studies are NOT required (EU/EEA rules):
• Long-acting locally applied products (therapeutically equivalence must be demonstrated, but no BE study, if no systemic effect is expected)
• Orally inhaled products (therapeutically equivalence must be demonstrated)
• Herbal drugs (other, separate regulatory provisions apply)
• Biosimilars (other, separate regulatory provisions apply)
• Homoeopathic medicinal products (other, separate regulatory provisions apply)
• Medicinal products eligible for a BCS-system based biowaiver procedure
• Medical gases
• Medicine with well-established/well-studied medical use
• Traditional (herbal) medicines
• *Simplified registration is possible (Decree #376, Order #460)*
• *Provisions in Annex 18 of Order #460.*

The respective provisions in the Ukrainian and EU Guidance on the Investigation of Bioequivalence are almost identical, but different from the provisions in Order #460.

The SEC has developed Draft amendments, recommendations and explanatory notes for applicants (1) to the MOH Order #460 to further harmonize it with Directive 2001/83/EC, and (2) the Guidelines on the investigation of bioequivalence. Furthermore, (3) product-specific guidance documents (reflecting those published by the EMA and FDA) and (4) recommendations for the proper selecting of reference comparator products in bioequivalence studies are in preparation, as well as a list of recommended reference products [10(b)].

**Activity 7.2.3**

A provision should be placed in all regulations on bioequivalence testing requiring applicants to present a sound justification to replace the necessity to perform a bioequivalence study by applying to use the BCS (Biopharmaceutics Classification system)-based biowaiver system.

**Activity 7.2.4**

Publish *“Product-specific bioequivalence guidance”* documents, like those published by the EMA and FDA, and refer to them in the Guidelines for Investigation of Bioequivalence [10].

Currently the SEC prepares such guidance: they are harmonized with the relevant provisions in the applicable Ukrainian and EU regulations.


**Activity 7.2.5**

Bioequivalence studies are phase I clinical studies and must be conducted by following ICH-GCP rules, as well as GLP rules concerning the bioanalytical part of the study [10,13]. Preparations for complying with the new Clinical trial regulation (EC) 536/2014 [35] should be started and the actual status of ICH-GCP implementation in Ukraine assessed.

**Activity 7.2.6**

Ukraine is a member of the PIC/S network and thus should introduce a simplified/abbreviated procedure concerning the verification of GMP Certificates issued by the competent bodies in other PIC/S Member states. Actually, except for GMP Certificates for centrally registered products in EU, the SAUMP needs to confirm the validity of this certificate. This may take several weeks.

**Activity 7.2.7**

Many manufacturers in Ukraine strive to join the WHO pre-qualification scheme. Medicinal products from the “WHO List of pre-qualified products” should receive MA in Ukraine by an “Abbreviated registration” process, as these products fulfil the (Internationally recognized) requirements concerning safety, efficacy, and quality. Furthermore, many of these pre-qualified medicines are for fighting against widespread dangerous diseases endangering national public health systems (HIV/AIDS, Tuberculosis, Influenza). This will also be beneficial for local manufacturers, because they will be able to participate in International tenders and may use the dossier, which needs to be established within the pre-qualification process, also in the national MAA process. The relevant provisions given in Order #460, Chapter V “Basic demands to the registration dossier materials”, Article 10.2, which refers only to WHO pre-qualified TB and HIV/AIDS drugs should be amended to “all pre-qualified products from the respective WHO list” [47].

**Activity 7.2.8**

Many EU Guidelines provide no, or only general information on many topics, leaving much space for interpretation and address some important issues only marginally. It is therefore useful to refer to provisions published by the WHO and/or FDA, as these are often much more detailed and can be used as supportive materials/references. They might also be considered in future updated or new regulatory provisions.

**Activity 7.2.9**

The provisions concerning bioequivalence and associated topics in the key regulatory documents, i.e. the Guideline on the Investigation of Bioequivalence” [10], Annex 18 of Order #460 [14], Decree #376 [19], and the Law of Ukraine on Medicines [28] need to be harmonized. Afterwards, they need to be harmonized with the key regulatory bioequivalence-related documents in EU/EEA, i.e. the Guideline on the Investigation of Bioequivalence” [13], Directive 2001/83/EC [4], and product-specific guidances [31]. This will be a major step forward towards mutually agreed Terms and Definitions, and it will also provide stakeholders (applicants) with a consistent, reliable frame of applicable, relevant regulatory provisions for investigating bioequivalence.
7.3 **Objective 3: Secure safe, effective, and of good quality generics**

**Activity 7.3.1**

Initiate a policy change concerning generic medicinal products in the course of the planned Healthcare reform in Ukraine: first priority should have the aspect of generic substitution, i.e. therapeutically equivalence and interchangeability within the national generic substitution policy. These terms are not within the scope of the MAA process in EU but regulated on a national level of the Member states.

**Activity 7.3.2**

Define the requirements medicinal products must fulfill for participating in the national procurement/reimbursement scheme. One key condition would be that the products must be safe, efficient, and of good quality. Quality is ensured by the proof that the product is manufactured under cGMP conditions, safety and efficacy are demonstrated by clinical studies, i.e. proof of bioequivalence (see for details in Chapter 7).

Currently the State register of medicines (within a pilot project) has been integrated into the “ProZorro electronic procurement system”. According to a report posted on ProZorro, the integration of the register into the system will allow state customers to choose the subject of procurement from the drop-down list under the international non-proprietary name (INN), which standardizes procurement items and eliminates errors in drug names. Integration of the evidence-based classification system, including the results of bioequivalence studies, into this IT system would ensure that all necessary information concerning decisions on procurement/reimbursement [6].

**Activity 7.3.3**

For generic/hybrid medicinal products complying with the conditions for procurement/reimbursement a list or website should be prepared showering those products considered as therapeutically equivalent and thus interchangeable [20-28]. [Refer to 4.2.3].

**In Chapter 9.2** a “Brief outline for a “Model regulation for generic substitution in Ukraine”, including alternatives from Germany, Ireland, and Sweden is presented taking into account relevant experiences in Ukraine, USA, Ireland, Sweden, and Germany.

**Activity 7.3.4**

Prescriptions must solely indicate the INN (International Non-proprietary Name) of the medicinal product on it, only in special cases the tradename can be used (Order #360) [56], if

- the drug has no INN
- the product is from biological origin and patent-free
- the product is a biosimilar
- the product is subject to subject-quantitative accounting (narcotics, psychotropic drugs, toxic and potent medicines listed in Annex 4),
- is released on preferential terms or free of charge, except of medicines listed in the Appendix to the Cabinet of Ministers of Ukraine Resolution # 863 from 9 November 2016, as amended, which are refundable [57]. NB. Supplement 6 of [56] lists those medicines (INN), which are not allowed to be prescribed.
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The recent amendment to Order #360 is Order #735 from 18 April 2018 [58] and its explanatory notes [59]. It implements an electronic prescription system and “Changes the rules of writing prescriptions for medicines and medical products”, including a new form for prescriptions in its Appendix I [60].

The original intention of the rule to use only INNs on the prescription was to curb influence of the manufacturers on the prescription behavior of the doctor. However, this led to a huge “collateral damage”, as now the pharmacist decides which product to supply: so, there is a conflict of interest, because he will prefer to dispense those products with the highest margin for himself. This provision needs to be amended to impose cost-control on the medicinal products dispensed by the pharmacist. Consequently, governments implemented so-called Reference price systems [25,26,28,30,61], based on reference groups for medicines with identical active principles (APIs) and the ATC-5 Classification system [62], as described in Chapter 9.2.

Activity 7.3.5

The results obtained from introducing a reference price system [63] for medicines to treat cardiovascular diseases, diabetes II, and bronchial asthma, should be used as the basis for possibly including additional groups of medicines based on identical active substances (APIs; Reference groups) and the ATC-5 Classification system of the WHO. Reference might be made to the envisaged update of the existing 2nd version of the “Medicinal Products Equivalence Reference Book - Ukrainian Orange Book”, the Ukrainian National List of Essential Medicines, lists of interchangeable medicines published by many RAs [22-26] and International organizations, like the WHO.

Activity 7.3.6

Define for each Reference group a reference price (i.e. the price for procurement by the government) to define the amount a patient must pay out-of-pocket if she/he prefers to buy more expensive originator product [30,62,63]. Eventually, all medicines on the most recent National Essential Drug List from July 2017, as the only list for procurement/reimbursement of medicines from public funds, should be the eligible for inclusion into reimbursement initiative.

Activity 7.3.7

For the sake of public safety, Ukrainian competent authorities should be supplied with sufficient evidence documents confirming that imported products are identical to the product manufactured in the exporting country. If not, the safety and efficacy might be different and thus presents a threat to patients in Ukraine, as e.g. galenic differences in the formulation of a product, like different excipients, can significantly alternate the dissolution profile of the product. In doubt, further evidence, like proof for bioequivalence, should be requested.

When assessing the marketing authorization application dossier, a CMC (Chemistry, Manufacturing, and Controls) review should be conducted to ensure the connection in quality between the originator’s drug and the generic drug, as well as of drug(s) used in clinical trials and the commercial product. Testing alone of the finished drug is insufficient for control of product quality [53].

Activity 7.3.8

On the Ukrainian pharma market are many medicinal products which were registered in the past without sufficient or even any proof of their safety, efficiency, and often quality. These products present
Introducing New Strategy on Bioequivalence in Ukraine

a threat to public health and measures need to be taken to remedy the situation. The existing marketing authorization dossiers of these products should be brought in line with European standards within a defined timeframe (possibly 5 years), taking into account the limited capacities of the SEC for the reviewing process and to ensure continuous access to these medicines for the patients. Within this period of time robust and conclusive scientific data on the products' safety, efficacy and quality must be demonstrated: product quality must be demonstrated by a GMP-compliant manufacturing, efficacy and safety by demonstrating bioequivalence (clinical study, comparative pharmacodynamic study, comparative clinical trial, or in-vitro dissolution). Under the assumption of a swift availability of an updated Medicinal Products Equivalence Reference Book - Ukrainian Orange Book, all interested parties, including consumers/patients, will be able to retrieve information on the regulatory status of all medicinal products marketed in Ukraine, so these products will receive a low scoring in the evidence-based classification system and thus be avoided by patients and eventually excluded from public procurement/reimbursement.

Activity 7.3.9

For the sake of improving public safety, the number of Official Medicines Control Laboratories (OMCLs) needs to be increased to 3-4 laboratories in various regions of Ukraine. It might be possible to upgrade already existing regional quality control laboratories to comply with EDQM requirements and to certify them later by applying e.g. ISO 17025:2017 or ISO 9001:2015 standards. This will significantly contribute to raise public safety.

Activity 7.3.10

An organizational unit at the MOH and/or SEC should be established charged with the responsibilities to monitor, retrieve, assess, and distribute actual, relevant information on the frequently changing legislative/regulatory framework in Ukraine and leading organizations, those of the ICH region. The actual guidelines and other regulatory provisions published by the WHO, FDA, and ICH organization should be monitored carefully, as they are an important source of information. As described in more detail in Chapter 4 (4.2.5), training and capacity building in the areas like investigation of bioequivalence, GCP-compliant conduct of clinical trials, biostatistics, and biosimilars needs to be promoted.

Activity 7.3.11

Move from a gradual harmonization to a process of implementing the acquis as a single block. The broad, general provisions in the Association Agreement in the pharmaceutical area leaves Ukraine with a number of alternatives for approximation and to identify its best way for harmonizing with the EU rules. Experience shows that the strategy of a “gradual approximation/harmonization of the regulatory/ legislative systems” in many CIS countries with the acquis communautaire has led to many inconsistencies, unclear provisions/rules, as well as discrepancies and unconformities: only defined parts of the regulations were implemented, but other parts not, leading to a patchwork of rules mixing both systems, basic definitions differ, already harmonized rules don’t reflect the actual (updated, amended) status of the rules in EU, etc. [44].

During their EU-accession process, States like the Czech Republic and Poland, opted for a comparably very fast adaptation of the acquis avoiding any time delays caused by long negotiations. However, to avoid chaos, long transition periods must be granted, minimum 5-10 years. Afterwards a fully compliant system will be in place.
Activity 7.3.12

Harmonization with the relevant EU regulations must be limited to those issues, which are regulated on the Community level in the EU. Many issues in the EU pharmaceutical legislation are regulated by the respective national DRAs of the Member states, like generic substitution. Ukraine may stick in defined cases to its national sovereign rights, like the creation of a list with interchangeable medicinal products, if deemed beneficial for the country.

Activity 7.3.13

Possible risks, existing or upcoming, as described in Chapter 5, must be taken into consideration and suitable measures to mitigate them, evaluated. A risk management plan should be established as soon as the implantation plan has been approved and the timelines fixed. The presented SWOT analysis in Chapter 5 could be a starting point.

The following Table 1 contains the “Detailed list of proposed activities”
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<tr>
<th>What shall be done/ achieved</th>
<th>Owner of process</th>
<th>Timings</th>
<th>Possible risks</th>
<th>How to mitigate risks</th>
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<tr>
<td><strong>Objective 1.</strong></td>
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</table>
| Activity 7.1.1 Align the Terms and Definitions concerning bioequivalence within the Ukrainian legislative/regulatory system [Ref. 4.1.1, 4.1.2, 4.1.3, 4.2.1] | MOH, SEC (Head of Departments)  
Taskforce/workgroup coordinating the experts  
External experts should be included “National Scientific Expert Committee for Generic Medicines” | Depending on the political will and extend of support from stakeholders: 1-2 years (mid/end of 2020) | Process will take too much time  
Difficult to reach mutual agreements with all stakeholders  
Legislative/regulatory rules change rapidly and frequently and thus need to be frequently updated/revised | Provide adequate, sufficient resources  
Assure political back-up  
Join networks of organizations in partner countries (“Twinning”) |
| Activity 7.1.2 Align the Terms and Definitions between Ukraine and EU/EEA Community legislation to get them comparable [4.1.1, 4.1.2, 4.1.3, 4.2.1-4.2.4] | MOH, SEC (Head of Departments)  
Task force/work group coordinating the experts  
External experts should be included “National Scientific Expert Committee for Generic Medicines” | Depending on the political will and support from stake-holders: 1-2 years (mid/end of 2020) | Process will take too much time  
Difficult to reach mutual agreement with all stakeholders  
Legislative/regulatory rules change rapidly and frequently | Provide adequate, sufficient resources  
Assure political back-up  
Join networks of organizations in partner countries  
(Twinning) |
| **Objective 2.**            |                 |         |               |                      |
| Activity 7.2.1 Define the medicinal products for which bioequivalence studies are required [4.1.2, 4.1.3, 4.2.2] | MOH, SEC (Head of Departments)  
Task force/work group coordinating the experts  
External experts from clinical research units should be included into the “National Scientific Expert Committee for Generic Medicines” | Depending on the political will and support from stakeholders: 1-2 years (mid/end of 2020) | Process will take too much time  
Difficult to reach mutual agreement with all stakeholders  
Legislative/regulatory rules change rapidly and frequently  
Not enough experts in the field | Provide adequate, sufficient resources  
Assure political back-up  
Join networks of organizations in partner countries  
(Twinning)  
Invite experienced, foreign experts from RAs and Industry |
| Activity 7.2.2 Define the medicinal products for which bioequivalence studies are NOT required [4.1.2, 4.1.3, 4.2.2] | MOH, SEC (Head of Departments)  
Task force/work group coordinating the experts  
External experts from clinical research units should be included into the “National Scientific Expert Committee for Generic Medicines” | Depending on the political will and support from stakeholders: 1-2 years (mid/end of 2020) | Process will take too much time  
Difficult to reach mutual agreement with all stakeholders  
Legislative/regulatory rules change rapidly and frequently | Provide adequate, sufficient resources  
Assure political back-up  
Join networks of organizations in partner countries |
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</table>
| Activity 7.2.3 Conditions to apply BCS-based bio waiver provisions must be justified [4.1.3, 4.2.2] | MOH, SEC (Head of Departments)  
Task force/work group coordinating the experts  
External experts from clinical research units should be included into the “National Scientific Expert Committee on Generic Medicines” | Depending on the political will and support from stakeholders: 1-2 years (mid/end of 2020) | • Not enough experts in the field  
• Process will take too much time  
• Difficult to reach mutual agreement with all stakeholders  
• Legislative/regulatory rules change rapidly and frequently | • Invite experienced, foreign experts from RAs and Industry  
• Provide adequate, sufficient resources  
• Assure political back-up  
• Join networks of organizations in partner countries  
• Invite experienced, foreign experts from RAs and Industry |
| Activity 7.2.4 Publish Product-specific bioequivalence guidances [4.2.2, 4.2.3]                | SEC (Head of Departments), release by the MOH  
External experts from clinical research units should be included into the “National Scientific Expert Committee for Generic Medicines” | After approval: 3-4 months                      | • Legislative/regulatory rules change rapidly and frequently  
• Only the most “important” products may be considered  
• Not relevant products may be chosen | • Carefully observe changes in the rules in the ICH-region  
• Adapt/adopt suitable, relevant changes  
• Close co-operation with the stake-holders, mainly from industry |
| Activity 7.2.5 Requirement to follow ICH-GCP rules in clinical trials [4.2.4]                  | All stakeholders in the sector, especially those performing clinical trials (research)  
Regulators from the SEC | 6-12 months                                   | • Not enough training capacities  
• No funds for inviting foreign trainers | • Join networks of organizations in partner countries  
• Invite experienced, foreign experts from RAs (“Twinning”) |
| Activity 7.2.6 Recognition of GMP Certificates from PIC/S members [4.1.3, 4.2.2]             | MOH (Head of Department)  
SEC | 6-12 months                                   | Resistance of the SAUMP to change the procedure  
Staff will be afraid to lose their job and will work to rule | • Try to find a mutually agreement  
• To keep staff in job, charge the SAUMP with other responsibilities |
| Activity 7.2.7 Abbreviated-registration for WHO pre-qualified products [4.1.2, 4.1.3, 4.2.2, 4.2.3] | MOH, jointly with SEC | Depending on the political will and support from stakeholders: 1-2 years (mid/end of 2020) | Procedure not in EU/EEA regulation  
Possible hindrance in the harmonization/approximation process | • Consult with colleagues from EU RAs  
• Identify similar provisions in other countries |
<table>
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<tr>
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<th>Timings</th>
<th>Possible risks</th>
<th>How to mitigate risks</th>
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<tbody>
<tr>
<td>Activity 7.2.8 Consider WHO and FDA recommendations as supportive material/reference [4.1.2, 4.2.1]</td>
<td>• All stakeholders in the sector</td>
<td>Ongoing</td>
<td>• WHO and FDA provisions are not part of MAAs in EU/EEA</td>
<td>• Use WHO and FDA recommendations as supportive documents with no national legal power</td>
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</tbody>
</table>
| Activity 7.2.9 Harmonize the key provisions concerning bioequivalence in Ukraine and EU/EEA; harmonizing of the Guideline on Investigation of bioequivalence with Order #460 makes the provisions in the guideline legally binding [4.1.1-4.1.3, 4.2.1] | • MOH (for approval of possible changes)  
• SEC (for preparing the necessary administrative documents) MOH for approval  
• External experts from clinical research units should be included into the “National Scientific Expert Committee for Generic Medicines” | Depending on the political will and support from stakeholders: 1-2 years (mid/end of 2020) | • Process will take a long time  
• Difficult to reach mutual agreement with all stakeholders  
• Legislative/regulatory rules change rapidly and frequently  
• A rapid resolution of this topic is necessary to provide applicants with secure, robust conditions in the MAA process | • Provide adequate, sufficient resources  
• Assure political back-up  
• Join networks of organizations in partner countries  
• Invite experienced, local and foreign experts from RAs and Industry |

Objective 3

| Activity 7.3.1 | MOH, supported by  
• SEC  
• Taskforce/workgroup coordinating the experts  
• External experts from EU/EES should be included | Depending on the political will and support from stakeholders: 2-3 years (end of 2021) | • Process will take too much time  
• Difficult to reach mutual agreement with all stakeholders  
• Legislative/regulatory rules change rapidly and frequently  
• Changes in the political will to support the project | • Provide adequate, sufficient resources  
• Assure political back-up  
• Join networks of organizations in partner countries  
• Invite experienced, foreign experts from RAs (“Twinning”) |
| Activity 7.3.2 | MOH in close co-operation with the SEC, and stakeholders in the sector, like Business Associations, Manufacturers, Patient organizations | Depending on the political will and support from stakeholders: 1-2 years (mid/end of 2020) | • Process will take too much time  
• Difficult to reach mutual agreement with all stakeholders  
• Legislative/regulatory rules change rapidly and frequently | • Provide adequate, sufficient resources  
• Assure political back-up  
• Join networks of organizations in partner countries |
<table>
<thead>
<tr>
<th>Activity 7.3.3 Preparation of a list of therapeutically equivalent/interchangeable products eligible for generic substitution for the new procurement/reimbursement system [4.2.3]</th>
<th>Owner of process</th>
<th>Timings</th>
<th>Possible risks</th>
<th>How to mitigate risks</th>
</tr>
</thead>
</table>
| • SEC for establishing the list (jointly with the “National Scientific Expert Committee on Generic Medicines”)
• MOH for its approval | Depending on the availability of the necessary resources: end of 2019 | • Changes in the political will to implement the provisions
• Lack of sufficient resources, like qualified external experts | • Maintain a timely information network for all stakeholders
• Provide adequate, sufficient resources
• Assure political back-up
• Join networks of organizations in partner countries |
| Activity 7.3.4 Amend the prescription instructions [4.2.3] | Owner of process | Timings | Possible risks | How to mitigate risks |
| • MOH
• “National Scientific Expert Committee on Generic Medicines" | Already in force [55-59], maybe amendments/further clarifications will be needed | • Medical professionals and suppliers may oppose
• Patient organizations may ask for changes | • Start a campaign to keep stakeholders and the public informed |
| Activity 7.3.5 Implement a Reference-price system [4.2.3] | Owner of process | Timings | Possible risks | How to mitigate risks |
| • MOH
• “National Scientific Expert Committee on Generic Medicines” | Depending on the availability of the necessary resources: end of 2019 | • Difficulties in receiving consent of all stakeholders;
• Manufacturers, wholesalers, pharmacists will ask for changes | • Start a campaign to keep stakeholders and the public informed
• Increase political pressure on those opposing the new rules |
| Activity 7.3.6 Define Reference groups (of medicines) based on INN/ATC-5 [4.2.3] | Owner of process | Timings | Possible risks | How to mitigate risks |
| • MOH, jointly with the “National Scientific Expert Committee on Generic Medicines” | Depending on the availability of the necessary resources: end of 2019 | • Resistance from the supplier side (manufacturers, Business Associations, Health Professionals Associations) | • Start a campaign to keep stakeholders and the public informed
• Seek advice from (foreign) external experts |
| Activity 7.3.7 Enforce the rules for imported products [4.2.3] | Owner of process | Timings | Possible risks | How to mitigate risks |
| • SEC, jointly with the MOH and Business Associations | Depending on the political will and resources at the SEC: mid 2019 | • Shortage of impacted medicines
• Problems with concerned foreign manufacturers and distributors in Ukraine | • Initiate a round-table with the affected parties to get their consent to change the rules |
| Activity 7.3.8 Develop a procedure for dealing with the “old” products on the market [4.2.3] | Owner of process | Timings | Possible risks | How to mitigate risks |
| • MOH, supported by the SEC and the “National Scientific Expert Committee on Generic Medicines” | End of 2013 (5-years sunset clause) | • Shortage of needed products
• Not sufficient resources at the SEC
• Political resistance initiated by affected manufacturers | • A concerted effort of all affected stakeholders might reduce the described risks |
<table>
<thead>
<tr>
<th>Activity 7.3.9</th>
<th>Develop a plan to increase the number of official medicines control laboratories (OMCLs)</th>
<th>MOH, supported by the SEC</th>
<th>5 years, depending on the availability of resources</th>
<th>Lack of sufficient resources both at the SEC and the MOH</th>
<th>Seek assistance from the EDQM/GEON network</th>
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</thead>
<tbody>
<tr>
<td>Activity 7.3.10</td>
<td>Install an Information Center at the SEC and/or MOH</td>
<td>MOH and SEC, All other stakeholders, in particular from the Industry and their Associations</td>
<td>Depending on the availability of the necessary resources and political will: mid of 2019</td>
<td>Lack of sufficient resources both at the SEC and the MOH</td>
<td>Start a campaign to keep stakeholders and the public informed</td>
</tr>
<tr>
<td>Activity 7.3.11</td>
<td>Switch from a gradual to approximation/harmonization process</td>
<td>MOH, SEC, Task force/work group coordinating the experts, External experts from EU/EES should be included</td>
<td>Depending on the political will and support from stakeholders: 1-2 years (mid/end of 2020)</td>
<td>Process will take too much time</td>
<td>Provide adequate, sufficient resources</td>
</tr>
<tr>
<td>Activity 7.3.12</td>
<td>Consider only those areas in the EU Community law, which are eligible for a possible harmonization/approximation</td>
<td>SEC and SEC together with the “National Scientific Expert Committee for Generic Medicines”</td>
<td>Depending on the political will and support from stakeholders: 1-2 years (mid/end of 2020)</td>
<td>Process will take too much time</td>
<td>Provide adequate, sufficient resources</td>
</tr>
<tr>
<td>Activity 7.3.13</td>
<td>Frequently identify possible risks</td>
<td>SEC and SEC together with the “National Scientific Expert Committee for Generic Medicines”</td>
<td>Ongoing</td>
<td>Possible risks may not be identified in-time</td>
<td>Raise awareness of all stakeholders for risks</td>
</tr>
</tbody>
</table>

**Notes:**
- **Activity 7.3.9**
  - Developed a plan to increase the number of official medicines control laboratories (OMCLs).
  - Owner: MOH, supported by the SEC.
  - Timings: 5 years, depending on the availability of resources.
  - Risks: Lack of sufficient resources both at the SEC and the MOH.
  - Mitigation: Seek assistance from the EDQM/GEON network.

- **Activity 7.3.10**
  - Installed an Information Center at the SEC and/or MOH.
  - Owners: MOH and SEC, All other stakeholders, in particular from the Industry and their Associations.
  - Timings: Depending on the availability of the necessary resources and political will: mid of 2019.
  - Risks: Lack of sufficient resources both at the SEC and the MOH.
  - Mitigation: Start a campaign to keep stakeholders and the public informed.

- **Activity 7.3.11**
  - Switched from a gradual to approximation/harmonization process.
  - Owners: MOH, SEC, Task force/work group coordinating the experts, External experts from EU/EES should be included.
  - Timings: Depending on the political will and support from stakeholders: 1-2 years (mid/end of 2020).
  - Risks: Process will take too much time.
  - Mitigation: Provide adequate, sufficient resources.

- **Activity 7.3.12**
  - Considered only those areas in the EU Community law, which are eligible for a possible harmonization/approximation.
  - Owners: SEC and SEC together with the “National Scientific Expert Committee for Generic Medicines”.
  - Timings: Depending on the political will and support from stakeholders: 1-2 years (mid/end of 2020).
  - Risks: Process will take too much time.
  - Mitigation: Provide adequate, sufficient resources.

- **Activity 7.3.13**
  - Frequently identified possible risks.
  - Owners: SEC and SEC together with the “National Scientific Expert Committee for Generic Medicines”.
  - Timings: Ongoing.
  - Risks: Possible risks may not be identified in-time.
  - Mitigation: Raise awareness of all stakeholders for risks.
8.0 IMPLEMENTATION

8.1 General reflections

The Action plan (road map) for implementing the proposed strategy, objectives, and scenarios depends on the strong, continuous political will of the Ukrainian government to foster compliance of the legislative/regulatory system of Ukraine with the EU acquis communautaire, which sets the criteria for countries intending to join the EU.

Most of the Actions described below can be implemented in parallel, depending on the available resources at the MOH and SEC, including the availability of external experts. Strategies are presented by taking into account their relevance and importance in the light of harmonization with the EU provisions. Strategies/Recommendations involving general changes to the legislative/regulatory system need to successfully pass the parliamentary hurdle and thus must be considered as a long-term strategy, whereas short-term recommendations could be implemented much faster, e.g. by Orders of the Minister of Health.

Changes in the Law of Ukraine On Medicines, and Decrees of the Cabinet of Ministers of Ukraine should be initiated on short notice, because the time horizon for such cases will possibly be not less than a year. During this period those changes can be envisaged which can be initiated within the competences of the MOH, i.e. by Orders of the MOH.

Several other CIS countries were, or are, in a similar situation like Ukraine in reforming their public healthcare systems, so it looks reasonable to get in contact with their regulatory authorities, but also with the competent bodies in EU/EEA (preferably in the framework of a Twinning programme), as well as the WHO and FDA.

Possible risks (as described in Chapter 5) should be carefully evaluated and a plan of measures developed to minimize them should they really occur.

The recommendations of the strategy are substantiated by those given in the report from September 2018 of the USAID-sponsored project “Strengthening Regulatory Systems to Improve medical product quality in low- and middle-income countries”: in particular, in its future priority areas the developing and implementing of guidelines for bioequivalence and the promoting of Official Medicinal Control Laboratories (OMCLs) is emphasized [64].

8.2 Establishing the necessary infrastructure for the implementation of the proposed activities, strategies, recommendations

To ensure the proper managing of the operative implementation of the proposed strategies, a taskforce/working group should be established and a “National Scientific Committee of Experts on Generic Medicines” supporting the taskforce. The taskforce should be supervised mutually by the Minister of Health and the Head of the SEC. They decide on all strategic, political issues in the project, like on priorities of the different objectives for implementation, including timelines, or which external representatives/experts from the key stakeholders should be invited to ensure scientific/technical/business-related input to pave the way for decisions to be taken by on the regulatory/political level. They are supported by the Head of the Department at the MOH charged with registration/marketing authorizations, and the corresponding Head of the Department at the SEC. They co-ordinate the realization of the envisaged strategies and appoint from their staff the best-qualified suitable professionals according to the individual, specific needs for each objective. The task force needs to work
according to defined rules, laid down in a statute: this will allow for an effective project control, i.e. by frequently comparing the planned goals with actual status.

A clear splitting of responsibilities between MOH and SEC deems necessary: responsibilities concerning the regulatory aspects, like provisions in the MAA process, go with the SEC. This applies to Terms and Definitions like “generic medicinal product”, “medicinal product”, “pharmaceutically equivalent”, “bioequivalence”. All scientific and administrative issues of harmonization/approximation of the legislative/regulatory frameworks in general, and in particular for the investigation of bioequivalence in Ukraine and EU, need to be considered by the SEC and prepared for approval by the MOH.

Responsibilities which non-regulatory issues, like “generic substitution”, “therapeutically equivalent”, “interchangeable medicinal products”, go with the MOH, because these include political aspects concerning public health. On the basis of the results of the scientific evaluations by the SEC in the MAA process, conclusions on questions on procurement/reimbursement will be taken. The “National Scientific Expert Committee on Generic Medicines” will be charged with the responsibility to support the taskforce by working on mutually agreed recommendations for addressing individual objectives.

Committee members should be representatives from the Business Associations (like ACC, EBA), manufacturers running drug development programs, scientists/managers from contract research service providers (CROs), medical and pharmaceutical professions, scientific institutions (National University of Pharmacy, Kharkiv), health economists, possibly patient organizations, and last not least support from the political representatives in the Parliament and Public health administration. The operational part should be managed mainly by SEC staff with experts from the concerned departments involved in the MAA process for generics, hybrids, and biosimilars.

Action1 in the following Chapter 9 describes the most relevant mandatory requirements for implementing the strategies.

8.3 Additional information on recent developments received during 10-14 December 2018 visit to Ukraine

8.3.1 Work done by the SEC since the first visit to Ukraine in September 2018

The SEC has started already several preparatory actions concerning the implementation of the proposed recommendations. This includes:

(1) Amending Annex 18 of Order #460 by stipulating that the provisions of the Guidelines “Investigation of Bioequivalence” should be the only reference for demonstrating bioequivalence
(2) About 40 “Product-specific guidelines for establishing bioequivalence” have been prepared and are expected to be published as separate documents, i.e. not as annexes to the guidelines “Investigation of Bioequivalence”
(3) A further stand-alone guidelines will be published on the selection of reference products for bioequivalence studies. This guideline is in public discussion; it takes into account the WHO selection criteria [31]
(4) First reflections concerning the legislative/regulatory provisions on generic substitution have been laid down in a white paper. These provisions are supposed to be published in a separate legislation, preferably they should be included into the legislation on social security issues
(5) It is planned to consider the provisions of the EMA “Guidance on triggers for inspections of bioequivalence trials EMA/745861/2016) [77] for the planning of inspections.
8.3.2 **Decree #1022 of the Cabinet of Ministers from 05 December 2018 [78]**

Decree #1022 of the Cabinet of Ministers from 5 December 2018 “On approval of State strategy of State policy implementation of medicinal products for the period till 2025 year” describes the goals and measures to improve access of the population to effective, safe, and good quality medicines at affordable prices. The presented provisions are based on WHO recommendations. This includes changes in the legislative/regulatory system, concerning e.g. (1) the marketing authorization application process, (2) the clear definition of those medicines eligible to be procured/reimbursed, i.e. the national List of Essential Medicines, (3) addressing several recommendations described in this report, like recognizing PIC/S Certificates from other competent authorities in other PIC/S Member states, (4) data exclusivity and patent-related rules, (5) training and capacity building measures, (6) measures to improve/control the quality of medicinal products, and (7) strict compliance with GCP, GLP (GxP) rules.

8.3.3 **Information from a parliamentarian roundtable (12 December 2018)**

Mr. V. Usenko informed on a meeting of the Parliamentary Committee on Healthcare held on 12 December 2018. It was confirmed that the comments from the Ukrainian Medical Expert Community (UMEC) on the first version of the report were included into the final version. It was also recognized that the roundtable (on 11 December 2018 at the SAFEMed office) with representatives from the key stakeholders, i.e. Business associations, pharmaceutical companies, “Ukrainian Agency for Health Technologies Assessment” (Prof. Kostantin Kosyachenko), WHO, and the Ukrainian Chamber of Commerce, mutually agreed with the report. Concerning the CMU Decree #1022: Due to the fact that all stakeholders agreed with the report, it is recommended to stick to the provisions in the report, because some of the provisions in the CMU Decree #1022, in particular on compulsory licences, will lead to long discussions which in turn might slow down the progress.

8.3.4 **Presentation of Prof. Dobrova (National University of Pharmacy in Ukraine, Kharkiv)**

Prof. Dobrova presented in an overview the Institute’s view on the key topics concerning the investigation of bioequivalence, also taking into account the new, actual Clinical Trial Regulation (EU) 536/2014 [35]. Four recommendations were given to:

1. Enforce capacity building in this area, i.e. by educating specialists for conducting investigations on bioequivalence by strictly following the actual applicable, relevant international standards;
2. Establish an open-source website for public information on all matters concerning clinical trials (like the EMA CT-database)
3. Ask for Governmental support for the reviewing/updating of the “Ukrainian Orange Book”
4. Continue the efforts to ensure harmonization of the regulatory provisions concerning bioequivalence in Ukraine and EU.

9.0 ROADMAP OF KEY ACTIONS

9.1 **10-Points Action Plan**

The following proposals for the roadmap are based on the strategy (scenarios, recommendations) described in Chapters 4, 6, and 7. It starts with a step-by-step approach describing the individual actions for implementing the proposed changes.
### Proposed Roadmap: Action 1

<table>
<thead>
<tr>
<th>ACTION</th>
<th>TASKS</th>
<th>Q1 2016</th>
<th>Q2 2016</th>
<th>Q3 2016</th>
<th>Q4 2016</th>
<th>Q1 2020</th>
<th>Q2 2020</th>
<th>Q3 2020</th>
<th>Q4 2020</th>
<th>2021</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Start preparatory works: (re-)confirm Top Management’s leadership and commitment to the strategies and objectives of the project</td>
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</tr>
<tr>
<td>1</td>
<td>Establish MOH and SEC joint steering committee</td>
<td>✔️</td>
<td>✔️</td>
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<td>✔️</td>
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<tr>
<td>1</td>
<td>Carefully evaluate the availability of the necessary sufficient, adequate resources (human, technical, financial, access to modern IT technology, and time). This includes the availability of qualified personnel for a longer period (2 years)</td>
<td>✔️</td>
<td>✔️</td>
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<tr>
<td>1</td>
<td>Check the availability of external experts and establish a close co-operation with key stakeholders (external experts, pharmaceutical companies and their business organizations/associations) by establishing a “National Scientific Expert Committee on Generic Medicines”</td>
<td>✔️</td>
<td>✔️</td>
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<tr>
<td>1</td>
<td>Establish a statute defining working instructions, project’s objectives, rationale, scope of work, code of conduct, selection criteria and payments of experts, ensuring impartial work of the taskforce, etc.</td>
<td>✔️</td>
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### Proposed Roadmap: Action 2

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<tr>
<th>ACTION</th>
<th>TASKS</th>
<th>Q1 2018</th>
<th>Q2 2018</th>
<th>Q3 2018</th>
<th>Q4 2018</th>
<th>Q1 2020</th>
<th>Q2 2020</th>
<th>Q3 2020</th>
<th>Q4 2020</th>
<th>2021</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Establish Working group, including the external experts</td>
<td>✔️</td>
<td>✔️</td>
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<td>✔️</td>
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<tr>
<td>2</td>
<td>Fine-tune strategic objectives, confirm the list of priorities and decide which actions might be addressed in parallel</td>
<td>✔️</td>
<td>✔️</td>
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<tr>
<td>2</td>
<td>For SEC to consider start evaluation with the NEML in coordination with NEML Expert Committee, necessary for future procurement and reimbursements</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
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<td>✔️</td>
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<tr>
<td>2</td>
<td>The MoH should start to prepare for the planned changes in the legislative/regulatory system (administratively by preparing the proposed amendments, which were developed by the SEC, for enacting, by informing the representatives of the concerned organizations, etc.)</td>
<td>✔️</td>
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<tr>
<td>2</td>
<td>Assign defined tasks to each member of the taskforce and the Committee, including timelines and control mechanisms</td>
<td>✔️</td>
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### Proposed Roadmap: Action 3

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<th>Q3 2018</th>
<th>Q4 2018</th>
<th>Q1 2020</th>
<th>Q2 2020</th>
<th>Q3 2020</th>
<th>Q4 2020</th>
<th>2021</th>
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<tbody>
<tr>
<td>3</td>
<td>SEC needs to prepare the necessary documents for the planned changes in the legislative/regulatory provisions for approval by the MoH</td>
<td>✔️</td>
<td>✔️</td>
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<tr>
<td>3</td>
<td>Harmonize/approximate the Terms and Definitions concerning the regulatory provisions in the MAA process, like “bioequivalence”, “generic product”, “Pharmacologically equivalent”, in the Law of Ukraine on Medicines, Decree #376, and Order #460, with those in EU, mainly Directive 2001/83/EC, if mentioned in the respective document</td>
<td>✔️</td>
<td>✔️</td>
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<tr>
<td>3</td>
<td>Harmonize the Ukrainian “Guideline on Investigation of Bioequivalence” and the corresponding guideline in EU, i.e. the 2 main differences concerning the selection of a reference product and that a non-EU reference product is recognized in the MAA process in Ukraine, be eliminated (or revised)</td>
<td>✔️</td>
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<tr>
<td>3</td>
<td>Brought Annex 1B in Order #460 in conformity with them and be defined as the only official reference concerning the investigation of bioequivalence</td>
<td>✔️</td>
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Proposed Roadmap: Action 4-7

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<tr>
<td>4</td>
<td>Remove from all legislative/regulatory documents on the regulatory provisions in the MAA process Terms and Definitions like “generic substitution”, “interchangeability”, “therapeutically equivalent” and move them to a separate regulation covering all aspects of generic substitution, procurement/reimbursement etc. These “non-regulatory” terms apply only to already registered products.</td>
<td>✔</td>
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<td>5</td>
<td>Remove from all legislative/regulatory documents provisions which apply only in Ukraine, like “Simplified procedure”, “In-bulk-products, “AFIs”, and the provisions in the MAA process with potential unlawful use of registration information and possible patent violations (data protection, patent protection)</td>
<td>✔</td>
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<td>6</td>
<td>Finalize which list of medicinal products and which classification system use</td>
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<td>6</td>
<td>Secure stakeholders agree on the applicable criteria for generic substitution (interchangeability)</td>
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<tr>
<td>7</td>
<td>List substitutable, inter-changeable (therapeutically equivalent) medicinal products published on the homepage of the MoH and SEC</td>
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Proposed Roadmap: Action 8 - 10

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<tr>
<td>8</td>
<td>Define conditions for procurement and reimbursement for the products on the list of substitutable, interchangeable (therapeutically equivalent) medicinal products</td>
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<td>8</td>
<td>Bring consensus on key cornerstone issues with concerned political organizations, patient organizations, health economists, manufacturers, wholesalers, researchers</td>
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<td>9</td>
<td>Stakeholders need to appoint a responsible person each at the MoH and the SEC to maintain the list; information on it must be actual, is e.g. doctors need to refer to it in their daily work, reliable, and easy-to-access</td>
<td>✔</td>
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<td>9</td>
<td>Updates should be planned each 6 months, except for actual safety information crucial to the health of patients or public health in general</td>
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<td>10</td>
<td>Implementation of identified strategies/objectives may be a source of possible risks</td>
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<td>10</td>
<td>Update, possibly revised/delete risks not relevant anymore or add new risks</td>
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<td>10</td>
<td>Develop and share with all stakeholder’s risk management plan</td>
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9.2 Outline for a “Model regulation for generic substitution in Ukraine”, including alternatives from Germany, Ireland, and Sweden

**Step 1.** Taking into account the results from the ongoing reimbursement program on the procurement of medicines of 3 therapeutic groups (cardiovascular, diabetes II, bronchial asthma), more medicines might be added, provided their eligibility to join has been ascertained. In a first approach the National Essential Medicines List (NEML) could serve as a good start.

**Step 2.** The regulatory status of the medicines from the NEML needs to be assessed and classified, mandatory for the further decision on generic substitution/interchangeability. This work should be conducted by the “National Scientific Expert Committee on Generic Medicines” to ensure that taken decisions are supported by all stakeholders. The classification scheme to be used could be the Practical guidelines “Theoretical justification and implementation of modern principles of therapeutic equivalence evaluation”, which were developed by Zupanets IA et al. and agreed by the MoH in 2017 [6]. The following proposal and recommendations (original text) were communicated by V. Usenko, MD, MBA, magister of quality assurance, Medical Director of Farmak JSC, Ukrainian Medical Expert Community
(UMEC). “The second medicinal products classification based on the evidence base medicine, therapeutic equivalence and type of the medicinal product (can be revised and updated in accordance to the current needs): 

**Code A – Original (innovative) medicinal product**

A.1 Medicinal product registered with full dossier (independent dossier)
A.2 Mixed marketing authorization medicinal product
A.3 Fixed combination medicinal product

**Code B – Generic medicinal product**

**B.1 Medicinal product, the interchangeability of which is proved by conducting in vivo study – bioequivalence**

B.1.1 Medicinal product, the interchangeability of which is proved by conducting in vivo study - bioequivalence (in comparison with original medicinal product).
B.1.2 Medicinal product, the interchangeability of which is proved by conducting in vivo study - bioequivalence (in comparison with generic medicinal product).

**B.2 Medicinal product, the interchangeability of which is proved by conducting in vitro study – dissolution test**

B.2.1 Medicinal product, the interchangeability of which is proved by conducting in vitro study – dissolution test (in comparison with original medicinal product)
B.2.2 Medicinal product, the interchangeability of which is proved by conducting in vitro study – dissolution test (in comparison with generic medicinal product)

**B.3 Medicinal product, the interchangeability of which is proved by conducting the comparative pharmacodynamic studies**

B.3.1 Medicinal product, the interchangeability of which is proved by conducting the comparative pharmacodynamic studies (with original medicinal product)
B.3.2 Medicinal product, the interchangeability of which is proved by conducting the comparative pharmacodynamic studies (with generic medicinal product)

**B.4 Medicinal product, the interchangeability of which is proved by conducting the comparative clinical studies**

B.4.1 Medicinal product, the interchangeability of which is proved by conducting the comparative clinical studies with original medicinal product
B.4.2 The interchangeability of which is proved by conducting the comparative clinical studies with generic medicinal product

**B.5 Medicinal product the interchangeability of which is proved only by pharmaceutical equivalence**

B.5.1 Medicinal product has proven pharmaceutical equivalence to original medicinal product
B.5.2 Medicinal product has proven pharmaceutical equivalence to generic medicinal product

**Code C – Medicinal product with well-established medical use and / or traditional (herbal) medicinal product**

C.1 Medicinal product with well-established medical use
C.2 Tradition(herbal) medicinal product
Introducing New Strategy on Bioequivalence in Ukraine

**Code D – Particular types of medicinal products which are subject to special registration requirements in Ukraine**

*D.1 Biological medicinal product*
D.1.1 Original (innovative) biological medicinal product
D.1.2 Biosimilar medicinal product (similar biological medicinal product)
D.1.3 Immunological medicinal product

*D.2 Other medicinal product types, which are subject to special registration requirement in Ukraine*

NB. Type D.2 contains products some of which detailed in Part III: Medicinal products (e.g. radio-pharmaceuticals and precursors) will be detailed as the next step of the development of classification.

This can help to differentiate with different types of products to avoid confusion and wrong interpretations and to put all non-original products in category generic. State Register of Drugs contains information on prescription status of the product (Rx or OTC) and SmPC. The one more info can be added as a PAR (Public Assessment Report). In this case products can be easily differentiated, and reimbursement category can be easily defined and integrated into the ProZorro electronic procurement system”. The combination of the provisions concerning the practical execution of generic substitution (on the pharmacy level) and the fundament for these provisions, i.e. the existence of an evidence-based classification system, cross-referencing medicinal products and their therapeutic equivalence, will be a suitable Model regulation for generic substitution in Ukraine”. Afterwards in the step the criteria for generic substitution, interchangeability, must be defined:

**Step 3.** Now it will be possible to define the criteria for generic substitution (interchangeability).

**Alternative 1 (Ireland):** The most recent approach (“Guide to interchangeable medicines”) was published by the Irish Health Products Regulatory Authority (HPRA) in June 2018 [26]. The key provisions (original text) include the

1. **Definition of an interchangeable medicine, which**
   a. Have the same qualitative and quantitative composition in each of their active substances
   b. Are in the same pharmaceutical form
   c. Have the same route of administration
   d. Have not more than two active substances.

2. **Defining the criteria for interchangeable medicines (next page)**

3. **Nine conditions which apply to the list of interchangeable medicines**

4. **Process for developing the list of interchangeable medicines.**

The list of interchangeable medicines is published on the HPRA homepage and frequently updated.
Criteria for interchangeable medicines

<table>
<thead>
<tr>
<th>CRITERION</th>
<th>TITLE</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Qualitative and quantitative composition</td>
<td>Qualitative and quantitative composition of active substances must be the same. As outlined in the Directive 2001/83/EC, Article 10.2, in the context of generic medicines, the different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy.</td>
</tr>
<tr>
<td>2</td>
<td>Pharmaceutical form</td>
<td>Pharmaceutical form must be the same or similar and suitable for interchangeability. As per Directive 2001/83/EC, in the context of generic medicines, Article 10.2, the various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form e.g. tablets and capsules.</td>
</tr>
<tr>
<td>3</td>
<td>Route of administration</td>
<td>Route of administration must be the same.</td>
</tr>
<tr>
<td>4</td>
<td>Bioavailability</td>
<td>An authorized generic medicine has demonstrated bioequivalence with the relevant reference medicine using bioavailability data. Waivers to the provision of bioavailability data are permitted under certain circumstances. Medicines will not be considered interchangeable where there is a difference in bioavailability which is clinically significant in terms of efficacy. Guidance on bioequivalence is listed at the end of this guide.</td>
</tr>
<tr>
<td>5</td>
<td>Number of active substances</td>
<td>Only medicines with two or less active substances can be included.</td>
</tr>
<tr>
<td>6</td>
<td>Medical device</td>
<td>Products where the medical device for administration of the medicine, if any, has significantly different instructions for use will not be considered interchangeable.</td>
</tr>
<tr>
<td>7</td>
<td>Biologicals</td>
<td>Biological medicines are excluded.</td>
</tr>
<tr>
<td>8</td>
<td>Safe substitution</td>
<td>Products will not be considered interchangeable if they cannot be safely substituted. This will be decided on a case-by-case basis.</td>
</tr>
</tbody>
</table>

Germany Case Study
In Germany guidelines on generic substitution (“Gute Substitutionspraxis, Good Substitution practice, GSP”) has been published by the German Pharmaceutical Association [3]. It describes in detail the basis for generic substitution. Therapeutic equivalence is defined as (1) pharmaceutical equivalent (same API, same dose/strength, comparable dosage form), (2) adequate pharmaceutical quality, and (3) bioequivalent (no mentioning of “same route of administration”). Two types of generic substitution are described: (1) first time administration of a generic, and (2) changing of the brand of the generic during an ongoing therapy. In case (1) no problems are expected, however, in case (2) severe problems may occur, when switching products with e.g. a narrow therapeutic bandwidth. Substitution during an
ongoing therapy of the following groups of medicinal products and/or dosage forms should be considered only after a positive risk/benefit assessment and done under strict medical supervision:

1. Groups of medicinal products with a potential risk for substitution
   - Antiarrhythmics – Antiepileptics – Immunosuppressives - Opioid-analgesics - Antiasthmatics - Anticoagulants – Lithium – Thyroid gland hormones – Antidepressives - Cardiac glycosides - Neuroleptics


For herbal products substitution is much more complex, as the active principle is the total plant extract (i.e. not a single, defined chemical entity). Substitution is possible only if the production processes (extraction, etc.) of both products are identical. Concerning Biologicals and Non-biological complex drugs (NBCDs), substitution, even of innovator-products, should be restricted to defined medical reasons (e.g. therapy-naïve patients) for safety reasons. In Germany the physician decides whether a generic substitution by the pharmacist is allowed or not by ticking (or not) a box “Aut-idem” on the receipt. Furthermore, a (legally-binding) list of medicinal products exists which are forbidden to be substituted (for patient’s safety). Drugs on this list are mainly those for treating chronic diseases (pain) and for the prevention of acute epileptic episodes:

<table>
<thead>
<tr>
<th>Antiepileptics:</th>
<th>Carbamazepine (retard tablets), Phenobarbital (tablets), phenytoine (tablets), Primidone (tablets), Valproic acid, also as sodium valproate und valproine acid and in combination with sodium valproate (retard tablets)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulants:</td>
<td>Phenprocoumon (tablets)</td>
</tr>
<tr>
<td>Cardiac glycosides:</td>
<td>beta-Acetyldigoxin (tablets), Digitoxin (tablets), Digoxin (tablets)</td>
</tr>
<tr>
<td>Immunosuppressives:</td>
<td>Ciclosporin (soft capsules and solution), Tacrolimus (hard capsules)</td>
</tr>
<tr>
<td>Opioid-Analgesics:</td>
<td>Buprenorphine (transdermal patches with different maximum application times, e.g. up to 3 days or up to 4 days) Hydromorphone (retard tablets with different daily application schemes, e.g. every 12 or 24 hours) Oxycodeone (retard tablets with different daily application schemes, e.g. every 12 or 24 hours)</td>
</tr>
<tr>
<td>Thyroid gland hormones:</td>
<td>Levothyroxine-sodium (tablets)</td>
</tr>
<tr>
<td></td>
<td>Levothyroxine-sodium + Potassium iodide (fixed combination, tablets).</td>
</tr>
</tbody>
</table>

In 2016 81% of all prescriptions were for medicines which were part of a reference price system. Patients are obliged to pay out-of-pocket between 5 and 10 € per prescription, and OTCs, treatments for minor ailments, and life-style medicines are nor reimbursed at all. Medicines are clustered in groups of therapeutically equivalent products, for which reference prices are defined. There is no positive list of reimbursed products, but a negative list for products which are not reimbursed. The system is complicated, thus slow, and changes frequently mostly because of (health-related) political issues. An up-to-date overview (from June 2018) is given.

**Sweden Case Study**

The Swedish Medical Products Agency (MPA) has on its homepage a list of “Substitutable Medicinal Products” [22], which is frequently updated and revised. Basic principles for substitution are, that “the products have the same active substance in the same amount and are otherwise medically equivalent”. NB. A new term medically equivalent has been introduced. The list is available in Swedish only.
The published list of substitutable medicines could be used as a reference for checking which product in which country is considered to be interchangeable.

**Step 4.** After a mutually agreed set of criteria for generic substitution (interchangeability) has been accomplished, the selection of products for the list of substitutable medicinal products can start. It will be of paramount importance that all affected stakeholders will take part in this process, i.e. consultations with the MAHs. The result of Step 4 will be a mutually agreed list of interchangeable medicinal products publish on the homepage of the MOH and SEC.

**Step 5.** Step 5 comprises all activities concerning the establishing of a Reference price system for interchangeable (therapeutically equivalent) products clustered in groups of medicines with identical active substances (APIs; Reference groups) and the ATC-5 Classification system of the WHO. Reference could be made to the envisaged update of the existing 2nd version of the “Medicinal Products Equivalence Reference Book - Ukrainian Orange Book”, the Ukrainian National List of Essential Medicines, and the lists of interchangeable medicines from Step 4. Eventually, the conditions for establishing a differentiated procurement and reimbursement system can be defined, like free-of-charge procurement of defined medicines for children and elderly patients, co-payments for products for treating minor ailments, etc.

**Step 6.** A system needs be in place to manage amendments to the list (to include new products, products leaving the market, updating e.g. safety issues, etc.), to maintain availability of the list, etc. The list should be reviewed and updated each half year.
10.0 REFERENCES

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[5(c)] EMA: Q&A Positions on specific questions addressed to the Pharmacokinetics working party (PKWP)
[5(d)] EMA: Q&A on generic medicines
[10(b)] SEC amendments-update on the bioequivalence guideline of 2016
[10(c)] Guideline on investigation of bioequivalence 2018 UKR
[11] MOH Order #426 of 26.08.2005, as amended, On approval of the procedure for conducting expert evaluation of registration materials pertinent to medicinal products, which are submitted for State registration (re-registration) and expert evaluation of materials about introduction of changes to the registration materials during the validity period of registration certificate
[14] MOH Order #460 of 07.23.2015 On making amendments to the procedure for the expertise of the registration materials for medicines submitted for State registration (re-registration), as well as the expertise of the materials on amendments to the registration materials during the registration certificate validity term, and approval of the verification procedure of the materials attached to the application for State registration of certain medicines in terms of their volume. PROCEDURE for the expertise of the registration materials for medicines submitted for State registration (re-registration) as well as the expertise of the materials on amendments to the registration materials during the registration certificate validity term
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[55] EMA: Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU-EEA and submitted in marketing authorization applications to the EU Regulatory Authorities. EMA/121340/2011. 16 April 2012

[56] MOH Order #360 from 19 July 2005 On approval of rules prescribing recipes for medicines and medical products, order delivery of medicines and medical products from pharmacies and their structural subdivisions, instructions on the procedure for the storage and destruction prescription forms

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[58] MOH Order #735 from 18 April 2018 On amendments to the Decree of the Ministry of Health of Ukraine from July 19, 2005, no. 360


[60] Order # 735 Appendix1 to the Rules of Issuing Prescriptions for Medicinal Products and Medical Goods


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[66] Regulation (EU) 726/2004 Laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. 31 March 2004


[71] Commission Regulation (EC) No 1084/2003 Concerning the examination of variations to the terms of a marketing authorization for medicinal products for human use and veterinary medicinal products granted by a competent authority of a member state. 03 June 2003


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[75] FDA: Biosimilars Action plan: Balancing Innovation and competition. July 2018

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1.0 Legislative/regulatory Overview

The Parliament, Verhovna Rada, is the sole legislative body on healthcare issues. The “Law of Ukraine on Medicines” [29] is a Framework Act, underpinned by several Governmental Decrees, and further regulations, guidelines, etc. to bring its policies into practice. It has been amended by Laws of Ukraine of:

- February 14, 1997 No 70/97-VR,
- June 30, 1999 No 783-XIV,
- January 19, 2006 No 3370-IV,
- November 16, 2006 No 362-V,
- May 17, 2007 No 1034-V,
- May 20, 2009 No 1364-VI,
- May 11, 2010 No 2165-VI,
- March 15, 2011 No 3141 VI
- May 12, 2011 No 3323-VI,
- September 08, 2011 No 3718-VI,
- November 03, 2011 No 3998-VI,
- November 17, 2011 No 4056-VI
- December 20, 2011 No 4196-VI
- March 13, 2012 No 4496-VI,
- April 13, 2012 No 4652-VI
- July 03, 2012 No 5029-VI,
- July 4, 2012 No 5038-VI,
- October 16, 2012 No 5460-VI
- April 04, 2013 No 183-VII
- August 12, 2014 No 1637-VII
- October 20, 2014 No 1707-VII
- December 28, 2014 No 77-VIII
- January 15, 2015 No 126-VIII
- March 19, 2015 No 269-VIII (amendment valid till 31.03.2019, see item 1, Section II)
- May 31, 2016 No 1396-VIII.

Directly related to individual Articles in the “Law of Ukraine on Medicines” are the Governmental Decrees (Resolutions by the Cabinet of Ministers), and (Executive) Orders of the Ministry of Health), which regulate defined issues in detail, i.e. how regulatory functions should be executed. The fourth layer of regulatory/legislative provisions is guidelines, which give advice of how to interpret, understand, and to comply with the applicable regulations. They are “straightforward recommendations” and therefore not legally binding. However, in case an applicant has chosen a different approach, i.e. not to follow the guideline, he needs to submit a conclusive justification for his decision. In EU guidelines get legally binding only when they are incorporated into the law(s) and/or regulation(s), like the ICH-GCP guideline when it was included into Directive 2001/20/EC, Article 1(4). In Ukraine legal documents must be registered/approved by the Ministry of Justice to get into power.

The key provisions ruling the State registration of medicinal products in Ukraine, some including the evaluation of bioequivalence, are:
Law of Ukraine on Medicines (as amended) [29] defines -among other issues- the basic terms in the area of State registration of medicinal products. It demands that the procedure(s) and fees for registration should be defined in more detail by a Decree of the Cabinet of Ministers. This was done by Decree #376 [19], followed by Order No. 426 [11], which is presently effective in the version of Order #460 [14] of the Minister of Health. The Law stipulates that medicinal products shall be marketed in Ukraine only after their State registration, that State registration requires an application submitted to the MOH, products are subject to re-registration after the expiry of validity of the registration certificate (5 years), and that after a positive decision of the MOH for registration, an individual registration certificate is issued, and the relevant information entered into the State register.

Concerning basic provisions governing the registration procedure, the requirements for the application documents, deadlines for the MOH to take decisions, confidentiality of data submitted by applicants, data and patent protection, reasons for rejection of application, and requirements for labelling, are given.

The Law distinguishes two additional categories of medicinal products, which might be registered by a “simplified” procedure: medicinal products authorized by Regulatory Agencies of countries with stringent regulatory systems [45] in the field of medicinal products (USA, Canada, Australia, Japan, Switzerland, EMA) (originally only medicinal product for the treatment of selected diseases, after the recent amendment of the Law now all medicinal products), and medicinal products subject to procurement under agreements between Ukraine and international organizations (WHO, UNDP; UNICEF; UK Crown agents ). However, the latter provision is valid only till 31 March 2019. The Law doesn’t give any reference to GMP, GCP, and bioequivalence, so in the scope of the actual project only its general provisions apply.

Decree #376 (as amended) [19] On Approval of Procedure for State registration (re-registration) of medicinal products and amounts of fees for their State registration (re-registration)
Amended by the Decrees of the Cabinet of Ministers:
No 503 of March 21, 2007,
No 1277 of October 31, 2007,
No 372 of April 17, 2008
No 1165 of November 14, 2011
No 717 of June 27, 2012
No 125 of March 18, 2015
No 597 of August 12, 2015 (valid through March 31, 2019)
No 312 of April 20, 2016
No 558 of August 8, 2016.

The Cabinet of Ministers (CMU) Decree transfers the general, basic, political provisions concerning the State registration system from the Law of Ukraine on Medicines into a self-contained document: e.g. a mandatory expert evaluation of the application documentation by the SEC is introduced, gives detailed information on the so-called “Simplified registration”, and the procedures foreseen for handling extensions and variations. It is obvious that the Decree intends to regulate the State registration procedures only in general and partly but to leave the issuing of detailed instructions for the State registration procedures (i.e. Orders) with the MOH.

Order #191 from 25.04.2005 includes “Guidelines on clinical trials MEDICINAL PRODUCTS Investigation of Bioavailability and Bioequivalence”, which was set forth in the State Pharmacopoeia of Ukraine, First edition, Supplement 2 (2008), as 5.14.2 “Bioavailability-
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ularity and bioequivalence studies of generic products’. By **Order #396** from 13.06.2014 an updated Guideline (CT-H-MO3Y 42-7.1:2014) “Medicines: A study on Bioequivalence” was introduced, which in-turn was updated/amended by **Order #22** from 12.01.2017 to the actual CT-H-MO3Y 42-7.1:2016 version [10(a)].

**Order #22** from 12.01.2017 puts into force Guideline ST-N MOZU 42-7.1:2016 “Medicinal products. Investigation of Bioequivalence”, developed by the SEC [10(a)]. This guideline gives detailed instructions for applicants; it is based on the respective EMA “Guideline on the Investigation of Bioequivalence” CPMP/QWP/EWP/1401/98 Rev.1,Cor.** [13(a)], its Appendix IV (EMA/CHMP/600058/2010/Corr.*) “Presentation of Biopharmaceutical and Bioanalytical Data in Module 2.7.1” [13(b)], and the “Questions & Answers: Positions on specific questions addressed to the Pharmacokinetics Working party (PKWP)” (EMA/18604/2008, Rev.13) [5(c)].

This guideline is the core source of information for applicants like its EU counterpart “Guideline on the Investigation of Bioequivalence” [13(a)]. Therefore, these two guidelines were compared in detail to identify possible differences, non-conformities and discrepancies. Recently the SEC has published 3 amendments to the Guideline on the Investigation of Bioequivalence [10(b)], and a new version of the guideline: **CT-N-MOZU 42-7.2:2018** [10(c)]. This is considered as a further step towards harmonization/approximation of the regulatory systems in Ukraine and EU/EEA within the Association Agreement.

(4) **Order #426** (as amended) [11] of the MOH from 26 August 2005 on the “Procedure for conducting expert evaluation of registration materials pertinent to medicinal products, which are submitted for state registration (re-registration) and expert evaluation of materials about introduction of changes to the registration materials during the validity period of registration certificate”. As amended by (MOH) Orders:

No. 95 of 01.03.2006
No. 536 of 11.09.2007
No. 543 of 25.09.2008
No. 3 of 04.01.2013
No. 470 of 07.07.2014
No. 566 of 11.08.2014
No. 460 of 23.07.2015.

**Order #460** [14] is a recent Amendment to Order #426 and its 28 Annexes give detailed instructions to applicants on the requirements of a registration dossier. In its **Annex 18, “Confirmation of the generic medicines equivalence”**, which has been significantly revised from earlier versions, provisions for demonstrating bioequivalence are given and thus will be a key object of evaluation in this project:

- **Annex 1** REGISTRATION FORM of a Medicine Submitted for State Registration
- **Annex 2** REGISTRATION FORM of a Homeopathic Medicine Submitted for State Registration
- **Annex 3** REGISTRATION FORM of a Medicine manufactured in line with the approved prescriptions which is submitted for State Registration
- **Annex 4** REGISTRATION FORM of an Active Pharmaceutical Ingredient submitted for State Registration (Re-Registration)
- **Annex 5** The Registration Dossier Structure (Common Technical Document Format)
- **Annex 6** General Demands to the Registration Dossier Materials (in Common Technical Document Format)
The guideline “On the investigation of bioequivalence” [10(a)] directly refers frequently to this Order, in particular its Annex 18.

2.0 Applicable, relevant legislative/regulatory provisions in the State registration procedures concerning bioequivalence

The results from bioequivalence studies are requested by the Drug Regulatory Authorities to ensure therapeutic equivalence (and possibly interchangeability) between a pharmaceutically equivalent test product and a reference product. Several in-vivo and in-vitro methods may be used to demonstrate bioequivalence [Annex 18 of Order #460; 14]. In this chapter the four test methods for evaluating (bio)equivalence are presented, the first three are in-vivo methods (in humans), the fourth in-vitro. The (recommended) first choice is always (1), a bioequivalence study with pharmacokinetic (PK) endpoints.
2.1 When bioequivalence studies are required and types of studies necessary

Article 3.2.2. in Annex 18 of Order #460 [14] states that “For the medicines which are at risk that possible differences in bioavailability may lead to significant pharmacological differences in clinical use of the generic medicine as compared with the reference medicine, the in vivo studies are conducted to prove the equivalence”. Then in Article 3.2.2.1 that “The risks that can lead to significant pharmacological differences in clinical use of the generic medicine as compared with the reference medicine cover the following”:

In-vivo studies

(1) Oral systemic medicines with immediate release if at least one of the following criteria can be applied:
   • use as an emergency medicine (serious patient condition requiring assured therapeutic intervention(s))
   • narrow spectrum of therapeutic action/window (the efficacy/safety limit), steep slope of the dose-response curve (the difference in bioavailability may cause the medicine toxicity due to inadequately high bioavailability or low efficacy, due to high rate of its elimination from the body in the case of low bioavailability)
   • published data are available that other equivalence study methods are not allowed for active substances of the generic medicines. Published data showing that problems in bioavailability exist with a specific drug, other drugs with a similar chemical structure and/or formulation
   • difficult physicochemical properties, like poor solubility, instability, poor permeability. In Article 3.2 is stipulated: “For a medicine the active ingredient of
   • which the patient obtains in an unsolvable form, the in-vivo and/or in-vitro studies are to be conducted to prove the equivalence”
   • it is known that the in vitro dissolution tests for a generic medicine can be influenced by the polymorphism of the active ingredient, the excipients or the manufacturing technology.

(2) Systemic medicines not intended for oral or parenteral use (such as transdermal patches, suppositories, nicotine chewing gums, testosterone gels and transdermal contraceptives)

(3) Systemic medicines with modified release (sustained or modified release formulations)

(4) Fixed combination systemic medicines for which the in vivo studies are conducted for at least one active substance

(5) Non-systemic medicines (“Non-solutions”), in particular, for oral, nasal, ophthalmic, dermatological, rectal or vaginal use without systemic absorption which are not solutions. In such cases bioequivalence is demonstrated by comparative clinical studies, or clinical trials using pharmacodynamic endpoints. In defined cases in vitro dissolution
tests, i.e. the application of the Biopharmaceutics Classification System (BCS)-based biowaiver system, may be acceptable [10(a),13(a),17,18].

Article 3.2.2.2 rules that in case pharmacokinetic studies cannot be conducted, because no measurable concentrations in a biological fluid can be detected,

(6) Comparative pharmacodynamic studies (blood pressure, heart rate, etc.) can be performed, or if no pharmacokinetic or pharmacodynamic parameters endpoint can be found,

(7) Comparative clinical trials should be considered.

**In-vitro studies**

Provisions concerning in-vitro dissolution tests, i.e. the possibility to use a BCS (biopharmaceutics Classification System)-based biowaiver system are given in Article 3.2.1.1 and will be discussed in the following Chapter 3.2.2.

### 2.2 When bioequivalence studies are not required

There are 3 cases when bioequivalence studies are not necessary to be performed:

(A) **Simplified registration possible** (Decree #376, Order #460)

(B) **Provisions given in Annex 18 of Order #460**

(C) **Application of the BCS (biopharmaceutics Classification System)-based biowaiver system is possible**

(D) **Medicine with well-studied medical use**

(E) **Traditional (herbal) medicine.**

(A) **“Simplified registration”** [Law of Ukraine on Medicines [29], Decree #376 [19], Order #460 [14]]

In addition to the “Standard” State registration procedures, a “Simplified registration” procedure for three categories of medicinal products is in place. These are:

(1) Medicinal products authorised by the EMA (centralized procedure)

(2) Medicinal products authorised by selected foreign agencies, and

(3) Medicinal products subject to procurement.

This means for the medicinal products in this category:

(1) No expert evaluation by the SEC, accelerated variations and re-registration procedures

(2) Only documents describing the applied quality control methods, commitment to manufacture the product to be brought to Ukraine under identical conditions as at the country of origin, instructions for use, and package mock-up sample. Furthermore, a “Master file” must be submitted. Generics fall in this category, too.

(3) Medicinal products urgently needed to fight epidemiological crisis. This provision expires on 31 March 2019. As for products in category (2) only a limited amount of documentation is requested, and the scope of evaluation by the SEC is reduced for checking the handed-in documentation.

(B) **Provisions in Annex 18 of Order #460** [14] to the Procedure for the expertise of the registration materials for medicines submitted for state registration (re-registration) and the expertise of the materials on amendments to the registration materials during the validity term of the registration certificate (item 2, section V). CONFIRMATION of the generic medicines equivalence:
(1) The new product is for parenteral use (e.g. intravenous, subcutaneous, intramuscular) as an aqueous solution and contains the same active ingredient(s) in the same molar concentration and the same or similar ingredients in comparable concentrations. The difference in the composition of the excipients (buffer solutions, preservatives, antioxidants) is acceptable provided that the evidence is presented in any way that in such concentrations they do not affect the safety and/or efficacy of the medicine.

(2) The new drug is a solution (e.g. syrup, elixir, tincture) for oral use and contains the same molar concentration as the reference medicine and contains essentially the same excipients in comparable concentrations. If it is known that the used excipients affect the gastrointestinal tract by penetrating into it and thus affecting the absorption and/or stability of the active substance in the gastrointestinal tract, the relevant data are to be provided on the impact of these excipients in selected concentrations on the safety and/or efficacy of the medicine.

(3) The new drug is a powder for the solutions preparation (reconstitution) and the obtained solution meets the requirements specified in sub-items (1) or (2) above.

(4) The medicine is a (medical) gas.

(5) The new drug is an otic or ophthalmic product made in the form of an aqueous solution containing the same active substance(s) in the same molar concentration(s) and essentially the same excipients in comparable concentrations as in the reference medicine. The difference in the composition of the excipients (including buffer solutions, preservatives, substances that adjust the density or thickeners) is acceptable provided that the applicant proves by any means that in such concentrations they do not affect the safety and/or efficacy of the medicine.

(6) The new medicine is a topical product of local action in the form of an aqueous solution containing the same active substance(s) in the same molar concentration(s), and the same excipients in comparable concentrations as in the reference medicine.

(7) The new medicine is an aqueous solution in the form of inhalation-nebulized preparations or nasal sprays used with practically identical devices and containing the same active substance(s) in the same molar concentration(s) and essentially the same excipients in comparable concentrations as the reference medicine. The difference in the composition of the excipients is acceptable provided that the applicant proves in any way that in such concentrations they do not affect the safety and/or efficacy of the medicine.

(8) The new drug is a systemic medicine in the form of an aqueous solution for rectal use containing the same active substance(s) in the same molar concentration(s) and essentially the same excipients in comparable concentrations as the reference medicine. The difference in the composition of the excipients is acceptable provided that the applicant proves in any way that in such concentrations they do not affect the safety and/or efficacy of the medicine.

“For cases specified in sub-items 2, 3, 5, 6, 7 and 8 of this sub-item, in the case of differences in the composition of excipients and if the applicant cannot provide information that in such concentrations they do not affect the safety and/or efficacy of the medicine and has no access to relevant data, he has to conduct the relevant studies to prove the absence of the impact of these excipients or of the auxiliary devices on the safety and/or efficacy of the medicine”. In other words, in-vivo studies need to be performed.

(C) Application of the BCS (biopharmaceutics Classification System)-based biowaiver system is possible [Annex 18 of Order #460; 14]
For defined drugs the application of the BCS-based biowaiver system can be used to replace the necessity to conduct an (in-vivo) BE study. The BCS-based biowaiver system was developed to reduce the need for clinical (i.e. in-vivo) BE studies by demonstrating bioequivalence by suitable data generated by in-vitro tests. This is achieved by establishing a system of drug substances based on their aqueous solubility and intestinal permeability characteristics (BCS Classes I-IV).

BCS-based biowaivers can be used to demonstrate bioequivalence:
1. Between products developed in clinical development programmes
2. Line extensions (of the same pharmaceutical form)
3. In the marketing application process for generics
4. Other post-approval changes that would otherwise require the conduct of a BE study.

In which cases the BCS-based biowaiver approach is applicable or not

BCS-based biowaivers are applicable to medicinal products with a high solubility and, either high (BCS Class I) or low permeability (BCS Class III).

**Applicable**
1. Immediate release, solid orally administered dosage forms
2. Suspensions delivering the drug into the systemic circulation
3. Fixed-dose combinations only when all drug substances of the combination meet the criteria concerning the classification (solubility, permeability), excipients, and in-vitro dissolution
4. Drug substances in test and reference product must be identical
5. In case of different excipients, it must be demonstrated that the in-vivo absorption is not affected. The acceptable differences in excipients which may affect absorption is limited to +/- 10%

**Not-applicable**
1. Drugs with a narrow therapeutic index
2. Drug substances in test and reference product differ, e.g. by different salts, ester, isomers
3. Drugs with buccal or sublingual absorption
4. Drugs from BCS Class II and IV.

The provisions when a BCS-based biowaiver approach can be used are defined in Annex 18 [14] and fully comply with the Guidelines on the BCS-based biowaiver approach, including examples of model drugs, etc. published by the ICH/EMA [17], FDA/CDER [18], and WHO [27]; e.g. EMA Guideline on the Investigation of Bioequivalence, Rev. 1, Corr.** [13(a)] and the corresponding Ukrainian guideline 10(a)] give detailed provisions for BCS-based biowaivers in the course of BE studies. The assessment of the provided data to demonstrate bioequivalence during the marketing authorization application must include a check to confirm that the use of the BCS-based biowaiver is justified.

Clinical studies evaluating bioequivalence are phase I studies (involving healthy volunteers); they need to be conducted by following the rules laid down in the Good Clinical Practice (GCP) rules [10(a,c),13(a),54,65]. The bioanalytical part of the study must be conducted in compliance with the Good Laboratory Practice (GLP) rules. This aspects of establishing bio-equivalence will be discussed in Chapters 5 and 6.
(D) **Medicine with well-studied medical use**

Article 1.4 stipulates that in case a medicinal product is in use for more than 10 years in Ukraine and/or EU and "no bioavailability issues associated with active substance or its forms" exist, the results of pre-clinical and clinical trials (CTD modules 4 and 5) can be replaced by literature data (public information).

(E) **Traditional (herbal) medicine**

Article 2.1 rules that for traditional (herbal) medicines the dossier needs not to contain preclinical and clinical data. Some restrictions apply, e.g. the drug must have been in use for more than 30 years and more than 15 years in Ukraine and/or EU.

### 3.0 Provisions concerning the requirement to demonstrate bioequivalence in the MAA process for generics and hybrid applications

The three key-players in the State registration process of medicinal products are the MOH, SEC and SAUMP:

The MOH manages the entire registration process; in essence, it receives the MAA documents, asks the SEC to evaluate the submitted documentation, like efficacy, safety, and quality of the product, and, based on the conclusions of the SEC, decides on the registration of the product. Afterwards, an Order confirming registration of the product is issued, a registration certificate prepared, and published in the official register.

The SEC conducts the scientific and administrative assessment of the supplied documents in the light of efficacy, safety, and quality of the product, executes the administrative procedures, like checks for the completeness of the documentation, request for additional information from the applicant, etc., and prepares all documents necessary for the MOH to issue the registration certificate.

The SAUMP’s role is to confirm (within the assessment process at the SEC) GMP-compliance at the manufacturing site.

The Law of Ukraine of Medicines [29] has no provisions on bioequivalence. Decree #376 (as amended) [19] stipulates: “Materials pertinent to pre-clinical and clinical trial of the medicinal product; in case of registration of generic medicinal products, materials verifying therapeutic equivalence (interchangeability) to the reference product assigned by the Ministry of Health of Ukraine according to the World Health Organization (WHO) recommendations, as well as results of expert evaluation of the materials”.

Order #460 [14] in its Section III “Types of medicines submitted for State registration and their relevant registration dossier materials”, defines the required documents to be submitted:

<table>
<thead>
<tr>
<th>Type of medicine</th>
<th>Module 1</th>
<th>Module 2</th>
<th>Module 3</th>
<th>Module 4</th>
<th>Module 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicine with a complete dossier (autonomous or mixed dossier*)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Generic</td>
<td>(✓)</td>
<td>(✓)</td>
<td>✓</td>
<td>(✓)</td>
<td>(✓)</td>
</tr>
<tr>
<td>Hybrid</td>
<td>(✓)</td>
<td>(✓)</td>
<td>✓</td>
<td>(✓)</td>
<td>(✓)</td>
</tr>
<tr>
<td>Biosimilar</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Well-studied medical application</td>
<td>(✓)</td>
<td>(✓)</td>
<td>✓</td>
<td>✗**</td>
<td>✗**</td>
</tr>
<tr>
<td>Fixed-combination (FDC)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Informed consent (MAH agrees that his data are used)</td>
<td>✓</td>
<td>✓</td>
<td>(✓)</td>
<td>(✓)</td>
<td>(✓)</td>
</tr>
</tbody>
</table>
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| Traditional medicine | (✓) | (✓) | (✓) | * ||** |
| Medicine form bulk product | ✓ | (✓) | ✓ | (✓) |

**Table 3** Documents required (by CTD Modules) for registration in Ukraine

*Module 4 and 5 with limited clinical + pre-clinical data
** public information (literature)
( ) complete (full) documentation not required. In case no pre-clinical and clinical data are provided, consent of the MAH is required to use his data
ANNEX B. GENERICS AND HYBRID MEDICINES: THE LEGISLATIVE/REGULATORY FRAMEWORK CONCERNING BIOEQUIVALENCE IN THE EU/EEA

1.0 Legislative/regulatory Overview

The foundation of Community pharmaceutical law, Directive 65/65/EEC, which was 10 years later amended by Directives 75/318/EEC and 75/319/EEC, together with a series of their successive amendments and further Directives, has been codified by assembling them into a single text, Directive 2001/83/EC (consolidated and amended). Directive 2001/83/EC, which till the end of 2012 has been amended for twelve times, is the key regulatory/legislative document ruling pharmaceuticals in the EU. The consolidated version (with Annexes listing e.g. repealed Directives and their amendments, correlation tables, etc.) is in [4].

Regulation (EC) 726/2004, as amended, [66] rules the Community (= Centralized) procedures for marketing authorization and supervision of medicines for human and veterinary use. Furthermore, it defines those products, which need to be authorized by the Community, like orphan medicines, advanced therapy products, biotech products, new active substances to treat AIDS, cancer, neurodegenerative disorders, diabetes, etc.

The European rules concerning the developing and registration/marketing authorization of medicinal products are laid down in the "Rules Governing Medicinal Products in the European Union" (current versions can be downloaded from the EudraLex website):

<table>
<thead>
<tr>
<th>Vol.</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vol. 1</td>
<td>Pharmaceutical Legislation. Medicinal Products for Human use</td>
</tr>
<tr>
<td>Vol. 2</td>
<td>Notice to Applicants. Medicinal Products for Human use</td>
</tr>
<tr>
<td>Vol. 3</td>
<td>Guidelines. Medicinal Products for Human use</td>
</tr>
<tr>
<td>Vol. 4</td>
<td>Good Manufacturing Practices (GMP). Medicinal products for Human and Veterinary use</td>
</tr>
<tr>
<td>Vol. 5</td>
<td>Pharmaceutical Legislation. Veterinary Medicinal Products</td>
</tr>
<tr>
<td>Vol. 6</td>
<td>Scientific notice to Applicants. Veterinary Medicinal Products</td>
</tr>
<tr>
<td>Vol. 7</td>
<td>Guidelines. Veterinary Medicinal Products</td>
</tr>
<tr>
<td>Vol. 8</td>
<td>Maximum residue limits. Veterinary Medicinal Products</td>
</tr>
<tr>
<td>Vol. 9</td>
<td>Pharmacovigilance. Medicinal Products for Human and Veterinary use</td>
</tr>
<tr>
<td>Vol. 10</td>
<td>Clinical trials. Medicinal Products for Human and Veterinary use</td>
</tr>
</tbody>
</table>

Table 5 Rules governing medicinal products in the European Union

NB. The respective regulations concerning the developing and registration of medicinal products in the USA are compiled in the FDA Guidance Documents (www.fda.gov/RegulatoryInformation/guidances). Q&A concerning generic drugs are under www.fda.gov/drugs/resourcesforyou/consumers/QuestionsAnswers.

During the previous decade’s considerable progress was achieved concerning the harmonization of the regulatory/legislative framework in the so-called “triad” areas, i.e. the USA, EU, and Japan. In particular, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human use (ICH) issued guidelines, like the (ICH)-GCP guidelines, which were mutually accepted and then implemented in all three regions. Despite of the legal status of a guideline, i.e. as a “straight forward recommendation” („soft law“), it has legal power in EU Member states and reasons for non-compliance must be stated and justified. Thus, the regulatory/legislative framework in the different triad regions is more or less the same, only some country-specific variations still exist, but there are no substantial differences left.
Concerning **generic and hybrid applications** the legal basis can be found in Article 6 of Regulation (EC) 726/2004 [66] and Article 10 of Directive 2001/83/EC [4]:

**Generic medicinal product**

According to Article 10 (1) of Directive 2001/83/EC the applicant is not required to provide the results of pre-clinical tests and clinical trials if he can demonstrate that the medicinal product is a generic medicinal product of a reference medicinal product which is or has been authorized under Article 6 of Directive 2001/83/EC for not less than 8 years in a Member State or in the Union. The period of 8 years from initial authorization of the reference medicinal product, providing a period of so-called “data exclusivity”, applies only for reference medicinal products for which the marketing authorization application has been submitted as of 30 October 2005 for MRP, DCP and national procedures, and as of 20 November 2005 for a centralized procedure according to the revised Community Legislation.

A generic medicinal product is defined in Article 10, 2b of Directive 2001/83/EC as: “**generic medicinal product**” shall mean a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy. In such cases, additional information providing proof of the safety and/or efficacy of the various salts, esters, or derivatives of an authorized active substance must be supplied by the applicant. The various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form. Bioavailability studies are not required from the applicant if he can demonstrate that the generic medicinal product meets the relevant criteria as defined in the appropriate detailed guidelines.

**Hybrid medicinal product**

Hybrid medicines are generics based on a reference medicine, but have different strength, a different route of administration or a slightly different indication from the reference medicine. “Hybrid applications under Article 10(3) of Directive 2001/83/EC differ from generic applications in that the results of appropriate pre-clinical tests and clinical trials will be necessary only in the following three circumstances:

1. where the strict definition of a ‘generic medicinal product’ is not met
2. where the bioavailability studies cannot be used to demonstrate bioequivalence
3. where there are changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration of the generic product compared to the reference medicinal product.

In such cases the results of tests and trials must be consistent with the data content standards required in the Annex to the Directive 2001/83/EC, as amended by Directive 2003/63/EC, i.e. “the results of appropriate pre-clinical tests or clinical trials shall be provided”. These applications will thus rely in part on the results of pre-clinical tests and clinical trials for a reference product (bibliographical data) and in part on new data (generated by the applicant) (“Mixed Marketing authorization application), [4, Annex I, Part II (7)].

Some guidance on the appropriate additional studies required is indicated in Annex IV of Chapter I of the Notice to Applicants [13(b)]. It should be noted that at the time of submission of the generic/hybrid application, the protection period of the reference medicinal product should have expired in order to allow the applicant to rely on the dossier of the reference medicinal product. This period of **market exclusivity** of the reference medicine is 10 years from the date of first authorization; the time...
period of data exclusivity is 8 years. However, the so-called Bolar exemption, which was introduced in the USA, but then adopted internationally, is in force both in Ukraine and EU, stipulating that even within the data protection period an applicant has the right to develop a medicinal product (but not to put it on the market!).

The type of applications mentioned above (“Mixed application”) refers to information that is contained in the dossier of the authorization of the reference medicinal product, for which a marketing authorization has been granted in the Union on the basis of a complete dossier in accordance with article 8(3), 10a, 10b or 10c of Directive 2001/83/EC.

The European Medicines Agency (EMA) assesses MAAs for generics only if

1. the reference medicine was centrally authorized, or
2. the generic medicine provides a significant innovation or advantage for patients [5(b)].

In general, all other MAA need to follow the National/MRP/DCP path, however, if the medicine constitutes (1) a significant therapeutic, scientific or technical innovation, or (2) the granting of a centralized authorization is in the interest of patients at Community level, the applicant can request that his MAA will be included into the centralized procedure.

As the safety and efficacy profile of the active substance(s) is already known from the reference medicine, the MAA needs to cover only

1. information on the product’s quality, and
2. proof that the new medicine “produces the same levels of the active substance in the human body as the reference medicine”.

In addition to the above general, basic rules, various rules have been published to properly address specific issues of certain types of medicines, like:

1. Orphan medicinal products
2. Medicinal products for children (pediatrics)
3. Advanced therapy medicinal products
4. Medicines for a geriatric population, etc.

2.0 Applicable, relevant legislative/regulatory provisions in the registration procedures concerning bioequivalence

The “Guideline on the investigation of bioequivalence” (CPMP/EWP/QWP/1401/98 Rev.1/Corr.**), effective from 01 August 2010, [13(a)] is the basic source of information for establishing bioequivalence in the course of an MAA. In addition, the EMA publishes “Product-specific bioequivalence guidance” documents, “summarizing in a standardized format the relevant study design principle for demonstration of bioequivalence” [33]. Corresponding guidance documents, both general and product-specific, have been published by the FDA [34]. The provisions of this guidelines, many of them harmonized with the ICH guidelines, should be read in conjunction with a series of guidelines providing more detailed information on specific aspects, like:

1. ICH E3 Clinical Study Report (ICH E3, CPMP/ICH/137/95) [67]
2. ICH E8 General considerations for clinical trials (ICH E8, CPMP/ICH/291/95) [68]
3. ICH E9 Statistical principles for clinical trials (ICH E9, CPMP/ICH/363/96) [69]
4. ICH M9 Biowaivers [17]
5. EMA Guideline on bioanalytical method validation [70]
6. Fixed combination medicinal products [48]
7. Modified release oral and transdermal dosage forms: Section I and II [49]
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(8) Clinical requirements for locally applied, locally acting products containing known constituents [50]
(9) EMEA Guideline on the role of pharmacokinetics in the development of medicinal products in the pediatric population [51].

The guideline stipulates [13(a)] that “In case bioequivalence cannot be demonstrated using drug concentrations, in exceptional circumstances pharmacodynamic or clinical endpoints may be needed. This situation is outside the scope of this guideline and the reader is referred to therapeutic area specific guidelines” [33]. In addition, in defined cases BCS-based biowaivers are applicable. BE studies conducted in the EU/EEA must be carried out in accordance with Directive 2001/20/EC, the (ICH) GCP rules, and the test products must have been manufactured in accordance with the GMP rules.

2.1 When bioequivalence studies are required and types of studies necessary

The four test methods (1) Comparative bioavailability (=bioequivalence) studies, in which the active ingredient(s) and/or its active metabolites are quantitatively determined in biological fluids, like blood (serum, plasma) or urine, (2) Comparative pharmacodynamic studies (blood pressure, heart rate, etc.), (3) Comparative clinical trials, and (4) in-vitro dissolution tests, for evaluating bioequivalence in EU are the same as in Ukraine and have been presented in Chapter 3.2.

For tablets, capsules and oral suspensions bioequivalence needs to be evaluated, unless a biowaiver is possible. Other types of applications also need to present the results from bioequivalence studies, namely:

(1) **Medicinal products with several strengths:** Depending on whether the pharmacokinetics are linear or non-linear and a list of biowaiver criteria is fulfilled, more than one BE-study may be required.

(2) **Fixed combinations** [48]: A BE study demonstrating safety and efficacy of the combination versus its individual constituents should be performed.

(3) **Variations:** In case a product has been re-formulated, or the manufacturing process changed a BE study is required, unless a conclusive correlation of in-vitro vs. in-vivo data can be demonstrated.

(4) **Medicinal products with different dosage forms:** When the test product contains a different salt, ester, ether, isomer, mixture of isomers, complex or derivative of an active substance than the reference medicinal product, bioequivalence should be demonstrated in vivo bioequivalence studies [13(a)].

(5) **Oral immediate release forms with systemic action:** (a) Orodispersable tablets (orodispersable films, buccal tablets/films, sublingual tablets, chewable tablets). Specific requirements apply, depending on the formulation (absorbed in the mouth or not, etc. (b) Oral solutions (in case excipients affect gastrointestinal transit).

(6) **Non-oral immediate release dosage forms with systemic action:** (a) Parenteral solutions (only in case excipients affect disposition of the active substance, like aqueous or oily solution). (b) Liposomal, micellar and emulsion dosage forms for intravenous use (special requirements apply, biowaivers may be possible). (c) Micelle-forming formulations (see b).
(7) **Modified release products with systemic action** [49]: (a) Modified release oral and transdermal dosage forms. (b) Modified release intramuscular or subcutaneous dosage forms.

(8) **Extensions**: Extensions concern changes in the active substance, route of administration, etc. and thus need a (full) new MAA.

(9) **Hybrid applications**: Hybrid medicines are generics based on a reference medicine, but have different strength, a different route of administration or a slightly different indication from the reference medicine.

### 2.2 When bioequivalence studies are not required

As both guidelines on the evaluation of bioequivalence in Ukraine [10(a,c)] and EU [13(a)] are essentially the same and are applicable only for immediate-release formulations with systemic action, the following medicinal products are out of the scope of said guidelines:

1. **Locally acting Locally applied products** [50] Therapeutically equivalence must be demonstrated, but no BE study, if no systemic effect is expected
2. **Orally inhaled products** [52] Therapeutically equivalence must be demonstrated
3. **Herbals** Active substance(s) are not as well defined as for chemical entities
4. **Biosimilars**
5. **Homoeopathic medicinal products**
6. **Medicinal products eligible for a BCS-system based biowaiver procedure**
7. **Medical gases**
8. **Medicine with well-established medical use**
9. **Traditional (herbal) medicines**.

### 3.0 Provisions concerning the requirement to demonstrate bioequivalence in the MAA process for generics and hybrid applications

The legal basis for a marketing authorization application (MAA) for medicinal products for human use is stipulated in Article 10 (1) generic applications) of Directive 2001/83/EC, as amended [4]. For full applications Article 8(3) applies, for fixed combinations Article 10b, for hybrids Article 10(3); extensions/variations (II) are ruled by Commission Regulation (EC) 1084/2003 [71] and 1085/2003 [72].

Both Ukraine and EU use the (ICH) CTD format for the MAA process. Annex I of Directive 2001/83/EC as amended, [4] presents a list of documents (following the CTD structure) to be submitted in the MAA process. Bioequivalence issues are located in Module 2 (“Summaries”), #2.7 “Clinical summaries”, and Module 5 (“Clinical study reports”), #5.2.1 “Reports of biopharmaceutics studies”.

In Part II of Annex I, under #2 “Essential similar medicinal products”, it is ruled that for generics application Modules 1, 2, 3 must be submitted, but not Modules 4 and 5 if the original marketing authorization holder consented that his data may be used by the applicant.

Mixed marketing applications are cases when the dossier contains “full” Modules 1-3, but modules 4 and 5 contain data of limited non-clinical and clinical studies from the applicant plus bibliographic references (Annex I, Part II, #7). Hybrid applications are such application forms.
ANNEX C. COMPARING THE APPLICABLE, RELEVANT LEGISLATIVE/ REGULATORY PROVISIONS CONCERNING BIOEQUIVALENCE IN UKRAINE AND THE EU/EEA; IDENTIFIED DIFFERENCES BETWEEN THE RELEVANT REGULATIONS

1.0 General differences

An in-depth report “On conformity of the process of state registration of medicinal products in Ukraine with the EU law and standards” was published within a project funded by the EBRD in 2016 [44]. The evaluations, observations and recommendations in the areas of legislation, organization of the registration process, and policy in the report were analyzed in the light of their relevance to the actual project’s topic “bioequivalence”.

The actual assessment of the regulatory/legislative framework with a focus on bioequivalence issues revealed that in general the applicable, relevant provisions in both systems are very similar. However, considerable differences were identified and recommendations, including a strategy (and roadmap) for their implementation, developed. The identified general differences in the regulatory systems are directly related to the evaluation of bioequivalence and its role in many areas and processes, like marketing authorization, procurement, reimbursement, price regulation, but also in drug safety and efficacy.

The EMA publishes “Product-specific bioequivalence guidance” documents, “summarizing in a standardized format the relevant study design principle for demonstration of bioequivalence” [33]. Corresponding guidance documents, both general and product-specific, have been published by the FDA [34]. No such guidance documents have been published in Ukraine.

2.0 Differences, discrepancies and nonconformities relevant to the scope of the project:

1. “Simplified procedure” for medicinal products authorized by Drug Regulatory Agencies from selected foreign countries with a Stringent Regulatory Authority (SRA) (WHO) [45] (U.S.A, Switzerland, Japan, Australia, Canada, EU-centralized procedure only) allows for registration in Ukraine of products which have not undergone scientific assessment in line with the requirements of Directive 2001/83/EC and thus contradicts EU legislation. It might thus be possible that drugs with a different safety profile, different dosages for the same indication are on the Ukrainian market. Secondly, medicinal products subject to procurement under agreements between Ukraine and international organizations (WHO, UNDP; UNICEF; UK Crown agents). However, the latter provisions are valid only till 31 March 2019.

2. Rules concerning Intellectual property, Patents, and Protection of registration data. In EU DRA’s are charged with the responsibility to ensure that only those medicinal products are on the market which are safe, efficacious, and of good quality. The originator’s product underwent a full evaluation of these requirements before entering into the market (by a “full dossier”), so, for generics it will be not necessary to re-evaluate safety and efficacy of the test product. Exceptions may apply e.g. in cases of newly reported unfavorable changes in the safety profile. Thus, the primary focus is on the quality aspects and bioequivalence. During the MAA process In EU the DRAs do not check for possible violations of data exclusivity and/or market exclusivity periods, nor for possible patent infringements. These issues are considered to be the obligation of the applicant, who needs to enforce his legal rights by himself (the DRA completely keeps out).

Directive 2001/83/EC, Article 10, 1, as amended, stipulates that the time period of data exclusivity is 8 years for a product which is or has been authorized in EU/EEA. A generic shall not be placed on the market until 10 years have been elapsed from the initial authorization (requesting a “full dossier”) of the reference product (market exclusivity) (may be extended to 11 years in defined cases).
In Ukraine any use of safety and efficacy data of the reference product in the MAA process for a generic is considered as an “unlawful use of registration information” and thus forbidden for a period of 5 years after registration of the reference product. These data can only be used if the MAH of the reference product gave his permission (Order #460(36) [14]). Violation of this provision is a reason for the SEC to reject the MAA. Furthermore, in the course of an MAA, the applicant needs to provide information on the patent situation (protection) of his product. SEC shall refuse State registration in case of violation of patents. Both provisions, the unlawful use of registration information and possible patent violations are not covered by EU Community law, in the first line Directive 2001/83/EC. In both Ukraine and EU data exclusivity rules are in place (8 years in EU, 5 years in Ukraine), but in Ukraine no market exclusivity exists. However, in both Ukraine and EU the so-called Bolar exemption is in force, stipulating that even within the data exclusivity (protection) period, an applicant has the right to develop a medicinal product (but not to put it on the market!). In EU this rule will be expanded in 2019 by the (1) “Manufacturing waiver” and the (2) “Stockpiling waiver”.

Supplementary Protection Certificates (SPCs)
According to the pharmaceutical regulatory rules in EU, manufacturers of generic drugs are not allowed to produce in EU generic products within the validity period of patents and/or so-called supplementary protection certificates, SPCs, of the originator. On the legal basis of Regulation 469/2009/EC [46] an SPC to prolong the patent protection period up to five years in order to compensate the manufacturer for the time elapsed between patent application and marketing authorization approval when he couldn’t generate revenues, might be granted.

Therefore, EU-based manufacturers of generics are forced to produce their products outside of EU to ensure that on the day after the originator’s patent (+SPC) expires their product is on the market (“Day-1-Launch”). Since 2015 in EU the discussion of implementing a so-called “Manufacturing waiver” is discussed, which would allow EU-based manufacturers to produce generics and biosimilars within the validity period of the patent/SPC, but only for export into third countries in case no SPC exists there (“Export waiver”). The actual initiative of the European Parliament aims to add to this Export waiver a so-called “Stockpiling waiver”, which will allow EU-based manufacturers of generics and biosimilars to produce in EU (but NOT to place them on the market in EU) medicinal products, which are still under patent/SPC protection. This will allow the MAHs to plan a “Day-1-Launch” of generics/biosimilars with a sufficient quantity of products (manufactured in EU). It is expected that both waivers will be implemented in EU in early 2019. In Ukraine no SPC-system exists.

(3) Definitions
a) Medicinal product

The Law of Ukraine on Medicines [29] in its Article 2, §3 defines a medicinal product as “Medicinal products shall include: API, “in bulk” products; finished medicinal products (medicinal preparations, drugs, medicaments); homoeopathic agents; agents used to detect and eliminate pathogenic organisms or parasites; cosmetic products and medicinal supplements to food products”.

Order #460 in its “Terms and Definitions” lacks a definition.

The Ukrainian Guideline “Investigation of bioequivalence” [10(a,c)] defines a Medicinal product as “any substance or combination of substances (one or more AFIs and excipients), which has the properties and is intended for treatment or prevention of disease in humans, or any substance or combination of substances (one or more AFIs and excipients), which can be designed for prevention of pregnancy, restoration, correction or change of physiological functions in humans by means of

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pharmacological, immunological or metabolic actions, or for establishing a medical diagnosis. Medicinal products include: AFIs, in bulk products; finished medicinal products (drug products, drugs, medicines); homeopathic products; products used for identifying causative agents of disease, as well as for combating causative agents of diseases or parasites; medicinal cosmetics and medicinal supplements to foodstuffs”.

Except for “finished medicinal products” and “homeopathic agents” all other mentioned types of products are not considered as a medicinal product in EU/EEA. These are regulated by separate rules in EU/EEA.

**Directive 2001/83/EC** defines a medicinal product as (a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings, or b) Any substance or combination of substances which may be used in or administered to human beings either with a view of restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolite action, or to making a medical diagnosis

b) **Active Substance, Active pharmaceutical ingredient**

**The Law of Ukraine on Medicines** defines “active pharmaceutical ingredient” (drug substance, active substance, substance) (hereinafter – API or active substance) as any substance or mixture of substances intended for use in the manufacture of a medicinal product and during this use becomes its active ingredient. Such substances have pharmacological or other direct effect on human body, as part of finished forms of medicinal products they are used for treatment, diagnosis or prevention of disease, for changing the condition, structures or organism’s physiological functions, for management, manipulation and relief of symptoms.

**Order #460, Article II, (1)** defines: active pharmaceutical ingredient (medicinal substance, active substance, substance) (hereinafter - API, active substance, substance), as any substance or mixture of substances to be used in the medicine manufacturing process which becomes its active ingredient during this process. Such substances have a direct pharmacological or other direct impact on human body. As a part of a finished medicine they are used for the disease treatment, diagnostics or prevention; for the change of state, structures or physiological functions of the body; for the symptoms care, treatment and relief.

The API may be: compact, covered with a shell, granulated, crushed to a certain extent or otherwise processed and presented under different names and in various forms (in particular, in pellets, granules and others).

**Guideline Investigation of Bioequivalence:** Active substance (active pharmaceutical ingredient), substance (active substance, drug, drug substance, substance): Any substance or mixture of substances intended for use in the production of a medicinal product, which becomes its active ingredient during such use. Such substances have pharmacological or other direct action on human body. As part of finished medicinal products they are used for treatment, diagnostics or prevention of disease, for change of body’s state, structures or physiological functions, for care, processing and symptomatic relief.

**Directive 2001/83/EC:** Any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in its production, becomes an active ingredient of that product intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or to make a
medical diagnosis. The Ukrainian definitions emphasize the usage of the API, whereas the EU definition refers more to the action of the API.

c) In-bulk products and APIs in Ukraine both need a MA, not in EU/EEA

3.0 Comparison of the relevant, applicable Guidelines on the investigation of Bioequivalence

The following guidelines and their directly interrelated provisions were compared:

EU

(1) Guideline on the Investigation of Bioequivalence, CPMP/QWP/EWP/1401/98 Rev.1/Corr.** [13(a)].

(2) Appendix IV [13(b)] to the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr. **): Presentation of biopharmaceutical and bioanalytical data in Module 2.7.1, EMA/CHMP/600958/2010/Corr.**

(3) Questions and answers: Positions on specific questions addressed to the Pharmacokinetics Working Party PKWP EMA/618604/2008, Rev. [5(c)].

UA

(1) Guideline Medicinal products. Investigation of bioequivalence. ST-N MOZU 42-7.1:2016 (enacted by Order no. 22 from 12 January 2017) [10(a)]. This guideline is in the process of being amended [10(b)] and has recently been replaced by the new version: CTN MOZU 42-7.2:2018 [10(c)].

(2) Order #426 (as amended) [11] of the MOH from 26 August 2005 on the “Procedure for conducting expert evaluation of registration materials pertinent to medicinal products, which are submitted for state registration (Re-registration) and expert evaluation of materials about introduction of changes to the registration materials during the validity period of registration certificate”.


(3) Provisions in Annex 18 of Order #460 to the Procedure for the expertise of the registration materials for medicines submitted for state registration (re-registration) and the expertise of the materials on amendments to the registration materials during the validity term of the registration certificate (item 2, section V). CONFIRMATION of the generic medicines equivalence.

General points to consider

(1) Compared to the respective EU guideline, the Ukrainian Guideline on Bioequivalence covers several more points, which are addressed in the EU guideline by separate provisions: it includes (as Appendix IV) the templates for presenting biopharmaceutical and bioanalytical data in Module 2.7.1 into the text as well as Terms and Concept Definitions, and in its Supplement 1 “Recommendations for Determining absolute and relative bioavailability” and “Recommendations for superbioavailable products”.

(2) The Ukrainian guideline is very similar to the EU guideline, however, there are some important differences, which are mainly amendments, clarifications, addenda, but also definitions, were necessary to be addressed in the guideline, because the national Ukrainian legal requirements must prevail.
In the “National Supplement” (for reference) the list of editorial changes and addenda with reference to the applicable terms in the EU rules is presented. “Changes have been made to this Guideline prompted by legal requirements and harmonized regulatory documents adopted in Ukraine”. In addition, several changes (modifications) addressing a specific issue in the actual text are inserted directly into the text (with a different font and marked by an *). This guideline [10(a)] will be revised regularly [10(b,c)] in accordance with any changes and addenda introduced to the EU guideline [13(a)].

List of differences, Editorial Changes and Addenda
In the following each individual item in the list is reviewed and commented; a summary of findings is in Chapter 6.3. Differences etc. are in italic.

General

1. Introduction
   1.1 Key provisions: Identical; definition of $t_{\text{max}}$ is added
   1.2 Generic medicinal products: in addition to Directive 2001/83/EC, Section III of Order #460 needs to be followed. Different wording
   1.3 Other application types: extensions and variations are included, but not described by these technical terms

2. Scope
   In justified cases instead of the concentrations of active substance, its metabolite may be measured. A note is added that Order #460 is applicable for the evaluation of bioequivalence.

3. Legislative Framework
   For the conduct of clinical trials, the ST-N MOZ guidelines harmonized with EU and ICH guidelines should be respected.
   The provisions in [5c] Q&A: Positions on specific questions addressed to the pharmacokinetics working Party (PKWP) should be taken into account
   Scientific advice might be asked for as stipulated in Orders #460 and #690[54]

4. Main guideline text

4.1 Design, Conduct and evaluation of bioequivalence studies: the reference product must be marketed in EU or with another reference medicinal product justified according to the requirements of Order #460. This a major difference between EU and Ukrainian rules.
   Results from pilot studies should also be compliant with the current legislation of Ukraine, not only with those in ICH E3
   Bioequivalence studies with a non-EU reference product should not be submitted and included in the list of studies, if submitting application in EU. This a major difference between EU and Ukrainian rules, explained by the volume of the Ukrainian market and low-level of interest on the part of manufacturers to promote original medicinal products on the Ukrainian market

4.1.1 Study design: Identical.

4.1.2 Reference and test medicinal products: Selection of the reference product must follow the requirements of Order #460. It is added “According to clause 6.1 of paragraph two of Directive 2001/83/EC, a medicinal product used as reference medicinal product should be part of a global license for the reference medicinal product, including its additional strengths, pharmaceutical forms, administration routes, marking, which have been implemented as changes to the registration dossier or changes requiring a new registration”.
   Selection of a reference product in an application for extension should take into account that a complete dossier is available from the initial approval. Packaging of Study medicinal products: Guideline ST-N MOZU 42.40:2016, harmonized with Annex 13 of the GMP EU rules, should apply.

4.1.3 Study subjects: Identical
Introducing New Strategy on Bioequivalence in Ukraine

4.1.4 Study conduct: Identical
4.1.5 Investigated characteristics
4.1.6 Strengths to be investigated
4.1.7 Bioanalytical Methodology
4.1.8 Evaluation
4.1.9 Active substances with narrow therapeutic index
4.1.10 Highly variable active substances or drug products
   For 3-or 4-period crossover design studies “additional conditions are presented in Appendix 2 of
   the guideline”.

4.2 In-Vitro Dissolution tests
4.2.1 In-vitro Dissolution tests complementary to bioequivalence studies: Identical
4.2.2 In-vitro dissolution tests in support of waiver on in-vivo tests for additional strengths: Identical

4.3 Study report
4.3.1 Bioequivalence study report: The study report should be written by taking into account both
   the relevant Guideline “Structure and Content of Clinical study reports” [67] and the
   “requirements of the current legislation of Ukraine”.
   The choice of the reference product should be in accordance with the provisions of Order #460
4.3.2 Other data to be Included in registration dossier: identical
4.4 Applications for Changes, which may occur during the registration certificate validity period:
   (this provision refers to “Variation application” in EU).
   The comparative medicinal product in a study supporting a variation application, the originator /
test product must have been approved “under complete and independent application, application
for well-established use, application for fixed combination or an informed consent application in
accordance with the current legislation of Ukraine”.

Appendix I Dissolution testing and similarity of dissolution profiles
1. General aspects of dissolution testing as related in bioavailability: Identical
2. Similarity of dissolution profiles: identical

Appendix II Bioequivalence Study requirements for different dosage forms
   Oral immediate release dosage forms with systemic action: Identical
   Orodispersable tablets: Identical
   Oral solutions: Identical
   Fixed combination dosage form: Bioequivalence studies should take into account the relevant
   EU Guideline [48] “and the provisions in Order #460.”
   Non-oral immediate release dosage forms with systemic actions: Identical
   Parenteral solutions: No bioequivalence study is needed if the test product is an aqueous
   intravenous solution containing the same active substance as the approved product “(reference
   medicinal product)”
   Liposomal, Micellar and emulsion Medicinal products for intravenous use: The currently
   approved product is the “reference medicinal product”.
   Modified release dosage forms with systemic actions: for locally acting locally applied medicinal
   products the currently approved product is the “reference medicinal product”.

Appendix III BCS-based Biowaiver procedure
I. Introduction: “variations” is used instead of “extension”. Biowaivers may be used also for
   products “available on the market”.
II. General requirements: Risks should be more critically reviewed for BCS Class III the rest of the
    sentence: than for BCS Class I products, is missing)
III. Active substance: Not applicable when the test product contains different “racemate” (included, not in EU Guideline), “mixture of isomers” (not included, but in EU Guideline)

IV. Medicinal product: Buffer solutions from both the European Pharmacopoeia “or the State Pharmacopoeia of Ukraine” can be used.

The following Appendix IV and the Supplements are only in the Ukrainian guideline:

**Appendix IV Presentation of Biopharmaceutical and Bioanalytical Data in section 2.7.1 of Module 2**

This appendix is a translation of “EMA: Appendix IV of the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1: “Presentation of Biopharmaceutical and Bioanalytical Data in Module 2.7.1” (EMA/CHMP/600058/ 2010/Corr.4) [13(b)]. It is not included in the EU “Guideline on the Investigation of bioequivalence” [13(a)]. It is stipulated that both the “current legislation of Ukraine” and the applicable provisions of the EU regulatory provisions, i.e. Directive 2001/83/EC [4], need to be followed.

**Supplement I Recommendation for determining absolute and relative bioavailability**

Provisions for the evaluation of “Absolute bioavailability”, “Relative bioavailability”, and “Recommendations for superbioavailable products” are given. Superbioavailability means that the test product has a better (higher) extend of absorption (AUC) than the reference product.

**Supplement 2 Possibility of using three-period crossover replicate design scheme to demonstrate C_{max} within-subject variability**

These provisions apply for highly variable drugs, as described in Chapter 4.1.10 of both guidelines and in Guideline [73].

**Terms and Concept definitions**

The EU guideline contains only 3 definitions:

1. Pharmaceutical equivalence: Identical
2. Pharmaceutical alternatives: Identical, despite “same active substance” is added
3. Pharmacokinetic parameters:
   - Cmax: added maximum plasma concentration “of analyte”
   - λz: “elimination” rate constant (terminal rate constant in EU guideline)
   - SmPc: Summary of product characteristics (missing)

The Ukrainian guideline contains more definitions, which are laid down in EU in Directive 2001/83/EC. On page 5 of the guideline it is written, that “The definitions of these terms may differ from those in other regulatory documents or the terms may have other meanings”.

Therefore, the definitions in the Ukrainian guideline [10(a,c)] need to be compared with those in Order #460 [14] and Directive 2001/83/EC [4].

**4.0 Specific differences concerning bioequivalence**

Demonstrating bioequivalence is fundamental for all aspects concerning generic/hybrid medicinal products in terms of pharmaceutical equivalence, pharmaceutical alternatives, therapeutically equivalent, interchangeability, but is also linked to the areas of generic substitution, marketing authorization, procurement/reimbursement systems, and pharmaceutical pricing [27,28,30,62].

The general regulatory/legislative provisions in the pharmaceutical area in ICH regions (USA, EU/EAA, Japan) and Ukraine are very similar, including the provisions in the respective guidelines/recommendations of the WHO. However, there are considerable differences in the definitions and
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terms. In particular, the concept behind generic medicinal products in EU/EEA, i.e. Directive 2001/83/EU, and the USA (FDA) is fundamentally different: in EU/EEA a product receives marketing authorization when it demonstrates a positive benefit-risk balance, whereas in the US the aspects of therapeutically equivalence and interchangeability within the national generic substitution policy is first [7,20].

In a first step the different definitions of (technical) terms need to be evaluated in order to come in a second step to a mutual understanding of the key stakeholders of these terms.

In the preceding chapters general differences and those between the Ukrainian and EU/EEAA guideline on the evaluation of bioequivalence are presented, the most important definitions are given in the overview below (UA Guideline refers to [10(a)]; EU Guideline to [13(a)]).

The most striking differences identified are:

1. **Definition of a generic medicinal product**
   The provisions of Order #460, Directive 2001/83/EC, Ukrainian and EU Guidelines on the evaluation of bioequivalence, WHO and FDA, request “Pharmaceutically equivalence” plus demonstrated bioavailability. However, in addition, Decree #376 and Order #460 request that the products are interchangeable. The FDA expects that the product is:
   1. **Pharmaceutically equivalent** to its reference listed drug (RLD), i.e., to have the same active ingredient, dosage form, strength, and route of administration under the same conditions of use.
   2. **Bioequivalent** to the RLD, i.e., to show no significant difference in the rate and extent of absorption of the active pharmaceutical ingredient, and, consequently,
   3. **Therapeutically equivalent**, i.e., to be substitutable for the RLD with the expectation that the generic product will have the same safety and efficacy as its reference listed drug for the same intended use.

2. **Definition of pharmaceutically equivalent**
   Pharmaceutically equivalent are medicinal products, which contain the same active ingredient (API), in the same strength (concentration) and dosage form, and, in addition, Order #460, WHO and FDA demand the use the same route of administration. Differences in e.g. in the manufacturing process or excipients may result in e.g. a different dissolution profile and thus pharmaceutical equivalence doesn’t necessarily imply therapeutic equivalence or bioequivalence. In both guidelines the definition is identical.

3. **Pharmaceutical alternatives**
   All 5 compared provisions in Table 4 request the same active ingredient (API). Order #460 and the FDA request the same amount (strength) of API and dosage form, the WHO and the Ukrainian and EU Guidelines on the evaluation of bioequivalence allow different dosage forms. Only WHO and FDA demand the “same route of administration”.

4. **Definition of Bioequivalence**
   Order #460, WHO and FDA have the same provisions, whereas the Ukrainian and EU Guidelines on the Investigation of Bioequivalence request “Pharmaceutically equivalent
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OR Pharmaceutical alternatives” (i.e. same or different of Administration). Directive 2001/83/EC has no definition of bioequivalence.

(5) **Therapeutically equivalent**
Therapeutic equivalence is based on 2 conditions: both products must be (1) pharmaceutically equivalent, and (2) after administration of the same molar dose produce similar effects for both safety and efficacy (shown by a bioequivalence study); therapeutically equivalent drugs are interchangeable.

As per definition by the FDA, two medicines that have the same clinical effect and safety profile are considered as therapeutic equivalent. These two drugs have nearly identical properties and thus can be interchanged. The “Approved Drug Products with Therapeutic Equivalence Evaluations” are published by the FDA in its “Orange Book” [23]; it is considered as a useful tool for choosing the right medicine by doctors.

A therapeutic equivalent medicine must have:
1. the same clinical effect and safety profile
2. be bioequivalent (same rate and extent of absorption of active substance(s)/active metabolite(s)
3. contain the same active ingredient at the same dosage as the original medication
4. utilize the same route of administration
5. be manufactured in accordance with the cGMP rules (to ensure good quality).

It is not necessary that these medicines have the same (1) Appearance (color, shape, size), (2) Packaging, (3) Release mechanisms, (4) Flavor, and/or (5) Preservatives.

Therapeutic equivalency is the basis for the ultimate goal of a generic medicine i.e. to be interchangeable with the reference product [12, 20-27]. No such reference is in the Law of Ukraine on Medicines [29], or Order #426 [11], but in Decree #376 [19] it is ruled that therapeutic equivalence (interchangeability) must be demonstrated according to “WHO recommendations” in the MAA process for a generic medicine, and Order #460 [14] uses the term in the Terms and Definitions of a generic product.

In EU/EEA, generic substitution issues are regulated on a national level, i.e. by the individual Member states.

In the marketing authorization application (MAA) process the Regulatory authorities (RAs) make sure that only those products will be on the market, which are of good quality (confirmed by a GMP-compliant manufacturing), and are efficacious and safe, proved by demonstrating bioequivalence of the originator’s and applicant’s product.

They should be therapeutically equivalent and interchangeable with the reference (comparator) product, as this is absolutely necessary in the daily medical-therapeutic practice to guarantee the proper safe and efficacious treatment of patients [3,12,20-26]. Interchangeability includes not only equivalence of the dosage forms, but also of the indications and instructions for use. However, the latter issues are not within the scope of the MAAA process.

(6) **Interchangeability** [2712,20-27,30,62]
Order #460 demands that the generic is pharmaceutically equivalent and that it is interchangeable with the reference product, proofed by “relevant studies”. Decree #376 requests that the test product is therapeutically equivalent and interchangeable according to the provisions of the WHO [15]. WHO and FDA stipulate that the
products must be therapeutically equivalent and can be interchanged with the comparator in clinical practice. Like therapeutically equivalence, interchangeability issues in EU are regulated by the individual Member states.

(7) Selection and definition of the Reference product
Directive 2001/83/EC and both Guidelines define that the reference product (comparator) must be authorized in EU/EEA with a full dossier (in addition the Ukrainian Guideline requests compliance with the provisions of Order #460). Order #460 and WHO request an innovator product with a full dossier, Decree #376 requires that the reference product is therapeutically equivalent (interchangeable) and selected by following WHO recommendations [15,31]. If a comparator product is not available, it should be selected by following WHO recommendations [15,31] from a “List of International comparator products after public consultation” [32]. Furthermore, it must be interchangeable in clinical practice. According to FDA rules the comparator must be selected from the Reference Listed Drug (RLD) [16,23].

EU Directive 2001/83/EC refers only to the term bioequivalence, there is no mentioning of “pharmaceutical and/or therapeutically equivalence”. Nevertheless, as part of the definition of bioequivalence, the EMA “Guideline on the Investigation of Bioequivalence” [13(a)] gives the following definitions of:

**Pharmaceutical equivalence**

“Medical products are pharmaceutically equivalent if they contain the same amount of the same active substance(s) in the same dosage forms that meet the same or comparable standards (quality), and

**Pharmaceutical alternatives**

Pharmaceutical alternatives are medicinal products with different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active moiety, or which differ in dosage form or strength.

The EMA Guideline On the investigation of bioequivalence in Articles 1.1 and 1.2 defines bioequivalence as:

“Two medicinal products containing the same active substance are considered bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailabilities (rate and extent) after administration in the same molar dose lie within acceptable predefined limits. These limits are set to ensure comparable in vivo performance, i.e. similarity in terms of safety and efficacy”, and in Directive 2001/83/EC, Article 10(2)(b) a **generic medicine** (according to) is defined as:

“A generic medicinal product is a product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance are considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy. Furthermore, the various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form”.

There is no reference, neither to therapeutic equivalence, nor to interchangeability, nor to the requirement of the FDA, the WHO, and Order #460 that the same route of administration must be utilized, only the term bioavailability is used. This may cause some uncertainties with the applicants and needs to be clarified.
Despite that the term therapeutic equivalence is not in the legal text, in the Note for Guidance on Locally acting Locally applied products [50] it is demanded that *therapeutically equivalence* must be demonstrated, “to ensure that the efficacy and safety profile of the test and reference products are sufficiently comparable so that a clinically relevant difference between products can be reliably excluded”.

As already mentioned, in EU aspects concerning “generic substitution” are subject to national regulation(s). Thus, in EU e.g. the Swedish [22] and Irish [26] RA have published on their website a list of therapeutically equivalent and thus interchangeable medicines.

“Product-specific bioequivalence guidance” documents, “summarizing in a standardized format the relevant study design principle for demonstration of bioequivalence” are frequently published by the EMA [33] and FDA [34]. No such guidance documents have yet been published in Ukraine.

However, the SEC has developed Draft amendments to the MOH Order #460 to further harmonize it with Directive 2001/83/EC, and the guideline on the investigation of bioequivalence. Furthermore, product-specific guidance documents (reflecting those published by the EMA and FDA) and recommendations for the proper selecting of reference comparator products in bioequivalence studies are in preparation, as well as a list of recommended reference products [10(b)].
### Definitions of the investigation of bioequivalence in Ukraine and EU plus supportive information from WHO and FDA rules

#### Generic medicinal product

<table>
<thead>
<tr>
<th></th>
<th>Order #460</th>
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<th>FDA</th>
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<td>The various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form</td>
<td>Bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies</td>
<td>Bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies</td>
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#### Pharmaceutically equivalent

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#### Pharmaceutical alternatives

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<th>UA and EU Guideline</th>
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#### Bioequivalence

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<th>FDA</th>
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<td>Same active ingredient (API)</td>
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### Therapeutically equivalent

<table>
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<tr>
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<th>Directive 2001/83/EC</th>
<th>UA/EU Guidelines</th>
<th>WHO</th>
<th>FDA</th>
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</thead>
<tbody>
<tr>
<td>NA; no reference in Order #426, Law on Medicines, but in Decree #376: documentation on the basis of WHO recommendations</td>
<td>NA; but defined in e.g. Guideline [B-24] on locally applied, locally acting products</td>
<td>NA; Regulated by the individual Member states</td>
<td>Pharmaceutically equivalent or alternatives</td>
<td>Pharmacologically equivalent</td>
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<td>Bioequivalent</td>
<td>Bioequivalent</td>
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<td>Same route of administration</td>
<td>Same route of administration</td>
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<td>Manufactured in compliance with cGMP</td>
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### Interchangeability

<table>
<thead>
<tr>
<th>Order #460; Decree #376</th>
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<th>UA/EU Guidelines</th>
<th>WHO</th>
<th>FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Order #460: Pharmaceutically equivalent; Proof that it can be interchanged in clinical practice</td>
<td>NA; In EU/EEA interchangeability is decided by the Member states</td>
<td>NA</td>
<td>Therapeutically equivalent</td>
<td>Therapeutic equivalent products can be interchanged</td>
</tr>
<tr>
<td>Decree #376: Therapeutically equivalent (interchangeable), according to the provisions of the WHO</td>
<td></td>
<td></td>
<td>Product can be interchanged with the comparator in clinical practice</td>
<td>Product can be interchanged with the comparator in clinical practice</td>
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### Reference product (comparator)

<table>
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<tr>
<th>Order #460; Decree #376</th>
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<th>UA and EU Guideline</th>
<th>WHO</th>
<th>FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Order #460: Innovator product with a full dossier</td>
<td>Must be authorized in EU/EEA with a full dossier</td>
<td>EU: Must be authorized in EU/EEA with a full dossier</td>
<td>Innovator product with a full dossier. If comparator product is not available, selection by following WHO recommendations [B-34; B-35] Must be interchangeable in clinical practice</td>
<td>Must be selected from the Reference Listed Drug (RLD)</td>
</tr>
<tr>
<td>Decree #376: should be therapeutically equivalent (interchangeable), and selected by following WHO recommendations</td>
<td>Should be part of a global marketing authorization</td>
<td>UA: must comply with Order #460. Should be part of a global marketing authorization</td>
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</table>

**Table 4** Comparison of important Terms and Definitions in the Ukrainian, EU, WHO, and FDA regulations

NA = not applicable
5.0 Summary and discussion of identified differences, nonconformities and discrepancies; Key points

The critical comparison/reviewing of the relevant, applicable legislative/regulatory provisions in Ukraine and the EU/EEC concerning the marketing authorization application process in general and those concerning bioequivalence, revealed that both systems are almost completely harmonized. However, significant differences exist:

1. within the relevant regulations in Ukraine, when e.g. different definitions for the same issue are given in the Law, Decrees, Orders, and Guidelines,
2. between the provisions in Ukraine and those of the EU/EEA, and
3. between the provisions from (1) and (2) and those from WHO and FDA.

Terms and Definitions must be consistent in all regulatory/legislative documents as they are the commonly agreed basis of understanding for all stakeholders and the fundament of all further considerations, strategies, and planning. Provisions from WHO and FDA were taken into consideration as supportive material, because they often contain more detailed and specific information than the respective national provisions.

5.1 Key differences concerning the Terms and Definitions in Order #460 [14], Directive 2001/83/EC [4], the Ukrainian [10(a,c)] and EU [13(a)] Guidelines on the Investigation of Bioequivalence, and WHO, FDA recommendations/rules

The overview in Chapter 4.0 presents the key differences: these differences, inconsistencies, and nonconformities comprise:

1. **Definition of a generic medicinal product**
   The provisions of Order #460, Directive 2001/83/EC, Ukrainian and EU Guidelines on the evaluation of bioequivalence, WHO and FDA, request “Pharmaceutically equivalent” plus demonstrated bioavailability. However, in addition to this Order #460 requests that the products are interchangeable. The FDA expects that the product is (1) pharmaceutically equivalent, (2) bioequivalent, and, consequently, (3) therapeutically equivalent, i.e. that the generic product will have the same safety and efficacy as its reference drug for the same intended use.
   Directive 2001/83/EC, Article 10(2)(b) defines: “A generic medicinal product is a product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance are considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy. Furthermore, the various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form”.

2. **Definition of Bioequivalence**
   Order #460, WHO and FDA have the same provisions, whereas the Ukrainian and EU Guidelines on the Investigation of bioequivalence request “Pharmaceutically equivalent or Pharmaceutical alternatives” (i.e. same or different way of administration); Directive 2001/83/EC has no definition of bioequivalence. The EU Guideline in Articles 1.1 and 1.2 defines bioequivalence as: “Two medicinal products containing the same active substance are considered bioequivalent if they are pharmaceutically equivalent or
pharmaceutical alternatives and their bioavailabilities (rate and extent) after administration in the same molar dose lie within acceptable predefined limits. These limits are set to ensure comparable in vivo performance, i.e. similarity in terms of safety and efficacy”.

(3) **Definition of pharmaceutically equivalent**
Pharmaceutically equivalent are medicinal products, which contain the same active ingredient(s) (API), in the same strength (concentration) and dosage form, and, in addition, Order #460, WHO and FDA demand the use the same route of administration. The “Guideline on the Investigation of Bioequivalence” defines: “Medicinal products are pharmaceutically equivalent if they contain the same amount of the same active substance(s) in the same dosage forms that meet the same or comparable standards (quality).

(4) **Pharmaceutical alternatives**
All 5 compared provisions request the same active ingredient (API). Order #460 and the FDA request the same amount (strength) of API and dosage form, the WHO and the Ukrainian and EU Guidelines on the Investigation of bioequivalence allow different dosage forms. Only WHO and FDA demand the “same route of administration”. The EU Guideline defines: “Pharmaceutical alternatives are medicinal products with different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active moiety, or which differ in dosage form or strength”.

(5) **Therapeutically equivalent**
Therapeutic equivalence is based on 2 conditions: both products must be (1) pharmaceutically equivalent, and (2) after administration of the same molar dose produce similar effects for both safety and efficacy (shown by a bioequivalence study); therapeutically equivalent drugs are interchangeable.
As per definition by the FDA, two medicines that have the same clinical effect and safety profile are considered as therapeutic equivalent. These two drugs have nearly identical properties and thus can be interchanged. Therapeutic equivalency is the basis for the ultimate goal of a generic medicine i.e. to be interchangeable with the reference product [3,12, 20-28,30]. No such reference is in the Law of Ukraine on Medicines [29], Order #460 [14], or Order #426 [11], but in Decree #376 [19] it is ruled that therapeutic equivalence (interchangeability) must be demonstrated according to “WHO recommendations” in the MAA process for a generic medicine. Again, in EU generic substitution issues are regulated on a national level, i.e. by the individual Member states.

(6) **Interchangeability** [3,12,20-28,30,62]
Order #460 demands that the generic is pharmaceutically equivalent and that it is interchangeable with the reference product, proofed by “relevant studies”. Decree #376 requests that the test product is therapeutically equivalent and interchangeable according to the provisions of the WHO. WHO and FDA stipulate that the products must be therapeutically equivalent and can be interchanged with the comparator in clinical practice. Like therapeutically equivalence, interchangeability issues are ruled in EU/EEA by the individual Member states.
(7) **Selection and definition of the Reference product**

Directive 2001/83/EC and both Ukrainian and EU Guidelines on the investigation of bioequivalence define that the reference product (comparator) must be authorized in EU/EEA with a full dossier (in addition the Ukrainian Guideline requests compliance with the provisions of Order #460). Order #460 and WHO request an innovator product with a full dossier, Decree #376 requires that the reference product is therapeutically equivalent (interchangeable) and selected by following “WHO recommendations” [B-17]. If a comparator product is not available, it should be selected by following WHO recommendations [31] from a “List of International comparator products after public consultation” [32]. Furthermore, it must be interchangeable in clinical practice. According to FDA rules the comparator must be selected from the Reference Listed Drug (RLD) [16,23].

In EU Directive 2001/83/EC there is no reference, neither to therapeutic equivalence, nor to interchangeability, nor to the requirement of the FDA, the WHO, and Order #460 that the same route of administration must be utilized, only the term bioavailability is used. This may cause some uncertainties with the applicants and needs to be clarified. In EU aspects concerning “generic substitution” are subject to national regulation(s) [13(a)]. Thus, in EU e.g. the Swedish and Irish RA have published on their website a list of therapeutically equivalent and interchangeable medicines [22,26].

(8) **Different requirements when bioequivalence studies are necessary**

In Annex 18 of Order #460 [14] a list of medicinal products is presented, which need to demonstrate bioequivalence in the registration process. This list is only partly compatible with the respective provisions in the Ukrainian [10(a)] and EU [13(a)] Guideline for Investigation of Bioequivalence. Terms, like “emergency medicine” are only in Annex 18 of Order #460.

(9) **Different requirements when bioequivalence studies are NOT necessary**

Like in (8) the list in Annex 18 of Order #460 for medicinal products for which no bioequivalence study is required (for registration), the listed products include those eligible for the “Simplified registration procedure” and the provisions laid down in Annex 18 of Order #460. Again, the provisions in the Ukrainian and EU Guideline for Investigation of Bioequivalence are identical, but significantly different from Order #460.

(10) **“Product-specific bioequivalence guidance”** documents, “summarizing in a standardized format the relevant study design principle for demonstration of bioequivalence published by the EMA and FDA [33,34] have not yet been published in Ukraine, but the SEC has prepared such “Guidance for industry” documents [10(b)]; they are expected to be published soon.

### 5.2 Identified differences in the general legislative/regulatory framework, interrelated to the scope of the project

(1) **Simplified procedure** for registration of medicinal products authorized by Drug Regulatory Agencies from selected foreign countries with a Stringent Regulatory Authority (SRA) (WHO, [45]) (U.S.A, Switzerland, Japan, Australia, Canada, EU-centralized procedure only) allows for registration in Ukraine of products which have not undergone scientific assessment in line with the requirements of Directive 2001/83/EC
and thus contradicts EU legislation. It might thus be possible that drugs with a different safety profile, different dosages for the same indication are on the Ukrainian market. Secondly, medicinal products subject to procurement under agreements between Ukraine and international organizations (WHO, UNDP; UNICEF; UK Crown agents). However, the latter provisions are valid only till 31 March 2019.

(2) **Provisions of data protection in the MAA process, data exclusivity, market exclusivity**

**In EU** RAs do not check for possible violations of data exclusivity and/or market exclusivity periods, nor for possible patent infringements during the MAA process. These issues are considered to be the obligation of the applicant, who needs to enforce his legal rights by himself (the RA completely keeps out). Directive 2001/83/EC, Article 10, 1, as amended, stipulates that the time period of data exclusivity is 8 years for a product which is or has been authorized in EU/EEA. A generic shall not be placed on the market until 10 years have been elapsed from the initial authorization (requesting a “full dossier”) of the reference product (market exclusivity) (may be extended to 11 years in defined cases).

**In Ukraine** any use of safety and efficacy data of the reference product in the MAA process for a generic is considered as an “unlawful use of registration information” and thus forbidden for a period of 5 years after registration of the reference product. These data can only be used if the MAH of the reference product gave his permission (Order no. 460 (36)). Violation of this provision is a reason for the SEC to reject the MAA. Furthermore, in the course of an MAA, the applicant needs to provide information on the patent situation (protection) of his product. SEC shall refuse State registration in cases of violation of patents. Both provisions, the unlawful use of registration information and possible patent violations are not covered by EU Community law, in the first line Directive 2001/83/EC.

In both Ukraine and EU data exclusivity rules are in place (8 years in EU, 5 years in Ukraine), but in Ukraine no market exclusivity exists. However, in both Ukraine and EU the so-called Bolar exemption is in force, stipulating that even within the data exclusivity (protection) period, an applicant has the right to develop a medicinal product (but not to put it on the market!). In EU this rule will be expanded in 2019 by the (1) “Manufacturing waiver” and the (2) “Stockpiling waiver”.

In Ukrainian legislation there is no provision to prolong the patent protection period up to five years in order to compensate the manufacturer for the time elapsed between patent application and marketing authorization approval when he couldn’t generate revenues (so-called Supplementary protection certificate, SPC) [46]. Thus, EU-based manufacturers of generic drugs cannot produce (in EU) generic products within the validity period of patents/SPC. They can produce only for export into third countries in case no SPC exists there (“Export waiver”). This waiver, the so-called “Manufacturing waiver”, and the “Stockpiling waiver”, will allow EU-based manufacturers of generics and biosimilars to produce and stockpile in EU (but NOT to place them on the market in EU) medicinal products, which are still under patent/SPC protection. It is expected that both waivers will be implemented in EU in early 2019. This will enable manufacturers to make a Day-1-Launch of their product(s) with a sufficient quantity of products (manufactured in EU).
(3) **Different Terms and Definitions**

**Medicinal product**
The Law of Ukraine on Medicines [29] and the Guideline on the Investigation of Bioequivalence [10(a)] define a medicinal product as an API, “in bulk” products; finished medicinal products (medicinal preparations, drugs, medicaments); homoeopathic agents; agents used to detect and eliminate pathogenic organisms or parasites; cosmetic products and medicinal supplements to food products”. Except for “finished medicinal products” and “homeopathic agents” all other mentioned types of products are not considered as a medicinal product in EU/EEA; they are regulated by separate rules in EU/EEA.

**Active pharmaceutical ingredient; active substance**
The Law of Ukraine on Medicines [29], Order #460 [14], and the Guideline on Investigation of Bioequivalence [10(a)] have similar, but different definitions of an API, focusing on the possible usage of the API, whereas the definition in Directive 2001/83/EC [4] reflects the action(s) of an API.
In Ukraine both in-bulk products and APIs need a marketing authorization, but not in EU/EEA.

(4) **Differences in the respective Ukrainian and EU Guidelines “On the Investigation of Bioequivalence”**

The Ukrainian guideline covers several more points, which are addressed in the EU guideline by separate provisions: it includes (as Appendix IV) the templates for presenting biopharmaceutical and bioanalytical data in Module 2.7, a Supplement 1 “Recommendations for Determining absolute and relative bioavailability” and “Recommendations for superbioavailable products”.
In the “National Supplement” (for reference) the list of editorial changes and addenda with reference to the applicable terms in the EU rules is presented. “Changes have been made to this Guideline prompted by legal requirements and harmonized regulatory documents adopted in Ukraine”. In addition, several changes (modifications) addressing a specific issue in the actual text are inserted directly into the text (with a different font and marked by an N).

The two major differences are that (1) not only a reference product marketed in EU can be chosen, but also a reference product according to the requirements of Order #460, and (2) that bioequivalence studies with a non-EU reference product might be included into the MAA dossier in Ukraine.
Generics and biosimilars have “the same roots”, as they are copies of the originator’s product, but due to their completely different way of production (chemical synthesis vs. use of genetically modified microorganisms) different regulatory/legislative rules must be applied. Thus, unlike generics, biosimilar products cannot be bioequivalent to the originator’s product and the principle of bioequivalence applies only in the sense of therapeutic equivalence for biosimilars.

The EMA has published a series of scientific guidelines for applicants seeking marketing authorization in the EU: General outlines are in “Overarching biosimilar guidelines” [37], which are complemented by product-specific guidelines (covering e.g. proteins, heparins, insulins/insulin analogues, etc.), and other related ones.

The legal basis is in Directive 2001/83/EC (Article 10(4), Annex I, Section 4, Part II): the similar nature of the two products must be demonstrated by comparative studies on the quality, safety, and efficacy. These comparisons are based on ICH Guideline Q5A-E Quality of Biotechnological products [74]. In contrast to generics, the same route of administration and dosage must be used. In defined situations it is possible to use a non-EEA authorized reference product. Like for generics, substitution (interchangeability) issues are within the remit of the EU member states. The increasing importance of biosimilars, which are often the only chance to treat specific diseases (cancer, genetic disorders) is highlighted by the recently (July 2018) FDA initiative “Biosimilars Action plan: Balancing Innovation and Competition” [75].

In Ukraine the entire regulatory/legislative provisions have been harmonized with those of the EU. In Order #460 (1.3 (3) the requirements for the MAA (CTD) documentation are specified and it stipulates that “the basic principles to be followed are set out in the EMA Guidelines or the MOH guidelines developed for specific type of biotech products”. The applicable regulatory provisions, which reflect the complementary EMA guidelines, can be retrieved from: http://www.dec.gov.ua/indexphp/ua/nastanovit}
Provisions for the evaluation of bioequivalence are laid down in the respective guidelines in Ukraine and EU. The practical approach includes the conduct of a phase I clinical trial, ruled by the respective Directive 2001/20/EC (“Clinical Trial Directive”) in EU [36], which has been replaced by the Clinical Trial Regulation (EU) 536/2014 [35], and Order #690, as amended [54], in Ukraine. Bioequivalence claims should be accepted by the RAs only if the underpinning clinical study was conducted under GCP conditions: Both regulations request that all clinical trials must be performed by following the GCP and good laboratory practice GLP) rules [65,10(a),13(a)]. Despite that the ICH-guidelines have the legal status of a “straightforward recommendation” (guidelines, “soft law”), these guidelines achieved legally binding power in EU when included into Directives 2005/28/EC [65], 2001/20/EC, and Regulation (EU) 536/2014, as well as into the national legal systems in the Member states.

1.0 Provisions for conducting clinical trials in the EU

The area of clinical trials is regulated by the so-called “Clinical Trial Directive” 2001/20/EC. This Directive represents the legal basis for the implementation of GCP within the EU Member states. Directive 2005/28 [65], amending Directive 2001/20/EC [36], stipulates that the ICH-GCP and GLP rules should “be taken into account”, the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects in its form of 1996 be followed, and it defines the requirements for authorization of the manufacturing or importation of Investigational Medicinal Products (IMP).


A number of guidelines has been issued in the context of the new regulation, detailing issues like:

1. Detailed Commission guidelines on good manufacturing practice for investigational medicinal products for human use, pursuant to the second subparagraph of Article 63(1) of Regulation (EU) no. 536/2014
3. Guideline on the responsibilities of the sponsor with regard to handling and shipping of investigational medicinal products for human use in accordance with Good Clinical Practice and Good Manufacturing Practice. Draft 26 April 2018 EMA/202679/2018. These guidelines need to be adopted within the harmonization process. Directives need to be transferred into national law and thus there are slight differences in the respective legal texts in each EU member state: nevertheless, said Directive (and its amendments) is the basis of the evaluations reported here.

**Legislative Basis, Core Documents**

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<tr>
<th>#</th>
<th>Document</th>
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<td>1</td>
<td>EUDRALEX The Rules Governing Medicinal Products in the EU, Vol. 10, Clinical trials, V30, January 2015</td>
<td>Compilation of legislative and guidance documents in the field of clinical trials</td>
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Table 5 The Rules governing medicinal products in the European Union

2.0 Provisions for conducting clinical trials in Ukraine

In Ukraine the planning, conduct, and reporting of clinical trials is governed by Order # 690 [54], as amended by Orders:

- #23 as of 12.07.2012
- #304 as of 06.05.2014
- #966 as of 18.12.2014
- #639 as of 01.10.2015.

This Order is harmonized with Directive 2001/20/EC [36], however, interview partners in formed that defined parts of the ICH-GCP rules are harmonized only partly (e.g. concerning adverse events). The results from clinical trials are (internationally) recognized only if the trial was performed under strict GCP conditions [55]. Five inspectors of the SEC perform GCP inspections in Ukraine, and participated.