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R E S E A R C H A R T I C L E

Marketing Authorization of Generic Drugs and Challenges

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A B S T R A C T

An Abbreviated New Drug Application (ANDA) contains data which when submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs, provides for the review and ultimate approval of a generic drug product. Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, low cost alternative to the American public. A generic drug product is one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics and intended use. All approved products, both innovator and generic, are listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (*Orange Book*).Generic drug applications are termed "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. Instead, generic applicants must scientifically demonstrate that their product is bioequivalent (i.e., performs in the same manner as the innovator drug). One way scientists demonstrate bioequivalence is to measure the time it takes the generic drug to reach the bloodstream in 24 to 36 healthy, volunteers. This gives them the rate of absorption, or bioavailability, of the generic drug, which they can then compare to that of the innovator drug. The generic version must deliver the same amount of active ingredients into a patient's bloodstream in the same amount of time as the innovator drug.

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

An Abbreviated New Drug Application (ANDA) is an application for a U.S. generic drug approval for an existing licensed medication or approved drug. The ANDA is submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs, which provides for the review and ultimate approval of a generic drug product. Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, low cost alternative to the American public. Electronic submissions of ANDAs have grown by 70% since November 2008. The Section IV challenge has been credited with suppressing new drug innovation. A generic drug product is one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics and intended use. All approved products, both innovator and generic, are listed in FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)[1].

Generic drug applications are termed "abbreviated" because they are generally not required to include preclinical (animal and in vitro) and clinical (human) trial data to establish safety and effectiveness. Instead, generic applicants must scientifically demonstrate that their product is bioequivalent (i.e., performs in the same manner as the innovator drug). One way scientists demonstrate bioequivalence is to measure the time it takes the generic drug to reach the bloodstream in 24 to 36 healthy volunteers. This gives them the rate of absorption, or bioavailability, of the generic drug, which they can then compare to that of the innovator drug. The generic version must deliver the same amount of active ingredients into a patient's bloodstream in the same amount of time as the innovator drug. In cases of topically active drugs, the bioequivalence of a drug can be demonstrated by comparing drugs dissolution or transdermal drug absorption is compared with the innovator drug. In cases of systemically active drugs, active drug blood concentration of that drug is compared with the innovator drug[2].

2. Objectives of the Study

The pharmaceutical industry is comprised of innovative and generic companies. The Innovative companies which are also referred to as “pioneer” or “ethical” companies develop innovative drugs, while the generic companies imitate these innovative drugs. Stringent regulations distinguish the pharmaceutical industry from other industries. Government Regulatory authorities control the development and sales of drugs in order to avoid hazards in which drugs have proved to be dangerous when used. Any drug/medicinal product have to be approved/ authorized by the respective regulatory authorities before it can be placed in the market. To get this approval/authorization, certain trials had to be conducted to prove the safety and efficacy of the drug/medicinal product.

The U.S. is the first country to identify the importance of generic drugs to reduce healthcare costs and introduced the generic drug approval process through the Hatch-Waxman Act. Before 1984, prior to the enactment of the Hatch-Waxman Act, the generic companies were required to duplicate the same health and safety tests conducted by the original applicant for obtaining a generic drug approval for drugs approved after 1962. In other words, a generic company could market a generic version of a new drug approved by FDA after 1962 only after it receives the approval of its full NDA for that product. The repetition of the complete testing resulted in duplicative, unnecessary, expensive, time consuming and ethically questionable pre-clinical and clinical trials. As a consequence, very few generic equivalents were introduced into the market due to the high expenditure for duplicative testing which also resulted in a prolonged monopoly for the patentee even after the patent has expired. To prevent this situation the US government introduced the Hatch-Waxman Act which provided Abbreviated New Drug. Application procedure (ANDA) to expedite the availability of less costly generic drugs by permitting FDA to approve generic versions of pioneer drugs without conducting the costly and duplicative pre-clinical and clinical trials. Further, the generic companies can copy the pioneer drugs that do not have patent protection. Commonly known as “Drug Price Competition¬Hatch-Waxman Act & Patent “The Hatch-Waxman Act is an act dealing¬Term Restoration Act” of 1984[3]. With the approval of generic drugs and associated conditions for getting their approval from FDA, market exclusivity, rights of exclusivity, patent term extension and Orange Book Listing.”

Filing process

Procedures for ANDAs submissions are set forth in FDA’s regulations in part 314 (21 CFR part 314). An ANDA is usually 3 submitted for a drug product that is the same as an already approved drug or listed drug. A *listed drug* is defined in § 314.3(b) as a new drug product that has an effective approval under section 505(c) of the FD&C Act for safety and effectiveness or under section 505(j) of the FD&C Act, which has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j) (5) of the FD&C Act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness (§ 314.161). An applicant submits an ANDA based on a listed drug, and the previously approved drug product on which the ANDA relies is officially known as the *reference listed drug* (RLD). A reference listed drug (RLD) is defined as the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application (§ 314.3(b)). FDA lists approved drugs that may be referenced in an ANDA in the *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book).4 The Orange Book is updated by a monthly cumulative 55 supplement[4].

On July 9, 2012, GDUFA was signed into law by the President to speed the delivery of safe and effective generic drugs to the public and reduce costs to industry. Under GDUFA, FDA agreed to meet certain obligations as laid out in the GDUFA Commitment Letter.5 Among these obligations is FDA’s commitment to performance metrics

for the review of new ANDAs that are submitted electronically following the electronic CTD (eCTD) format. For example, FDA has committed to review and act6 on 90 percent of original ANDA submissions within 10 months from the date of submission in Year 5 of the program, which begins on October 1, 2016. To meet these performance goals, FDA is issuing this guidance to assist ANDA applicants in improving the quality of submissions, to increase the number of original ANDAs acknowledged for receipt upon initial submission, and to decrease the number of review cycles. FDA is committed to providing comprehensive assistance in the early stages of the application process so that an original ANDA will contain all information necessary for FDA to complete its review in one review cycle[5].

New Drug Application (NDA)--This is the formal step a drug sponsor takes to ask that the FDA consider approving a new drug for marketing in the United States. An NDA includes all animal and human data and analyses of the data, as well as information about how the drug behaves in the body and how it is manufactured. When an NDA comes in, the FDA has 60 days to decide whether to file it so that it can be reviewed. The FDA can refuse to file an application that is incomplete. For example, some required studies may be missing. In accordance with the Prescription Drug User Fee Act (PDUFA), the FDA's Center for Drug Evaluation and Research (CDER) expects to review and act on at least 90 percent of NDAs for standard drugs no later than 10 months after the applications are received. The review goal is six months for priority drugs.

Drug Review Steps:

1. Preclinical (animal) testing.
2. An investigational new drug application (IND) outlines what the sponsor of a new drug proposes for human testing in clinical trials.
3. Phase 1 studies (typically involve 20 to 80 people).
4. Phase 2 studies (typically involve a few dozen to about 300 people).
5. Phase 3 studies (typically involve several hundred to about 3,000 people).
6. The pre-NDA period, just before a new drug application (NDA) is submitted. A common time for the FDA and drug sponsors to meet.
7. Submission of an NDA is the formal step asking the FDA to consider a drug for marketing approval.
8. After an NDA is received, the FDA has 60 days to decide whether to file it so it can be reviewed.
9. If the FDA files the NDA, an FDA review team is assigned to evaluate the sponsor's research on the drug's safety and effectiveness.
10. The FDA reviews information that goes on a drug's professional labeling (information on how to use the drug).
11. The FDA inspects the facilities where the drug will be manufactured as part of the approval process.
12. FDA reviewers will approve the application or issue a complete response letter.

The Role of User Fees

Since PDUFA was passed in 1992, more than 1,000 drugs and biologics have come to the market, including new medicines to treat cancer, AIDS, cardiovascular disease, and life-threatening infections. PDUFA has allowed the Food and Drug Administration to bring access to new drugs as fast as or faster than anywhere in the world, while maintaining the same thorough review process.

Under PDUFA, drug companies agree to pay fees that boost FDA resources, and the FDA agrees to time goals for its review of new drug applications. Along with supporting increased staff, drug user fees help the FDA upgrade resources in information technology. The agency has moved toward an electronic submission and review environment, now accepting more electronic applications and archiving review documents electronically[6].

The goals set by PDUFA apply to the review of original new human drug and biological applications, resubmissions of original applications, and supplements to approved applications. The second phase of PDUFA, known as PDUFA II, was reauthorized in 1997 and extended the user fee program through September 2002. PDUFA III, which extended to Sept. 30, 2007, was reauthorized in June 2002.

PDUFA III allowed the FDA to spend some user fees to increase surveillance of the safety of medicines during their first two years on the market, or three years for potentially dangerous medications. It is during this initial period, when new medicines enter into wide use, that the agency is best able to identify and counter adverse side effects that did not appear during the clinical trials.

On September 27, 2007, President Bush signed into law the Food and Drug Administration Amendments Act of 2007 which includes the reauthorization and expansion of the Prescription Drug User Fee Act. The reauthorization of PDUFA will significantly broaden and upgrade the agency's drug safety program, and facilitate more efficient development of safe and effective new medications for the American public.

3. The Quality of Clinical Data

The Food and Drug Administration relies on data that sponsors submit to decide whether a drug should be approved. To protect the rights and welfare of people in clinical trials, and to verify the quality and integrity of data submitted, the FDA's Division of Scientific Investigations (DSI) conducts inspections of clinical investigators' study sites. DSI also reviews the records of institutional review boards to be sure they are fulfilling their role in patient protection. "FDA investigators compare information that clinical investigators provided to sponsors on case report forms with information in source documents such as medical records and lab results," says Carolyn Hommel, a consumer safety officer in DSI[7]. DSI seeks to determine such things as whether the study was conducted according to the investigational plan, whether all adverse events were recorded, and whether the subjects met the inclusion/exclusion criteria outlined in the study protocol. At the conclusion of each inspection, FDA investigators prepare a report summarizing any deficiencies. In cases where they observe numerous or serious deviations, such as falsification of data, DSI classifies the inspection as

"official action indicated" and sends a warning letter or Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) to the clinical investigator, specifying the deviations that were found.

The European Medicines Agency operates as a decentralized scientific agency (as opposed to a regulatory authority) of the European Union and its main responsibility is the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use. More specifically, it coordinates the evaluation and monitoring of centrally authorised products and national referrals, developing technical guidance and providing scientific advice to sponsors. Its scope of operations is medicinal products for human and veterinary use including biologics and advanced therapies, and herbal medicinal products.

The agency is composed of the Secretariat (ca. 600 staff), a management board, six scientific committees (human, veterinary and herbal medicinal products, orphan drugs, paediatrics and advanced therapies) and a number of scientific working parties. The Secretariat is organised into five units: Directorate, Human Medicines Development and Evaluation, Patient Health Protection, Veterinary Medicines and Product Data Management, Information and Communications Technology and Administration. The Management Board provides administrative oversight to the Agency: including approval of budgets and plans, and selection of Executive Director. The Board includes one representative of each of the 27 Member States, two representatives of the European Commission, two representatives of the European Parliament, two representatives of patients' organisations, one representative of doctors' organisations and one representative of veterinarians' organisations. The Agency decentralises its scientific assessment of medicines by working through a network of about 4500 experts throughout the EU. The EMA draws on resources of over 40 National Competent Authorities (NCAs) of EU Member states[8].

Centralized marketing authorizations and CHMP/CVMP

The centralized procedure allow companies to submit a single application to the Agency to obtain from the European Commission a centralised (or 'Community') marketing authorisation (MA) valid in all EU and European Economic Area (EEA)-European Free Trade Association (EFTA) states (Iceland, Liechtenstein and Norway). The centralised procedure is compulsory for all medicines derived from biotechnology and other high-tech processes, as well as for human medicines for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions, and viral diseases, and for veterinary medicines for use for growth or yield enhancers. The centralized procedure is also open to products that bring a significant therapeutic, scientific or technical innovation, or is in any other respect in the interest of patient or animal health. As a result, the majority of genuinely novel medicines are authorized through the EMA.

For products eligible for or requiring centralized approval, a company submits an application for a marketing authorization to the EMA. A single evaluation is carried out through the Committee for Medicinal Products for Human Use (CHMP) or Committee for Medicinal Products for Veterinary Use (CVMP). If the relevant Committee concludes that the quality, safety and efficacy of the medicinal product is sufficiently proven, it adopts a positive opinion. This is sent to the European Commission to be transformed into a marketing authorisation valid for the whole of the EU. A special type of approval is the paediatric-use marketing authorisation (PUMA), which can be granted for medical products intended exclusively for paediatric use. The CHMP and CVMP are obliged by the Regulation to reach decisions within 210 days, though the clock is stopped if it is necessary to ask the applicant for clarification or further supporting data. This compares well with the average of 500 days taken by the U.S. FDA[9].

From Community to Union - the institutions

The European Economic Community institutions were founded in the aftermath of the Second World War, to bring European nations closer together, and establish an economic basis for peace and stability for the generations to come. In 50 years, the Community's institutions have grown larger and more numerous, but they still form the constitutional framework within which Member States work towards the ever closer union envisaged by its founders. In the early years, the Commission would propose, the European Parliament would advise, the Council of Ministers would decide and the Court of Justice would interpret. However, the European Single Act (1986*), the Maastricht Treaty on European Union (1992*), and the Treaty of Amsterdam of (1997*), have changed the way they work, and extended their remit beyond purely economic matters to encompass public health, social policy, research, and consumer and environment protection. The 1957 Treaty of Rome empowered the European Parliament only to deliver opinions on European Commission proposals for legislation, under the "consultation" procedure. Decisions were taken by the Council of Ministers, which was not obliged to take these opinions into account. The 1986 Single European Act gave Parliament more say in the drafting of Community legislation, by introducing the "co-operation procedure". However, the Council still had the final word. Under the "co-decision" procedure, incorporated in the Treaty in Maastricht and revised in Amsterdam, no draft text can become law without the formal agreement of both the European Parliament and the Council. In other words, as far as the procedure is concerned, these two institutions are now on an equal footing[10]. The Treaty of Amsterdam, which entered into force on 1 May 1999, thus made some significant institutional changes. Here are some examples.

- The role of the European Parliament, as a genuine co-legislator with the Council, was recognized by streamlining the co-decision procedure and extending the areas to which it applies. Overall, the number of procedures by which Parliament helps to shape legislation was reduced to three, i.e. co-

decision, assent and consultation. Parliament was also empowered to make proposals for its own electoral procedure, based on principles common to all Member States.

- The areas in which the Council of Ministers takes decisions by a qualified majority voting was also extended, which should facilitate decision-making.
- A more effective and efficient Commission, which plays a central role in the institutional structure as initiator, administrator, mediator, negotiator and guardian of the Treaties.
- The powers of the Court of Justice have been extended and clarified as regards safeguarding fundamental rights, action by the Union on asylum and immigration, and cooperation in police and judicial matters.

Types of procedure

There are several alternative procedures to choose from depending on which countries the product is going to marketed in and the type of medicine.

Centralized procedure:

In the European Union (EU), a company may submit a single application to the European Medicines Agency (EMA) for a marketing authorisation (licence) that is valid simultaneously in all EU Member States, plus Iceland, Liechtenstein and Norway. This is called the centralised (or community) authorisation procedure, and is mandatory for certain types of medicines and optional for others. (The precise scope is set out in Annex I of Regulation (EC) No 726/2004 (external link). Further information about European applications can be found on the EMA website (external link).

Clarification regarding Centrally Authorized Products (national notifications):

Although the EMA is the main point of contact for issues regarding EU licenses, there are occasion in which marketing authorisation holders (MAH) may need to liaise directly with National Agencies when required by the EMA (eg conditions of approval) .

One of such requirements can be to submit Education Materials. MAH needing to use education materials in the United Kingdom will need to approach the MHRA and seek our opinion on those. To ensure these types of submissions are promptly assessed, we request the MAHs to notify the MHRA by email when the education materials are dispatched. This email notification should mention product name, active substance, centralised procedure number (EMEA/H/C/….), date of the dispatch and confirm department/address to which it was sent (e.g. Area 8 - Submission Centre for CAPs). Other authorisation procedures are used for medicines that do not fall within the mandatory scope of the centralised procedure, these are:

National procedure:

Each EU Member State has its own procedures for the authorisation of medicines that fall outside the scope of the centralised procedure. Applicants must submit an application to the competent authority of the Member State. In the UK, this is the MHRA. Applicants will receive assessment reports for major, standard and complex national initial applications. The assessment report will be sent to the applicant with the request for further information at the initial assessment stage. Following the applicant's submission of responses, a new assessment report (containing the assessment of the responses only) will be sent to the applicant. These reports will help applicants better understand the context and basis of the comments raised by assessors[11].

Decentralized procedure:

Using the decentralized procedure, companies may apply for simultaneous authorization in more than one EU country of products that have not yet been authorised in any EU country and that do not fall within the mandatory scope of the centralized procedure.

Mutual recognition procedure:

In the mutual recognition procedure, a medicine is first authorised in one EU Member State, in accordance with the national procedures of that country. Following this, further marketing authorisations can be sought from other EU countries in a procedure whereby the countries concerned agree to recognise the validity of the original, national marketing authorisation.

Types of application

Applications for new active substances are described as 'full applications'. Applications for medicines containing existing active substances are described as 'abbreviated' or 'abridged applications'. The legal basis for all types of application is set out in Directive 2001/83/EC and in Regulation (EC) No726/2004.

Marketing authorization via national procedure:

Applicants following the National Procedure will be granted a marketing authorization that is valid only in the Netherlands. It is granted by the MEB. Furthermore, this marketing authorization is not based on recognition of another marketing authorization for the same product awarded by an assessment authority of another EU/EEA Member State. This means that the medicinal product to which the dossier relates can only be placed on the market in the Netherlands.

The National Procedure can also serve as the first phase of a Mutual Recognition procedure if the Netherlands is going to act as the reference member state (RMS) in that procedure. It is not always possible for applicants to follow the National Procedure. In the case of medicinal products in the category for which the Centralised European procedure is compulsory, that procedure must be followed. In addition, the National Procedure is not available in the case of medicinal product dossiers where the same applicant has already obtained marketing authorisation in one of the other Member States of the EU/EEA or has already submitted an application for marketing authorisation in one of the other Member States of the EU/EEA and the application is under consideration. In the latter case, applicants must follow a Mutual Recognition procedure[11].

Marketing authorization for a product

Applicants wishing to follow a National Procedure must submit a marketing authorisation dossier to the MEB Agency. The MEB will assess the risk/efficacy ratio of the medicinal product. The MEB has up to 210 days to reach a final decision. This period may be suspended to allow the company to answer questions. Companies can also give

verbal explanations relating to the dossier they have submitted. If the decision is favourable, the Summary of Product Characteristics, the package leaflet and the label text (including layout) will be determined when the marketing authorization is granted. Decisions to grant national marketing authorizations are recorded in a register of medicinal products.

Guidelines for medicinal products with a known active ingredient: A known active ingredient is one which has already been used in another medicinal product that has been granted marketing authorization in the EU/EEA. When certain conditions are met the dossier for a medicinal product containing a known active ingredient does not have to contain preclinical or clinical test results. If this is the case, the applicant must show that the medicinal product is a "generic" version of a reference medicinal product. The reference medicinal product itself must have been granted marketing authorization in the EU/EEA at least eight years previously.

A generic medicinal product is a medicinal product that has the same qualitative and quantitative composition in respect of the active ingredients and the same pharmaceutical form, and that has been shown to be bioequivalent to the reference medicinal product. The various salts, esters, ethers, isomers, mixtures of isomers, complexes and derivatives of an active ingredient are regarded as the same active ingredient, unless their safety or efficacy properties are markedly different. If this is the case, the applicant must submit additional data to show that the various salts, esters or derivatives of an authorised active ingredient are sufficiently safe and/or effective. The various oral immediate-release pharmaceutical forms are regarded as a single pharmaceutical form[12].

Line extensions

A line extension is an application for a product that only differs in pharmaceutical form and/or strength from one or more other pharmaceutical products for which the applicant either holds a marketing authorization, or has submitted a marketing authorization application. A line extension therefore requires a separate marketing authorization application, and the holder/applicant of this marketing authorization is the same as for the other products in the 'range'.

Applicants should also consult the relevant European guidelines for more information about the requirements governing dossiers for line extensions. They can be found at Eudralex - Volume 2.

Duplex marketing authorizations

A duplex marketing authorisation is a marketing authorisation for a product of which the dossier is identical to that of a product which is already authorised. In principle, this concerns a standard marketing authorisation, and the dossier must meet the known legal criteria. In a duplex marketing authorisation procedure, the MEB can waive a full evaluation, and the proof of authorisation (marketing authorisation) can be quickly issued. The Medicines and Healthcare Products Regulatory Agency (MHRA) is a UK government agency which is responsible for ensuring that medicines and medical devices work and are acceptably safe. The Medicines and Healthcare products Regulatory Agency was formed in 2003 with the merger of the Medicines Control Agency (MCA) and the Medical Devices Agency (MDA). In April 2013, it merged with the National Institute for Biological Standards and Control (NIBSC) and was rebranded, with the MHRA identity being used for the parent organization and one of the centres within the group. It is an executive agency of the Department of Health[13].

The MHRA is divided into three main centers:

- MHRA Regulatory (the regulator for the pharmaceutical and medical devices industries)
- Clinical Practice Research Datalink
- National Institute for Biological Standards and Control

History:

In 1999, the Medicines Control Agency (MCA) took over control of the General Practice Research Database (GPRD) from Office for National Statistics. Medicines Control Agency (MCA) and the Medical Devices Agency (MDA) merged in 2003 to form the Medicines and Healthcare products Regulatory Agency (with a lower case "products" at that time). In April 2012, the GPRD was expanded and relaunched as the Clinical Practice Datalink (CPRD). In April 2013, the MHRA merged with the National Institute for Biological Standards and Control (NIBSC) and was rebranded, with the MHRA identity being used for the parent organisation and one of the centres within the group. At the same time the CPRD was formally declared a separate centre of the MHRA, too.

Roles:

1. Operate post-marketing surveillance for reporting, investigating and monitoring of adverse drug reactions to medicines and incidents with medical devices.
2. Assessment and authorization of medicinal products for sale and supply in UK.
3. Oversee the Notified Bodies that ensure medical device manufacturers comply with regulatory requirements before putting devices on the market.
4. Operate a quality surveillance system to sample and test medicines to address quality defects and to monitor the safety and quality of unlicensed products.
5. Investigate internet sales and potential counterfeiting of medicines, and prosecute where necessary.
6. Regulate clinical trials of medicines and medical devices.
7. Monitor and ensure compliance with statutory obligations relating to medicines and medical devices.
8. Promote safe use of medicines and devices.
9. Manage the Clinical Practice Research Datalink and the British Pharmacopoeia.

MHRA hosts and supports a number of expert advisory bodies, including the Commission on Human Medicine which replaced the Committee on the Safety of Medicines in 2005, and the British Pharmacopoeia Commission. As part of the European system of approval, MHRA or other national bodies can be the rapporteur or co-rapporteur for any given pharmaceutical application, taking on the bulk of the verification work on behalf of all members, while the

documents are still sent to other members as and where requested.

Funding

The MHRA is funded by the Department of Health for the regulation of medical devices, whilst the costs of medicines regulation is met through fees from the pharmaceutical industry.[3] This has led to suggestions by some MPs that the MHRA is too reliant on industry, and so not fully independent.[4] The European Medicines Agency (EMA) is a European Union agency for the evaluation of medicinal products. From 1995 to 2004, the European Medicines Agency was known as European Agency for the Evaluation of Medicinal Products.[1]

Roughly parallel to the U.S. Food and Drug Administration (FDA), but without FDA-style centralization, the European Medicines Agency was set up in 1995 with funding from the European Union and the pharmaceutical industry, as well as indirect subsidy from member states, in an attempt to harmonize (but not replace) the work of existing national medicine regulatory bodies. The hope was that this plan would not only reduce the €350 million annual cost drug companies incurred by having to win separate approvals from each member state but also that it would eliminate the protectionist tendencies of states unwilling to approve new drugs that might compete with those already produced by domestic drug companies. The EU is currently the source of about one-third of the new drugs brought onto the world market each year[14].

Based in London, the EMA was born after more than seven years of negotiations among EU governments and replaced the Committee for Proprietary Medicinal Products and the Committee for Veterinary Medicinal Products, though both of these were reborn as the core scientific advisory committees.

The European Medicines Agency operates as a decentralized scientific agency (as opposed to a regulatory authority) of the European Union and its main responsibility is the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use. More specifically, it coordinates the evaluation and monitoring of centrally authorised products and national referrals, developing technical guidance and providing scientific advice to sponsors. Its scope of operations is medicinal products for human and veterinary use including biologics and advanced therapies, and herbal medicinal products. The agency is composed of the Secretariat (ca. 600 staff), a management board, six scientific committees (human, veterinary and herbal medicinal products, orphan drugs, paediatrics and advanced therapies) and a number of scientific working parties. The Secretariat is organised into five units: Directorate, Human Medicines Development and Evaluation, Patient Health Protection, Veterinary Medicines and Product Data Management, Information and Communications Technology and Administration. The Management Board provides administrative oversight to the Agency: including approval of budgets and plans, and selection of Executive Director. The Board includes one representative of each of the 27 Member States, two representatives of the European Commission, two representatives of the European Parliament, two representatives of patients' organisations, one representative of doctors' organisations and one representative of veterinarians' organisations. The Agency decentralises its scientific assessment of medicines by working through a network of about 4500 experts throughout the EU. The EMA draws on resources of over 40 National Competent Authorities (NCAs) of EU Member states.

The actual application

The results of the testing program are codified in an FDA-approved public document that is called the product label, package insert or Full Prescribing Information. The prescribing information is widely available on the web, from the FDA, drug manufacturers, and frequently inserted into drug packages. The main purpose of a drug label is to provide healthcare providers with adequate information and directions for the safe use of the drug.

The documentation required in an NDA is supposed to tell the drug's whole story, including what happened during the clinical tests, what the ingredients of the drug formulation are, the results of the animal studies, how the drug behaves in the body, and how it is manufactured, processed and packaged. Currently, the decision process for FDA approval lacks transparency; however, efforts are underway to standardize the benefit-risk assessment of new medicines. Once approval of an NDA is obtained, the new drug can be legally marketed starting that day in the U.S.

Once the application is submitted, the FDA has 60 days to conduct a preliminary review which will assess whether the NDA is "sufficiently complete to permit a substantive review". If the NDA is found to be insufficiently complete (and reasons for this can vary from a simple administrative mistake in the application to a requirement to reconduct much of the testing), then the FDA rejects the application with the issue of a Refuse to File letter which is sent to the applicant explaining where the application has failed to meet requirements[15].

Types of ANDA:

Para I: A Para I filing for the launch of generic drug is made when the innovator has not made the required information in the Orange book.

Para II: A Para II filing is made when the drug is already off patent.

Para III: A Para III filing is made when the applicant does not have any plans to sell the generic drug until the original drug is off patent.

Para IV: A Para IV filing for the launch of generic drug is made when the applicant believes its product or the use of its product does not infringe on the innovator's patents or where the applicant believes such patents are not valid or enforceable.

Table 1: Describing Age Group of urinary tract infections with type 2 diabetes mellitus

Age Group	Patients	Percentage	P-Value	Results
20-30	03	2.7%	0.002894	$P < 0.05$

30-40	10	9.0%	0.00001	P < 0.05
40-50	37	33%	0.00001	P < 0.05
50-60	32	29%	0.00001	P < 0.05
60-70	22	20%	0.00001	P < 0.05
70-80	05	4.5%	0.00001	P < 0.05
Above 80	01	0.9%	0.002894	P < 0.05

Based on gender affected by UTI in patients with type2 diabetes mellitus

Gender	Frequency	Percentage	Result	P-Value
Male	47	42.7%	0.00001	P < 0.05
Female	63	57.3%	0.00001	P < 0.05

Table 3: Describing symptoms of UTI in patients with type-2 diabetes mellitus

Symptom S	Frequency	Percentage	Results	P-Value
Fever	30	27.27%	0.00001	P < 0.05
Dysuria	90	81.81%	0.00001	P < 0.05
Abdominal Pain	70	63.63%	0.00001	P < 0.05
Frequency	100	90.90%	0.00001	P < 0.05
Haematuria	10	9.09%	0.00001	P < 0.05
Urgency	95	86.36%	0.00001	P < 0.05
Pelvic Pain	80	72.72%	0.00001	P < 0.05
Vomiting	55	50.0%	0.00001	P < 0.05
Rectal Pain	70	63.63%	0.00001	P < 0.05

Table 4: Multi variables analysis for factors associated with UTI among diabetic patients

Areas	Frequency	Percentage	P-value	Results
Rural	65	59.09%	0.00001	P<0.05
Urban	45	41.0%	0.00001	P<0.05
Drinking Status				
Yes	25	22.7%	0.00001	P<0.05
No	85	77.3%	0.00001	P<0.05
FBS				
<126 mg/dl	32	29.1%	0.00001	P<0.05
>126 mg/dl	78	70.9%	0.00001	P<0.05

Table 5: Organisms isolated from urine samples in type 2 diabetic patients

Organism isolated from Urine samples	Total No. of Isolates	Percentage
Escherichia coli	22	43.1%
Klebsiella species	18	35.2%
Pseudomonas aeruginosa	02	3.92%
Streptococcus viridians	01	1.96%
Staphylococcus species	02	3.92%
Acetobacter species	01	1.96%
Candida species	05	9.8%
Enterococcus species	2	3.96%

Table 6: Drug sensitivity pattern of organisms sourced from the urine samples of type-2 diabetic patients with UTI

Organism isolated from Urine sample	No. of Isolates	Sensitivity							
		AK	N	O	I	TZP	G	D	M
Escherichia coli	22	20	15	10	05	05	00	00	00
Klebsiella species	18	15	08	15	00	05	00	00	00
Pseudomonas Aerginosa	02	02	00	02	01	02	00	00	00
Streptococcus viridians	01	01	00	01	01	01	00	00	00
Staphylococcus Aureus	02	00	01	00	00	01	00	00	01
Acetobacter species	01	01	00	01	01	01	00	00	01
Enterococcus species	02	01	02	02	02	02	00	00	00

Total Percentage		79.1%	54.1%	67.3%	20.8% 35.4%	0%	0%	4.1%

4. Conclusion

Urinary tract infections are common among patients with type-2 diabetes mellitus. UTI are more severe caused by more resistant pathogens and is associated with worse outcomes in patients with diabetes on basis of gender, age and duration of diabetes were found to have increased risk factors for developing UTI in diabetes. Females are more effected with UTI than in males. Based on age group, above 40 years age increases the risk for UTI in type 2 diabetes .E.coli was the most common organism causing UTI in type-2 diabetes mellitus. Now a days, klebsiella species, pseudomonas aerginosa and fungal infections were also causing more factors developing in UTI. Treatment should be offered only to symptomatic cases and antibiotic treatment in such cases serves mostly to increase bacterial resistance. Treatment should be tailored according to severity of infection and culture results. Complicated cases of UTI are infrequent, but are more common in diabetes. The proper management is crucial as prompt diagnosis and correct use of antibiotics is vital for treatment. Prolonged antibiotic management is necessary to prevent reccurence of UTI .Future research in this regard, will hopefully to use preventive measures to decrease the risk of UTI in diabetic patients.

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