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THE BIOEQUIVALENCE OF GENERIC MEDICINES LEADING TO REFERRALS IN THE EU: THE IMPACT OF GUIDANCE

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Tiivistelmä/Referat – Abstract

Tutkimuksessa perehdyttiin lääkkeiden myyntilupamenettelyissä tapahtuneisiin ristiriitatilanteisiin, referraaleihin eli niin sanottuihin lähetemenettelyihin EU:ssa. Tarkemmin keskityttiin geneeristen lääkeaineiden bioekvivalenssitutkimuksia eli biologista samanarvoisuutta koskeviin referraaleihin. Biologinen samanarvoisuus alkuperäisvalmisteeseen verrattuna on geneerisillä lääkevalmisteilla edellytys myyntiluvalle. Tutkimuksen tarkoituksena oli selvittää, miten vuonna 2010 päivitetty biologisen samanarvoisuuden viimeisin ohjeistus on vaikuttanut referraalien määrään tai syihin.

Aineistona käytetiin Euroopan lääkeviraston, EMA:n, julkaisemia julkisia dokumentteja, joista löytyy tietoa referraaleista, kuten julkiset arviointilausunnot, muut julkiset dokumentit ja tilastot. Aineiston perusteella luotiin lista kaikista referraaleista, joissa pääsyy koski biologista samanarvoisuutta. Tapauksia, joissa referraaliin johti bioekvivalenssiin liittyvä syy, oli yhteensä kolmekymmentäkahdeksan (38). Valmistelistaa tutkittiin tarkemmin jakamalla tapaukset referraalin ajankohdan ja tarkemman referraalin syyn perusteella ja vertailtiin syitä päivitetyn ohjeiston sisältöön.

Suurin yksittäinen tutkimuksessa esille noussut referraalin syy koskien biologisen samanarvoisuuden tutkimuksia, oli ruokailun vaikutuksen huomioiminen. Ruokailun vaikutuksesta on julkaistu kattavampi ohjeistus vuoden 2010 Bioequivalence Guidelinessa. Ruokailulla on merkitystä tiettyjen lääkeaineiden biologiseen hyötyosuuteen. Biologisen hyötyosuuden tutkimisessa paastotutkimukset ovat kaikista herkimpiä. Tutkimuksessa valitaan ruokailu tai paasto alkuperäisvalmisteen valmisteyhteenvedon ohjeistuksen perusteella.

Referraalien suurentunut määrä vuosina 2005 – 2010 oli yhteydessä samanaikaisen geneeristen myyntilupien määrän voimakkaalla kasvulla. Muun muassa geneerisen substituution vaikutuksesta geneeristen myyntilupahakemusten määrä kasvoi moninkertaisesti. Referraalien määrä ei kuitenkaan noussut suhteessa yhtä paljon. Siitä voi päätellä, että uusi biologisen samanarvoisuuden ohjeisto on vähentänyt biologista samanarvoisuutta koskevien referraalien osuutta.

Tutkimusta suunniteltaessa oli tarkoitus selvittää myös referraaleja, jotka koskevat GCP:tä eli Good Clinical Practise -tarkastuksia eli tarkastuksia, joita viranomaiset tekevät kliinisiä tutkimuksia suorittavien tutkimusyksiköihin. Näitä tapauksia oli kuitenkin vain seitsemän, eikä niistä voinut tehdä johtopäätöksiä pienen aineiston takia. Pääosin näissä referraaleissa ei löytynyt myyntiluvan estäviä ongelmia tutkimuspaikkojen toiminnassa.

Avainsanat – Nyckelord – Keywords
bioekvivalenssi, biologinen samanarvoisuus, referraali, geneerinen, Guideline on the Investigation of Bioequivalence

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Tiivistelmä/Referat – Abstract

Subject of this study was referrals in marketing authorisation procedures of medicines, in particular related with bioequivalence studies. The focus was in bioequivalence studies of the generic medicines. Referrals are processes in which controversial questions related with marketing authorisations are solved. Bioequivalence studies are required from the generic medicinal products against the original product. Purpose of the study was to find out if the latest renewed bioequivalence guidance from the year 2010 has had an influence in the number of referrals or the reasons for referral.

Research material for the case study has been collected mainly from the European Medicines Agency's public files where information of the referrals can be found via public assessment reports and other public documents and statistics. A list of all the referrals in which the main reason for referral was related with the bioequivalence studies, altogether thirty eight (38) cases, was created and the product list was further investigated against the updated bioequivalence guidance and categorised according to the year of the referral as well as the detailed description of the reason for referral.

As a conclusion of the study, one major group of referrals related with bioequivalence study, was noted: the fed and fasting conditions during bioequivalence studies. The bioequivalence guidance from the year 2010 included improved guidance regarding the fed and fasting conditions. Some medicinal products have a different bioavailability depending weather they have been taken with or without meal. Usually fasting conditions is the most sensitive condition to study bioequivalence. Recommendations of the SPC (Summary of Product Characteristics) of the original medicine are followed when choosing fed or fasting conditions for the study.

There was found a connection with the rise of the referral cases was and the fast increase of the generic marketing authorisation applications from year 2005 to year 2010. One reason for the number of generics was the generic substitution. However, it was noted that number of referrals did not increased the same amount and share of the bioequivalence referrals was smaller after introducing the new bioequivalence guideline.

In this study, also referrals regarding Good Clinical Practise (GCP) were briefly reviewed since some bioequivalence related referrals dealt with deficiencies in the Contract Research Organisations (CRO's). Authorities are responsible for inspecting these facilities in order to guarantee the reliability of the clinical studies as well as safety and efficacy of the studies. However, there were only seven referrals regarding CRO's and therefore it was not possible to make deep conclusions based on these cases due to the narrow material. However, in most of these referral cases the outcome was that there were not such neglects which would have been criteria for suspension of the marketing authorisations.

Avainsanat – Nyckelord – Keywords
bioequivalence, referral, generic, Guideline on the Investigation of Bioequivalence

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Concepts and Terms

Bioavailability	Biological availability, defined by FDA as “the rate and extend to which the active ingredient is absorbed from a drug product and becomes available at the site of action” (Hauschke 2007).
Bioequivalence	The rate and extent of absorption of the [generic] drug do not show a significant difference from the rate and extent of absorption of the [reference] drug when administered at the same dose of the therapeutic ingredient (EMA 2010). Pharmaceutical products produce similar therapeutic effect and their concentration vs. time profiles are similar (Hauschke 2007).
Therapeutic equivalence	Medicinal product contains the same active substance or therapeutic moiety and clinically has the same efficacy and safety as the product whose efficacy and safety has been established. There may be differences in absorption rate if not therapeutically significant (Hauschke 2007).
Bioequivalence study	“To demonstrate that different formulations or regiments of drug product are similar to each other in terms of their therapeutic benefit (efficacy) and non-therapeutic side-effects (safety)” (Patterson 2006).
Biowaiver	Exemption from performing bioavailability studies on certain basis

	"BCS-based biowaiver is restricted to highly soluble drug substances with known human absorption and considered not to have a narrow therapeutic index" (EMA 2010).
BCS	Biopharmaceutics Classification System categorizes drug substances into four classes based on their solubility and permeability (EMA 2018).
CRO	Contract Research Organisation
EPAR	European Public Assessment Reportis "a set of documents describing the evaluation of a medicine authorised via the centralised procedure and including the product information, published on the European Medicines Agency website" (EMA 2020)
Generic medicine	Medicine developed to be the similar than the originally authorised medicine. Efficacy and safety relies on the studies of the originator. Can be marketed only after originator's exclusivity period has expired (EMA 2019c). Same qualitative and quantitative composition in active substance and same pharmaceutical form as the reference medicinal product, bioequivalence with the reference medicinal product demonstrated by bioavailability studies, applied via article 10(1) of Directive 2001/83/EC (EC 2001).

Hybrid medicine	Similar than generic application except in certain circumstances also pre-clinical and clinical studies are required to support the application - definition of a generic medicinal product is not met - bioavailability studies cannot be used to demonstrate bioequivalence - differences in the active substance, indications, strength, pharmaceutical form or route of administration compared to the reference medicinal product Applied via article Article 10(3) of Directive 2001/83/EC (EC 2019a, EMA 2019c)
Marketing authorisation	A medicinal product has to apply a marketing authorisation before it can be marketed. (Fimea 2019b). Authorisation is granted by a competent authority.
Non-compliance	Failure to satisfy the prescribed requirements within the Good Clinical Practice (GCP) (EC 2006) GxP compliance (Good Practise in pharmaceutical development in general) is required in all areas of developing and manufacturing medicines; in addition to GCP there are requirements for Good Laboratory Practise (GLB) and Good Manufacturing Practise (GMP) as well as Good Distribution Practise (GDP). Authorities have tools to share information regarding compliance e.g. via

	EudraGMDP database which includes information and certificates regarding the manufacturing. GxP covers all steps in manufacturing.
Reference product / originator	“A medicinal product which has been granted a marketing authorisation by a Member State or by the Commission on the basis of a complete dossier, i.e. with the submission of quality, pre-clinical and clinical data in accordance with Articles 8(3), 10a, 10b or 10c of Directive 2001/83/EC and to which the application for marketing authorisation for a generic/hybrid medicinal product refers, by demonstration of bioequivalence, usually through the submission of the appropriate bioavailability studies.” “the reference medicinal product means a medicinal product authorised under Article 6, in accordance with the provisions of Article 8. Article 6 lays down the principle that no medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued.” (EC 2019a, EMA applications 2019c)
Referral	“A procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines. In a referral, the European Medicines Agency (EMA) is requested to conduct a scientific assessment of a particular medicine or class of

	medicines on behalf of the European Union (EU)" (EMA 2019e)
• Article 29(4) referrals	"This type of referral is triggered when there is a disagreement between Member States regarding a marketing authorisation application being evaluated in a mutual-recognition or decentralised procedure, on the grounds of a potential serious risk to public health." (EMA 2019f) If Member States cannot agree on the recognition of an authorisation already granted in a mutual recognition procedure or a final assessment and a product in a decentralised procedure due to a potential serious risk to public health, the objections must be referred to the Coordination Group (CMDh). In case if the Member States cannot reach an agreement, the matter is referred to the CHMP (EC 2019a)
• PSRPH	Potential serious risk to public health
• Article 31 referrals	"This type of referral is triggered when the interest of the Union is involved, following concerns relating to the quality, safety or efficacy of a medicine or a class of medicines." (EMA 2019f)

1 INTRODUCTION

This study is handling marketing authorisations for medicines in specific situations where there are conflicts during the marketing authorisation procedure. The focus is on cases where studies related to bioequivalence have been questioned. Proof of bioequivalence is required for generic products in order to proof their similarity towards the original medicine. Study focuses only on human generic medicines within the area of European Union (EU). Marketing authorisations within the European frame include also the European Economic Area (EEA), Norway, Iceland and Liechtenstein with the 28 Member States of the European Union. These countries have adopted the so-called Union acquis on medicinal products (EC 2019a).

According to the legislation (EC 2001), generic medicine "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 law, which allows medical substitution, came into to effect in April 2003 (Finlex 2003). Generic medicines and the generic substitution caused a fall in prices of medicines and therefore the price became an important competitive advantage. The principles regarding the generic substitution can be different (Verbeeck & Musuamba 2012). Generic substitution means that the patient can have an affordable generic version of his medicine after the data exclusivity of the original medicine "the originator" has expired (EMA 2011).

The marketing authorisation procedure of the generics differs from the procedure of the original medicines. Original medicines usually gain their marketing authorisation via centralised procedure, which is a procedure where a marketing authorisation is applied as a single marketing authorisation to whole EU and in addition to countries in the EEA (EMA 2019a). For new active substances the medicinal product's safety and efficacy is reviewed, whereas in generic marketing authorisations the main focus is in similarity compared with the original medicine.

The marketing authorisation of generic medicines is granted via the Mutual Recognition Procedure (MRP) or the Decentralised Procedure (DCP) where the equivalence with the original marketing authorisation has to be proven. Marketing authorisation documentation, so-called dossier, is not as comprehensive regarding clinical sections, but includes documentation of the bioequivalence studies. In addition to European procedures, the national procedure still exists, but most of the marketing authorisations are granted via EU procedures and therefore the marketing authorisations in the EU are quite streamlined without so many purely national requirements.

Generic substitution has had an impact on the number of marketing authorisation applications since it was followed by a multiplication of generic applications in the EU countries. In Finland generic substitution started in 2003. “Generic substitution means the replacement by pharmacy personnel of the medicinal product prescribed by a doctor or a dentist with the cheapest or nearly cheapest generic medicine suitable for substitution” (Fimea 2019a).

Generic medicines have lower prices and each EU country has its own principles for handling generic substitution since it is a national matter. Since more affordable medicines can bring savings in health care costs, governments are supporting generics by reimbursement of medicines. In Finland there is a reference price system which “applies to reimbursable medicinal products that are included in the sphere of generic substitution” (Hila 2015). “Reference price groups are based on the Finnish Medicines Agency's interchangeable drug list and on the pharmaceutical companies' price notifications” (Hila 2015).

In case of disagreement between the EU Member states, the marketing authorisations will be handled in EU working groups and if consensus cannot be achieved, the final decision is made by the European Commission. The uncertainty related to bioequivalence is a major reason for rejection or suspension of the marketing authorisation. As the bioequivalence guideline was renewed in 2010, it raised the question whether it has had an impact to the way how bioequivalence studies have been conducted.

The main purpose of the study is to find out how the new Bioequivalence Guideline has influenced the number of referrals of which reason for referral is related with the bioequivalence. In addition, it was studied if some particular type of products that had more tendency to trigger a referral. Some aspects like the effect of fed and fasting conditions and the pharmaceutical form were studied further. The referrals covered also cases related with the GCP (Good Clinical Practise inspections). The purpose was to find out what kind of defiencies in bioequivalence studies by the COR's (Contract Research Organisations) lead to referral. The renewed Bioequivalence Guideline was compared with the previous guidance and the purpose was to find out in what areas it had improved and did those improvements have an impact.

2 LITERATURE REVIEW

2.1 History and current status

In Europe there has been guidelines regarding bioequivalence already in 1991. The Commission of the European Communities tried to harmonise the marketing approvals of generic medicines in within the former European Community (EC) and created European Note for Guidance related to bioavailability and bioequivalence assessment (EMA 2000). In the history, before 1991, the registration documentation was not as comprehensive as it is nowadays; documentation was based mainly on the scientific literature and the first European guidelines on pharmacokinetic studies and the marketing authorisation were assessed nationally in each European country. In this study, the focus is in guidance related with bioequivalence studies.

In 2001 EMA's Committee of Proprietary Medicinal Products (CPMP) published the first Note for Guidance on the Investigation of Bioavailability and Bioequivalence which came into effect on January 2002. The first guidelines covered only the immediate release oral medicinal products with systemic action and so were much more concise compered to modern guidelines (Verbeeck & Musuamba 2012). The new Bioequivalence Guideline came into effect 1st of August 2010. The purpose was to give more detailed information since the first guideline had proven to be quite ambiguous.

Generic medicines may gain marketing authorisation for drug substances after the original products, so called originator's, data exclusivity period has expired (EMA 2019b). Data exclusivity period is eight years (and before year 2005, six or ten years) (EC 2004, EMA 2019b). During the data exclusivity period of the originator, generic, hybrid or biosimilars cannot obtain a marketing authorisation relying on data of the originator.

Even though the guidance is quite streamlined in the EU countries, the challenge has been the interpretation of the guidelines as well as several referrals regarding the bioequivalence studies. Problematic areas are some Biopharmaceutics Classification System (BCS) based biowaivers, for instance the use of metabolite instead of parent drug plasma concentrations and bioequivalence assessment of highly variable drugs (Verbeeck & Musuamba, 2012). According to Bioequivalence guideline highly variable

drugs are defined as “those whose intra-subject variability for a parameter is larger than 30%” (EMA 2010).

This study has focus only in the EU guidelines. Globally there are differences between major health authorities (Verbeeck & Musuamba, 2012). Other major authorities in addition to EMA are FDA (USA), Canada, Asia and Rest of the World, which have their own regulations.

2.2 Bioequivalence studies

Bioequivalence studies are required in cases where there is a possibility that bioavailability is different, and the therapeutic effect is not similar between two products (Hauschke 2007). When studying the bioequivalence of a generic product against the originator product, the reference product, the study is usually carried out with a two-period, two-sequence crossover design. Study design is described in general level since this review concentrates more on the regulatory referral procedures.

Generic products has to be proven similar with the originator in clinical studies, unless a biowaiver is acceptable. According to year 2010 bioequivalence guideline, most important is to “demonstrate equivalence in biopharmaceutics quality between the generic medicinal product and the reference medicinal product in order to allow bridging of preclinical tests and of clinical trials associated with the reference medicinal product.” Only exemptions are waivers of bioequivalence studies (via in vitro dissolution tests or clinical studies (EMA 2010).

Demonstrating the bioequivalence applies the changes in approved marketing authorisation dossier as well. Bioequivalence guideline includes advice regarding variation applications. In case of changes in formulation or the manufacturing method (if it affects the bioavailability), a bioequivalence study is required, if not justified in other ways (EMA 2010).

In the new guideline it is reminded that after changes in product that might affect the bioavailability, new studies have to be made (García-Arieta 2012). Such cases could be for example formulation changes or a change in the manufacturing method.

Bioequivalence studies are usually completed with healthy volunteers, both men and women (EMA 2019b, Patterson 2006). Subjects will be given test and reference formulations. Between these doses there must be a so called wash out period in order to guarantee that there is no or very little amount of drug in the subject's body.

The AUC and Cmax are the most important of these measures which help to achieve the efficacy and safety of the drug (Patterson 2006). Sample size in is usually n ≤ 30 subjects and 2 x 2 cross-over trial, described in the Table 1, is typical design to bioequivalence studies. The pharmacokinetic characteristics have been explained in the Table 2.

Table 1. 2 x 2 cross-over study according to Patterson (2006)

Sequence Group		**Period**		**No. of Subjects**
	1	Washout	2	
1 (Reference formulation - Test formulation)	**R**		**T**	n / 2
2 (Test formulation – Reference formulation)	**T**		**R**	n / 2

Table 2 Main pharmacokinetic measures

AUC	Area under the curve of the drug plasma concentration from administration to last observed concentration versus time. (Hauschke 2007) It is a characteristic of the of extent of the drug absorption.
Cmax	Maximum plasma concentration of the drug (Hauschke 2007)
Tmax	Time from administration to maximum plasma concentration peak (Hauschke 2007) (Hauschke 2007)

2.3 Fasting or Fed Conditions in Bioequivalence Studies

In the referrals of this study, the fed and fasting conditions were the most common defined subject of the referrals. Fed and fasting conditions have become more important part of the bioequivalence studies after generic substitution - especially important is evaluating the effect of food in case of modified release formulations (Hauschke 2007).

Taking a medicine with a meal may affect to the absorption of the active ingredient (Patterson 2006). Fed and fasting conditions may change the drug absorption in various ways. In bioequivalence studies, the effect of meal is taken into consideration when needed. There are several factors that may have an influence on absorption of the medicine as can be seen in the Figure 1.

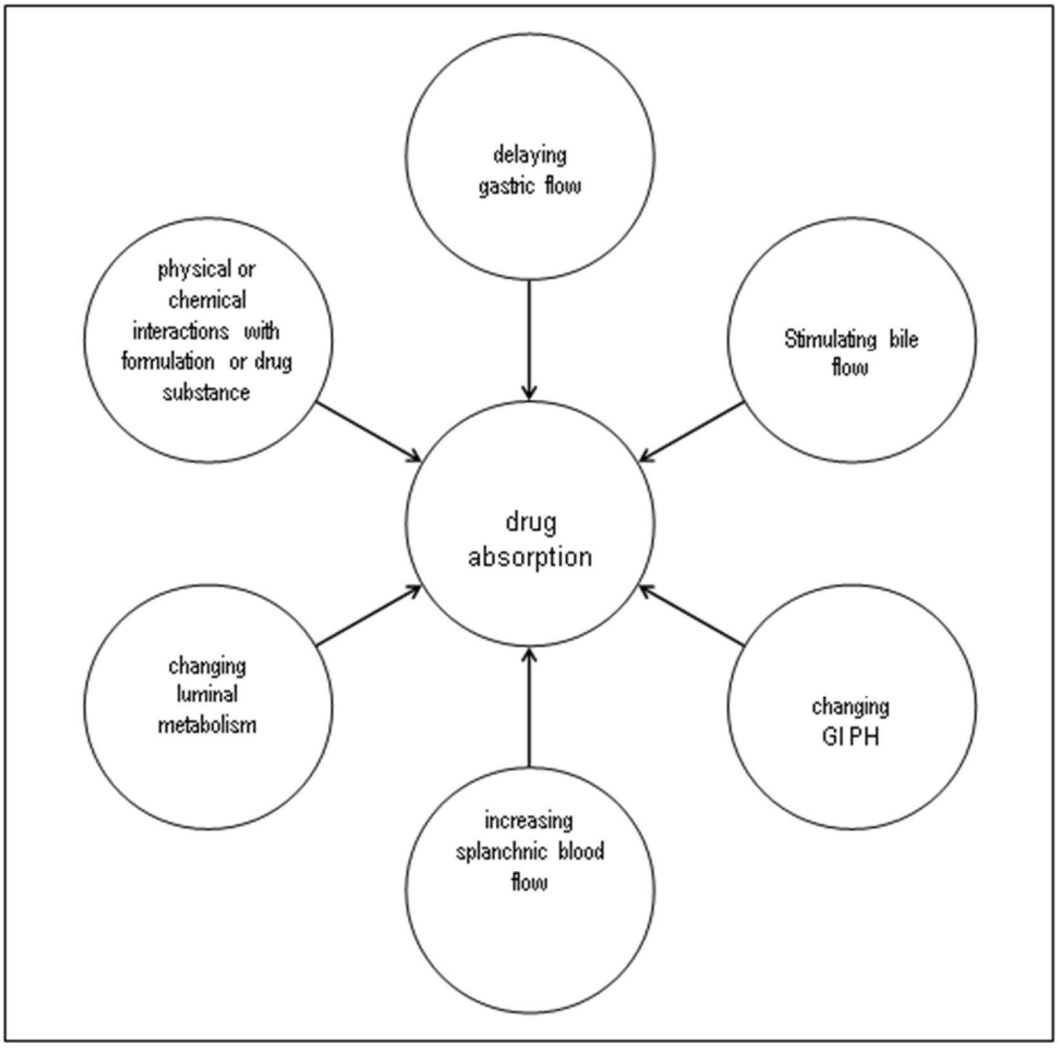

Figure 1 The effect of fasting or fed conditions (Patterson, 2006)

An open-label, randomised, 2 x 2 cross-over trial with healthy volunteers is a typical study setting for finding out the effect of food (Patterson 2006). The food effect should be taken into consideration early as in the pharmaceutical development phase (Hauschke 2007). According to Wonnemann et al. (2006) the pH dependency is one of the most important reasons for the food interactions especially with some modified release products (Hauschke 2007). In this study the food effect is investigated in more depth since it came out in the study as one major factor triggering the referral.

2.4 Guidelines and instructions

Medicinal industry is guided by several laws and guidance documents at different levels. “Guideline on the Investigation of Bioequivalence” defines the scope for bioequivalence studies (EMA 2010). The former guidance was “Note for guidance on the investigation of bioavailability and bioequivalence" which came to act in January 2002 (and replaced the former guideline from December 1991 (EMA 2010). Hierarchy is described in the Figure 2 in basic levels so that the strongest guidance are the directives, which have an influence on lower levels.

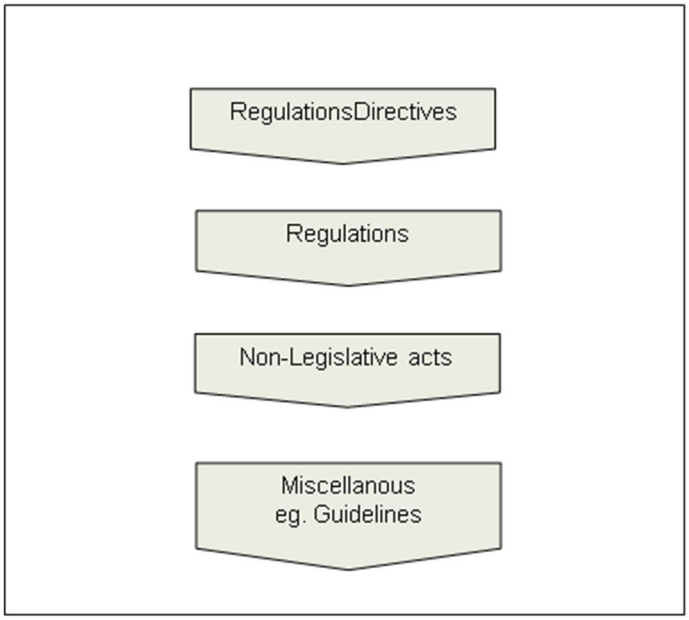

Figure 2. Hierarchy of the legislation and guidance in EU (ec.europa.eu/health, Eudralex vol 1)

Bioequivalence guideline is a guidance published by European Medicines Agency. It applies to Marketing Authorisation submitted in accordance with the Directive 2001/83/EC, under Art. 8(3) (full applications), Art 10b (fixed combination), Art. 10 (1) (generic applications), Art 10(3) (hybrid applications) and line extension and variations in accordance with Commission Regulations No 1084/2003 and 1085/2003 (EMA 2010). Guidance to carry bioequivalence studies should is based on the Directive 2001/20/EC of the European parliament and of the European Council (EMA 2010).

The Guideline on the Investigation of Bioequivalence should be read in connection with Annex I of Directive 2001/83/EC and several other relating guidelines such as: Guideline for Good Clinical Practice, Modified Release Oral and Transdermal Dosage Forms: Sections I and II, and guidelines for other specific pharmaceutical forms as fixed combinations, inhaled products and locally applied and acting products (EMA 2010). Those which were related to this study have been presented in this thesis.

Many areas of bioequivalence studies have been covered in more detailed manner in the renewed guidance. In the new guideline on the Investigation of Bioequivalence (EMA 2010) especially, specific cases are covered better than in the old. In this study the focus is in the areas which were found in the referral cases.

Also, a product specific guidance has been planned. Concept paper on the development of product-specific guidance on demonstration of bioequivalence by Pharmacokinetics Working Party (PKWP) has been on consultation and separate guidelines according to active substance already exists (EMA 2013).

Referrals can be started in case of potential serious risk to public health. What is a potential serious risk has been defined in the Guideline on the definition of a potential serious risk to public health (EC 2006b) as “a situation in which exceptional cases the concerned Member State can refuse to recognise a marketing authorisation in a mutual recognition procedure, or a draft assessment report, a draft summary of products characteristics, and a draft of the labelling and package leaflet from the reference Member State in a decentralised procedure“. Raising major objections on a potential serious risk to public health comment means that in “exceptional cases the concerned Member State can refuse to recognise a marketing authorisation in a mutual recognition procedure, or a draft assessment report, a draft summary of products characteristics, and a draft of the labelling and package leaflet from the reference Member State in a decentralised procedure”.

The term ‘risk related to the use of the medicinal product’ is defined in point 28 of Article 1, first indent of Directive 2001/83/EC as ”‘any risk relating to the quality, safety or efficacy of the medicinal product as regards to patients' health or public health” (or any risk of undesirable effects on the environment). The term ‘risk-benefit balance’ is defined

in point 28a of Article 1of that Directive as “an evaluation of the positive therapeutic effects of the medicinal product in relation to the risks as defined in point 28, first indent”.

A potential serious risk to public health (PSRPH) is defined as a situation where there is a significant probability that a serious hazard resulting from a human medicinal product in the context of its proposed use will affect public health.” (EC 2006b). PSRP, or so-called major objection, triggers referral procedures, which will be paid attention to later in this study.

2.5 Excipients

In the new guideline it is noted that “excipients are known not to affect bioavailability” (EMA 2010). In the new guideline a quantitative proportionality is required between the amounts of the excipients (Morais 2010). Guideline also clarifies that different salts or derivatives of a medicinal product are not suitable.

The guideline stresses the importance of excipients in oral solutions (García-Arieta 2012). Locally acting generic medicines may include different excipients than the original medicine, but differences in the composition should be justified (EMA 2010). The new guideline states that a waiver does not apply for intravenous aqueous solutions, if there are differences in excipients that interact with the drug. In the renewed guidance it is reminded about the significance of different viscosity when different, but comparable, excipients have been used. The new guideline detailed guidance for using excipients since excipients may affect bioavailability.

2.6 Pharmaceutical form

The year 2010 bioequivalence guideline defines criteria for proving the bioequivalence of different pharmaceutical forms in annexes and in separate more specific guidelines (EMA 2010). Guideline mentions the pharmaceutical forms, which may be applicable to a biowaiver for instance eye drops, nasal sprays and cutaneous solutions. Specific guidelines give instructions to the bioequivalence study or waiver according to the pharmaceutical form, for instance for products for local use (EMA 2009, EMA 1995).

Regarding modified release oral and transdermal dosage forms, bioequivalence studies are required in accordance with several guidelines. There is the Guideline on Modified Release Oral and Transdermal Dosage Forms Section II (EMA 2014) .The second is the Note for guidance on the clinical requirements for locally applied, locally acting products containing known constituents (EMA 1995). In addition there is the Guideline on the Requirements for Clinical Documentation for Orally Inhaled Products (OIP) (Including the Requirements for Demonstration of Therapeutic Equivalence between two Inhaled Products for Use in the Treatment of Asthma and Chronic Obstructive Pulmonary Disease (COPD) in Adults and for Use in the Treatment of Asthma in Children and Adolescents) (EMA 2009).

2.7 Modified release (Controlled Release, CR) dosage forms

The category controlled or modified release product includes many different pharmaceutical forms, such as mentioned in the Note for Guidance on Modified Release Oral and Transdermal Dosage Forms (2004) delayed-release, prolonged-release, multiphasic modified release and so on. In EMA's guidance the terms used for different modified release products can be found from the European Pharmacopeia (Ph. Eur). In Nordic countries terms depot and entero have been used commonly (Juslin 1998) but the term modified release includes different modified release formulations and is used in EMA's guidance.

Modified release product can be divided into two main groups; long-affecting products and locally-acting products (Juslin 1998). Benefits of the modified release form are for instance steady plasma concentration and fewer side effects compared to the conventional oral pharmaceutical form. To certain modified release oral forms, the amount of food in the moment of taking the medicine may have great impact. In this study, several referral cases were found where fed and fasting conditions of modified release was the main reason of referral. These are presented later in Tables 7 and 8 .

There are many reasons why investigating the modified release product is challenging. (Aulton 2000). In sustained release products, maintenance dose has to be released at wanted rate and plasma concentration must stay at therapeutic range for a long time and

designing such product is difficult. Compared to conventional medicines, sustained release products include a chemical or physical barrier, which should function similarly with the generic compared with the originator. Many factors may have an influence on the release and absorption of sustained release products: gastro-intestinal, pH, enzyme activities, gastric and intestinal transit rates as well as food. Products may be complex and include more than one modified release layer.

In bioequivalence studies of a sustained release product, the food effect should be the same given immediately after high fat meal in single dose study where same dose is given to subjects in the study (Hauschke 2007). The high-fat and high-caloric meal is described in EMA's guideline (EMA 2010). Delayed release products for instance entero-coated, bioequivalence studies are necessary because of the food effect on the absorption.

There is a separate guideline for investigating modified release oral and transdermal dosage forms: "Note for Guidance on Modified Release Oral and Transdermal Dosage Forms Section II (Pharmacokinetic and Clinical Evaluation)" by CHMP coming to effect first time already in January 2000. The latest version is from June 2015. In the guideline advice can be found regarding "oral formulations, from which the active substance is released slower or delayed than immediate release dosage forms and with transdermal dosage forms" (EMA 1999). In this guidance, requirements for modified and delayed release products have been recommended both in fed and fasting conditions so the recommendations have already been in force long before the year 2010 bioequivalence guidance. However, in the more recent bioequivalence guideline, special recommendations have been written in much more detail. In the year 2000 guidance, in the section "Applications for Modified Release Forms Essentially Similar to a Marketed Modified Release Form" advice for generic modified release products is presented. The new guidance presents some dosage forms as orodispersible tablets micelle forming formulations and modified release suspensions, complexes and matrix forms as their own examples. The affect of excipients has been added in several sections as well. The renewed guidance also included recommendations on BCS-based biowaivers.

"The bioequivalence approach considering usual acceptance limits (80.00 – 125.00 percent) is applicable for generic MR products" as well (EMA, 2014). In the year 2010

Bioequivalence Guideline there are recommendations on highly variable drug products, which will apply if the acceptance standard does not fall inside the usual acceptance limits (EMA 1999, EMA 2010).

In bioequivalence studies of modified release products, recommendation is that delayed release formulations can be studied as immediate release formulations but taking into consideration the delayed release characteristics. With entero-coated formulations after meal studies should be included (EMA 1999). The orally administered products should be studied by comparing two formulations which have the same pharmaceutical form. Single and multiple dose studies are suitable for prolonged release products and studied product should have at least the same prolonged release properties as the reference product. How to study the effect of food regarding the generic modified release products is presented in the Figure 3.

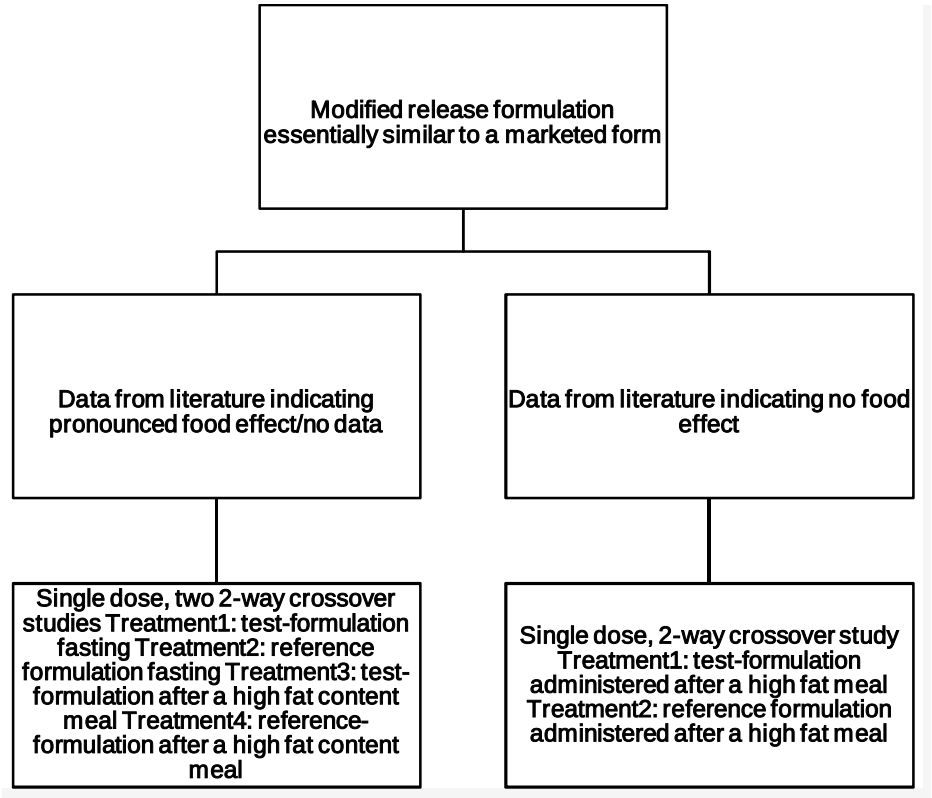

Figure 3 Studying the effect of food (according to EMA, Modified Release, 1999)

The reference product choice is recommended to be the “The marketed immediate release product of the same active substance” and as the same salt form (EMA 2004).

In the guidance it is also noted that formulation of the modified release product may have an influence into the food effect. The food effect is most reliable when studied after high fat meal before the dose.

2.8 Fasting or fed conditions

In generics, reference products SPC (Summary of Product Characteristics) is always followed also when it comes to taking the medicine with meal. If, in the SPC, administration with food is mentioned but not the composition of the meal, high-fat, high-calorie meal should be used (García-Arieta 2012).

The revised bioequivalence guideline includes more detailed information about fed conditions in bioequivalence studies (EMA 2010) in addition to the specific guidance regarding the modified release products. Already the year 2001 bioequivalence guidance noted the importance of the food effect regarding modified (controlled release, CR) products (Hausche 2007).

2.9 Biopharmaceutics classification system

Biopharmaceutics classification system determines the need for bioequivalence study based on the characteristics of the medicinal product and pharmaceutical form. Some products may apply an exception, a waiver, of the bioequivalence studies (Hauschke, 2007).

Biopharmaceutical Classification System is founded on United States Pharmacopoeia (USP). In the USA and Europe, 85 percent of the most sold drugs are oral in pharmaceutical form, so the Biopharmaceutical Classification System has an importance. Class II and III bioequivalence waivers are more demanding than class I, on the other hand their purpose is to facilitate the workload of the regulatory field (Patel Wagh 2010).

The new guideline, ICH M9 draft guideline on biopharmaceutics classification system based biowaivers, is still a draft version. It will give more detailed advice for biopharmaceutics classification system (BCS)-based biowaivers as shown in the Table

3. In the Table 4, there are examples of active ingredients which have been categorised by their BSC class.

Table 3 Biopharmaceutics Classification System (according to Wu, C.-Y. & Benet, L. 2005)

	High Solubility	Low Solubility
High Permeability	**Class I**: high solubility, high permeability (rapid dissolution for biowaiver)	**Class II**: low solubility, high permeability
Low Permeability	**Class III**: high solubility, low permeability	**Class IV**: low solubility, low permeability

Table 4 Classification of orally administrated drugs according to the BSC (tel & Wagh 2010)

Drug	Solubility (mg/ml)	Permeabilty (*10⁻⁴cm/sec)	Dose (mg)	BCS class
Atenolol	26.5	0.20	100	3
Carbamazepine	0.01	4.30	200	2
cimetidine	1.00	0.26	200	3
Furosemide	0.01	0.05	40	4
Hydrochlorthiazide	1.00	0.04	50	3
Propranolol	33	2.91	40	1
Verapamil	83	6.80	80	1

2.9.1 BCS-Biowaiver

According to the guideline, for immediate release drug, which is highly soluble drug and which does not have a narrow therapeutic index, if the composition of the product (including excipients) is similar, a biowaiver may be possible (EMA 2010).

The latest bioequivalence guidance defines the biowaiver, which has been extended to class III drugs (EMA 2010). According the bioequivalence guideline, waivers are possible only for such locally-acting and locally-applied products, which are formulated as solutions with the same qualitative and quantitative composition, or with minor differences in excipients (García-Arieta 2012). Regarding additional strengths, in new guidance, it is more clearly stated when a waiver is possible (EMA 2010).

Appendix 2 of the 2010 bioequivalence guidance defines the study requirements for different dosage forms (EMA 2010). There are certain pharmaceutical forms which usually do not require bioequivalence studies and may apply a waiver if detailed conditions will be met. Such are for instance: parenteral solutions, locally acting locally applied products and solutions, for instance eye drops, nasal sprays or cutaneous solutions.

Also, in some cases where there are several strengths, bioequivalence studies for only one or two strengths might be enough depending on the proportionality in composition between the different strengths and other product related issues (EMA 2010).

The purpose of the biowaiver is to reduce the need unnecessary bioequivalence studies and can be used only for certain products such as immediate release, solid orally administered dosage forms or suspensions delivered to the systemic circulation (EMA 2018).

2.10 Recommendations for study design

In the Guideline of the Investigation of Bioequivalence from January 2010 study design, the classical single dose two-way cross-over design is recommended as it is more sensitive to formulation differences (EMA 2010). The 90 percent confidence interval within an 80 –125 percent acceptance interval should be used. In the new guideline, number of subjects in the bioequivalence study has been defined as twelve (12) at least (García-Arieta 2012). In the guideline it is also clearly stated that “all treated subjects should be included in the analysis” (EMA 2010).

Completely all exceptional cases covering guideline would be impossible to prepare.
In complex cases, case to case evaluation is in place “for example non-linear or highly variable pharmacokinetics, narrow therapeutic index, presence of enantiomers or active metabolites” (EMA 2010). Different guidelines complete each other and form quite comprehensive network of guidance, if the information can be found easily.

2.11 GCP Guideline

Guidance for Good Clinical Practice is given in several sources. The main guideline is the Commission Directive 2005/28/EC “Good Clinical Practice (GCP) which “is an international ethical and scientific quality standard” (EMA 2016)). In addition, in European commission site there are clinical guidelines (in Eudralex, Volume 10). “Until the Clinical Trials Regulation becomes applicable sponsors should follow the documents relevant to the Clinical Trials Directive” (EC 2019b). Clinical Trials Regulation should become applicable in 2010 and replace Clinical Trials Directive (2001/20/EC).

Clinical research units are under supervision by authorities. The research and clinical protocol have to be received before the study can start (EMA 2016, WHO 2005). All studies related with the GCP should have approval from independent research ethic

committee (IEC) or Institutional review board (IRB). (EMA 2016, WHO 2005). The study should include a research protocol (detailed description of the research) and a clinical protocol (objectives, design, methodology, statistical considerations, organisation of the study). In addition, all the volunteers should give a freely given Informed consent before the clinical study starts. (EMA 2016, WHO 2005).

Clinical studies, including bioequivalence studies, should be reliable in what comes to the clinical practise as well as recording the data. Data integrity plays important role and is one sector to which authorities focus, everything must be strictly recorded, and information of the whole study should be traceable (WHO 2005). Medicinal products used in studies should be manufactured according to Good Manufacturing Practise (GMP), and the handling and storing the samples should be according to guidance.

3 EXPERIMENTAL PART: BIOEQUIVALENCE REFERRALS

3.1 Study methods

The study is a concise literary review and a desk reseach and analysis. Also case study was considered since it is a method which gives comprehensive view of the phenomenon in real life and the subject of the thesis could be seen as a whole in stead of many individual cases. However the subjects covered all the cases during the time period in question and desk research was most suitable method. The goal was to find answers to the question, has the renewed bioequivalence guideline (EMA 2010) had an impact on the number of referrals and how the procedures had been influenced by the guidance. In addition it was investigated further if there were any particular factors, like the pharmaceutical form, which had had any influence (Aaltola & Valli, 2001a).

The website of the European medicine's Agency offers a tool to investigate the referrals since all public documents, for instance public assessment reports (PARs) or Questions and Answers (QA) documents regarding marketing authorization procedures are published (list and hyperlinks to PARs and QA documents can be found in the Appendix 1). The study includes all the Art 29(4) referrals where bioequivalence study was the main reason for referral that means that all the cases where there has been a doubt of

the public health risk relating to bioequivalence studies in accordance to marketing authorization applications of the generic medicines were included in this study.

Focus in this review is only in cases inside EU. Marketing authorisation system for generics and requirements for bioequivalence studies outside Europe are somewhat different even there are also similarities. First the products were screened by using the search in EMA's web pages and having criteria as Human (medicines), referrals article 29(4) and article 31 and search term: bioequivalence. Public assessment reports and public information about referrals were used to find final conclusions of the referrals concerning the bioequivalence.

From the EMA's pages was found a table including article 29(4) referrals. From that the cases were screened at first with the criterion "European Commission decision made".

3.2 Thesis procedure in practice

Those referrals have been included which, in the base of the public documents, have dealt the problems relating to bioequivalence studies.

After comparing results from the two different methods to search the referrals in question, it was noticed that in the Excel sheet from EMA's web site all the cases had not been noticed. Therefore, the criterion was changed as "CHMP opinion provided" instead of "Commission decision made".

The cases were screened from the first "raw data" on basis of the true reason for referral. Reason for the referral was searched from public documents, mainly from the public assessment reports. On the basis of that the main reason for referral was: inadequate bioequivalence studies of the generic medicine compared with the originator, the final cases were included into this study. The process is described as seen in the Figure 4 and 5.

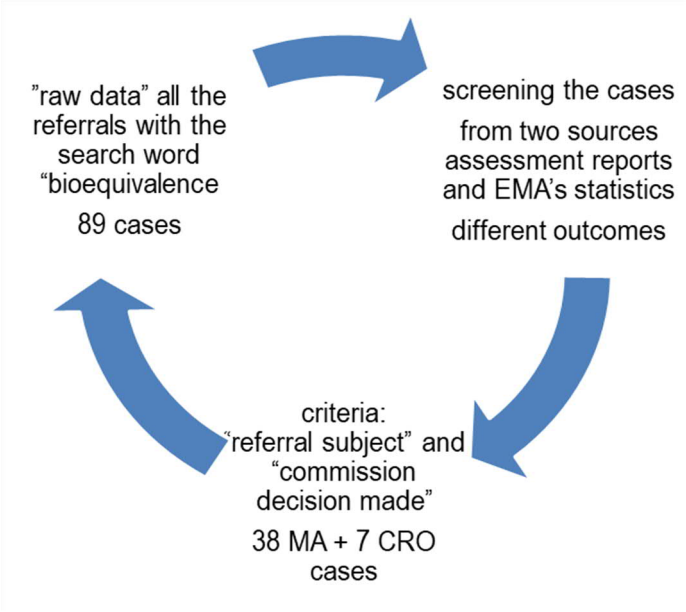

Figure 4 Selection of the cases

The results have been categorized by different themes in order to find explanations to the research questions. That was done by reading the assessment reports and finding information of the cases that fulfilled the screening criteria from public documents. By classifying the material with different themes, it is easier to find the core information (Aaltola & Valli, 2001b). Acquired data was organised into tables where it can easily be compared in numerical form and more detailed information can be included (Aaltola & Valli, 2001b). In order to find an answer to the question whether the renewed guidance has had an influence, tables with multiple variants for example cross tabulation has been used (Aaltola & Valli, 2001b).

In addition, with the search word: referral and Article 31 referral, there were only seven cases which concerned a CRO where had been inadequate bioequivalence studies. Since the number was so low, these cases are mentioned only briefly. Since only public information about the problems in CRO places and GCP inspections could be included, this study can rely on the cases, which have proceeded to referral procedure and have been published by the authorities.

Data of all the referrals regarding bioequivalence studies was collected into an Excel sheet. All data was collected from the EMA’s pages and from the public assessment

reports and QA documents concerning bioequivalence referrals. Following criteria was chosen for collection of data: Product name or CRO, year of the application (left out since not all the information available from public AR;s), type of referral (Article number), referral start date (referral to CMDh or arbitration procedure at CHMP, according to which was available in the public assessment report), referral outcome, referral subject per assessment report or QA document in short, but as precise as it was possible.

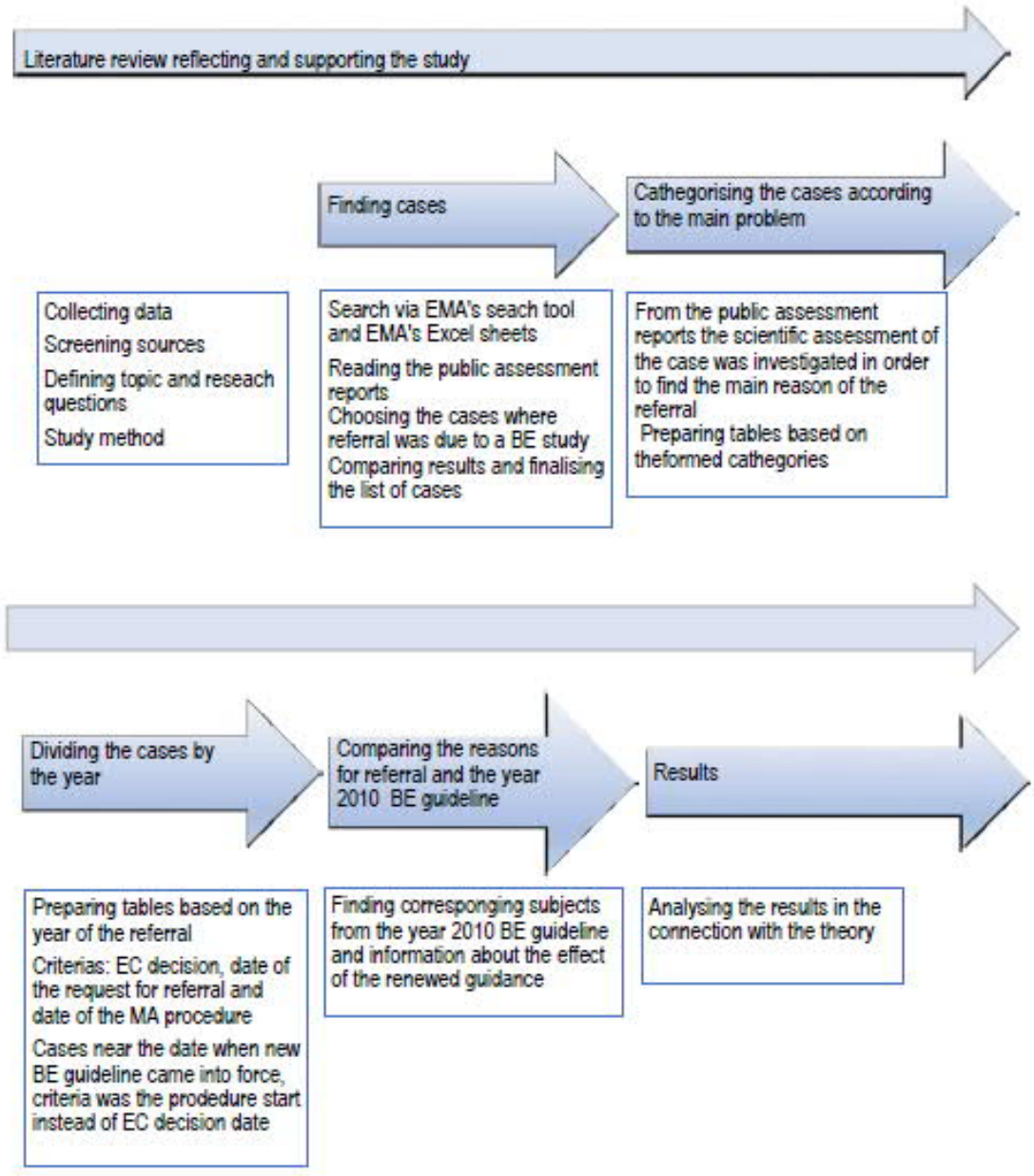

Figure 5 Description of the thesis process

When marketing authorisation application had been applied, was left out from the data since it was not always notified in the public assessment or other public documents. In addition, some of the referrals concerned already authorised products of which bioequivalence studies were questioned while the product was already on the market. It was considered that the time of the referral was adequate criterion to divide the cases to those before and those after the renewed guidance was published.

4 RESULTS

4.1 Article 29(4) referrals

As a result of screening the cases for this study, altogether forty (40) article 29(4) cases were found where bioequivalence studies were the main reason for referral. This was less than half of the preliminary cases (appr. 90 referrals) since for most of them did not meet the criteria. Of these, thirtyeight (38) were related with bioequivalence studies for generic marketing authorisation application and two dealt with deficiencies in CRO place used for marketing authorisation application, which will be discussed more in accordance with article 31 cases. In the Table 5 article 29(4) referrals relating with bioequivalence studies have been introduced by dividing them into groups per main reasons for referral. Questions concerning fasting or fed conditions, thirteen (13) cases, and general bioequivalence problems, which were not defined in more accurate way in public documents, formed the biggest two groups. There were altogether fourteen (14) referrals where detailed reason could not be found and referred only as problems in bioequivalence studies.

Number of article 29(4) cases related with marketing authorisation procedure was thirty-eight (38) of which approximately 30 percent were due to inadequate studies related with the fed conditions. Most of the cases, 29 of 38 marketing authorisation related article 29(4) cases, ended positivel. Both GCP related cases had a positive outcome as well, so the total number of positive referrals was 31 of total 40 cases.

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Table 5 Article 29(4) referrals

Main reason for referral								
Pharmaco-kinetic parameters / narrow therapeutic drug (n=1)	**Release profile and effect of food (fed and fasting conditions) (n=1)**	**Indication and dose (n=1)**	**Proof of bioequivalence in general and difference in composition and/or pharmaceutical form (n=1)**	**Proof of bioequivalence in general or not defined (n=1)**	**Only in-vitro studies not sufficient (waiver not applicable) (n=1)**	**Bioequivalence Study not carried out using corresponding strengths or dosing (n=1)**	**Direct comparative data with the reference medicine missing (related with formulation) (n=1)**	***GCP related* (n=1)**
Rigevidon 150 µg levonorgestrel and 30 µg ethinylestradiol coated tablet, positive	Diclofenac epolamine 50 mg tablets, **negative**	Fentanyl-ratiopharm and associated names 25/50/75/100 µg/h Matrixpflaster[2], positive	Docetaxel Teva Generics 20 mg and 80 mg, powder and solvent for solution for infusion, positive	Betavert N 8 mg or 16 mg tablet, betahistine dihydrochloride, positive	Mometasone Furoate Sandoz 50 micro gram/dose nasal spray, positive	Glimepirida Parke-Davis and assocoated names 2, 3 and 4 mg tablets, positive	Paclitaxel Hetero and associated names 6 mg/ml concentrate for solution for infusion, **negative**	Tibolona Aristo and associated name 2.5 mg tablets, positive (EMEA/H/A-29/1389)
	Didanosine 200, 250 and 400 mg gastro-resistant capsules, positive	Fentanyl-ratiopharm and associated names 25/50/75/100 µg/h TTS[2], positive	Okrido 6 mg/ml oral solution, prednisolone sodium phosphate, positive	Canazole 1% w/w cream, clotrimatzole, **negative**		Perlinring and associated names 0.120mg/0.015mg per 24 hours vaginal delivery system, etonogestrel/ ethinylestradiol, positive		Tibocina and associated name 2.5 mg tablets, positive (EMEA/H/A-29/1390)
	Doxagamma and associated names 4mg prolonged release tablets[1], doxazosin, positive		Teicoplanin Hospira 200 or 400 mg powder and solvent for injection, **negative**	Ciclosporin IDL 25 mg, 50 mg and 100 mg, capsules, **negative**		Simvastatin Vale 20mg/5ml and 40mg/5ml oral suspension, positive		

	Doxastad and associated names 4 mg prolonged release tablets[1], positive			Fluoxetin NM 20 mg capsules, positive				
	Doxazosin Retard Arrow and associated names 4 mg prolonged release tablets[1], positive			Galantamine Stada and associated names 8, 16 and 24 mg prolonged released tablets, **negative**				
	Doxazosin Winthrop and associated names 4mg prolonged release tablets[1], positive			Lisonorm 5 mg / 10 mg tablet, amlodipine / lisinopril, positive				
	Isotretinoin and associated names 10 and 20 mg soft capsules, **negative**			Loratadine Sandoz 10 mg tablets, **negative***				
	Lansoprazole 15 mg and 30 mg gastro-resistant capsules, hard, positive			Mifepristone Linepharma 200 mg tablet, positive				
	Methylphenidate Hexal 18, 36 and 54 mg prolonged-release tablet[3], positive			Pantoprazole Bluefish 20 and 40 mg tablets[4], positive				
	Methylphenidate Sandoz 18, 36 and 54 mg prolonged-release tablet[3], positive			Pantoprazole Olinka (EMEA/H/A-29/1170) 20 and 40 mg tablets[4], positive				

	Myoson and associated names 50 mg and 150 mg film coated tablets[6], tolperisone hydrochloride, positive			Pantoprazole Olinka (EMEA/H/A-29/1169) 20 and 40 mg tablets[4], positive				
	Merison and associated names 50 mg and 150 mg film coated tablets[6], tolperisone hydrochloride, positive			Prokanazol 100 mg capsule, itraconazole, **negative**				
	Cardoreg 4 mg prolonged release tablets and associated names[5] (doxazosin) , positive, EC decision			Sabumalin 100 µg/dose metered dose aerosol inhaler[5], salbutamol, positive				
				Sanohex 100 µg/dose metered dose aerosol inhaler[5], salbutamol, positive				
1	13	2	3	14	1	3	1	2

[1, 2, 3, 4, 5, 6] same or similar dossier

Total number of cases	40
Marketing authorisation related cases	38
Number of positive outcome	31
Number of negative outcome	9

4.2 Referrals before and post the new guidance

The cases were divided into two groups based on either the day the marketing authorisation procedure start or the day when the referral procedure had been launched (request for a referral date) or the Commission Decision date. Since similar information could not be found in public assessments reports, timing the procedure had to be made in various ways depending which data was available. Altogether, dividing the cases by date, related with the guidance used at that time, gave adequately correct result. The year 2010 Bioequivalence Guideline came into force on 1st of August 2010 and the cases have been split to referrals before and post that date.

Usually, in marketing authorisation applications, legislation to be followed is on the base on the date when the marketing authorisation procedure starts. That information was not to found from all the PAR's and therefore the date of referral start (in this connection CMDh request for referral) was more appropriate date to be used for dividing the cases. The information found from the PAR's was not always consistent and in few cases only the day of the marketing authorisation procedure start was found and therefore that date was chosen to separate the case into pre or post 2010 group as shown in the Table 6.

Table 6 Referrals before and after year 2010 Bioequivalence Guideline

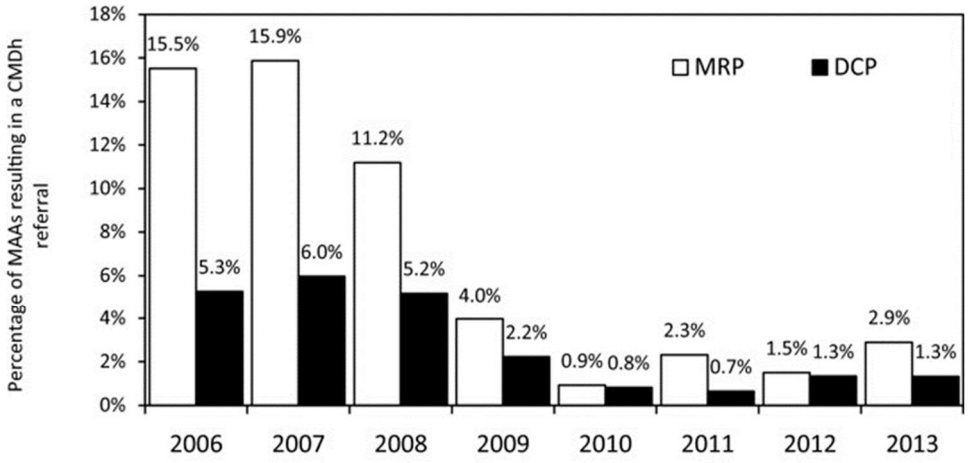
Procedure before before 1.8.2010		Procedure after 1.8 2010	
Product name	**EC decision**	**Product name**	**EC decision**
Fluoxetin NM 20 mg capsules, positive	9.6.1998	Canazole 1% w/w cream, clotrimatzole, negative	15.9.2010
Rigevidon 150 µg levonorgestrel and 30 µg ethinylestradiol coated tablet, positive	10.5.2005	Galantamine Stada and associated names 8, 16 and 24 mg prolonged released tablets, negative, (arbitration on 26.3.2010)	21.2.2011
Cardoreg 4 mg prolonged release tablets and associated names[5] (doxazosin), positive	11.10.2006	Mifepristone Linepharma 200 mg tablet, positive	11.9.2012
Doxagamma and associated names 4mg prolonged release tablets[1], doxazosin, positive	11.10.2006	Mometasone Furoate Sandoz 50 micro gram/dose nasal spray, positive	8.10.2012
Doxastad and associated names 4 mg prolonged release tablets[1], positive	11.10.2006	Glimepirida Parke-Davis and assocoated names 2, 3 and 4 mg tablets, positive	19.11.2012
Doxazosin Retard Arrow[1] and associated names 4 mg prolonged release tablets[1], positive	11.10.2006	Simvastatin Vale 20mg/5ml and 40mg/5ml oral suspension, positive	27.5.2013
Doxazosin Winthrop and associated names 4mg and associated names 4 mg prolonged release tablets[1], positive	11.10.2006	Okrido 6 mg/ml oral solution, prednisolone sodium phosphate, positive	5.9.2013
Lansoprazole 15 mg and 30 mg gastro-resistant capsules, hard, positive	18.9.2007	Methylphenidate Hexal 18, 36 and 54 mg prolonged-release tablet[3], positive	9.10.2013
Fentanyl-ratiopharm and associated names 25/50/75/100 µg/h TTS[2], positive	23.10.2007	Methylphenidate Sandoz 18, 36 and 54 mg prolonged-release tablet[3], positive	9.10.2013
Fentanyl-ratiopharm nd associated names 25/50/75/100 µg/h Matrixpflaster[2], positive	23.10.2007	Didanosine 200, 250 and 400 mg gastro-resistant capsules, positive	20.11.2013
Lisonorm 5 mg / 10 mg tablet, amlodipine / lisinopril, positive	12.11.2008	Myoson and associated names 50 mg and 150 mg film coated tablets[6], tolperisone hydrochloride, positive	23.4.2015
Sabumalin 100 µg/dose metered dose aerosol inhaler, salbutamol[5], positive	12.3.2009	Merison and associated names 50 mg and 150 mg film coated tablets[6], tolperisone hydrochloride, positive	25.6.2015
Sanohex 100 µg/dose metered dose aerosol inhaler[5], salbutamol, positive	12.3.2009	Diclofenac epolamine 50 mg tablets, negative	22.9.2016
Betavert N 8 mg and 16 mg tablet, betahistine dihydrochloride , positive	2.6.2009	Perlinring and associated names 0.120mg/0.015mg per 24 hours vaginal delivery system, etonogestrel/ethinylestradiol, positive	18.12.2018
Prokanazol 100 mg capsule, itraconazole, negative	14.7.2009	Paclitaxel Hetero and associated names 6 mg/ml concentrate for solution for infusion, negative	11.1.2019

Loratadine Sandoz 10 mg tablets, negative	6.8.2009		
Teicoplanin Hospira 200 or 400 mg powder and solvent for injection, negative, (DCP procedure start in 2005)	29.1.2010		
Isotretinoin and associated names 10 and 20 mg soft capsules, negative, (MRP procedure start 24.2.2010)	18.05.2011		
Pantoprazole Bluefish 20 and 40 mg tablets[4], positive, (referral request 30.7.2009	30.3.2010		
Pantoprazole Olinka (EMEA/H/A-29/1170) 20 and 40 mg tablets[4], positive, (referral request 30.7.2009	30.3.2010		
Pantoprazole Olinka (EMEA/H/A-29/1169) 20 and 40 mg tablets[4], positive, (referral request 30.7.2009	30.3.2010		
Docetaxel Teva Generics 20 mg and 80 mg, powder and solvent for solution for infusion, positive, DCP start 30.1.2009, referral request 20.5.2010	7.7.2011		
Ciclosporin IDL 25 mg, 50 mg and 100 mg capsules, negative (referred to the CHMP for arbitration on 2 December 2008)	22.7.2010		

[1, 2, 3, 4, 5, 6] same or similar dossier

Due to the fact that public assessment reports as well as other public documents did not include the same details and there was some inconsistency with the form of published data, it was not possible to compare the cases with the same variants. In some documents, the date of referral start was mentioned, whereas in some MRP or DCP procedures only start or only the initial authorisation date. To achieve some logic to the comparison, the cases were chosen on the base of which the final European Commission (EC) decision, if could be found. Some of the referrals may end with consensus already in earlier phases during the referral procedure via discussions in the CMDH or CHMP groups and no official EC decision is needed.

Number of referrals in the period after the new guidance does not seem to be much less but considering that the total amount of procedures has risen during the years, the proportion of the bioequivalence referrals of the generic applications is significantly lower as seen also in the Figure 6. The trend can be seen in the Figure 7 and 8 as well. In the year 2006 there was 5 bioequivalence referrals and 419 generic MRP or DCP procedures and in 2013 the number were 5 bioequivalence referrals towards 933 generic MRP or DCP procedure. During the year 2010 there were 8 bioequivalence referrals and 1439 generic MRP or DCP procedures. In 2010 there was the highest peek in the number of marketing authorisation applications via mutual recognance procedure.



Total number of MAAs per year

MRP	535	441	411	378	325	259	266	207
DCP	57	386	733	1304	1452	1381	1198	1052

Figure 6 Percentage of procedures resulting in CMDh referral per year (Ebbers, H.C. et. al. 2015)

In the article by Ebbers et. al. it was indicated that “the frequency of referrals has decreased in recent years” (Ebbers, H.C. et. al. 2015). The same study had categorized bioequivalence referrals into two groups, bioequivalence not demonstrated where the reasons for referral were: “bioequivalence parameter outside predefined border, endpoint not met for bioequivalence / TE studies, post hoc widening of acceptance -requirements-, exclusion of outliers not supported” and bioequivalence not investigated in sub-groups where the main reasons for referral were related with: “Including dose, fasting / fed condition group, or patient category. Discussions on the acceptability of biowaivers of studies, extrapolation of different dose strengths included in the bioequivalence studies”. During the study period 2006 – 2013 it was found that the percentage of all the referrals, the clinical bioequivalence referrals represented thirty three (33) percent of which bioequivalence was not demonstrated was thirty eight (38) percent and where bioequivalence was not investigated in sub-groups was twenty four (24) percent.

In the Figure 7 and 8 these statistics are presented. The information has been found from the EMA’s web pages (HMA 2019b) and from the numbers of referrals in this study.

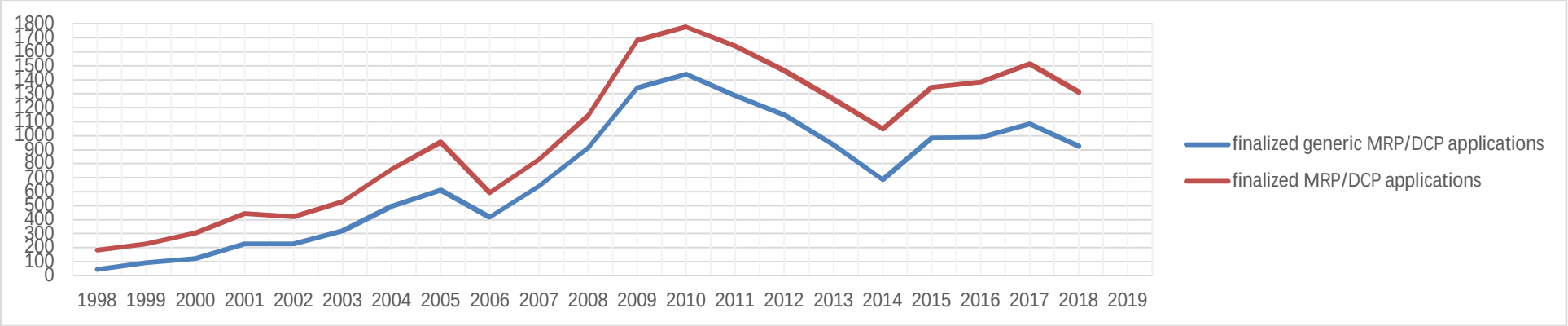


Figure 7 Number of referrals vs no. of generic MA procedures between 1998 – 2019 (influence on the referrals) (adapted from HMA statistics)

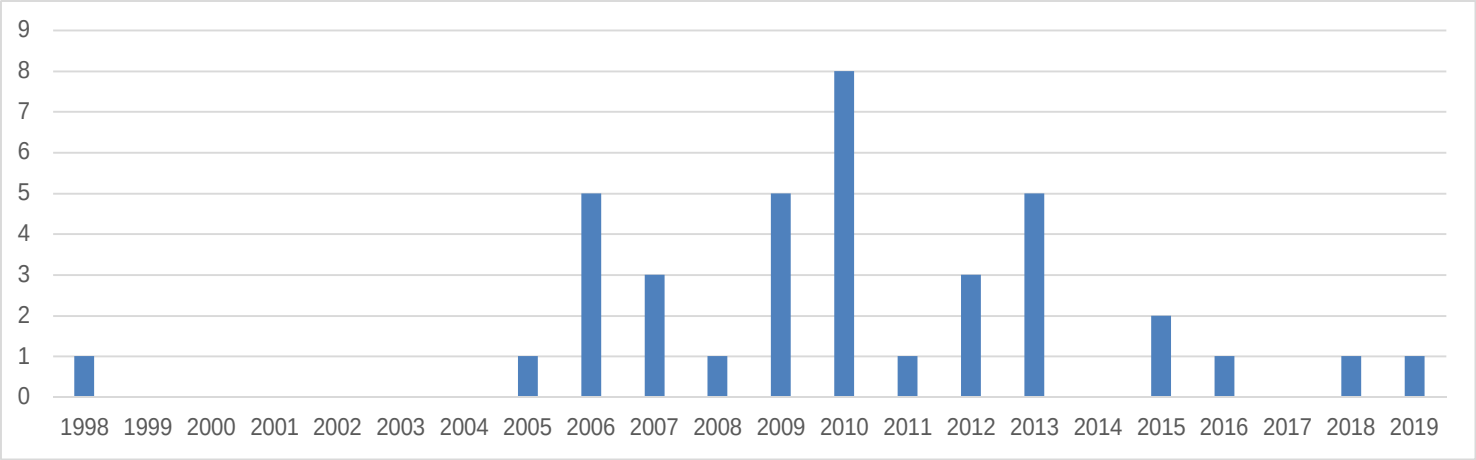


Figure 8 Number of referrals vs number of generic marketing authorisation procedures 1998 – 2019 (adapted from HMA statistics)

5 REFERRAL CASES ACCORDING TO PHARMACEUTICAL FORM

Referral cases were studied further to find out if the pharmaceutical form had had any influence on the reasons for triggering the referral. Cases have been sorted by dosage form according to year 2010 Bioequivalence Guideline (see Table 7 and 8). According to Bioequivalence Guideline, the main types for pharmaceutical dosage forms are: oral immediate release dosage forms with systemic action (tablets, capsules and oral suspensions, orodispersible tablets, oral solutions etc.), non-oral immediate release dosage forms with systemic action (parenteral solutions, liposomal, micellar and emulsion dosage forms for intravenous use and so on), modified release dosage forms with systemic action: (modified release oral and transdermal dosage forms, modified release intramuscular or subcutaneous dosage forms etc.) and locally acting locally applied products (oral, nasal, pulmonary, ocular, dermal, rectal, vaginal etc. administration) and in addition gases, which were not present in the studied cases (EMA 2010).

Table 7 Referrals according to different dosage forms

	pre August 2010 positive	**pre August 2010 negative**	**post August 2010 positive**	**post August 2010 negative**
Modified release dosage forms with systemic action	Cardoreg 4 mg prolonged release tablets[5] and associated names (doxazosin)		Methylphenidate Hexal 18, 36 and 54 mg prolonged-release tablet[3]	Galantamine Stada and associated names 8, 16 and 24 mg prolonged released tablets
	Doxagamma and associated names prolonged release tablets[1] (doxazosin)		Methylphenidate Sandoz 18, 36 and 54 mg prolonged-release tablet[3]	
	Doxastad and associated names prolonged release tablets[1] (doxazosin)		Didanosine 200, 250 and 400 mg gastro-resistant capsules	
	Doxazosin Retard Arrow and associated names prolonged release tablets[1] (doxazosin)		Perlinring and associated names 0.120mg/0.015mg per 24 hours vaginal delivery system, etonogestrel/ ethinylestradiol	
	Doxazosin Winthrop and associated names 4mg prolonged release tablets[1]			
**	Lansoprazole 15 mg and 30 mg gastro-resistant capsules, hard			
	Fentanyl-ratiopharm and associated names 25/50/75/100 µg/h TTS[2]			
	Fentanyl-ratiopharm nd associated names 25/50/75/100 µg/h Matrixpflaster[2]			
number of cases	**8**		**4**	**1**
Oral immediate release dosage forms with systemic action	Fluoxetin NM 20 mg capsules	Ciclosporin IDL 25 mg, 50 mg and 100 mg capsules	Myoson and associated names 50 mg and 150 mg film coated tablets[6], tolperisone hydrochloride	Diclofenac epolamine 50 mg tablets
	Rigevidon 150 µg levonorgestrel and 30 µg ethinylestradiol coated tablet	Loratadine Sandoz 10 mg tablets	Merison and associated names 50 mg and 150 mg film coated tablets[6], tolperisone hydrochloride	Isotretinoin and associated names 10 and 20 mg soft capsules

	Lisonorm 5 mg / 10 mg tablet, amlodipine / Lisinopril	Prokanazol 100 mg capsule, itraconazole	Mifepristone Linepharma 200 mg tablet	
	Betavert N 8 mg and 16 mg tablet, betahistine dihydrochloride		Glimepirida Parke-Davis and assocoated names 2, 3 and 4 mg tablets,	
	Pantoprazole Bluefish 20 and 40 mg tablets[4]		Simvastatin Vale 20mg/5ml and 40mg/5ml oral suspension	
	Pantoprazole Olinka (EMEA/H/A-29/1170) 20 and 40 mg tablets[4]		Okrido 6 mg/ml oral solution, prednisolone sodium phosphate	
	Pantoprazole Olinka (EMEA/H/A-29/1169) 20 and 40 mg tablets[4]			
number of cases	7	3	6	2
Locally acting locally applied products	Sabumalin 100 µg/dose metered dose aerosol inhaler[5], salbutamol			Canazole 1% w/w cream, clotrimatzole
	Sanohex 100 µg/dose metered dose aerosol inhaler[5], salbutamol			
number of cases	2	-	-	1
Non-oral immediate release dosage forms with systemic action:	Docetaxel Teva Generics 20 mg and 80 mg, powder and solvent for solution for infusion	Teicoplanin Hospira 200 or 400 mg powder and solvent for injection		Paclitaxel Hetero and associated names 6 mg/ml concentrate for solution for infusion
			Mometasone Furoate Sandoz 50 micro gram/dose nasal spray,	
number of cases	1	1	1	1
number of cases of all dosage forms	**18**	**4**	**11**	**5**

[1, 2, 3, 4, 5, 6] same or similar dossier

Modified release form formed about one third of all (13 of 38) the cases. It is obvious that many of the processes leading to a referral were other than conventional dosage forms and that might have been one reason for difficulties in bioequivalence studies. In other dosage forms except modified release, there were no significant difference between pre and post year 2010 in number of referral cases, but number of modified release form was higher before year 2010 (eight cases) than after 2010 (five cases). Nevertheless, it should be noted that proportion of referrals is smaller after year 2010 due to the rise in

application numbers during the period investigated and because many generic procedures are clone applications, so called duplicates (similar documentation), it is hard to estimate the real number of different cases. Based on the information found from the public files, many of the bioequivalence studies were similar between referrals of the same active substance. However, in this study the figures rely on the numbers of different referral procedures that have their own EU-procedure number. In public assessments it was not mentioned if the applications were identical. In some cases, it was obvious that the bioequivalence study had been the same.

Table 8 Prolonged release products with fasting or fed conditions as referral reason

Before August 2010	**After August 2010**
Cardoreg 4 mg prolonged release tablets5 and associated names (doxazosin)	Methylphenidate Hexal 18, 36 and 54 mg prolonged-release tablet[2]
Doxagamma and associated names prolonged release tablets1	Methylphenidate Sandoz 18, 36 and 54 mg prolonged-release tablet[2]
Doxastad and associated names prolonged release tablets1	Didanosine 200, 250 and 400 mg gastro-resistant capsules
Doxazosin Retard Arrow and associated names prolonged release tablets1	
Doxazosin Winthrop and associated names 4mg prolonged release tablets1	
Lansoprazole 15 mg and 30 mg gastro-resistant capsules, hard	
Number of cases 6	Number of cases 3

[1, 2] same or similar dossier

The number of prolonged release product form in referral cases related with fed and fasting conditions is small and definite conclusions cannot be made. Since five (5) doxazosin procedures had the same or similar dossier, actually before the year 2010, the prolonged release cases consisted of two (2) different dossiers. After the year 2010 prolonged release dosage form cases formed of only three (3) procedures and two of them were also simultaneous procedures, so the number of different cases is actually only two (2). Therefore, it could be said, that there were about the same amount of cases with prolonged release form leading to a referral before and after the renewed guidance.

Altogether nine (9) cases, and actually four (4) different documentations, related with food and fed conditions had modified release as the pharmaceutical form. This forms anyhow one major group of all the pharmaceutical forms, which had food effect related or as the reason for referral.

It implies that modified release dosage form is more challenging dosage form for performing the bioequivalence. However, the guidance after August 2010 and thereafter has been improved. The improvement of the guidance did not show notable change after the year 2010 guideline came into effect due to the low number of cases.

6 CASES REGARDING GCP

GCP inspections are carried out by authorities and their purpose is to investigate "documents, facilities, records, quality assurance arrangements and other material" which is related to clinical trials. Inspections can be done in accordance of ongoing "marketing authorisation procedure follow-up measures, variation applications, re-examinations or safety updates" (PSUR, periodic Safety Update Report) (EMA 2012).

GCP related referrals take place after a signal from an inspection carried by an authority and are followed by a process where all marketing authorisation dossiers related to that particular site have to be identified. Authorities have to evaluate if the findings could jeopardise the safety and efficacy of the medicinal product in case of clinical, including bioequivalence, studies have been carried out in the place and during the time frame when the deficiencies have been noted.

Procedure for re-evaluation of the sites, which were included into this study were Article 31 referrals, which is due to a Union interest or Article 29(4) referrals, when an ongoing marketing authorisation procedure is in question.
"The European Medicines Agency (EMA) acts as a co-ordinator for GCP inspections but national EU authorities are responsible for doing the inspections" (EMA 2019h).

In a Reflection paper on advice to applicants / sponsors / cross of bioequivalence studies, a more detailed advice is given regarding to quality of the clinical studies, especially for generic industry (EMA 2008). It covers many areas which came across as deficiencies

in referral procedures such as: “data Verification & Quality, qualification of the facilities, availability of audit certificates, production site (for example location, GMP license/inspection, QP activities), traceability, conditions of administration, labelling, traceability, storage and transport conditions of the biological samples”.

Cases found were few and are presented in more detail in the table of the GCP referrals (Appendix 3). A short review of cases is shown in Table 9.

Table 9 GCP related referrals

Name	Location	Article	Commision decision	Reason for referral	Outcome
Tibolona Aristo and associated names	Sofia, Bulgaria	Article 29(4)	5.3.2014	no evidence of adequate transfer and storage of the study PK samples, , no documentation was made available regarding to reidentification of study samples, no documentation on the equipment (freezer) where samples were stored or the storage conditions. results of the bioequivalence study are reliable and demonstrates the bioequivalence	positive
Tibocina and associated names	Sofia, Bulgaria	Article 29(4)	5.3.2014	no evidence of adequate transfer and storage of the study PK samples, , no documentation was made available regarding to reidentification of study samples, no documentation on the equipment (freezer) where samples were stored or the storage conditions. results of the bioequivalence study are reliable and demonstrates the bioequivalence positive	positive
Semler Research Center Private Ltd	Karnataka, India	Article 31	22.9.2016	several issues such as substitution and manipulation of subjects' clinical samples, critical deviations e.g. Quality management and reliability of data alternative studies resulted positive outcome for some of the related medicines	partially positive (alternative studies were provided for some of these medicines)
Micro Therapeutic Research Labs	Chennai, India and Tamil Nadu, India	Article 31	23.6.2017	Critical findings e.g. serious doubts on the reliability of the data of bioequivalence studies serious concerns related to the suitability of the quality management system at both sites and of the reliability of data submitted in applications for marketing authorisations in EU	negative
Alkem Laboratories Ltd	Taloja, India	Article 31	8.9. 2016	misrepresentation of data during the conduct of two different trials, The findings cast doubts on the quality management system in place at the site, and thus on the reliability of the data of bioequivalence studies for part of the products an alternative studies have been provided that support a positive benefit-risk balance can remain in the market	partially positive
Cetero Research Center	Houston (Texas, USA)	Article 31	20.2.2013	laboratory analyses of bio-analytical studies could not be considered reliable	negative
GVK Biosciences	Hyderabad, India	Article 31	16.7.2015	data manipulations of electrocardiograms critical deficiencies in the quality system lack of GCP training, data integrity, for part of the products	partially positive (bioequivalence has been established by other studies)

Even though there were not many GCP related referral cases, each of these referrals influenced various medicinal products and therefore have significance among other referrals. Bioequivalence Guideline, however, is not the main guidance regarding the GCP but the Guideline for Good Clinical Practice (GCP) and these should be read in connection with the guideline. The reasons of the referrals relating to the CRO places were also quite serious, even so the outcome was positive in most cases. However, some deficiencies have to be found before a referral procedure can be launched. The reasons have been collected in the Figure 9.

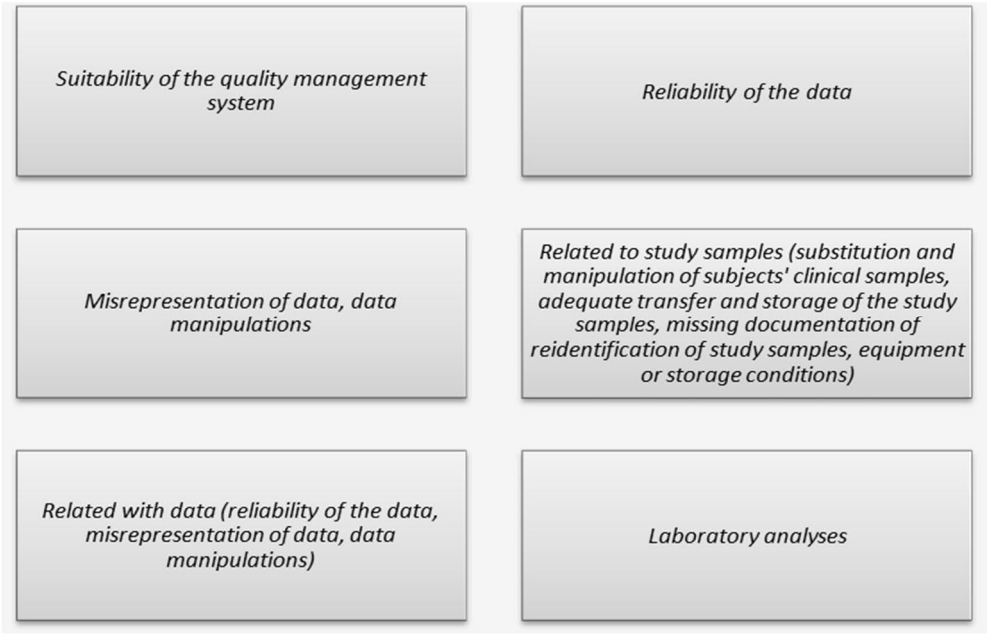


Figure 9 The main reasons of Art. 31 referrals

The legislation behind the guidance is the Clinical Trial Directive (Directive 2001/20/EC) and the GCP Directive (Directive 2005/28/EC) (EMA 2019e).

For that reason, these GCP cases have not been included into the comparison of cases related into bioequivalence problems by Article 29(4) and are only briefly reviewed. Tibolona Aristo and associated names and the parallel procedure Tibocina and associated names cases have been included only in this review even it is Article 29(4) procedure since it is purely GCP related case. Not to mention, all the GCP cases were dated after the renewed Bioequivalence Gdeline.

7 DISCUSSION

Most of the material for this study was based on the public documentation of the generic marketing authorisations and referrals. It was both an advantage as a challenge since the published documentation was available, but in many cases it did not offer the expected information.

“Since 1995, same year Finland joined the EU, the Agency has published European public assessment reports (EPAR). Publication of information has been increased by the Agency” (EMA.eu, Transparency). Doing this study, it was noticed that the level of detailed information in the public assessment reports has become common within the recent years, whereas in the oldest PARs there was quite limited information and in some cases it was even difficult to find the reason for referral. There was also some contradiction between found information comparing the assessment reports and Excel tables of the referrals produced by the Agency. These cases were probably only minor mistakes. Cases taken into this study were collected in many different ways, via searches in the EMA’s web pages and using published tables by EMA so the reliability of the data should be adequate. Since the public assessment reports varied a lot with regard to detailed information, it was not possible to find out all the specific reasons for referral for all the cases.

The renewed Bioequivalence Guideline from the year 2010 does not cover everything but it would be impossible to prepare such guideline, which would give answers to every specific case. However, the renewed guideline is more detailed and more comprehensive than previous ones. However, it is not a new guideline anymore since it is already almost a decade old. Guidelines usually need continuous updating. Nevertheless, the Bioequivalence Guideline is supported by many other guidelines and by many Q & A’s by EMA, for instance Questions & Answers: positions on specific questions addressed to the Pharmacokinetics Working Party. Together with other relating advice from the authorities, bioequivalence guidance can be complemented.

Though the number of applications has dramatically been growing, especially after year 2005 (when for instance generic switching became more common in EU countries), the number of referrals has remained almost same, so the proposition of the referral has

indeed decreased. In the year 2010, when the new bioequivalence guidance came into force, there was not much increase in the number of referrals compered to number of applications, but after the year 2010, the number of marketing authorisation applications started to diminish after the very fast growth during 2005 and 2010. This could be due to the fact that especially around 2005 many Reference Member State (RMS) countries, including Finland, were overloaded with generic applications and could not start new procedures and applicants were advised to seek new willing RMS countries.

The subject of the study was so complex that it was not possible to include all the possible areas in the frames of this concise thesis for specialisation studies. In a wider research, it could have been taken into consideration which countries raised the questions leading to the referrals and are there national differences. In a referral procedure several countries are involved; the reference country, the country/countries who started the referral, and naturally all the countries participating in CMDh / CHMP activities are involved with the assessment and decision-making process.

Number of biowaivers was not considered since such number was not included in EMA's statistics of marketing authorisation applications. Could the proportion of biowaivers have been growing and therefore affected to the number of referrals related to bioequivalence studies? At least the year 2010 guideline included more specific guidance for applying biowaiver and the class III medicines had been included into guidance as well. It would interesting to know how many biowaivers there has been per year and have they become more common over the years.

Cases were looked in more depth on the basis of the pharmaceutical form. It was noted that conventional dosage forms formed approximately half of the cases, but others had somewhat more challenging pharmaceutical form such as modified release form, which is more difficult to study since for instance the effect of food may have more influence.

The cases could have been categorized according to the active substance in order to find out if the referral was related with the properties of the active substance. Studies of dose-proportionality were left in less attention due to the limited scope of this study but would be one interesting area, which was one topic mentioned in the referrals.

Found GCP inspection referrals were quite low in number, but each of them affects a wide range of marketing authorisations and a referral is caused by a potential serious public health risk so therefore their meaning cannot be overlooked, even how they are not very common. Also ,the subjects of referral related to GCP inspections were quite alarming, because it was almost in every case related with the reliability of documentation during the bioequivalence studies performed by the CRO's. Data integrity is emphasized in every guidance regarding manufacturing of medicines and clinical studies, and the reliability of data of clinical trials should be self-evident. GCP-related cases and guidance could have been investigated further in a wider review.

Total number of referrals compared with the number of generic applications is quite small and in many cases, referrals have ended positively. Aside from the fact that many controversial cases do not proceed to referral but are agreed already during the marketing authorisation procedure. However, that is a sign that even though referral is based on potential serious public health concern, generally marketing authorisation applications follow the guidance and are of good quality.

8 CONCLUSION

The reasons for referrals were found as an indicator, which could show how well the guidance had been used, understood or interpreted during the time period of a particular referral. It was found that the guidance had an impact and especially in cases where due to pharmaceutical form or the feed and fasting consitions inspecting the bioequivalence is generally more demanding. In the cases dealing with GCP referrals the reasons were different, mainly related with the reliability of the data and the quality system and not similar with the product related referrals. In stead of Bioequivalence Guideline, the Good Clinical Practice Guideline deals with ethical and quality standard issues.

The main reasons for referral were mostly described in detail, expect in some, especially older, cases. In addition, in some cases, there were several reasons, which had led to the referral. Other factors, such as the number of generic marketing authorisations per year, were taken into concern and the impact of guidance could be interpreted reflecting the number of referrals to the total number of generic marketing authorisation

applications. Fed and fasting conditions were found to be the main reason. It is one area in bioequivalence studies where the guidance had been improved already before year 2010 Guideline, but which still required more detailed instructions. Since all the cases are unique, exclusive guidance might not even be possible but case to case consideration will always be needed.

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APPENDIX 1

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https://www.ema.europa.eu/en/documents/referral/cardoreg-4-mg-article-29-referral-annex-i-ii-iii_en.pdf

Cetero Research
QA:
www.ema.europa.eu/en/documents/referral/questions-answers-review-medicines-which-studies-have-bioequivalenceen-conducted-texas-based-cetero-research_en.pdf
AR:s for related products:
www.ema.europa.eu/en/documents/referral/assessment-report-cilazapril-teva_en.pdf
www.ema.europa.eu/en/documents/referral/assessment-report-leflunomide-actavis_en.pdf
ema.europa.eu/en/documents/referral/assessment-report-leflunomide-apotex_en.pdf
www.ema.europa.eu/en/documents/referral/assessment-report-fenofibrato-pensa-fenofibrato-ranbaxy_en.pdf

Ciclosporin IDL
www.ema.europa.eu/en/documents/referral/questions-answers-referral-ciclosporin-idl-associated-names-capsules-containing-ciclosporin-25-mg-50_en.pdf

Diclofenac epolamine
www.ema.europa.eu/en/documents/referral/diclofenac-Article-29-referral-assessment-report_en.pdf

Didanosine
www.ema.europa.eu/en/documents/referral/questions-answers-didanosine-associated-names-didanosine-gastro-resistant-capsules-200-250-400-mg_en.pdf

Docetaxel Teva Generics and associated names
www.ema.europa.eu/en/documents/referral/docetaxel-teva-generics-Article-29-referral-assessment-report_en.pdf

Doxagamma and associated names
www.ema.europa.eu/en/documents/referral/opinion-following-Article-292-referral-doxagamma-4-mg-prolonged-release-tablets-associated-names_en.pdf

Doxastad and associated names www.ema.europa.eu/en/documents/referral/opinion-following-Article-292-referral-doxastad-4-mg-prolonged-release-tablets-associated-names_en.pdf

Doxazosin Retard Arrow and associated names
www.ema.europa.eu/en/documents/referral/opinion-following-Article-292-referral-doxazosin-retard-arrow-4-mg-prolonged-release-tablets_en.pdf

Doxazosin Winthrop and associated names
www.ema.europa.eu/en/documents/referral/opinion-following-Article-292-referral-doxazosin-winthrop-4-mg-prolonged-release-tablets-associated_en.pdf

Fentanyl-ratiopharm Matrixpflaster and associated names
www.ema.europa.eu/en/documents/referral/opinion-following-Article-294-referral-fentanyl-ratiopharm-25/50/75/100-mg/h-matrixpflaster-associated-names-international-non-proprietary-name-inn-fentanyl-background_en.pdf

Fentanyl-ratiopharm TTS and associated names
www.ema.europa.eu/en/documents/referral/opinion-following-Article-294-referral-

fentanyl-ratiopharm-25/50/75/100-mg/h-tts-associated-names-international-non-proprietary-name-inn-fentanyl-background-information_en.pdf

Fentrix
www.ema.europa.eu/en/documents/referral/questions-answers-referral-fentrix-associated-names-25-50-70-100-microgram/hour-fentanyl-transdermal-patch_en.pdf

Fluoxetin NM
www.ema.europa.eu/en/documents/referral/opinion-following-Article-10-referral-fluoxetin-nm-international-non-proprietary-name-inn-fluoxetine_en.pdf

Galantamine Stada and associated names
www.ema.europa.eu/en/documents/referral/questions-answers-galantamine-stada-associated-names-galantamine-8-16-24-mg-prolonged-released_en.pdf

Glimepirida Parke-Davis and assocoated names
www.ema.europa.eu/en/documents/referral/glimepirida-parke-davis-Article-294-referral-assessment-report_en.pdf

GVK Biosciences
www.ema.europa.eu/en/documents/referral/gvk-biosciences-Article-31-referral-gvk-biosciences-final-assessment-report-following-re-examination_en.pdf

Isotretinoin and associated names
www.ema.europa.eu/en/documents/referral/isotretinoin-Article-29-referral-assessment-report_en.pdf

Ketoprofene Ethypharm LP
www.ema.europa.eu/en/documents/referral/summary-information-opinion-pursuant-Article-10-council-directive-75/319/eec-amended-kactoprofane-ethypharm-lp-international-non-proprietary-name-inn-ketoprofen-background_en.pdf

Lansoprazole and associated names
www.ema.europa.eu/en/documents/referral/opinion-following-Article-294-referral-lansoprazole-associated-names-international-non-proprietary_en.pdf

Lisonorm
www.ema.europa.eu/en/documents/referral/opinion-following-Article-294-referral-lisonorm-associated-names-international-non-proprietary-name_en.pdf

Loratadine Sandoz 10
www.ema.europa.eu/en/documents/referral/questions-answers-referral-loratadine-sandoz-10-loratadine-10-mg-tablets-final_en.pdf

Mephatrim
www.ema.europa.eu/en/documents/referral/questions-answers-referral-mephatrim-trimetazidine-35-mg-modified-release-tablets_en.pdf

Merison and associated names
www.ema.europa.eu/en/documents/referral/merisone-associated-names-Article-294-referral-assessment-report_en.pdf

Merisone and associated names
www.ema.europa.eu/en/documents/referral/merisone-associated-names-Article-294-referral-assessment-report_en.pdf

Methylphenidate Hexal
www.ema.europa.eu/en/documents/referral/methylphenidate-hexal-Article-29-referral-assessment-report_en.pdf

Methylphenidate Sandoz
www.ema.europa.eu/en/medicines/human/referrals/methylphenidate-sandoz

Micro Therapeutic Research Labs
www.ema.europa.eu/en/documents/referral/micro-therapeutic-research-Article-31-referral-chmp-assessment-report_en.pdf

Mifepristone Linepharma
www.ema.europa.eu/en/medicines/human/referrals/mifepristone-linepharma

Mometasone Furoate Sandoz
www.ema.europa.eu/en/documents/referral/questions-answers-mometasone-furoate-sandoz-mometasone-furoate-nasal-spray-50-microgram/dose_en.pdf

Myoson and associated names
www.ema.europa.eu/en/documents/referral/myoson-associated-names-Article-294-referral-assessment-report_en.pdf

Okrido
www.ema.europa.eu/en/documents/referral/questions-answers-okrido-prednisolone-sodium-phosphate-oral-solution-6-mg/ml_en.pdf

Paclitaxel Hetero and associated names
www.ema.europa.eu/en/documents/referral/paclitaxel-hetero-associated-names-Article-294-referral-assessment-report_en.pdf

Pantoprazole Bluefish
www.ema.europa.eu/en/documents/referral/questions-answers-referral-pantoprazole-bluefish-pantoprazole-20-40-mg-tablets_en.pdf

Pantoprazole Olinka (EMEA/H/A-29/1169)
www.ema.europa.eu/en/documents/referral/questions-answers-referral-pantoprazole-olinka-pantoprazole-20-40-mg-tablets-ema/h/29/1169_en.pdf

Pantoprazole Olinka (EMEA/H/A-29/1170)
www.ema.europa.eu/en/documents/referral/questions-answers-referral-pantoprazole-olinka-pantoprazole-20-40-mg-tablets-emea/h/29/1170_en.pdf

Perlinring and associated names
www.ema.europa.eu/en/documents/referral/perlinring-Article-294-referral-assessment-report_en.pdf

Prokanazol
www.ema.europa.eu/en/documents/referral/questions-answers-referral-prokanazol-capsules-containing-itraconazole-100-mg_en.pdf

Rigividon
www.ema.europa.eu/en/documents/referral/opinion-following-Article-292-referral-rigevidon-international-non-proprietary-name-inn_en.pdf
Sabumalin
www.ema.europa.eu/en/documents/referral/questions-answers-referral-sabumalin-salbutamol-metered-dose-aerosol-inhaler-100-mg/dose_en.pdf

Sanohex
www.ema.europa.eu/en/documents/referral/questions-answers-referral-sanohex-salbutamol-metered-dose-aerosol-inhaler-100-mg/dose_en.pdf

Semler
www.ema.europa.eu/en/documents/referral/semler-Article-31-referral-chmp-assessment-report_en.

Simvastatin Vale
www.ema.europa.eu/en/documents/referral/questions-answers-simvastatin-vale-associated-names-simvastatin-oral-suspension-20-mg/5-ml-40-mg/5-ml_en.pdf

Teicoplanin Hospira
www.ema.europa.eu/en/documents/referral/questions-answers-referral-teicoplanin-hospira-powder-solvent-injection-containing-200-400-mg_en.pdf

Tibolona Aristo and Tibocina and associated names / GCP inspection
www.ema.europa.eu/en/documents/referral/tibolona-aristo-tibocina-associated-names-Article-294-referral-assessment-report_en.pdf

Trimetadizine-ratiopharm
www.ema.europa.eu/en/documents/referral/questions-answers-referral-trimetadizine-ratiopharm-trimetazidine-35-mg-modified-release-tablets_en.pdf

APPENDIX 2

Table of the GCP referrals

Name and place of the research centre	referral type	reason for referral	year	conclusion
Semler Research Center Private Ltd, Karnataka, India bioanalytical site Bangalore, India	Article 31	Between 29 September and 9 October, FDA performed a GCP inspection that identified several issues at Semler's bioanalytical site, including the substitution and manipulation of subjects' clinical samples WHO also inspected the site between 27 – 31 January 2015 and found critical deviations. Quality management and reliability of data	notification of referral 27 April 2016	alternative studies were provided for some **o**f these medicines. These studies show bioequivalence, and therefore, the CHMP recommended that these medicines can remain on the market **PARTIALLY POSITIVE**
Micro Therapeutic Research Labs, Chennai, India and Tamil Nadu, India	Article 31	Critical findings were identified following GCP inspections by the Austrian Federal Office for Safety in Healthcare (BASG) and the Health Care Inspectorate of the Netherlands (IGZ) from 8-12 February 2016 serious doubts on the reliability of the data of bioequivalence studies The findings raise serious concerns related to the suitability of the quality management system at both sites and of the reliability of data submitted in applications for marketing authorisations in EU	Between 1st and 14th December 2016 request for referral	suspension of the marketing authorisations for all remaining medicinal products concerned by this referral procedure, as bioequivalence vis-à-vis the EU reference medicinal products has not been demonstrated. For marketing authorisations of a medicinal product considered critical, the suspension may bioequivalence deferred in the relevant EU Member State(s) for a period which shall not

		Member States in the time period from June 2012 (date of the oldest study inspected) to June 2016		exceed twenty-four (24) months from the Commission Decision. For all other marketing authorisation applications subject to this referral the CHMP considers that the applicants did not submit information which allows establishing bioequivalence to the EU reference medicinal product, and therefore the marketing authorisation applications do not currently fulfil the criteria for authorisation. **NEGATIVE**
Alkem Laboratories Ltd., Taloja, India,	Article 31	On 23 June 2016, the European Medicines Agency (EMA) recommended the suspension of a medicine (Riluzole Alkem), for which studies were conducted at the Alkem Laboratories Ltd site in Taloja, India, and has required companies to provide new data for another medicine before it can bioequivalence authorised in the EU. The recommendations followed a joint routine inspection by German and Dutch authorities in March 2015, which revealed misrepresentation of data during the conduct of two different trials performed in 2013 and 2014 at the Taloja site. The findings cast doubts on the quality management system in place at the site, and thus on the reliability of the data of bioequivalence studies conducted between March 2013 and March 2015.	referral start 1 April 2016.	Riluzole Alkem, a medicine for amyotrophic lateral sclerosis (ALS) which has yet to be marketed in the EU, should now be suspended. Ibuprofen Orion, a painkiller currently under evaluation by national authorities, cannot bioequivalence authorised on the basis of studies carried out at Alkem Laboratories Ltd. So far, no alternative studies from other sources have been provided. • Cefuroxime Ingen Pharma, currently under evaluation by national authorities, can still bioequivalence considered for authorisation, as studies from other sources

				have been provided. • Cefuroxime Alkem and Cefuroxime Krka (antibiotics) can remain on the market in the EU, as alternative studies have been provided that support a positive benefit-risk balance. **PARTIALLY POSITIVE**
Tibolona Aristo and Tibocina and associated names, Sofia, Bulgaria	Article 29(4)	GCP inspection 18-19 June 2013 findings classified as critical: no evidence of adequate transfer and storage of the study PK samples at the clinical site was provided for a period of 75 days (date of first blood collection until last date of shipment to analytical site). In addition, no documentation was made available regarding to reidentification of study samples when transferred from the dry ice box into the freezer and no documentation on the equipment (freezer) where samples were stored or the storage conditions. The CHMP acknowledged that with regard to GCP compliance, these findings must be considered as a critical deficiency.	referral start 5 August 2013.	The CHMP therefore concluded that while notable deviations from GCP requirements were identified during the conduct of the bioequivalence study, the totality of the available evidence confirms that the results of the bioequivalence study are reliable and demonstrates the bioequivalence of the proposed products and the reference product. **POSITIVE**
Cetero Research, Houston (Texas, USA)	Article 31	Inspection by The US Food and Drug Administration concerns over the way laboratory analyses of bio-analytical studies, were conducted at this facility in the period from April 2005 to June 2010. results of the studies concerned could not bioequivalence considered reliable.	01 August 2012	The CHMP recommended the suspension of the marketing authorisations until adequate bioequivalence data is made available **NEGATIVE**.

GVK Biosciences, Hyderabad, India	Article 31	The French Agency on medicinal products (ANSM) conducted an inspection on 19-23 May 2014 data manipulations of electrocardiograms between July 2008 and 2013 critical deficiencies in the quality system lack of GCP training data integrity	referral on 4 August 2014	category 1 products: (products for which MAHs have not provided any biowaiver request or bioequivalence study in other facilities or MAHs have not responded) In conclusion, in the absence of demonstration of the bioequivalence the efficacy and safety of the concerned category 1 medicinal product cannot be established, and the benefit-risk balance cannot be considered positive category 2 products (MAHs have provided biowaiver request, the biowaiver request is acceptable, For the remaining medicinal products in category 2 suspension of the concerned marketing authorisations Category 3 products (MAHs have provided data from other bioequivalence studies) for most the bioequivalence has been established by other studies, for the rest of the products, absence of the demonstration of bioequivalence and the

				efficacy and safety of these medicinal products cannot be established **PARTIALLY POSITIVE**
4 x India 2 x Bulgaria 1 x USA	5 x Article. 31 2 x Article. 29(4), 7 cases	critical deviations in general 2 x suitability of the quality management system 3 x reliability of the data 2 x misrepresentation of data, data manipulations 3 x related to study samples (substitution and manipulation of subjects' clinical samples, adequate transfer and storage of the study samples, missing documentation of reidentification of study samples, equipment or storage conditions) 5 x related with data (reliability of the data, misrepresentation of data, data manipulations) 1 x laboratory analyses	between 2012 - 2016	2 x positive 3 x partially positive 2 x negative outcome