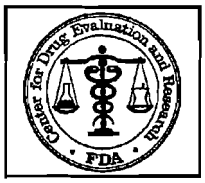

Center for Drug Evaluation
and Research (CDER)

Reviewer Guidance

Validation of Chromatographic Methods

November 1994
CMC 3

TABLE OF CONTENTS

REVIEWER GUIDANCE[1]

VALIDATION OF CHROMATOGRAPHIC METHODS

I. INTRODUCTION

The purpose of this technical review guide is to present the issues to consider when evaluating chromatographic test methods from a regulatory perspective. The document discusses the points to note and weaknesses of chromatography so that CDER reviewers can ensure that the method's performance claims are properly evaluated, and that sufficient information is available for the field chemist to assess the method. Analytical terms, as defined by the International Conference of Harmonization (ICH), 1993, have been incorporated in this guide.

Chromatographic methods are commonly used for the quantitative and qualitative analysis of raw materials, drug substances, drug products and compounds in biological fluids. The components monitored include chiral or achiral drug, process impurities, residual solvents, excipients such as preservatives, degradation products, extractables and leachables from container and closure or manufacturing process, pesticide in drug product from plant origin, and metabolites.

The objective of a test method is to generate reliable and accurate data regardless of whether it is for acceptance, release, stability or pharmacokinetics study. Data are generated for the qualitative and quantitative testing during development and post-approval of the drug products. The testing includes the acceptance of raw materials, release of the drug substances and products, in-process testing for quality assurance, and establishment of the expiration dating period.

Validation of a method is the process by which a method is tested by the developer or user for reliability, accuracy and preciseness of its intended purpose. Data thus

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[1]This guidance has been prepared by the Analytical Methods Technical Committee of the Chemistry Manufacturing Controls Coordinating Committee (CMC CC) of the Center for Drug Evaluation and Research at the Food and Drug Administration. Although this guidance does not create or confer any rights for or on any person and does not operate to bind FDA or the industry, it does represent the agency's current thinking on the validation of chromatographic methods. For additional copies of this guidance, contact the Division of Communications Management, HFD-210, CDER, FDA, 5600 Fishers Lane, Rockville, MD 20857 (Phone: 301-594-1012). Send one self-addressed adhesive label to assist the offices in processing your request. An electronic version of this guidance is also available via Internet the World Wide Web (WWW) (connect to the FDA Home Page at WWW.FDA.GOV/CDER and go to the "Regulatory Guidance" section).

generated become part of the methods validation package submitted to CDER.

Methods validation should not be a one-time situation to fulfil Agency filing requirements, but the methods should be validated and also designed by the developer or user to ensure ruggedness or robustness. Methods should be reproducible when used by other analysts, on other equivalent equipment, on other days or locations, and throughout the life of the drug product. Data that are generated for acceptance, release, stability, or pharmacokinetics will only be trustworthy if the methods used to generate the data are reliable. The process of validation and method design also should be early in the development cycle before important data are generated. Validation should be on-going in the form of re-validation with method changes.

II. TYPES OF CHROMATOGRAPHY

Chromatography is a technique by which the components in a sample, carried by the liquid or gaseous phase, are resolved by sorption-desorption steps on the stationary phase.

A. High Performance Liquid Chromatography (HPLC)

HPL chromatographic separation is based on interaction and differential partition of the sample between the mobile liquid phase and the stationary phase. The commonly used chromatographic methods can be roughly divided into the following groups, not necessarily in order of importance:

1. Chiral
2. Ion--exchange
3. Ion--pair/affinity
4. Normal phase
5. Reversed phase
6. Size exclusion

1. Chiral Chromatography

Separation of the enantiomers can be achieved on chiral stationary phases by formation of diastereomers via derivatizing agents or mobile phase additives on achiral stationary phases. When used as an impurity test method, the sensitivity is enhanced if the enantiomeric impurity elutes before the enantiomeric drug.

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