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Bioequivalence - What Patent Lawyers Need To Know

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March 20, 2013

Overview

- Bioequivalence (BE) – General Concept
- BE Requirements for ANDA filers
- Challenging Bioequivalence Standards
- Bioequivalence and Patents
- Invalidating BE Claims in PIV Patent Litigation

Why Bioequivalence?

- Required for FDA approval of an ANDA for the generic version of a brand name drug.
- FDA recommends substitution by state formularies only for bioequivalent products.

FDA Definitions Used in Bioequivalence Determinations

- Pharmaceutical equivalents
- Bioavailability
- Therapeutic equivalents
- Bioequivalence

Pharmaceutical Equivalents

- Drug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), have the same dosage form and route of administration and are identical in strength or concentration.
- May differ in shape, release mechanisms and packaging.

Bioavailability

- Bioavailability is the rate and extent to which the active ingredient becomes available at the site of drug action.
- Bioavailability is typically measured as AUC and C_{max}.
- C_{max} measures the rate of absorption.
- AUC measures the extent of absorption.

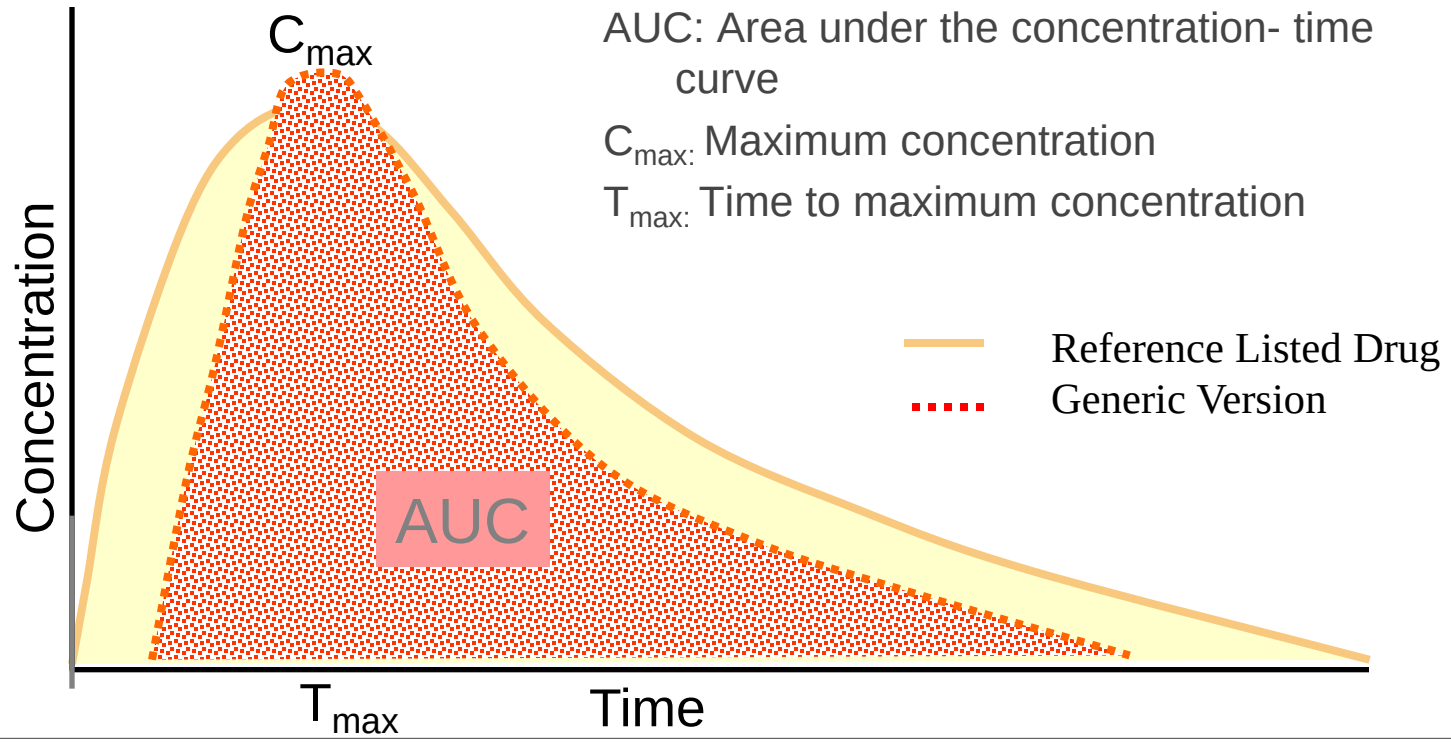
Therapeutic Equivalents

- Drug products are considered therapeutic equivalents if they are all of the following:
  - Bioequivalent
  - Approved as safe and effective
  - Adequately labeled
  - Manufactured in compliance with current Good Manufacturing Practice regulations
- Therapeutic equivalents are expected to have the same clinical effect and safety profile.

Bioequivalence

- Drug products are considered bioequivalent if they are pharmaceutical equivalents whose rate and extent of absorption are not significantly different when administered to patients or subjects at the same molar dose under similar experimental conditions.
- Bioequivalence may be demonstrated through in vivo or in vitro test methods or other tests set by FDA.

Pharmacokinetic Studies: Key Measurements



AUC: Area under the concentration- time curve

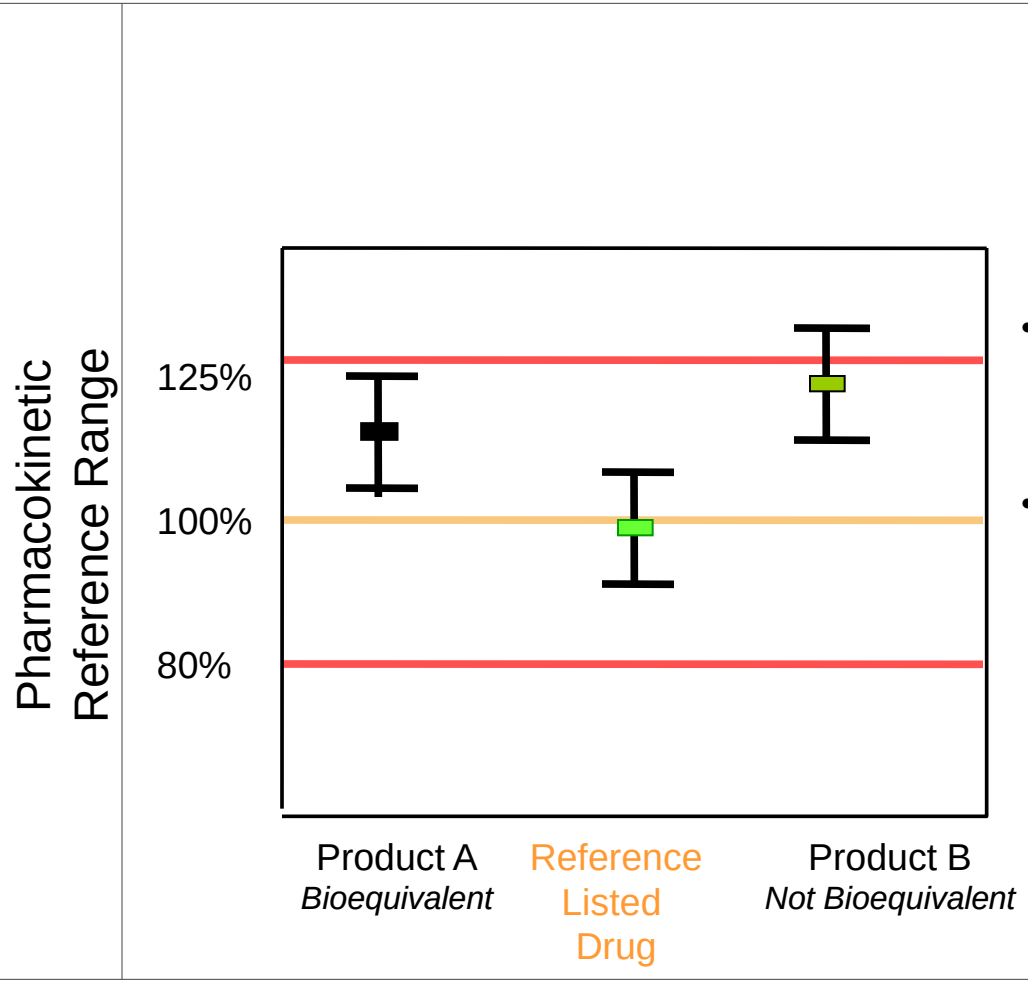
$C_{max:}$ Maximum concentration

$T_{max:}$ Time to maximum concentration

Reference Listed Drug

Generic Version

FDA Requirements for Bioequivalence



- Product A is bioequivalent to the reference drug; its 90% confidence interval for AUC and C_{max} fall within 80% to 125% of the reference drug
- Product B is not bioequivalent to the reference drug; its 90% confidence interval for AUC and C_{max} fall outside of 80% to 125% of the reference drug

Generic Products

- A bioequivalency rating is given to, and designated by, the manufacturer of the generic drug product who originally submitted the ANDA.
- Generic prescriptions typically may be filled with the most cost efficient generic product.
- Most state formularies require the generic to be AB-rated.

BE Guidelines for Specific Products

- In 2007, FDA published a guidance and launched a website for designing BE studies for specific products
  - **http://www.fda.gov/cder/handbook/index.htm**
- Streamlines process by allowing direct access to information
- Provides recommendations and the current FDA mindset - not statutory requirements

Challenging Bioequivalence Standards

- Citizen petitions and the Administrative Procedures Act court challenges.
- FDA is given wide discretion and courts will typically defer to FDA's bioequivalence rulings. *See*, *e.g.*, *Schering Corp. v. FDA*, 51 F.3d 390 (3d Cir. 1995).

Wellbutrin XL® Citizen Petition

- Biovail argued that FDA should require ANDA filers to conduct additional bioequivalence testing.
- Sought comparisons to Wellbutrin IR and SR, in addition to Wellbutrin XL®.
- FDA rejected argument – ANDA filers only need to prove bioequivalence to RLD.
- Filing citizen petitions to challenge BE standards becoming more common, e.g., Arava® and Adderall XR®.

Ambien CR®

- Brand company had argued that FDA should require more extensive BE measurements
- August 2009 BE Guidance
  - Required AUC from time 0-1.5 hours after administration to meet the 80/125 test
  - Reasoning was that this was a sleep medication and that effectiveness in the first 1.5 hours required a BE AUC

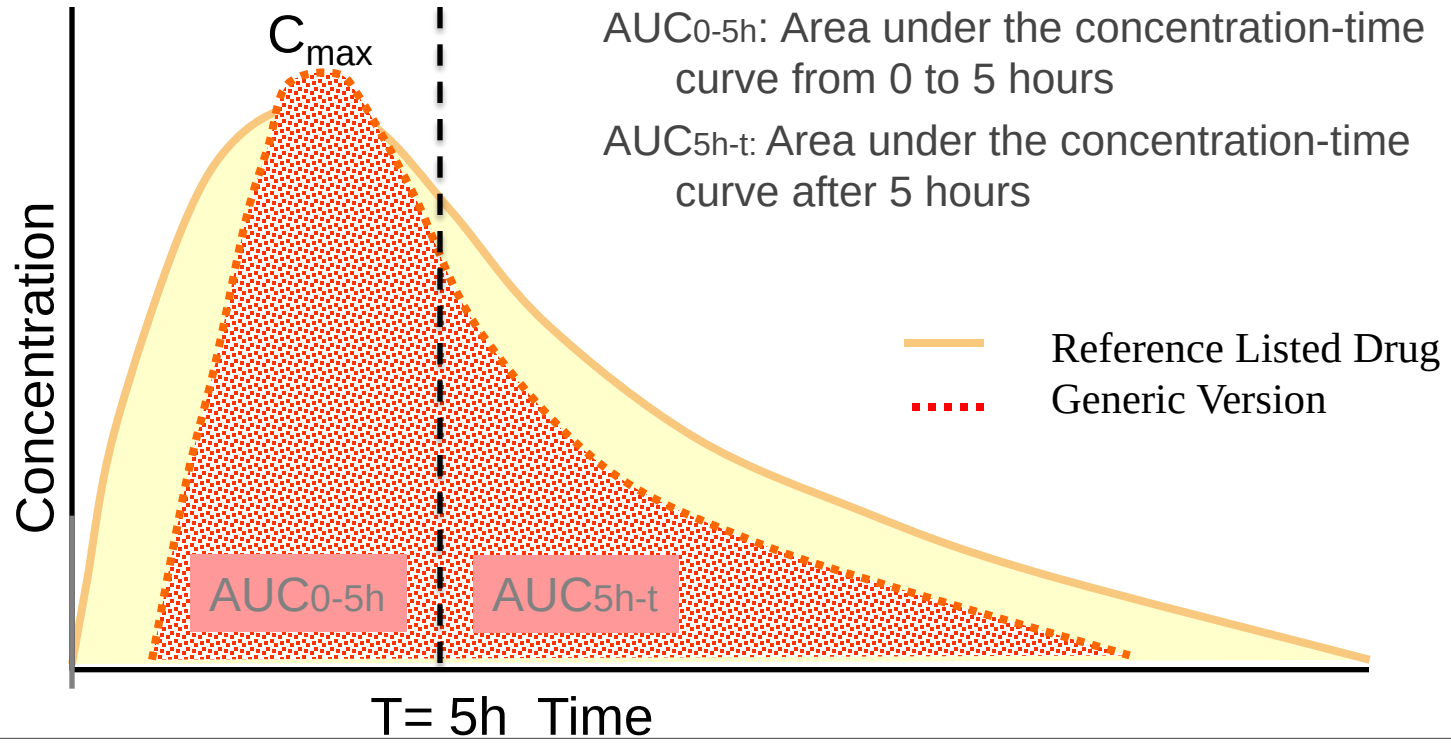
Adderall XR®

- October 2005 – Shire files citizen petition requesting FDA to require partial AUC measurements for generic drugs referencing Adderall XR®
  - $AUC_{0\text{-}1}$, $AUC_{1\text{-}2}$, $AUC_{2\text{-}3}$, $AUC_{3\text{-}4}$
- March 2012 – Shire files supplement requesting additional partial AUC measurement requirements
  - $AUC_{0\text{-}1.5h}$, $AUC_{1.5h\text{-}t}$
- June 2012 – FDA responds with partial approval
  - FDA-2005-P-0120-0030

Adderall XR® (cont.)

- FDA acknowledged that it was important to use partial AUC metrics for the specialized dosage form because the dosage form:
  - (1) contained IR and DR components
  - (2) was designed to achieve both rapid onset and sustained activity throughout the day
  - (3) did not show unusual accumulation at steady state
- Required two additional metrics: $AUC_{0\text{-}5h}$ and $AUC_{5h\text{-}t}$

Partial AUCs required for generic products referencing Adderall XR®



$AUC_{0\text{-}5h}$: Area under the concentration-time curve from 0 to 5 hours

$AUC_{5h\text{-}t}$: Area under the concentration-time curve after 5 hours

Reference Listed Drug

Generic Version

Anticompetitive Conduct?

- A meritless citizen petition submitted to impose delay may raise antitrust issues
- On the eve of ANDA approvals relating to Arava®, Sanofi-Aventis filed a citizen petition for more stringent BE studies – denied by FDA six months later
- Drug wholesaler brought action under § 2 of the Sherman Act
- Jury trial resulted in a defense verdict after the jury concluded that the Citizen Petition was not "objectively baseless."
- Court denied motion for JNOV or new trial
  - *Louisiana Wholesale Drug Co., Inc. v. Sanofi-Aventis, 2009 WL 2708110 (S.D.N.Y. Aug. 28, 2009)*

Bioequivalence and PIV Litigation

- Impact of FDA's Bioequivalence Rules on Claim Construction
- Bioequivalence and Infringement
- Invalidating Bioequivalence Claims

Bioequivalence-Type Patents

- More recent development
- Claims focus on pharmacokinetic ("PK") characteristics:
  - In vitro properties
  - In vivo properties
  - True BE claims – adopt 80/125 test

Bioequivalence-Type Patents

- Examples of products with PK patents listed in the Orange Book:
  - Adderall XR® (mixed amphetamine salts)
  - Concerta® (methylphenidate)
  - Wellbutrin XL® (bupropion)
  - OxyContin® (oxycodone)

Bioequivalence and Claim Construction

- Construction of claims directed towards in vivo characteristics may be impacted by FDA's bioequivalence rules.
- Perspective of one of ordinary skill in the art
- "About"
- "Mean"
- Single vs. multiple dose studies

Bioequivalence and Infringement

- Generics often in a box
- Individual data when a mean is not claimed
- Population size for in vivo tests
- Failure to prove in vivo release characteristics

Bioequivalence and Infringement

- Doctrine of Equivalents
  - Insubstantial differences between product and claim
  - Function-Way-Results test
- Bioequivalence vs. doctrine of equivalents

Bioequivalence and Validity

- Patents claiming in vitro or in vivo characteristics present unique validity issues.
- Anticipation
- Inherency
- Obviousness
- Written Description

Bioequivalence and Validity

- Anticipation arguments typically involve finding the identical formulation in the art and arguing that the claimed PK values are inherent properties.
- Limits of current inherency law
- Difficulties of proof and variability
- Identical compositions have identical properties

Bioequivalence and Validity

- Obviousness and *KSR v. Teleflex.*
- Rejected rigid T-S-M test.
- Creativity of one of skill in the art.
- Obvious to try may be enough if there are design or market pressures and a finite number of predictable solutions.
- Problematic for XR patents.

Bioequivalence and Validity

Obviousness arguments typically involve a similar, but not identical, prior art formulation.

- For example, a formulation with a different API with similar pharmacological properties.
- Argue that it would be obvious to modify the formulation to achieve the claimed PK values.
- Need to demonstrate why the claimed PK values would have been known to be optimal.
  - XR formulations that replicate IR.

Bioequivalence and Validity

- Secondary considerations may be used to rebut obviousness.
  - Copying
  - Commercial success

In re Cyclobenzaprine 676 F.3d 1063 (Fed. Cir. 2012)

- Cephalon, Inc.
  - 7,387,793 patent directed to a modified-release dosage form of skeletal muscle relaxant
  - 7,544,372 patent directed to a method of relieving muscle spasms with formulation disclosed in '793 patent
- Mylan and Par
  - ANDA for generic versions of extended-release cyclobenzaprine hydrochloride
  - PIV alleging noninfringement or patent was invalid or unenforceable
- D. Del. found Cephalon's patent claims to be invalid as obvious over the IR dosage form
- Fed. Cir. reversed and vacated D. Del.'s invalidity judgment

In re Cyclobenzaprine 676 F.3d 1063 (Fed. Cir. 2012)

- D. Del. found claims were obvious because the claimed extended-release PK profile was bioequivalent to the immediate-release PK profile
- Fed. Cir. held district court erred because it was also required to consider whether it was obvious that a bioequivalent PK value would produce a therapeutically effective formula
  - Cyclobenzaprine had no known PK/PD relationship for any formulation
  - Skilled artisans could not predict whether any particular PK profile would produce a therapeutically effective formula

In re Cyclobenzaprine 676 F.3d 1063 (Fed. Cir. 2012)

- Fed. Cir. held the district court erred when it found the patent claims were obvious before it evaluated proof of objective considerations
- "'[S]econdary considerations' must always when present be considered en route to a determination of obviousness." Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1538 (Fed. Cir. 1983).
- Secondary considerations are not after-the-fact considerations but rather have broader applicability

In re Cyclobenzaprine 676 F.3d 1063 (Fed. Cir. 2012)

- Fed. Cir. held the district court erred when it shifted the burden of persuasion to Cephalon to prove secondary considerations of nonobviousness
- There is no formal burden-shifting framework
- The burden of proof is placed *only* on the party challenging invalidity and does not shift to the patentee to prove nonobviousness

Bioequivalence and Validity

- Written description
  - Given the variability of biology and PK, patent specification must sufficiently support the claimed values, especially where wide ranges are claimed.

Any questions?

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