

An Approach to Abbreviated New Drug Applications (ANDA) and
Question based Review (QbR)

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List of Abbreviations

ANDA	Abbreviated New Drug Application
API	Active pharmaceutical ingredient
BA	Bioavailability
BE	Bioequivalence
CBER	Center for Biologics Evaluation and Research
CDC	Centers of Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practice
CMC	Chemistry, Manufacturing and Controls
CoA	Certificate of Analysis
CTD	Common Technical Document
DMF	Drug Master File
eCTD	Electronic Common Technical Document
EOB	Electronic Orange Book
ESTRI	Electronic Standards for the Transfer of Regulatory Information
EWG	Expert Working Group
FDA	Food and Drug Administration
FDAMA	Food and Drug Administration Modernization Act
FD&C Act	Federal Food, Drug and Cosmetic Act
GDEA	Generic Drug Enforcement Act
GPhA	Generic Pharmaceutical Association
HHS	US Department of Health & Human Services
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IIG	Inactive Ingredients Database
IND	Investigational New Drug
MaPPS	Manual of Policies and Procedures
MMA	Medicare Prescription Drug Improvement & Modernization Act
NCE	New Chemical Entity
NDA	New Drug Application
NIH	National Institute of Health
NME	New Molecular Entity
NTI	Narrow Therapeutic Index
OCI	Office of Criminal Investigations
OGD	Office of Generic Drugs
ONDQA	Office of New Drug Quality Assessment
ONDC	Office of New Drug Chemistry
OTC	Over-The-Counter
PTO	Patent and Trademark Office
PTR	Patent Term Restoration
QbR	Question-based-Review
QOS	Quality Overall Summary
RLD	Reference Listed Drug
TOC	Table of Content
US	United States

USC	United States Code
USP	United States Pharmacopeia
USPTO	United States Patent and Trademark Office
XML	Extensible Markup Language

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1. Introduction and Scope

In 2007 the sales of US generic pharmaceutical manufacturers accounted for 58.5 billion dollars while at the same time the brand pharmaceutical manufacturer sales accounted for 228 billion dollars. With a growth of more than 7 % the generic industry is growing faster than the world pharmaceutical market [69].

Generic drugs save consumers between \$8 billion and \$10 billion each year according to a 1998 study by the Congressional Budget Office. 8,730 of the 11,487 drugs listed in the FDA's Orange Book have generic counterparts. Generic medicines account for 65% of all prescriptions dispensed in the United States [69].

Because generic manufacturers don't have the same development costs, they can sell their product at substantial discounts. Also, once generic drugs are approved, there is greater competition, which keeps the price down. In 2006, the average retail price of a generic prescription drug was \$32.23 whereas the average retail price of a brand name prescription drug was \$111.02 [69].

Generics drug substitution therefore is important factor providing for significant healthcare savings.

To market a generic product, generic companies must submit an Abbreviated New Drug Application (ANDA). The Drug Price Competition and Patent Term Restoration Act of 1984, more commonly known as the Hatch-Waxman Act, made ANDAs possible by creating a compromise. Generic drug companies gained greater access to the market for prescription drugs, and innovator companies gained restoration of patent life of their products lost during FDA's approval process

Within this thesis, the specific terms and requirements related to the filing of an Abbreviated New Drug Application are discussed.

On introduction of the regulatory framework of ANDAs special consideration is given to the meaning of (Reference) Listed Drug, patent protection, patent certification requirements and market exclusivity. In this context, also the handling of the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations List, better known as Orange Book, is explained.

The availability and termination of the 30-months stay of approval as result of a patent infringement litigation and 180-day exclusivity are discussed in detail considering previous FDA interpretation of the statute, statutory amendments and current guidance.

A separate section is foreseen for the content and format of an Abbreviated New Drug Application. Information on the compilation of Modules 1, 2, 3 and 5 is provided. Requirements for electronic submission in eCTD format are strived.

The new Pharmaceutical Quality Assessment System called Question based Review (QbR), that is the requested format for the Quality Overall Summary in Module 2.3 since the beginning of 2007, is discussed in the last section of this thesis.

2. US Regulatory Environment

2.1 US Government and Legal Structure

2.1.1 Structure of US Government

The Constitution of the United States provides for separation of powers by creation of three separate branches of government, the legislative branch as well as the executive and the judicial branch [1, 2]. The main tasks of the three branches are summarized in the following:

- Legislative Branch - In the United States the power to legislate belongs to Congress. The function of the legislative branch is to make new laws and amend existing laws.
- Executive Branch - The executive branch is organized into departments (e.g., Department of Health and Human Services), agencies such as the Food and Drug Administration, and other entities (e.g., commissions). The departments are assigned responsibility for specific areas of public affairs and enforce the law within these areas. One of the primary functions of the executive branch is to enforce and administer laws passed by the Congress and signed by the President.
- Judicial Branch - The judicial power of the United States is established in the Supreme Court and the federal courts. The task of the judicial branch is the application of law, e.g. by deciding suits brought before the courts.

While the President is the head of the executive branch, and as such, responsible for executing, enforcing, and administering the laws, he also may influence the lawmaking process of the Congress by either approving a bill (draft law passed by Congress), which then may enter immediately into force, or preventing a bill from becoming law by means of a veto [2]. A bill that has become law may only be declared invalid by the United States Supreme Court if the court decides that the law violates the Constitution [2].

2.1.2 The Executive Branch - Regulatory Authority

2.1.2.1 History and Structure

Beginning as the Division of Chemistry in 1867 and after July 1901 named as the Bureau of Chemistry, the Food and Drug Administration (FDA) was established as a government agency in 1930 [3, 8]. The FDA belongs to the US Department of Health & Human Services (HHS), the United States government's principal agency for protecting the health of the public and providing essential human services, including - in addition to the FDA - further agencies, such as the National Institutes of Health (NIH), the Centers of Disease Control and Prevention (CDC) or the Indian Health Service (HIS), to name a few [3, 9].

The general tasks of the FDA are depicted in the FDA's Mission Statement [10]. Accordingly, FDA is responsible for "*protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation*". Moreover, it is FDA's aim "*to advance the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable as well as to provide independent and objective information to the public in order to improve their health.*"

To cope with this broad range of duties the agency's specific responsibilities are assigned to eight different offices/centers [4] amongst them the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) [9].

The CDER, the largest of FDA's five centers, is responsible for assessment of drugs before marketing, safety observation during the use of marketed drugs (pharmacovigilance),

monitoring drug information and advertising as well as establishing standards for drug quality, the manufacturing processes, safety and efficacy [13]. The CDER consists of the Office of New Drug Quality Assessment (ONDQA), responsible for the assessment of new drug applications (NDA) and the Office of Generic Drugs (ODG), which is responsible for Abbreviated New Drug Applications (ANDA) [13].

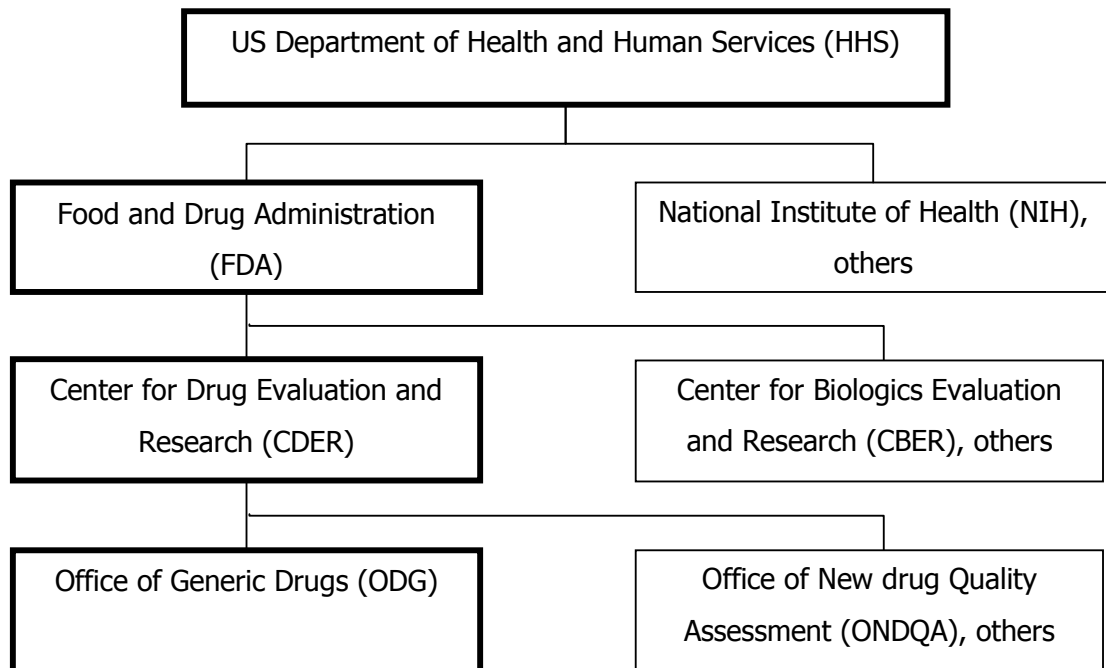


FIGURE 1: ORGANIZATION OF REGULATORY AUTHORITY, FOOD AND DRUG ADMINISTRATION

2.1.3 Rulemaking and Enforcement Actions

As part of the executive body the mission of the FDA is to enforce/administer laws enacted by the US Congress [3, 6, 7, 14]. This duty is carried out by means of:

- developing and announcing regulations that translate the laws into rules which establish or modify the way the agency regulates the products under its field of responsibility
- enforcing these regulations.

2.1.3.1 FDA's Rulemaking

Rulemaking refers to the process that a government agency uses to create, modify, or delete rules in the Code of Federal Regulations (CFR). As in general the laws constitute rather broad provisions, the US departments or regulatory agencies like the FDA have to subsequently create more detailed regulations. Regulations or rules either explain law, describe an agency's organization, or add scientific expertise and implementation detail [5].

Upon proposal of a new regulation by the FDA or revision of an existing one, the upcoming rule is made available to the public for review by an announcement published in the Federal Register, thereby asking for early public input on the proposed regulation. Before drawing up the final rules, which are also published in the Federal Register, the comments made by the public are considered carefully. The final regulation then becomes part of the Code of Federal Regulations which is revised annually [3, 5]. The CFR is divided into 50 titles the FDA's part of which interprets the Federal Food, Drug and Cosmetic Act, the basic food and drug law of the U.S., and its related statutes [5].

2.1.3.2 FDA's Enforcement Actions

FDA's law enforcement actions comprise civil action (e.g. a lawsuit filed in court), criminal action and administrative action. Administrative action, for example, includes the approval of New Drug Applications [14].

Criminal actions are enforced by FDA's Office of Criminal Investigations (OCI). For example OCI executes search warrants, arrest warrants and conducts physical surveillance [11]. The OCI also conducts the majority of criminal investigations related to the Food, Drug & Cosmetic Act.

The FDA enforcement report is published weekly and contains information on actions taken in connection with agency regulatory activities [12].

2.1.4 Legal hierarchy – Laws, Regulations and Guidance

The legal hierarchy distinguishes 3 major categories that are either binding or non-binding [2]:

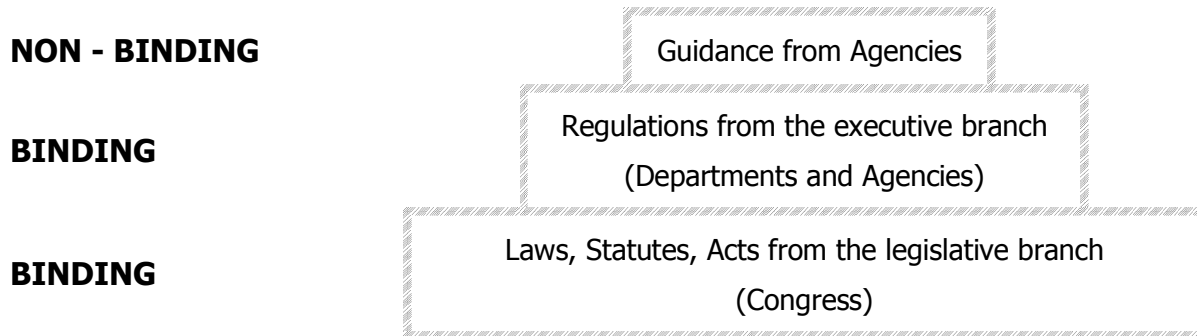


FIGURE 2: HIERARCHY OF LEGAL STRUCTURE

Laws from the legislative branch (Congress) – After enactment of a new law by the Congress and President it is incorporated into the United States Code (USC), which organizes laws into Titles, Chapters and Sections. For example 21 USC 301 et seq. corresponds to Title 21, section 301 et seq., known as the Federal Food, Drug and Cosmetic Act (FD&C Act). The FD&C Act includes its amendments e.g. Drug Price Competition and Patent Term Restoration Act of 1984, more commonly known as the Hatch-Waxman Act [2, 3].

Regulation from the executive branch (Departments and Agencies) – The Federal Regulations are organized into the Code of Federal Regulations or CFR (refer also to section 2.1.3.1). Similar to the USC the CFR is structured into Titles, Chapters and Sections. The regulations proposed by the FDA interpret the Food, Drugs and Cosmetics Act and related statutes. Section 21 of the CFR contains most of the regulations related to food and drugs. Amongst other things the regulations document the majority of actions required by applicants for filing of new drug applications (e.g. 21 CFR Part 314 which relates to applications for FDA approval to market a new drug) [3, 5].

Guidance Documents and Letters to Industry (Agencies) - Agencies also publish Guidance Documents or Guidelines. Guidance Documents represent the Agency's current thinking on a particular subject. Unlike regulations or laws, guidance documents are not enforceable. *These documents are prepared by FDA review staff and applicants/sponsors to provide guidelines to the processing, content, and evaluation/approval of applications and also to the design, production, manufacturing, and testing of regulated products* [3]. However, an alternative approach to a particular Guideline may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

This series of Letters to Industry informs generic drug product manufacturers on the Agency's view with respect to the Drug Price Competition and Patent Term Restoration Act of 1984. Guidelines and Letters to Industry are published on FDA's web page for Guidance Documents (<http://www.fda.gov/cder/guidance/index.htm>).

Manual of Policies and Procedures (MaPPS) from Agencies – *MaPPS provide official instructions for internal practices and procedures followed by CDER staff to help standardize the drug review process and other activities* [3]. Furthermore, MaPPs define activities of drug sponsors (e.g. MAPP 5225.1 - Guidance on the Packaging of Test Batches [5, 7]).

Due to public availability of MaPPs CDER operations, office policies, definitions and staff responsibilities become more transparent. CDER's Manual of Policies and Procedures is published at <http://www.fda.gov/cder/mapp.htm>.

2.2 Brief Overview of American Drug Law History

A view on the American Drug Law is always a view on the Drug Law History. Introductory tutorials and seminars by the FDA often start with an overview describing historical triggers and major achievements of the American Drug Law.

Besides the purely educative purpose, a basic knowledge and understanding of the American Drug Law History is important, since legal acts and amendments are often referred to synonymously for the provisions implemented by that Act (e.g. provisions made by the Hatch-Waxman Act) [16]. Moreover, FDA Rules and Guidance Documents often present the Agency's current thinking in comparison to previous interpretations and provisions.

A brief, chronological overview of the drug law and the content of its amendments is provided in the following.

American Drug Law goes back on a long history. Regulation of food in the United States dates from early colonial times. Federal controls over the drug supply began with inspection of imported drugs in 1848 [8, 16]].

1906 - Food and Drugs Act. The foundation for modern food and drug law was laid, when Congress adopted the Food and Drugs Act of 1906. The Food and Drugs Act was the first nationwide consumer protection law, which made it illegal to distribute misbranded or adulterated foods, drinks and drugs [8, 15, 16].

1938 – Federal Food, Drug and Cosmetics Act (FD&C Act). The Food, Drug, and Cosmetics Act was established in 1938 as the result of a public health disaster. A liquid formulation of Sulfanilamid containing poisonous anti-freeze killed 107 people, most of them children. As a consequence, the Act required companies to prove the safety of new drugs before putting them on the market. Further, the Act introduced toughened criminal sanctions and authorized factory inspection and sample collection. Subsequent Acts only amended the 1938 - Food, Drug, and Cosmetics Act which therefore can be considered the fundament of today's Drug Law [8, 15, 16].

1962 – Kefauver-Harris Drug Amendments. The Kefauver-Harris Drug Amendments was adopted after the Thalidomide disaster. It introduced tightened safety requirements and required manufacturers to prove the effectiveness of their products before marketing them. The law required that all drugs introduced between 1938 and 1962 had to be reviewed for effectiveness retrospectively. Additionally, it made good manufacturing requirements for drug manufacturers statutory [8, 15, 16].

1984 - Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Act). The Hatch-Waxman Act established the ability for generic companies to file an Abbreviated New Drug Application. At the same time, it allows brand-name companies to apply for up to five additional years of patent protection for the new medicines they developed to make up for time lost while their products were going through FDA's approval process.

Therewith the Hatch-Waxman Act eliminated duplicative, unnecessary clinical testing and sped-up the approval of generic drugs [8, 15, 16].

1997 - Food and Drug Administration Modernization Act (FDAMA).

The FDAMA mandated wide-ranging reforms in agency practices. Amongst others ANDAs are affected by labelling changes, paediatric exclusivity and chemistry supplement changes [8, 15].

2003 – Medicare Prescription Drug Improvement & Modernization Act (MMA).

The MMA made significant changes to the generic drug approval process designed to provide more certainty to the generic drug approval process and to speed up the market access of generic of drugs [15, 16].

Key provisions established by the MMA are:

- Statutory basis for single 30-month stay
- Revision of 180-day triggers to first commercial marketing
- Elimination of issues where multiple first filers block one another to market

3. Regulatory Framework and Basis of ANDAs

3.1 Regulatory Framework

The current regulatory framework for generics in the United States is governed by the Drug Price Competition and Patent Term Restoration Act of 1984, more commonly known as the Hatch-Waxman Act, and the Medicare Prescription Drug Improvement & Modernization Act (MMA) of December 2003 [6, 16, 17]. Moreover, the FDA Generic Drugs Final Rule and Initiative of June 2003 implemented new regulations and review procedures to speed up the approval process of generic drugs [16, 18].

The **Hatch-Waxman Act** created section 505(j) of the FD&C Act which was codified under title 21 of the CFR in section 314 (21 CFR 314). Section 505(j) provides the statutory basis allowing pharmaceutical companies to file Abbreviated New Drug Applications (ANDAs) instead of providing a full new drug application comprising the whole range of preclinical and clinical studies [16, 22]. At the same time, the Hatch-Waxman Act allows brand-name companies to apply for up to five additional years of patent protection for new medicines to compensate for time lost while their products were going through FDA's approval process [6, 16, 19].

Provisions of the Hatch-Waxman Act that protect products of innovator companies comprise:

- **Market exclusivity** of up to 5 years
- **Patent Term Restoration** of up to 5 years and a maximum of 14 years of total marketing exclusivity

Benefits of the Hatch-Waxman Act for generic manufacturers include:

- Implementation of **Abbreviated New Drug Applications** to access generic market approval
- Establishment of **bioequivalency** as the basis for approving generic drugs
- Providing manufactures of generics with an **exemption for pre-patent expiry development and testing** including the use of the brand name drug to perform studies required for the approval process
- **180-day generic exclusivity**

With publication of the **Generic Drugs Final Rule and Initiative** in June 2003 [18] FDA revised its interpretation of the Hatch-Waxman Act by improving the implementing regulations with regard to generic drugs. In preparing the Final Rule, the agency carefully reviewed comments submitted by pharmaceutical and food additive manufacturers, biotechnology companies, and trade associations. The agency also worked closely together with the Patent and Trademark Office (PTO) to ensure that FDA's and PTO's regulations will complement each other. The final rule became effective on August 19, 2003, i.e. 60 days after the publication date as of June 18, 2003 [16, 18].

Under FDA's previous interpretations of the Hatch-Waxman Act, brand-name companies have been able to file patents on packaging, ingredient combinations, and other matters in order to get repeated 30-month stays (see 3.4) causing a delay in approval of generic applications. The access to generic drugs was significantly deferred by repeated applications of automatic 30-month stays on later-issued patents. Multiple 30-month stays have even led to delays in generic entry of an additional 4 to 40 months [16, 18].

The final rule facilitates the market entry of generic medicines by

- allowing a maximum of one 30-month stay per Abbreviated New Drug Application instead of the previously possible multiple and overlapping 30 month stays
- clarifying the types of patents that must and must not be submitted to FDA for listing in the Orange Book
- revising the information required to be submitted on patents and consolidating all patent information on declaration forms to make those submissions more informative and precise

The **Medicare Prescription Drug Improvement & Modernization Act** which was signed into law in December 2003 changed provisions of the FD&C Act that were originally added by the Hatch-Waxman Act. Substantial changes relate to 30-month stays and the timing of approval of ANDAs (as discussed in 3.4) [16, 20].

Regarding generics the MMA provides for:

- **Single 30-month** stays on a statutory basis
- **First commercial marketing** to trigger the 180-day exclusivity
- **Forfeiture mechanisms** to avoid scenarios where multiple first filers block one another to market
- **Modifications** to be included **in a single drug application** on a statutory basis. For example, different strengths may be included in a single generic application, whereas different dosage forms (i.e., tablets, capsules) must be in separate applications.

3.2 Basis for Submission

The legal definition of ANDAs is provided in 21 CFR 314.3: "*Abbreviated application means the application described under § 314.94, including all amendments and supplements to the application*" [21].

An "Abbreviated New Drug Application" is called abbreviated because results from (pre-)clinical safety and efficacy studies are usually not required. Instead reference is made to the data on file for an already approved reference drug (see 3.2.2) [16, 17].

The legal basis for the filing of an ANDA is laid down in section 505(j) of the FD&C Act, which was implemented by the Hatch-Waxman Act (see 3.1). Regulatory action required for the submission of an Abbreviated New Drug Application by the applicant is provided in the corresponding section of the CFR, that is subpart C or sections 314.92 to 314.99 [16, 17, 18, 19].

The content and format of an abbreviated application is described in section 314.94 of the CFR [21]. The compilation of an ANDA according to the current requirements will be discussed in detail in section 4 of this thesis.

The *basis for an Abbreviated New Drug Application* is a specific requirement which needs to be included in the submission of an ANDA according to 314.94(a)(3) [21].

An ANDA is usually submitted for a drug product that is the same as a drug product previously approved by the FDA [21]. The previously approved drug product is known as the Reference Listed Drug (RLD - see also 3.2.2).

According to the regulation, the *basis for Abbreviated New Drug Application submission* is generally substantiated by the following particulars:

- (i) *reference to the name of the Listed Drug, including its dosage form and strength and*
- (ii) *a statement as to whether the Listed Drug is entitled to a period of marketing exclusivity.*

However, as stipulated in § 314.92 an Abbreviated New Drug Application may only be submitted for drug products that are the same as the (Reference) Listed Drug [16, 21]. As further detailed in § 314.92(a)(1) the term "same as" means, the drug product and Listed Drug:

- shall contain the identical active ingredients
- shall be identical in strength, dosage form, and route of administration
- shall have identical conditions of use.

Although drugs approved in ANDAs are generally the same as the RLD, certain changes are permitted which are set forth in § 314.93(b) as follows [16, 21]:

- a difference in dosage form
- a difference in strength
- a different route of administration
- substitution of one active ingredient for one of the active ingredients in a listed combination drug.

In order to obtain permission to file an ANDA with any of these changes, an ANDA suitability petition has to be submitted in accordance with 21 CFR 10.20 and in the format specified in §10.30 (see 3.2.3) [16, 21].

3.2.1 Listed Drug

As per the definition given in section 314.3 Listed Drug means *a new drug product that has an effective approval under section 505(c) of the Act for safety and effectiveness or under section 505(j) of the Act* [21, 22]. Thus, ANDAs are allowed to refer to a new drug filed by the New Drug Application (NDA) procedure according to 505(b) or to refer to another generic drug filed by ANDA procedure. However, as required by the definition in Section 314.3, the approved NDA or ANDA should not have been withdrawn from sale due to problems in terms of safety or effectiveness. As set forth in the same paragraph a drug product is deemed to be a Listed Drug on the date of effective approval of the application or abbreviated application, but not when tentative approval is granted [21]. The Listed Drug status can be inferred from the listing of the drug product in the current edition of FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" or any current supplement thereto [23].

Each strength of an approved drug is regarded a separate Listed Drug. Consequently, each strength proposed in an ANDA should refer to the corresponding Listed Drug, although the reference standard for purposes of bioequivalence may be only one strength. Generally, a single application can be used to seek approval for different strengths of the same Listed Drug. Moreover, an applicant may submit an amendment or supplement to obtain approval of a different strength which has not been included in the initially submitted application and is not required to file a separate application for the additional strength. This is explicitly permitted under the Act, as amended by the MMA (see section 505(j)(2)(D)(ii) of the Act) [20].

3.2.2 Reference Listed Drug

3.2.2.1 Definition of Reference Listed Drug

A Reference Listed Drug (RLD) as defined in 21 CFR 314.3 means the medicine that has been approved by the FDA and is listed in FDA's Approved Drug Products with Therapeutic Equivalence Evaluations, better known as the Orange Book (see 3.2.2.2) [23]. Upon submission of an ANDA generic companies must designate an RLD to which the *in vivo* bioequivalence and, in some instances, the *in vitro* bioequivalence of the applicant's product is compared [21].

3.2.2.2 Reference of Listed Drugs in the Orange Book

The FDA's Approved Drug Products with Therapeutic Equivalence Evaluations list, commonly known as the Orange Book, catalogues drug products approved on the basis of adequate safety and effectiveness by the FDA. The main criterion for the inclusion of any product is that it has an effective approval, i.e. after approval of the application it has not been withdrawn for safety or efficacy reasons [23].

The Orange Book comprises a list of four parts:

- (1) approved prescription drug products with therapeutic equivalence evaluations;
- (2) approved over-the-counter (OTC) drug products;
- (3) drug products approved by the Center for Biologics Evaluation and Research
- (4) approved products not marketed and drug products with their approvals withdrawn.

While drug product listed in Part 1 to 3 comprise all approved drug products currently marketed, the drug products listed in part 4 either have never been marketed (e.g. products for exportation or military use) or have been discontinued from marketing for other than safety or efficacy reasons [23].

In the beginning, that is in January 1979, the Approved Drug Products with Therapeutic Equivalence Evaluations List was distributed by the FDA with the intent to provide recommendation to Federal States regarding drug product selection by setting forth FDA's

evaluations of the therapeutic equivalence of drug products that have been approved. At that time, it included only currently marketed prescription drug products [23].

The 1984 Amendments of the Hatch-Waxman Act required the Agency to publish an up-to-date list of all marketed drug products, OTC as well as prescription, that have been approved for safety and efficacy. OTC drug products and drug products with approval under Section 505 of the Act administered by the Center for Biologics Evaluation, previously excluded from the List, are mentioned in the Approved Drug Products with Therapeutic Equivalence Evaluations List from the 7th edition onwards [23].

Under the terms of recommending acceptable candidates for drug product selection, FDA applies specific criteria for the evaluation of therapeutic equivalents. Drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical efficacy and safety profile when administered to patients under the conditions specified in the labelling. The therapeutic equivalents evaluation date is usually the same as the approval date [23].

The coding system for therapeutic equivalents evaluations provides for two basic categories indicated by the first letter of code:

- "A" codes – Drug products that are considered to be therapeutically equivalent to other pharmaceutically equivalent products.
- "B" codes – Drug products that are currently considered to not be therapeutically equivalent to other pharmaceutically equivalent products.

In the meaning of the Orange Book coding system a drug product is rated "A" (therapeutically equivalent) when there are no known or suspected bioequivalence problems or rated "B" when bioequivalence problems have not been resolved. For drug products, which are rated "AB", actual or potential bioequivalence problems have been resolved with adequate in vivo and/or in vitro evidence supporting bioequivalence [23].

In the published version of the Orange Book the Reference Listed Drug is identified by the symbol "+" in the prescription and over-the-counter drug product lists [23].

The publication includes the name of the drug product, dosage form, strength, Reference Listed Drug status, applicants name and the final approval date.

In addition, the addendum to the Orange Book contains drug patent and exclusivity information including patent numbers and patent expiration dates as well as exclusivity codes and expiration dates. Moreover, for a use patent, the Orange Book includes a code identifying the indication covered by patent [23, 24].

3.2.2.3 Reference Standard for Bioequivalence Testing

The Reference Listed Drug is the drug product identified by FDA in the prescription drug product and OTC drug product lists as reference standard to which all generic versions must be shown to be bioequivalent. By designating a single Reference Listed Drug as standard for bioequivalence, FDA intends to avoid possible significant variations among generic drugs and their brand name counterpart resulting from comparison to different Reference Listed Drugs [23].

Title 21 Part 320 of the CFR lays down the requirements for bioavailability and bioequivalence [25]. In the meaning of § 320.1(e) the term "bioequivalence" describes the absence of a significant difference in the rate and extent to which active ingredients or the active moiety of pharmaceutical equivalents or pharmaceutical alternatives become available at the site of drug action.

According to 21 CFR Part 320.1 pharmaceutical equivalents are defined as drug products in identical dosage forms [25]:

- containing the identical amount of identical active ingredients (i.e. same salt or ester of the same active moiety)
- meeting the same batch requirements for identity, strength, purity, and quality, but
- not necessarily containing the same inactive ingredients.

As implied by the meaning of bioequivalence the generic product which is tested for bioequivalence should comply with the above definition of pharmaceutical equivalent or pharmaceutical alternative (identical therapeutic moiety, but not necessarily in the same amount or dosage form or in different salt or ester). Due to this requirement, the identification of an appropriate Reference Listed Drug can be considered a key for development of a generic drug and in planning ANDA submissions, respectively.

3.2.2.4 Using the Orange Book

The Orange Book serves the generic applicant as a source of information relating to the following topics [24]:

- Selection of the Reference Listed Drug
- Obtaining drug patent information, including patent numbers, patent expiration dates and for a use patent, the code identifying the indication covered by the patent
- Identification of exclusivity information, including exclusivity codes and expiration dates.

The Orange Book is available to the generic applicant in a paper version from the US Government Printing Office published as annual edition with monthly cumulative supplements [24]. Furthermore, the annual edition and monthly cumulative supplements are provided in downloadable PDF-format at the Electronic Orange Book (EOB) web page (annual edition on EOB web page: <http://www.fda.gov/cder/ob/docs/preface/eclink.htm>). The PDF annual and cumulative supplements duplicate previous paper versions.

Since February 2005, daily update on Abbreviated New Drug Applications and patent information is provided on the Electronic Orange Book version (<http://www.fda.gov/cder/ob/default.htm>). The EOB can be searched by active ingredient, proprietary name, application holder, application number as well as by patent [24].

3.2.3 Citizen Petitions

Petition for not listed products or Listed Drugs not designated a Reference Listed Drug – As already mentioned under 3.2.2.2 the Orange Book does not include drug products that were not being marketed on September 24, 1984, despite the fact that FDA had previously approved them for safety and efficacy. Products that have been discontinued at a later time point are to be found in the "Discontinued Section" and do not have RLD status.

When an ANDA applicant wishes to refer to a listed drug that is not designated as the Reference Listed Drug or a Listed Drug that has been voluntarily withdrawn from sale in the United States, the application must be accompanied by a citizen petition under 21 CFR 314.93 and 21 CFR 314.122 [21, 23]. The petition should be submitted in accordance with § 10.25(a) and the format specified in § 10.30 [26]. To support its petition the petitioner has to provide all available information regarding the reasons for which marketing of the drug product was discontinued. FDA may approve or reject the petition for reasons of safety or efficacy of the drug product [21].

Upon approval of the petition, the not listed product or Listed Drug will be designated as an additional Reference Listed Drug. The petitioner will need to cite the new Reference Listed Drug on submission of its Abbreviated New Drug Application [21].

Petition to request a change from a Listed Drug – Although drugs approved in ANDAs are generally the same as the RLD, the following changes described in § 314.93 are permitted [21]:

- a different dosage form
- a difference in strength
- a different route of administration
- substitution of one active ingredient for one of the active ingredients in a listed combination drug.

In order to obtain permission to file an ANDA with any of these changes, an ANDA suitability petition has to be submitted in accordance with 21 CFR 10.20 and in the format specified in §10.30 [21, 26]. The petitioner has to demonstrate that the difference does not adversely effect the safety and effectiveness of the drug product.

Suitability petitions must be submitted to the FDA and approved before submission of the ANDA. The Agency usually handles ANDA suitability petitions in 90 days as set forth under § 314.93(e) [21].

For utilizing an approved suitability petition as basis of submission the applicant must provide a copy of the respective approval letter as required by 314.94(a)(3)(iii) [21].

In case the proposed drug product differs from the RLD and the applicant does not intend to submit an ANDA suitability petition, there is still the option of submitting a NDA according to 505(b)(2) generally relying on references to studies conducted by others and/or on published literature.

3.3 Market Exclusivity and Patent Protection

Provisions of the Hatch-Waxman Act protect innovator drug products by market exclusivity and patent term restoration each of up to 5 years [21, 27]. While exclusivity is awarded by the FDA, patents are awarded by the United States Patent and Trademark Office (USPTO) [16, 28, 32].

3.3.1 Market Exclusivity

New drug exclusivity is implemented by provisions under section 505(j)(5)(F) of the Act codified in 21 CFR 314.108 [27]. This section of the Act provides for specific time periods, known as new drug product exclusivity or market exclusivity, during which an ANDA cannot be submitted or the effective date of approval for an ANDA must be delayed.

As per section 505(c)(3)(E) and 505(j)(5)(F) of the Act a 5-year period of exclusivity is granted for new chemical entities (NCE) not previously approved by FDA [22, 27]. These sections of the Act expressly state that no ANDA may be submitted during the exclusivity period and that such applications may be submitted after 4 years only if they contain a certification of patent invalidity or non-infringement. Under the same sections it is laid down that certain drugs or changes to drugs such as a change in dosage form or strength, new indications or routes of administration can receive 3 years period of exclusivity [22, 27]. However, approval of three-year exclusivity requires new clinical investigations (other than bioavailability studies).

Drug products with paediatric indication can qualify for additional 6 months of exclusivity as an incentive to sponsors to conduct more studies regarding the use of drugs in the paediatric population. This attaches to either a NCE exclusivity period or a patent if agreed before the patent is expired. The paediatric exclusivity is provided for in 505A of the Act [27].

For the sake of completeness it should be mentioned that 7 years of market exclusivity are granted for new orphan indications [22, 29].

3.3.2 Patent Protection and Patent Term Restoration

Patent applications are filed with the USPTO, which is part of the US Department of Commerce [16, 28]. The patent confers *"the right to exclude others from making, using, offering for sale, or selling the invention throughout the United States or importing the invention into the United States"* [30].

Hence, the role of the USPTO is only to grant patents or to register trademarks but not to protect the inventions. The patentee itself has to protect its intellectual property rights against others making use of its invention [30].

Generally, the period of validity of a new patent is 20 years from the date of filing of the patent application [30, 31].

Patents may only be enforced via lawsuits. If a patent is infringed, the patentee may sue for relief in the appropriate federal court. The patentee may ask the court for a restriction to prevent the continuation of infringement and may also ask the court for an award of damages because of the infringement. In such an infringement suit, the defendant may raise the question of the validity of the patent, which is then decided by the court [30].

Patent Term Restoration (PTR) enacted by the Hatch-Waxman Act in 1984 compensates patent holders for marketing time lost while developing the product and awaiting FDA approval by extending the patent term up to five years [31, 32]. The exact number of days recovered is based on the NDA review time and half the Investigational New Drug (IND) testing time, but total marketing exclusivity for a given drug cannot exceed 14 years [31]. Patent extension must be claimed within 60 days of NDA approval [31]. The regulations governing the Patent Term Restoration program are located in the Code of Federal Regulations, 21 CFR Part 60 [33]. The

FDA assists the Patent and Trademark Office in determining a product's eligibility for patent extension, but the PTO determines the period of patent extension [31, 32, 33].

3.3.3 Patent Information required with an NDA

3.3.3.1 Patent information to be submitted by the NDA Applicant or Patent Holder

Patent information is required to be filed by the NDA applicant/ NDA holder or patent holder under section 505(b) and (c) of the Act [22] and the Code of Federal Regulations § 314.53 [21]. Section 505(b)(1) of the Act requires all NDA applicants to file, as part of the NDA, *the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug* [22]. If a patent is issued after the filing date but before approval of the application, the applicant needs to amend the application later on to include the aforementioned information.

For patents issued after approval of the application, the holder is required to file such information under section 505(c)(2) of the Act not later than thirty days after the date of issuance of that patent [22].

In essence of CFR 314.53 the NDA applicant/ NDA holder or patent holder is required to file patents claiming for:

- the drug substance (ingredient);
- the drug product (formulation and composition); and
- the method of use.

Upon submission of the patent information, FDA is directed by the Act to publish the information of the aforementioned patents in the Orange Book [22]. This does not apply to process patents and patents claiming packaging, metabolites or intermediates.

3.3.3.2 Patent information to be submitted with an ANDA

According to section 505(j)(2) of the Act ANDAs are required to include certifications on the status of all patents applicable to the listed drug [22]. Section § 314.94(a)(12) of the CFR describes the patent certification requirements for ANDAs as interpreted by the FDA [21]. Section 314.94 [21] presents an overview on the provisions that will be discussed in turn:

- § 314.94(a)(12) (i) Patents claiming drug, drug product, or method of use
- (ii) No relevant patents
 - (iii) Method of use patent
 - (iv) Method of manufacturing patent
 - (v) Licensing agreements.

(i) Patents claiming drug, drug product, or method of use. As per § 314.94(a)(12)(i), a patent certification shall be submitted for each patent issued by the USPTO that claims the listed drug product, the drug substance thereof or a use of the Reference Listed Drug, i.e. those patents required to be filed under § 314.53 of the CFR and listed in the Orange Book (see also 3.3.3.1) [21, 37].

In case such a patent is existing four types of certifications may be applicable which are differing in the statement to be made by the applicant with regard to the patent status [21, 37].

TABLE 1: TYPE OF PATENT CERTIFICATIONS AND EFFECTS ON ANDA APPROVAL

Certificate	Patent Status	Statement	Effects ANDA Approval
Paragraph I	Patent existing but not submitted.	The patent information has not been filed.	ANDA may be approved immediately
Paragraph II	Patent listed but expired.	The patent has expired.	ANDA may be approved immediately
Paragraph III	Patent listed not expired.	The date on which the patent expires.	ANDA may be approved on patent expiry date
Paragraph IV	Patent listed not expired.	The patent is invalid, unenforceable or will not be infringed.	Possibility of law suit and 180 day exclusivity (see sections 3.4 and 3.5.)

A Paragraph I Certification has to be filed in cases where the applicant believes that a patent exists but the patent owner has not filed patent information with FDA. According to the rule, the ANDA applicant has to certify that, "in its opinion and to the best of its knowledge," no patent information has been submitted to the FDA. A Paragraph II Certification is filed if a patent listed in Orange Book has expired at the time of application. ANDAs containing Paragraph I and Paragraph II certifications may be approved immediately if the application is otherwise approvable [21, 27, 37].

In situations where listed patents have not yet expired it is at the option of the applicant to either file a Paragraph III Certification or a Paragraph IV Certification. By submitting a Paragraph III Certification the applicant decides to accept delay of the ANDA approval until the expiry date of the respective patent. ANDAs including a Paragraph III Certification may obtain tentative approval that will become effective after the date of patent expiry [16, 21, 37].

In contrast, applicants who submit a Paragraph IV Certification challenge the patent assuming that the latter is invalid, unenforceable or that the patent will not be infringed by the manufacture, use or sale of the drug for which the ANDA is submitted. Inclusion of a Paragraph IV Certification permits the Applicant to file its ANDA 4 years after approval of a new chemical entity, that is 1 year before actual expiry of the 5 year exclusivity [16, 21].

Section 505(j)(5)(B)(iv) of the Act established a financial incentive for generic companies to file Paragraph IV Certifications and therewith to challenge listed patents by offering a 180-day period of generic marketing exclusivity [36, 37]. The implementation of the 180-day exclusivity is discussed separately in section 3.5 of this thesis.

(ii) No relevant patents. The applicant is required to submit a patent certification under § 314.94(a)(12)(ii), if the applicant believes that no relevant patent exists [21, 27].

As stated in the CFR, the applicant makes a patent certification under § 314.94(a)(12)(ii) if *in the opinion of the applicant and to the best of its knowledge, there are no patents that claim the listed drug referred to in the application or that claim the use of the listed drug* [21]. However, when the applicant is aware of or believes that a patent covers the listed drug the patent certifications under § 314.94(a)(12)(i) apply (see above) [27].

The word 'relevant' refers to those patents defined by section 505(j)(2)(A)(vii) of the Act [22], i.e., patents that claim the listed drug, or drug substance thereof, as referred to in the ANDA, or that claim a use of the listed drug or drug substance for which the ANDA applicant seeks approval and for which patent information is required to be filed under section 505(b) and (c) of the Act and § 314.53 [21, 22].

The rule does not require ANDA applicants to conduct patent searches in addition to the information given in the Orange Book [27]. However, a patent search could reveal the existence of an unlisted, but valid, patent and thus prevent an unnecessary expenditure of resources by applicants and FDA on a product that might not be marketable [27]. A patent search might also enable ANDA applicants to avoid an unnecessary patent infringement litigation.

(iii) Method of use patent. The rule requires an applicant to make a patent statement according to paragraph iii) when a method of use patent *does not claim a use for which the applicant is seeking approval* (see also section 505(j)(2)(A)(viii) of the Act) [21, 22]. This situation occurs when the applicant excludes any indications that are covered by the use patent from the product information of its product. In such a case, the applicant is not entitled to submit a Paragraph IV Certification and thereby the access to benefits arising from a Paragraph IV Certification is controlled [27].

If, however, there are listed patents that present both a product and method of use claim, the applicant may file a Paragraph IV Certification with respect to the product patent and a statement that the product proposed in the application does not involve a patented method of use.

(iv) Method of manufacturing patent. This section simply states that an applicant is not required to make a certification with respect to any patent that claims only the method of manufacturing of the listed drug as these are non-relevant with regard to the requirements under section 505(b) and (c) of the Act and § 314.53 of the CFR regulating the filing of patent information [21, 22].

(v) Licensing agreements. If the ANDA is intended for a drug or a method of using a drug claimed by a patent and the applicant has signed a licensing agreement with the patent owner, the applicant is required to include in its application a Paragraph IV Certification as to that patent and a licensing statement according to this paragraph. In case the NDA holder and patent owner are different legal persons it is not required that the NDA holder gives consent to the license agreement [21].

3.4 30-month stay

The ANDA applicant who has included a Paragraph IV Certification in its application is required to send a 'Notice of certification of invalidity or non-infringement of a patent' also known as 'notice of certification' to each owner of the patent in question and to the holder of the approved NDA to which the ANDA refers [20, 37, 38].

Section 314.95 of the CFR describes the current requirements with regard to the sending of the notice and the information to be included in the notice by the applicant [21]. According to that regulation the applicant is obliged to send the notice not on submission of the ANDA but when it receives from FDA an acknowledgement letter stating that its ANDA is sufficiently complete to permit a review of the entire dossier [21]. In case an ANDA is amended to include a Paragraph IV Certification, e.g. a change from a Paragraph III Certification to a Paragraph IV Certification, the applicant shall send the notice of certification together with the amendment [21]. In any case the applicant is required according to § 314.95(b) to subsequently amend its ANDA to include a statement that the notice has been provided to each owner of the patent and the holder of the NDA and that the notice met the content requirements given in paragraph 314.95(c) [21].

The submission of an ANDA for a drug product that is claimed in a patent is an infringing act and, therefore, may be followed by patent infringement litigation [38]. If the innovator company decides to sue the generic applicant for the patent infringement, it must do so within 45 days from receipt of notice according to section 505(j)(5)(B)(iii) of the Act [22, 38]. In such cases, the FDA will delay the approval of the ANDA up to 30 months for pending resolution of lawsuit. FDA approval can only come into effect when the 30-months period has elapsed, or the generic applicant wins during patent litigation [20, 38].

Under the Hatch-Waxman Act, brand-name companies have been able to file patents on packaging, ingredient combinations, and other matters in order to get repeated 30-month stays in approval of generic applications thereby significantly delaying the access to generic drugs. As outlined in the following the MMA introduced significant improvements in the field of ANDAs, e.g. by providing a statutory basis for a single 30-month stay and benefits in terms of timing of ANDA approvals [37, 38].

3.4.1 Availability and Termination of the 30 month stay

Amendments by the MMA concerning the availability and termination of 30-month stays made in section 505(j)(5)(B)(iii) of the Act apply to patents submitted to FDA on or after August 18, 2003 [20]. The effective date for this provision means that the MMA supersedes the Generic Drugs Final Rule and Initiative. In order to clarify the agency's view with regard to these changes, FDA issued a Guidance in October 2004 [20] which specifically discusses the availability and termination of 30-month stays.

3.4.1.1 Availability of 30 month stays

With respect to such patents submitted to FDA on or after August 18, 2003, a 30-month stay on an ANDA containing a Paragraph IV Certification to the patent will ensue if:

- The patent was submitted before the date the ANDA was submitted to FDA, and
- The patent owner or NDA holder initiates a patent infringement action on the patent within 45 days of receipt of the certification notice.

Consequently, no 30-month stay of approval will result from a patent subject to the MMA, if the patent was submitted to FDA on or after the date the ANDA including a Paragraph IV Certification to the patent was submitted. Because of this limitation, in most cases, ANDAs will not be subject to more than one 30-month stay [20].

From the FDA Guidance issued in October 2004 [20] it becomes also clear that there are still certain circumstances in which multiple 30-month stays are possible. For example if the same ANDA containing a Paragraph IV Certification also contains a Paragraph III Certification for a different listed patent which was submitted on or after August 18, 2003 but before the filing of the ANDA, a second 30-month stay may be available against the ANDA if the Paragraph III Certification is amended to a Paragraph IV Certification.

3.4.1.2 Termination of the 30 month stay

The MMA further identifies the impact of a district court decision on the termination of a 30-month stay of approval [20, 22].

Consequently, a 30-month stay will be terminated and approval of an ANDA may be made effective, as of any of the following dates:

- The date that the district court decides that the patent at issue is invalid or not infringed, or
- The date of a settlement order or consent decree signed and entered by the district court stating that the patent that is the subject of the certification is invalid or not infringed, or

- The date on which the court of appeals decides that the patent is invalid or not infringed, or the date of a settlement order or consent decree signed and entered by the court of appeals stating that the patent is the subject of the certification is invalid or not infringed (only in cases where the district court decided that the patent has been infringed, and this decision is reversed on appeal).

In conclusion, a district court decision to that effect terminates the 30-month stay of approval, thus allowing FDA to render a final approval of an ANDA if it is otherwise ready for approval.

3.5 180 Day Exclusivity

Section 505(j)(5)(B)(iv) of the Act provides an incentive for generic manufacturers filing a Paragraph IV Certification to challenge patents that may be invalid, not infringed or unenforceable, thereby possibly triggering a patent action against them by the patent owner [22, 34, 36]. According to this section of the Act the first generic applicant to submit an application containing a Paragraph IV Certification will enjoy 180 days of generic exclusivity, since all subsequent applications - although including a Paragraph IV Certification - will be made effective on the date that is 180 days after the date of the first commercial marketing of the drug by the first applicant [22].

This exclusivity protecting a first-to-file applicant whose ANDA contains a Paragraph IV Certification from competition by subsequent generic applicants referring to the same RLD is commonly known as "180-day exclusivity" [36]. As the price of a generic drug strongly decreases with the market entry of multiple generics it provides an incentive for generic firms to challenge weak or inappropriately listed patents.

Under the old law of the Hatch-Waxman Act, subsequent ANDAs for the same drug product could not be approved by FDA until the 180-day exclusivity period of the "first-to-file" applicant had expired. The 180-day exclusivity period was triggered by

- (i) the commercial launch of the first-to file applicant's ANDA product, or
- (ii) the date of a decision of a court holding the challenged patent(s) either invalid or not infringed,

whichever was earlier [34, 35, 38]. The old law allowed for interpretation of a "patent-based" 180-day exclusivity, whereby the exclusivity was associated to the first-to-file challenge for each Orange Book listed patent. In situations where different applicants challenged different Orange Book-listed patents for the same drug product FDA adopted a complicate "shared exclusivity" approach under which the first-to-file applicants with a Paragraph IV Certification for each listed patent shared the 180-day exclusivity period based on that patent [39, 40].

Because the clock was triggered by the first court decision in the applicant's favour, the first-to-file applicant had to launch directly on approval following that court decision in order to take advantage of its 180-day exclusivity, bearing the risk that the decision might be reversed on appeal.

The MMA has revised the provisions under the Hatch-Waxman Act related to the 180-day exclusivity by establishing [16, 20]:

- commercial marketing as only trigger for 180-day exclusivity (exceptions by interim arrangements)
- "product-based" 180-day exclusivity
- forfeiture provisions.

While the old law allowed for "patent-based" 180-day exclusivity, the new regulations provide for "product-based" 180-day exclusivity [16, 40]. Product-based exclusivity is associated to the first-to-file challenge on a particular product irrespective of the Orange Book-listed patent referred to by the challenge. Under the new law shared exclusivity is only possible in situations when more than one ANDA application is filed on the same day by more than one ANDA applicant (see 3.5.1).

By virtue of the MMA specific forfeiture provisions such as failure of the first-to-file applicant to market its generic product or withdrawal of its Paragraph IV Certification(s) eliminate scenarios where the access to market is blocked [16, 40]. It shall be noted that once the first-to-file applicant forfeits its 180-day exclusivity, no subsequent ANDA applicant will be eligible for 180-day exclusivity. Any subsequent ANDA filer may launch its generic product immediately provided that any patent issues are resolved and final FDA approval is received [16, 40].

3.5.1 Shared Exclusivity by multiple Submissions on the same Day

Under the Hatch-Waxman Act as initially interpreted by the agency the ANDA applicant had to be sued and win its patent litigation in order to qualify for the exclusivity, what is also known as "successful defence" requirement [34]. The chance that multiple ANDA applicants qualify for 180-day exclusivity was therefore extremely low and from 1984 to 1998, only three ANDA applicants were assigned the 180-day exclusivity [39]. To improve the situation in 1998 the FDA published a guidance eliminating the "successful defence" requirement [34]. Consequently, the number of assignments of 180-day exclusivity significantly increased as well as the chance of having multiple applicants qualify for 180-day exclusivity in cases where multiple ANDAs containing a Paragraph IV Certification to the same patent were submitted on the same day [36].

Same day patent challenges generally occur upon expiration of 4 years of a 5-year exclusivity period under section 505(j)(5)(D)(ii) permitting submission of ANDAs containing a Paragraph IV Certification. Multiple submissions on the same day may also occur when a new patent is issued by the Patent and Trademark Office and submitted to FDA within 30 days of issuance by the NDA sponsor after ANDAs have been submitted [36].

However, as the possibility of multiple applications for 180-day exclusivity on the same day were not addressed by the law at that time, FDA adopted in 1999 a complicate "shared exclusivity" approach under which each first-to-file applicant shared the 180-day exclusivity period (see 3.5). [39, 40].

With publication of the Guidance for Industry in July 2003 [36], FDA adopted a multiple first applicant approach concerning the qualification for 180-day exclusivity *"by considering all substantially complete ANDAs, amendments, and supplements containing a Paragraph IV Certification to a listed patent that are submitted to the OGD document room on the same day as being first applicants, when no Paragraph IV Certification to the patent has been submitted on any previous day"*.

During the exclusivity period, FDA may approve any other first applicant's ANDA, but no other ANDAs. Any first applicant whose ANDA is approved after the exclusivity has been triggered will share in the remaining period of exclusivity [36]. Once the 180-day exclusivity period has expired, FDA may approve all subsequent ANDAs.

3.6 DMF Filing

A drug master file (DMF) usually contains proprietary information about a drug substance, a component, or a container/closure system [41].

Rather than providing the information directly to the applicant, the manufacturer may choose to hold a DMF. The DMF holder provides the information directly to the FDA [41]. If reference to a DMF is made a letter of authorization is usually issued by the manufacturer, which must be included in the application and listed on the application form (Form FDA 356h - refer to section 4.1).

A DMF may contain information required in an application about the following areas [41]:

- Manufacturing site, facilities, operating procedures, and personnel (Type I)
- Drug substance, drug substance intermediate, and materials used in the preparation, or drug product (Type II)
- Packaging materials (Type III)
- Excipient, colorant, flavour, essence, or materials used in the preparation (Type IV)
- FDA accepted reference information (Type V)

The above mentioned letter of authorization from the DMF holder is granting the FDA authorization to refer to information in the DMF during the review of the application. The letter of authorization should be printed on the DMF holder's letterhead and dated and signed with an original signature. It should cite the DMF holder's name, drug name, and DMF number [41].

A DMF for Active Pharmaceutical Ingredients must be stamped received by the Agency prior to submission of an ANDA that relies upon said DMF [42].

3.7 Amendments / Supplements

In case a change to the product applied for would lead to a significant difference as compared to the listed drug cited in the initial submission (e.g., different active ingredient, dosage form, route of administration) a new application should be filed for the different drug product and the new ANDA should refer to the separate listed drug with the desired characteristics (e.g., active ingredient, dosage form, route of administration) if identifiable in the Orange Book. The applicant is not allowed to submit a supplement or amendment to its pending or approved application to seek approval for such a change [20].

Each strength of an approved drug is to be considered a separate listed drug. Each strength proposed in an ANDA should reference the corresponding listed drug (although the reference standard for purposes of bioequivalence may be only one strength). Generally, a single application can be used to seek approval for different strengths of the same listed drug.

Consequently, an applicant may submit an amendment or supplement to seek approval of a different strength from that for which the application was initially submitted and is not required to file a separate application for such a change. This is expressly permitted under the Act, as amended by the MMA (see section 505(j)(2)(D)(ii) of the Act) [20, 22].

4. Content and Format of ANDAs

4.1 Overview and General Requirements

The content and format of an Abbreviated New Drug Applications are described under 21 CFR 314.94 [21].

The particular requirements are presented in the order of paragraph (a) of this section in the table below. The applicant is obliged to submit three copies of its ANDA, a complete copy which contains all requested information and is referred to as archival copy, a review copy and a field copy [21, 44].

TABLE 2: CONTENT AND FORMAT OF ANDAS

Archival Copy - Requirement/ Title acc. to 21 CFR § 314.94(a)	Review Copy		Field Copy	Location within CTD***
	Chem.*	Bio.**		
(1) Application form.	X	X	X	Module 1
(2) Table of contents.	X			Module 1
(3) Basis for Abbreviated New Drug Application submission.	X	X		Module 1
(4) Conditions of use.	X			Module 1
(5) Active ingredients.	X			Module 1
(6) Route of administration, dosage form, and strength.	X			Module 1 & 5
(7) Bioequivalence.		X		Module 2 & 5
(8) Labelling.	X	X		Module 1
(9) Chemistry, manufacturing, and controls.	X		X	Module 2 & 3
(10) Sample statement required under § 314.50(e)(1) and methods validation package as per (e)(2)(i).				Sample on request
(11) Other information as described in § 314.50(g), e.g. reference to information submitted previously.				Module 2 & 3, as applicable
(12) Patent certification	X			Module 1

* chemistry/microbiology

** bioequivalence

*** Common Technical Document

When paper format is submitted, the applicant is requested to submit three copies of the application according to §314.94(d) as further detailed below:

1. **Archival copy** - The archival copy is a complete copy of an application and is intended to serve as the official reference source for the Agency. The archival copy is maintained during the review of the application to permit individual reviewers to refer to information that is not contained in their particular technical sections of the application. After an application is approved, the archival copy is retained by the Agency and serves as complete and sole copy of the approved application [21, 43].

2. **Review copy** - The review copy is used to evaluate the application. It is usually divided into two parts containing the scientific information needed for chemistry/microbiology review and bioequivalence review conducted by different scientific reviewers. Beside the information on chemistry, manufacturing and controls, the part for chemical/microbiological review should contain additional information as indicated in table 2 (see above). Descriptive information on the analytical procedures enabling FDA's laboratories to perform the respective tests should also be included. Required patent information is limited to a copy of patent certification according to §314.94(12)(i)(A) or 505(j)(A)(vii) of the Act pertaining to patents claiming the drug, drug product, or method of use (for details refer to section 3.3.3.2). The part for bioequivalence review should contain information about the basis of submission, labelling and bioequivalence of the proposed drug (please refer to table 2). Both parts are required to contain the application form described in section 314.50(a) and section 314.94(a)(1) (see table 2 above) [21, 43].
3. **Field Copy** The field copy is used to enable pre-approval inspection by the FDA. The field copy should hence contain the technical section of the chemistry, manufacturing and controls part for drug substance and drug product according to section 314.50(d)(1) as required in section 314.94(a)(9) of the CFR. Inclusion of the application form is required as for all other copies. Furthermore, it needs to include a confirmation that the field copy is a true copy of the technical information contained in the archival and review copies of the abbreviated application as described in section 314.94 (a)(9) of the CFR. [21, 43].

Each application should be submitted in colour-coded jackets. Information about the volume size and identification, the jacket specifications (including colour coding), the size and quality of paper for text, and mailing instructions can be retrieved from the internet [44, 45].

In the past, ANDAs were structured according to FDA's guidance for industry "Organization of an ANDA (February 1999)", which contained a model for an ANDA table of contents and detailed description of the content and format of ANDA applications, the so called "traditional format".

Nowadays, the organization of an ANDA should follow the format of the Common Technical Document (CTD) as established by the International Conference on Harmonisation (see below). The "ANDA checklist for CTD and eCTD format" [46] is currently referred to by FDA as guide for structure and content of ANDA applications (for eCTD see section 4.6) [44].

Although, at this time, the FDA can not refuse an ANDA on grounds of using the traditional format, FDA encourages applicants to submit their ANDAs in the CTD format and preferably as electronic CTD [44].

The Common Technical Document was agreed upon in November 2000 by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The ICH brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry to achieve greater harmonisation in the interpretation and application of technical guidelines and requirements for product registration in the three regions. The implementation date for the Common Technical Document in the three regions was July 2003 [47].

The Common Technical Document is divided into four separate sections. The four sections address the application organisation (M4), the Quality section (M4Q), the Safety section (M4S) and the Efficacy section (M4E) of an application [48]

Relating to the topics of Quality, Safety and Efficacy ICH has agreed upon a range of common scientific and technical standards published in the respective "Q", "S" or "E" Guidelines [48].

Most of these guidelines have already been implemented nationally and therefore provide for a common basis of the content of new drug applications in the three ICH regions. The national implementation status of the individual guidelines can be viewed at the ICH web-page [48].

Despite the general harmonization of the content and format of new applications in the three ICH regions, a few regional distinctions regarding the content and location of information need to be considered. Moreover, Module 1 contains administrative and prescribing information such as application forms or the proposed label for use in the specific region. Module 1 requirements vary by region and by the type of application as specified by the relevant regulatory authorities. The discussion in this thesis will focus on the special requirements applicable to ANDAs [42].

4.2 Content and Format of Module 1 - Regional Requirements

Following the implementation of the CTD-format, the administrative and prescribing information according to section 505(j)(2)(A) of the Act and section 314.94 of the CFR is contained in Module 1 [21, 22, 42, 44]. The "ANDA checklist for CTD or eCTD format" contains a complete list of documents to be included in this section [44, 46].

The content and format to be followed in the preparation of individual documents of Module 1 can be obtained from current FDA presentations published on the homepage of FDA or the Generic Pharmaceutical Association (GPhA) [42, 44]. Table 3 below combines the document requirements according to the ANDA checklist and auxiliary information for the preparation of Module 1 taken from the presentations [42, 44, 46].

TABLE 3: CONTENT AND FORMAT OF MODULE 1

CTD Section	Format and Content of Module 1
1.1	Application Form (356h) [50] The form contains seven major sections to be filled in by the ANDA applicant: (1) applicant information, (2) product description, (3) application description, (4) establishment information, (5) content of the application (individual items applicable for ANDAs), (6) certification that the provided information is true to the best of knowledge, to update specific parts of the application as needed, to submit required safety reports to comply with all applicable laws and regulations, and (7) original signature of responsible official
1.2	Cover Letter (only for paper submission) The application should include a signed and dated cover letter with a clear, brief introductory statement. Any issues or previous communication with the Agency should be addressed. Table of Contents (TOC) is to be structured according to the table in CTD format referenced in the ANDA checklist. Required for paper submissions.
1.3.2	Field Copy Certification (original signature, paper submission only) Example: (Name of applicant) certifies that the field copy is a true copy of the technical section of the application described in 21CFR 314.50(l)(3) and contained in the archival and review copies of the application.
1.3.3	Debarment Certification according to GDEA (Generic Drug Enforcement Act) 1. Debarment Certification Confirmation not to use the services of any person debarred under section 306 of the Act. 2. List of Convictions statement All ANDA applicants should include a non-conviction statement or, if necessary, they must include information about any convictions (of the company or affiliated persons) that could have led to debarment.

CTD Section	Format and Content of Module 1
1.3.4	Financial Certifications Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) or Disclosure Statement (Form FDA 3455). It is not necessary to include a financial disclosure form (Form FDA 3455) with ANDAs unless the application contains an in vivo bioequivalence study.
1.3.5	
1.3.5.1	Patent Information Patents listed for the RLD in the Orange Book.
1.3.5.2	Patent Certification 1. Patent Numbers 2. Patent Certification acc. to §314.94(a)(12) 3. Expiration of Patents 4. Exclusivity Statement The submission and approval of ANDAs may be affected by exclusivity granted to the RLD. A statement should be included even if the product is not entitled to exclusivity.
1.4.1	References 1. DMF Letters of Authorization allowing FDA to review DMFs (see section 3.6) 2. Letter of Authorization (US Agent) must be submitted by all firms residing outside of the United States. This letter must be on the applicants letterhead and grant authority for a designated US firm and individual to act as an intermediary between FDA and the applicant.
1.12.11	Basis for Submission The Reference Listed Drug as designated in the Orange Book. For utilizing an approved Suitability Petition as Basis of Submission the applicant must provide a copy of the approval letter for the Suitability Petition. 314.93
1.12.12	Comparison between Generic Drug and RLD-505(j)(2)(A) (1) conditions of use, (2) active ingredient, (3) inactive ingredients, (4) route of administration, (5) dosage form, (6) strength If differences exist between the proposed drug and the RLD and approval of an ANDA suitability petition has been obtained (see 3.2.3), these differences should be explained and a copy of the suitability petition approval letter should be included.
1.12.14	Environmental Impact Analysis Statement The applicant should submit a signed statement regarding compliance with all federal, state and local environmental laws. ANDA applicants may claim a categorical exclusion under 25.31(a).
1.12.15	Request for Waiver of in-vivo BA/BE Study(ies) The applicant should submit a BA/BE waiver request for any strength or dosage form in which a in-vivo BA/BE study is not performed.

CTD Section	Format and Content of Module 1
1.14.1	Draft Labelling
1.14.1.1	4 copies of draft product label and all drug product labelling* (each strength and container)
1.14.1.2	1 side by side labelling comparison of containers and carton with all differences annotated and explained
1.14.1.	1 package insert (content of labelling) submitted electronically
	All ANDAs submitted after June 8, 2004, are required to provide their labelling in electronic format, Structured Product Labelling according to Guidance for Industry [51]
	*The term product labelling is a collective term that includes the package insert, vial labels, and carton labelling.
1.14.3	Listed Drug Labelling
1.14.3.1	1 side by side labelling (package and patient insert) comparison with the RLD with all differences annotated and explained
1.14.3.3	1 RLD label and 1 RLD container label

4.3 Content and Format of Module 2

Module 2 contains the Summary of Module 3 as well as the Overview and Summary of Module 5. Non-clinical and toxicological information summarized in section 2.4 and 2.6 and non-clinical study reports located in Module 4 can be omitted for ANDAs [44, 46].

The Quality Overall Summary (QOS), also referred to as Module 2.3, should include sufficient information from each section of Module 3 to provide the reviewer with an overview [42]. The Office of Generic Drugs (OGD) developed a "Question-based Review" (QbR) for its chemistry, manufacturing, and controls (CMC) evaluation of Abbreviated New Drug Applications. ANDA applicants are encouraged to submit a Quality Overall Summary that answers the QbR questions with every ANDA submission starting from January 2007. A model Quality Overall Summary in the QbR format can be found on the OGD webpage providing an example for an immediate release tablet and an extended release tablet [42].

The requirements and implementation of the QbR will be discussed in more detail in section 5 of this thesis.

The applicant of an ANDA is obliged to provide in Module 2.7 the Clinical Summary containing the results of bioavailability/bioequivalence studies. The Overview of Module 2.5 only needs to be submitted if deemed necessary by the applicant [42, 44, 46].

The Division of Bioequivalence has developed new data summary tables enabling the applicants to submit their data to the Office of Generic Drugs in a concise format consistent with the Common Technical Document. The completed tables should be sent along with the bioequivalence part of the ANDA submission. The tables and instructions on how to fill the tables are available on the OGD web site [19].

4.4 Content and Format of Module 3

The content and format of the chemistry, manufacturing and controls part mainly is subject to ICH Guidelines [52, 53]. The format follows the ICH-CTD standard for Module 3 as described in the M4Q (R1) Guideline [54]. The majority of ICH Quality guidelines have meanwhile been adopted by FDA [52]. Despite this common basis a few regional aspects specific to FDA are to be considered for the compilation of Module 3 as outlined in the below overview:

TABLE 4: CONTENT AND FORMAT OF MODULE 3 SPECIFIC TO FDA [42, 44, 46].

CTD Section	Regional aspects to be considered for Module 3
DRUG SUBSTANCE	
3.2.S.2	<u>Manufacturer</u> Type II DMF number for Active Pharmaceutical Ingredients (APIs) DMF number to be included in this section, i.e. the DMF for APIs referred to in this section must be stamped when received by FDA prior to submission of the ANDA.
3.2.S.4	<u>Control of Drug substance</u> Sample Statement Statement to be included that samples of the drug substance will be submitted upon request from authority acc. to CFR 314.94(a)(10) as required under § 314.50(e)(1) and (e)(2)(i)21.
DRUG PRODUCT	
3.2.P.1	<u>Description and Composition of the Drug Product</u> Inactive ingredients and amounts appropriate per Inactive Ingredients Database (IIG) According to 314.94(a)(9)(i) the applicant should identify and characterize the inactive ingredients in the proposed drug product and demonstrate that these do not adversely affect the safety of the drug product applied for. Proof of safety can be provided in the following ways: <ul style="list-style-type: none">• <i>Inactive Ingredients Database.</i> By referencing to inactive ingredients present in FDA-approved drug products listed in IIG and considered to be safe, if the proposed inactive ingredients are used in a similar dosage form at a similar strength. For each inactive ingredient present in the drug product this information should be provided in a tabular format.• <i>Citation of a control number.</i> Applicable for flavours and colours not previously approved (not listed in IIG) for which the supplier requested FDA's evaluation of the formulation and it's use and was assigned a control number.• <i>Pharmacology/ Toxicology Studies</i> to justify the safety of an inactive <i>ingredient</i> (Studies included in 3.2.P.4).
3.2.P.3.1	<u>Manufacture</u> Facilities should be identified by full address, function and responsibility of each site involved in the manufacture, testing and packaging of finished product and API in order to enable request for inspection by FDA. cGMP Certification. Signed certification to be provided here. For further details please refer to section 5 on QbR.

CTD Section	Regional aspects to be considered for Module 3
3.2.P.3.3	<u>Description of Manufacturing Process and Controls</u> Blank Master Production Batch Records for largest intended production runs. The maximum production batch size may not be more than 10x the theoretical yield of the exhibit batch. Reprocessing Statement. The manufacturer needs to confirm that no reprocessing procedures are used in the manufacture of the drug product as reprocessing steps require prior approval by the Agency.
3.2.P.4	<u>Controls of Excipients</u> The source of all inactive ingredients needs to be stated within a table.
3.2.P.4.1	<u>Specifications (Inactive Ingredients)</u> Suppliers specification plus drug manufacturer's/ applicant's specification.
3.2.P.4.4	<u>Justification of Specification</u> Certificate of Analysis (CoA) Suppliers CoAs plus drug manufacturer's/ applicant's CoAs. CoAs of the excipients batches used in the manufacture of biobatches are most appropriate, copies of chromatograms and spectra may be included. Pharmacology/ Toxicology Studies are to be submitted here to justify the safety of an active ingredient if not demonstrated otherwise (see above).
3.2.P.5.3	<u>Validation of Analytical Procedures</u> Sample Statement Statement to be included that samples of the drug product will be submitted upon request from authority acc. to CFR 314.94(a)(10) as required under § 314.50(e)(1) and (e)(2)(i)21.
3.2.P.5.4	<u>Batch Analysis</u> CoAs of the finished product of all executed batches.
3.2.P.7	<u>Container Closure System</u> Packaging Configuration and Sizes including engineers drawings with exact dimensions for all dosage units.
3.2.P.8	<u>Stability Summary and Conclusions</u> Proposed expiration period. The applicant may propose a tentative 24 months expiration period based upon 3 months of accelerated stability.
3.2.P.8.3	<u>Stability Data</u> Accelerated stability data covering four time points, i.e. 0, 1, 2, and 3 months, should be submitted: for the exhibit batches. The storage conditions acc. to ICH (40°C and 75% R.H.) shall be applied. This data need to be provided even if the product fails under accelerated conditions.

REGIONAL INFORMATION – DRUG SUBSTANCE

3.2.R.1.S Executed batch records for drug substance

3.2.R.2.S Comparability Protocols (optional: plan for assessing the effect of specific CMC changes on the identity, strength, quality, purity, and potency of a specific drug product)

3.2.R.3.S Methods Validation Package (3 copies)

REGIONAL INFORMATION – DRUG PRODUCT

3.2.R.1.P.1 Executed batch records for drug product with equipment specified, including packaging records

For Solid Oral Dosage Forms the exhibit batch must be a minimum of 100,000 units or 10% of the proposed production batch.

The exhibit batch shall be packaged completely in containers proposed for marketing.

For parenteral products it is mandatory that a minimum of 10% of the exhibit bulk is packed in each vial size (container) proposed for marketing.

3.2.R.1.P.2 Information on Components

– Name and address of sources of active substance, non-compendial excipients and container closure system

– Name/address and function of contract facilities

– COAs from the component manufacturer and the test results for the same batch from the drug product manufacturer

3.2.R.2.P Comparability Protocols (optional: plan for assessing the effect of specific CMC changes on the identity, strength, quality, purity, and potency of a specific drug product)

3.2.R.3.P Methods Validation Package (3 copies)

4.5 Content and Format of Module 5

The format of the clinical part follows the ICH-CTD standard for Module 5 as described in the M4E (R1) Guideline [55]. ICH efficacy guidelines regulate general aspects on clinical trials such as [52]:

E3	Structure and Content of Clinical Study Reports
E6 (R1)	Good Clinical Practice
E8	General Consideration of Clinical Trials
E9	Statistical Principles for Clinical Trials
E10	Choice of Control Group and Related Issues in Clinical Trials
E11	Clinical Investigation of Medicinal Products in the Paediatric Population
E12	Guidelines for Clinical Evaluation by Therapeutic Category

Specific bioavailability (BA) / bioequivalence (BE) requirements are subject to national regulations in the US. The detailed discussion of this requirements, however, is not within the scope of this thesis.

According to section 314.94(a)(7)(i) the ANDA applicant is obliged to submit information showing that the proposed drug product is bioequivalent to the Reference Listed Drug to which reference is made [16, 21]. Bioequivalent drug products show no significant difference in the rate and extent of absorption of the active moiety. Regulatory requirements for documentation of bioequivalence are provided in part 320 of the CFR, which contains two subparts. Subpart A covers general provisions and definitions, while subpart B describes general bioequivalence requirements [25]. The regulation is supplemented by several FDA Guidance documents which provide further explanation and recommendation for the planning and documenting of bioequivalence studies. An overview of topics covered by regulations and FDA Guidance is outlined in the table below:

TABLE 5: REGULATORY REQUIREMENTS WITH REGARD TO BIOEQUIVALENCE

Title acc. to 21 CFR 320		Guidance for Industry [53]
§ 320.23	Basis for demonstrating in vivo BA or BE	Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations
§ 320.24	Types of evidence to establish BA or BE	
§ 320.25	Guidelines for conduct of in vivo BA studies	
§ 320.26	Guidelines on design of single-dose BA studies	
§ 320.27	Guidelines on design of multiple-dose in vivo BA studies	
§ 320.22	Criteria for waiver of in vivo study requirements	Statistical Approaches to Establishing Bioequivalence
320.35	Requirements for in vitro batch testing of each batch	Food-Effect Bioavailability and Fed Bioequivalence Studies
		Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System.
		Dissolution Testing of Immediate Release Solid Oral Dosage Forms

Title acc. to 21 CFR 320		Guidance for Industry [53]
320.35	Analytical methods for an in vivo BA study	Bioanalytical Method Validation
320.63	Retention of BE samples	Handling and Retention of Bioavailability and Bioequivalence Testing Samples

In addition to general topics, FDA provides guidance on how to design bioequivalence studies for specific drug products in the "Individual Product Bioequivalence Recommendations", which is currently issued as Draft Guidance for Industry on the FDA web site [56]. The tabular listing can be searched by API name.

Recommendations in the above mentioned Guidances include:

- Study design
- Analytes to measure (in appropriate biological fluid)
- Criterion/basis of Bioequivalence
- Bioequivalence Waiver
- Dissolution test method and sampling times.

If a waiver of BA/BE studies is applied for and the respective request for a waiver of in-vivo BA/BE Study is included in Module 1.12.15 (see section 4.2), Module 5 is not needed [42].

4.6 Submission in Electronic Format

As of 1 January 2008 all applicants submitting electronically are required to send their submissions in the Electronic Common Technical Document (eCTD) format [57]. Applicants who would like to submit electronically, but who are unable to submit in eCTD format by the official start-date, can ask for an eCTD waiver [57].

Electronic applications submitted before January 2008 were organized according to the so called "traditional format" (see section 4.1).

The eCTD format is an electronic standard that provides a harmonised technical solution for the transfer of regulatory information contained in the Common Technical Document from Industry to Agencies across ICH regions [58]. The information to be included in the technical sections of Modules 1 to 5 follows the provisions laid down in the ICH M4 Guidelines (refer to section 4.1 of this thesis).

In 1994, the ICH Multi-disciplinary Group 2 (M2) Expert Working Group (EWG) was established to develop "Electronic Standards for the Transfer of Regulatory Information (ESTRI)" that meet the requirements of the pharmaceutical companies and regulatory authorities [58]. For that purpose the ICH M2 EWG has published a number of technical Guidances so called "Specifications" [58, 59].

The second specification developed by the ICH M2 EWG was the Electronic Common Technical Document Specification, which is based on Extensible Mark-up Language (XML) technology and lists the criteria that will make an electronic submission technically valid. The focus of the specification is to provide the ability to transfer the registration application electronically from industry to a regulatory authority while at the same time also facilitating the creation, review, lifecycle management and archival of the electronic submission [59].

Based on ICH CTD and eCTD specifications the FDA has published Guidance on "Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications" which provides recommendations on how to

organize electronic applications to FDA [57, 60]. This guidance refers to a series of technical specifications which should be followed for the preparation of an electronic application in accordance with the eCTD format. The specifications are published on the Electronic Common Technical Document web site of the FDA [57].

Applicants may make a sample submission reviewed by FDA to resolve any technical issues with the eCTD submission prior to the actual submission. The sample submission is however not considered an official eCTD submission [57].

Before submission of the actual ANDA the applicant should request a "Pre-Assigned Application number". A step-by-step description of the procedure to be followed is provided on the web site of the FDA: http://www.fda.gov/cder/Regulatory/ersr/preassigned_application.htm.

5. Question based Review (QbR)

The Office of Generic Drugs developed a "Question-based Review" (QbR) for its chemistry, manufacturing, and controls (CMC) evaluation of Abbreviated New Drug Applications. QbR was designed with the expectation that ANDA applications would be organized according to the Common Technical Document (CTD). A template for QbR is provided that contains standardized review questions for the compilation of the Quality Overall Summary in Module 2.3. The template in word format as well as a model Quality Overall Summary in the QbR format can be found on the OGD webpage [42, 61].

ANDA applicants are encouraged to submit a Quality Overall Summary that answers the QbR questions with every ANDA submission starting from January 2007 [42, 61].

5.1 Development and Rationale

5.1.1 Impetus of the QbR

Two major objectives which led to the development of the Question based Review (QbR) can be identified [62, 65, 66].

The first motivation for developing the QbR resulted from the increasing review workload encountered by the OGD during the last years. As shown in Figure 4 the OGD received only a total of 307 ANDAs in the year 2001 while this number increased to 449 ANDAs in 2003 and almost 800 ANDAs in the year 2006 - the last year before the QbR approach was practically implemented in the submission and review process of ANDAs at FDA [62].

Since the increase in ANDAs and associated CMC supplements results in an increasing review workload, the change of the review system to use limited resources more efficiently became a necessity to enable OGD's review work in the future [62].

Office of Generic Drugs

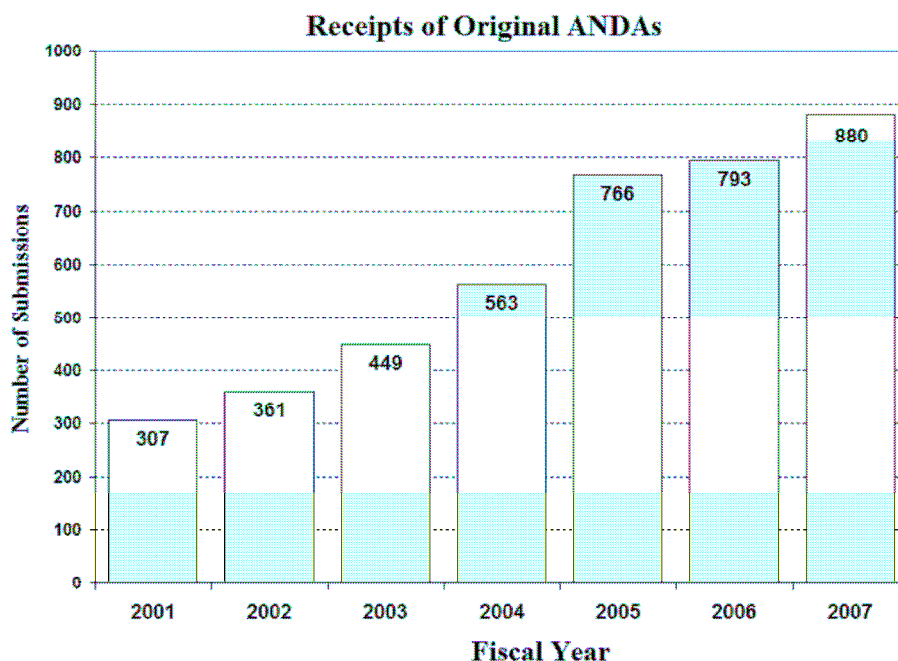


FIGURE 3: NUMBER OF ANDAs SUBMITTED TO THE OFFICE OF GENERIC DRUGS FROM 2001 TO 2007 [67]

The second motivation for developing the QbR derives from the discrepancy between the objectives of the "*Current Good Manufacturing Practices (cGMPs) for the 21st Century Initiative*" and formerly applied chemistry, manufacturing and controls (CMC) review practices. Brief background information about cGMP and the *cGMPs for the 21st Century Initiative* to better understand the context of the QbR is described in the following sections [61, 62].

5.1.2 cGMPs for the 21st Century Initiative

The requirements for Current Good Manufacturing Practices (cGMP) are stipulated in the Code of Federal Regulations sections 210 and 211 [64, 67]:

- 21 CFR 210 - Current Good Manufacturing Practice in manufacturing, processing, packing, or holding of drugs.
- 21 CFR Part 211 - Current Good Manufacturing Practice for Finished Pharmaceuticals.

An ANDA applicant has to mandatory include a **cGMP Certification** in Module 3.2.P.3.1 of its application at the time of submission (see also section 4.4). The cGMP compliance of generic manufacturers is assessed on the basis of inspection of the facilities, sample analyses, and compliance history conducted by FDA inspectors during the approval process. Failure to comply with cGMPs can lead to issuance of a warning letter or other regulatory actions against the company or worst case to non approval of the application by FDA [67].

In August 2002, the FDA announced the *cGMPs for the 21st Century Initiative* with the long term goal to enhance and modernize the cGMPs regulation [64].

The objectives and concepts outlined by this initiative include [64]:

- **early adoption of new technological advances** by the pharmaceutical industry
- application of **modern quality management techniques** by industry, including implementation of quality systems approaches, to all aspects of pharmaceutical production and quality assurance
- implementation of **risk-based approaches** that focus both industry and Agency attention on critical areas
- improvement of **FDA's drug quality regulatory programs**, in part, by further integrating enhanced quality systems approaches into the Agency's business processes and regulatory policies concerning review and inspection activities

Work results and ongoing activities of the initiative are presented in the final report to the initiative of September 2004 and on FDA web site: A Risk-Based Approach to Pharmaceutical Current Good Manufacturing Practices (cGMP) for the 21st Century Previous Reports, Guidances and Additional Information (<http://www.fda.gov/Cder/gmp/>).

Achievements that have resulted from the cGMPs for the 21st Century Initiative so far are [64]:

- adoption of a quality systems model for agency operations which is incorporated into the FDA Staff Manual Guide
- development of a quality systems guidance for cGMP regulation which has resulted in the Guidance for Industry on Quality Systems Approach to Pharmaceutical cGMP Regulations. This guidance works in concert with the new Pharmaceutical Quality Assessment System
- implementation of risk-based management plans such as the FDA's Strategic Action Plan, the Risk-based Model for Inspectional Oversight and the Part 11 Guidance, to name a few [64]. Worth mentioning in the context of QbR is the ONDC Pharmaceutical Quality Assessment System, which has been developed by the Office of New Drug Chemistry (ONDC - recently reorganized in the ONDQA), implementing a new risk-based pharmaceutical quality assessment system to replace its current CMC review process [64].
- Science-based regulation of product quality. This new system will encourage the implementation of new technologies, such as process analytical technology (PAT), and facilitate continuous manufacturing improvements via implementation of an effective quality system (also refer to PAT Guidance [68]).

In the next phase of the Initiative under the leadership of the FDA Council on Pharmaceutical Quality additional guidance on quality systems for pharmaceutical manufacturing will be developed in order to meet the initial goal to enhance and modernize the regulation of pharmaceutical manufacturing and product quality [64].

5.1.3 Development of the QbR

In the first phase of development of the QbR the essential aspects of the CMC review process used for ANDA review at that time were identified and compared with the goals of the cGMPs for the 21st Century Initiative. This comparison revealed the key scientific questions that were not being addressed before [62, 65, 66]:

TABLE 6: COMPARISON OF OBJECTIVES OF cGMPs FOR THE 21ST CENTURY INITIATIVE AND PREVIOUS CMC REVIEW PRACTICE

"Desired state" acc. to the Initiative	CMC review practice before the QbR
Product quality and performance: - by scientific understanding of how formulation and manufacturing process factors affect product quality and performance (Quality by design), and - by design of effective and efficient manufacturing processes	Product quality and performance: - ascertained mainly by end product testing - little understanding of complex problems (e.g. process scale up)
Product specifications (performance-based): - based on mechanistic understanding - impact of formulation and process factors on product performance - continuous improvement and continuous "real time" assurance of quality	Product specifications: - derived empirically from testing batches - irrelevant specifications - testing to document quality - deviations and out of specification investigation
Assessment (risk-based assessment): - the scientific understanding of how formulation and manufacturing process affect product quality - the capability of process control strategies to prevent or mitigate risk of producing a poor quality product	Assessment: - products treated equally - too much review time on low risk products - same time for high-risk products such as complex dosage forms or narrow therapeutic index (NTI) drugs
Regulatory policies (science-based): - recognize the level of scientific knowledge supporting product applications, and - encourage the voluntary development and implementation of pharmaceutical innovation	Regulatory policies: - regulatory consistency among all applicants is a hurdle to recognize the level of scientific knowledge

In the following phase the most important scientific and regulatory questions on critical pharmaceutical attributes essential for generic drug product quality were identified. Best practices of the previous review system were preserved. A risk-based approach was included to maximize economy of time, effort and resources [62].

Before its implementation the QbR was subject to wide consultation in order to ensure high quality of the review [62].

5.1.4 Objectives of the QbR

The purpose of the QbR hence can be summarized by the following objectives [62, 65, 66]:

1. Effective allocation of limited review resources
 - to reduce CMC review time in order to cope with increasing workload
 - to ensure generic drug product quality, especially with regard to more complex dosage forms and narrow therapeutic index (NTI) drugs
2. Implementation of the goals of the cGMPs for the 21st Century Initiative such as
 - quality by design
 - performance base specifications
 - risk-based approaches / risk based assessment
 - science-based regulatory policies to reduce CMC supplements and facilitate continuous improvement

5.2 Concept of Implementation

In order to achieve the above mentioned objectives the QbR has been realized to incorporate the following principles:

➤ **Standardized Review Questions**

A template is provided for QbR [61] that contains standardized review questions. As such, the new QbR template establishes the best practices of the CMC review system as a standardized method for the entire office [62].

Due to the design of questions reviewers can quickly account for common cases and prior knowledge enabling reviewers to spend less effort on low-risk products. Equally, the questions enhance the mechanistic understanding of how formulation and manufacturing process variables affect pharmaceutical quality. The QbR thereby provides for an in-depth review of more complex dosage forms and NTI drugs [62, 65, 66].

In addition, the formalized QbR questions increase the transparency of drug product quality assessment providing generic companies clear direction to improve the quality of their submissions. Such transparency encourages the more rapid "first-cycle" approvals and minimizes the inefficient and time consuming "multiple-cycle" approvals, particularly in the case of simple drug products [62, 65, 66].

Taken together, the QbR enables generic companies and reviewers to focus on critical pharmaceutical attributes. Standardized review questions enhance the quality of reviews. Scientifically important CMC deficiencies in ANDA submissions can be identified by reviewers in the most efficient manner.

➤ **Quality by Design and performance-based specifications to assure pharmaceutical quality**

To encourage Quality by Design and application of more relevant specifications the QbR incorporates review questions on the product development report from which reviewers will learn how drug substance and formulation variables affect the performance and stability of the drug product [62, 65, 66]. In addition, it includes a critical comparison of the proposed generic drug product and RLD formulations essential to the approval of therapeutically equivalent products. Eventually, these new practices will contribute to the goal that product quality and performance are achieved and assured by the design of effective and efficient manufacturing processes [62, 65, 66].

➤ **Risk-Based assessment and science-based regulatory policies**

QbR contains a risk assessment section to determine the level of risk associated with the manufacture and design of the drug product. By introduction of simple risk assessment systems some products may be classified in a lower risk category with the benefit of relaxed post-approval CMC supplement requirements for these products. The risk assessment, which utilizes the pharmaceutical development report, considers the degree of dosage form complexity and therapeutic index as well as the level of scientific understanding of the manufacturer of how formulation and manufacturing process factors affect product quality [62, 65, 66].

The new system allows for regulatory relief regarding supplements of minor and incremental changes to the manufacturing process and controls. Furthermore, it encourages continuous improvement of manufacturing processes and the implementation of "real time" assurance of quality [62, 65, 66].

5.3 Achievements of QbR in practice

As of January 2007, OGD encouraged ANDA applicants to submit a Quality Overall Summary in the QbR format with every ANDA submission. In July 2007 already more than 90% of ANDA submissions were submitted in the new format.

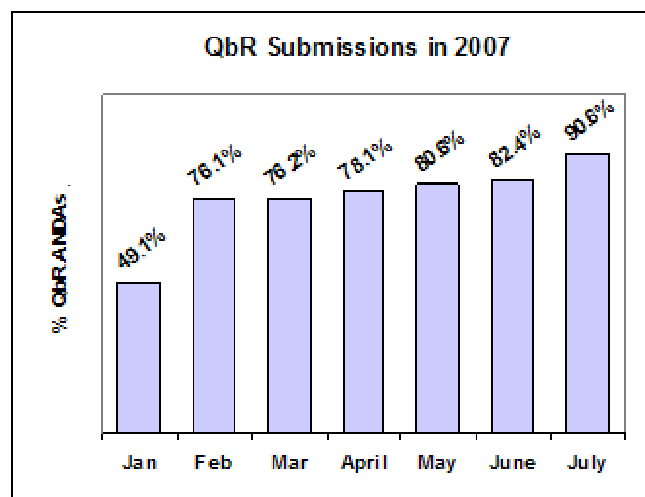


FIGURE 4: ANDAs SUBMITTED TO THE OFFICE OF GENERIC DRUGS IN QbR FORMAT STARTING FROM JANUARY 2007 AS PERCENTAGE OF TOTAL ANDAs SUBMITTED DURING THAT PERIOD

As outlined previously the Question based Review has been designed as an assessment system
 (1) to more effectively allocate limited review resources as well as
 (2) to concretely and practically assess the implementation of FDA's cGMPs for the 21st Century and Quality by Design.

The achievements of the QbR with regard to the first point (effectiveness of review) may be assessed by the following measures:

TABLE 7: EVALUATION OF EFFECTIVENESS OF REVIEW

Objective	Measures	Evidence
Effectiveness of review	Regulatory review period for ANDAs	Reduced review period
	Number of first-cycle approvals versus number of multiple-cycle approvals	Increasing number of first-cycle approvals
	Number of receipts of CMC supplements versus risked-based post-approval waivers	Decreasing number of supplements

The achievements of the QbR with regard to the second objective have to be seen in the context of the FDA's cGMPs for the 21st Century Initiative. QbR is intended to practically assess the implementation of the cGMPs for the 21st Century Initiative but in addition to that QbR provides a tool promoting the implementation of the same. Therefore, the implementation status of the cGMPs for the 21st Century Initiative is an important criterion of assessment. The following measures are considered to evaluate the effect of QbR in the implementation of the cGMPs for the 21st Century Initiative:

TABLE 8: EVALUATION OF QbR WITH REGARD TO IMPLEMENTATION OF THE cGMP INITIATIVE

Objective	Measures	Evidence
Quality by design / Risk-based assessment	Number of submission containing a pharmaceutical development report that demonstrates sufficient product and process understanding to qualify for risk-based assessment	Increased utilization of risk-based assessment
	Number of receipts of CMC supplements versus risked-based post-approval waivers	Decreasing number of supplements
	Number of product recalls	Decreasing number of product recalls

Evaluation of the QbR by the measures described above at this time is not feasible, since the data available in the public domain are insufficient with regard to the type of data and not up-to-date.

Besides the evaluation of empiric data, the following benefits may be recognized on the basis of the design of QbR alone:

- QbR establishes the best practices of the CMC review system as a standardized method for the entire office. It enables reviewers to better recognize those deficiencies that affect product quality in CMC information.
- Formalized QbR questions increase the transparency of drug product quality assessment providing generic companies direction to improve the quality. It encourages generic applicants to share their pharmaceutical development knowledge.

6. Summary

In the United States, applications to market a generic are filed by so called "Abbreviated New Drug Applications (ANDA)". The application is called abbreviated because results from (pre-)clinical safety and efficacy studies are usually not required. Instead, reference is made to the data on file for an already approved reference drug

The current regulatory framework for generics in the United States is governed by the Drug Price Competition and Patent Term Restoration Act of 1984, more commonly known as the Hatch-Waxman Act, and the Medicare Prescription Drug Improvement & Modernization Act (MMA) of December 2003. The legal basis for the filing of an ANDA is laid down in section 505(j) of the Food, Drugs & Cosmetics Act which is codified in 21 CFR 314.

After introduction of the United States legal system and regulatory authority the specific terms and requirements related to the filing of an Abbreviated New Drug Application are discussed within this thesis.

An ANDA usually is submitted for a drug product that is the same as a drug product previously approved by the FDA. The approved drug product, usually an innovator drug, when referred to in a generic application, is called the Reference Listed Drug.

According to the Regulation the term "same as" means the drug product and the Reference Listed Drug:

- shall contain identical active ingredients
- shall be identical in strength, dosage form, and route of administration
- shall have identical conditions of use.

Provisions of the Hatch-Waxman Act protect the innovator drug products by market exclusivity and patent term restoration. Consideration, consequently, is given to patent certification requirements. In case a patent exists that claims the drug, drug product, or method of use the applicant is requested to file a patent certification with regard to the patent status. The different types of patent certifications are discussed. By submitting a so called Paragraph IV Certification the applicant challenges the patent assuming that the latter is invalid, unenforceable or will not be infringed. Inclusion of a Paragraph IV Certification permits the Applicant to file its ANDA 4 years after approval of a new chemical entity, that is 1 year before actual expiry of the 5 year exclusivity.

The submission of an ANDA containing a Paragraph IV Certification is an infringing act and, therefore, may be followed by a patent infringement litigation. In such cases, the FDA will delay the approval of the ANDA up to 30 months for pending resolution of lawsuit. As part of the thesis the availability and termination of the 30-month stays is discussed considering statutory amendments and current guidance.

As provided by the Food, Drugs & Cosmetics Act, the first generic applicant to submit an application containing a Paragraph IV Certification is eligible to an incentive of 180 days of generic exclusivity. This exclusivity, commonly known as "180-day exclusivity", protects the first-to-file applicant, whose ANDA contains a Paragraph IV Certification, from competition by subsequent generic applicants referring to the same Reference Listed Drug. This thesis elucidates FDA's previous interpretations of the statute regarding 180-day exclusivity, it explains the latest statutory amendments and current guidance.

A separate section is given to discussion of the content and format of an Abbreviated New Drug Application. Information considered helpful in the compilation of Modules 1, 2, 3 and 5 is provided. Requirements for electronic submission in eCTD format are outlined.

Finally, attention is paid to the new Pharmaceutical Quality Assessment System called Question based Review (QbR), which is the requested format for the Quality Overall Summary in Module 2.3 since the beginning of 2007. Development and rationale of the QbR are described in the context of the *cGMPs for the 21st century Initiative*. The design of the QbR is discussed and an evaluation of achievements is proposed.

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