BUILDING A BETTER PRODUCT USING THE 505b(2) PATHWAY

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4TH ANNUAL SYMPOSIUM: DEVELOPMENT OF GENERICS AND 505 b(2)
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DISCUSSION POINTS

- Understanding 505 b(2)
  - Why 505 b(2)
  - What changes can be supported by 505 b(2)
  - Considerations for identifying the concept
- Case study – Methylphenidate HCl
- Examples – using all available data
- Conclusions
QUICK PRIMER...THE REGULATORY PATHWAYS

505 b(1) NDA
Full application – Data from studies conducted by and for sponsor

505 b(2) NDA
Hybrid between ANDA [505 (j))] and NDA [505 b(1)]

505 (j) ANDA
Appropriate for drug products that are same as approved products – BE requirement

“Where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference”

Adapted from www.camargopharma.com
505 b(2) – BETWEEN NDA AND ANDA

- Like a stand alone NDA, a 505 b(2) application must satisfy the requirements for safety and effectiveness of the drug product.
  - Application can rely on the finding of safety and effectiveness of the listed drug only to the extent the product seeking approval and the listed drug are the same.
  - Establishing the “scientific bridge” with the reference listed drug
- Like an ANDA application, 505 b(2) applications are subject to patent certification requirements
- Depending on approval conditions, marketing exclusivity conditions may be allowed for a 505 b(2)
SEEKING HIGHER VALUE PRODUCTS – 505 b(2) BUSINESS DRIVERS

VALUE OF PRODUCTS AT RISK 2004–2020

Source: IMS Health, MIDAS, Market Segmentation, Jun 2010
Copyright IMS Health; All rights reserved

Ref: Ken Phelps, Generic companies seek new revenue streams; www.camargopharma.com
505 b(2) APPROVALS: TREND 2004 TO 2016

- Increasing opportunities for higher value products
- Market differentiation – niche products
- Lower development risk
- High profit potential
- Potential for market exclusivity

## CHANGES THAT SUPPORT SUBMISSION OF A 505 B(2)

<table>
<thead>
<tr>
<th>Change</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of administration</td>
<td>Intravenous to Oral, Oral to Transdermal etc</td>
</tr>
<tr>
<td>Dosage Strength</td>
<td>Higher or Lower</td>
</tr>
<tr>
<td>Dosage Form</td>
<td>Oral to Transdermal, Lotion to Foam, Solution to Chewable etc</td>
</tr>
<tr>
<td>Dosing Regimen</td>
<td>2x or 3x daily to 1x daily or weekly</td>
</tr>
<tr>
<td>Change in Active Ingredient</td>
<td>New salt, Racemate, Enantiomer, Complex etc</td>
</tr>
<tr>
<td>Combination Product</td>
<td>Switch of one DS from a previously approved combo, new combo of previously approved drugs</td>
</tr>
<tr>
<td>New Chemical Entity</td>
<td>Prodrug of previously approved drug</td>
</tr>
<tr>
<td>Indication</td>
<td>New indication, new patient population</td>
</tr>
<tr>
<td>Rx to OTC</td>
<td>Previously approved drug changed to OTC or changes to existing OTC product</td>
</tr>
</tbody>
</table>
# CHANGES THAT SUPPORT SUBMISSION OF A 505 B(2)

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<th>Change</th>
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<tbody>
<tr>
<td>Formulation changes leading to bio-inequivalence</td>
<td>Controlled release products, Other formulation changes excluding 505 (j) applications</td>
</tr>
<tr>
<td>Drug Device Combination products</td>
<td>Drug + device, Two drugs + device, Drug + biologic (in all cases, primary mode of product action must be drug)</td>
</tr>
<tr>
<td>Naturally derived or recombinant active</td>
<td>New manufacturing source (not biologics)</td>
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**SOURCES OF DATA FOR REFERENCE**

- Sponsor owns the data
- FDA Approval packages (approved labeling)
- *Extensive guidelines are available in* “Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products”
- Studies published in reputable, peer reviewed journals
  - Multiple studies, different investigators
  - Significant details on study plan including statistical analysis and appropriate study end points
  - Definitive efficacy conclusion
- Central databases e.g.:
  - TOXNET
  - Adverse Event Reporting System
- Body of evidence from patient use

Adapted from: Drug Repositioning, Bringing New Life to Shelved Assets and Existing Drugs, Ed: Michael J Barratt and Donald Frail, 2012
IDENTIFYING RIGHT CONCEPT – DRUG REPURPOSING

- Life cycle management opportunities within big Pharma
  - Licensing opportunities
- Internal resources focused on therapeutic areas with ability to identify value opportunities
  - Patent expirations
  - Clinical unmet needs
  - Develop proof of concept ideas
    - Add meaningful improvements to mature products
- New technology platforms
  - Integration of bioinformatics, systems biology, computational science
  - Integrate data mining and knowledge management to develop testable hypotheses.
IDENTIFYING THE RIGHT CONCEPT

- What is the rationale for the product
  - What is the problem? Unmet need? How does it help the patient?
  - Does the solution allow for a differentiated product?
- Is the proposed solution viable from a technical perspective?
  - Does the science make sense? Is the technology available and accessible?
- What is the clinical and regulatory viability?
  - What is the clinical data required for approval? Can the clinical data provide differentiation to allow for eventual claims?
- What is the commercial viability?
  - COG’s, substitution and competition, what is needed for reimbursement?
LEADING TO A TARGET PRODUCT PROFILE (TPP)

- “A Target Product Profile is a strategic development process tool.”
- A TPP is a summary of a drug development program described in terms of labeling concepts.
- A TPP can be prepared by a sponsor and then shared with the appropriate FDA review staff to facilitate communication regarding a particular drug development program.
- “The TPP is a dynamic summary that changes as knowledge of the drug increases.”
  - It is a snapshot of the development plan at a specific point in time.
- Submission of a TPP is voluntary.

AN UNDER UTILIZED DEVELOPMENT TOOL

- Review of 808 NDA and BLA applications from 2008 – 2015
  - 87 applications used TPP’s
    - 58 were 505 b(1)
    - 22 were 505 b(2)
    - 11 were BLA
- Subset of data analyzed against controls
  - Median difference of 30 days from first submission to approval for applications that reference TPP

Ref: Breder, Du, Tyndall. Trends in Biotechnology, July 2017
METHYLPHENIDATE HYDROCHLORIDE
CASE STUDY

CONCERTA®
QUILLIVANT®XR
APTENSIO®XR
COTEMPLA®XR ODT
METHYLPHENIDATE HYDROCHLORIDE FOR TREATMENT OF ADHD SYMPTOMS

- Original approval for IR product in 1955
- Sustained release products have been available since 1982
- Short acting stimulant with half life of 2-3 hours and duration of action of 1-4 hours
  - BID or TID dosing was commonly used to manage symptoms
- Compound is well absorbed from GI tract

CONCERTA®: MARKET RESEARCH INDICATED THAT AN IMPROVED SUSTAINED RELEASE PRODUCT IS DESIRABLE

- Sustained release (SR) products available on the market were considered to be clinically less effective than multiple doses of immediate release (IR) product
  - SR products were not well accepted in clinical practice. Reason for lower efficacy was unknown (efficacy based on measures of behavior and attention)
  - 8 hr duration of action for marketed SR product did not provide full day coverage
- Efficacy issues: Short duration of action leading to multiple doses throughout the school day – peak and trough effects
- Compliance issues:
  - Frequently missed doses due to need for multiple administrations
  - Delayed administration of afternoon dose may impact sleep and/or appetite due to elevated plasma levels at end of day
- Privacy issue:
  - Dosing in public settings and logistical difficulty of taking a dose in school or after school

Why is the existing SR product not considered clinically effective?

What is the ideal in vivo profile to address the shortcomings of existing SR products?

Clinicians hypothesized that

- Lower $C_{\text{max}}$ obtained from SR products may not be clinically effective
- Can the sustained plasma concentration of drug induce tachyphylaxis (acute tolerance to the drug)

Three dosing regimens were studied with placebo

- Twice a day dosing (with IR product)
- Flat dosing (large bolus followed by small constant doses)
- Ascending dosing (small bolus followed by small increasing doses)

Study conducted in children with diagnosis of ADHD and under treatment with methylphenidate (5 to 15 mg daily dose) (n=38; 7-12 years of age)

- Doses were administered as capsules at 30 min intervals

Study conducted in a laboratory school setting and after each classroom session, teachers completed evaluation using SKAMP rating scale

- SKAMP scale is a systematic measure of behaviors considered to classroom manifestations of ADHD symptoms
Ascending dosing regimen becomes as efficacious as b.i.d regimen by the afternoon – suggesting a large bolus may not be required to achieve significant improvement in symptoms

Flat dosing regimen loses efficacy in the afternoon

CONCERTA®: DOSING REGIMENS TESTED – STUDY 2

Two experimental t.i.d dosing regimens were studied where timing of second bolus dose was varied.

Simulated plasma methylphenidate concentrations for 30 mg total daily dose delivered by various dosing regimens.

TID – AM: Middle bolus delivered 2 h after first dose and TID – PM: middle bolus delivered 6 h after first dose.

CONCERTA®: WHAT IS THE IDEAL TARGET PRODUCT PROFILE FOR DELIVERY OF METHYLPHENIDATE

- Rapid onset of action, followed by an ascending drug profile
- Once a day dosing
  - Avoid intermittent dosing throughout the day
  - Avoid efficacy fluctuations associated with peak – trough plasma levels
- Provide duration of effect for 12 hours

PUSH-PULL™ TRILAYER TECHNOLOGY WAS DEVELOPED TO DELIVER THE ASCENDING RELEASE PROFILE (CONCERTA®).

Before Operation

Drug Overcoat (To provide rapid onset)
Rate Controlled Membrane

Drug Compartment #1

Drug Compartment #2

Push Compartment

During Operation

Orifice/Exit Port

CONCERTA® ADMINISTERED QD MAINTAINS DURATION OF ACTIVITY COMPARABLE TO TID ADMINISTRATION OF IR PRODUCT
SUMMARY OF SKAMP FINDINGS IN LABORATORY SCHOOL SETTING

Concerta® Prescribing Information; McNeil Pediatrics™, November 2010
QUILLIVANT® XR: EXTENDED RELEASE ORAL SUSPENSION OF METHYLPHENIDATE HYDROCHLORIDE

- Approved in 2012
- Extended release powder for reconstitution as an oral suspension (dosing dispenser provided with product)
- RLD = Methylphenidate HCl Oral Solution
- One Phase 3 study

Ref: Prescribing Information for Quillivant® XR, February 2015
Ref: US Patent 8,465,765;
QUILLICHEW® XR: EXTENDED RELEASE CHEWABLE TABLETS (METHYLPHENIDATE HYDROCHLORIDE)

- Approved in 2015
- Extended release chewable tablets
- RLD = Immediate Release Methylphenidate chewable tablet
- One Phase 3 study

Ref: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207960s000lbl.pdf
Methylphenidate is bound to a ion exchange resin – sodium polystyrene sulfonate

Methylphenidate-ion exchange resin complex is coated with a water insoluble, permeable, pH-independent barrier coating

Pediatric friendly formulation which allows for precise dosage adjustment with the suspension, ease of administration with chewable tablets

Once a day dosing – fast onset of action
APTENSIO® XR

- Multiparticulate bead formulation – 40% of drug load is immediate release portion, 60% is extended release
- Approved in 2015
- RLD = Ritalin SR
- 2 clinical safety and efficacy studies conducted

Ref: APTENSIO® XR approved label accessed On 18 Sep 2017
COTEMPLA® XR - ODT

- Extended release orally disintegrating tablet for once a day administration
- Methylphenidate is ionically-bound to the sulfonate of polystyrenesulfonate particles.
- RLD = Ritalin SR
- Approved in 2017

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205489s000lbl.pdf
Understand the value proposition from a scientific perspective
XURIDEN®

- Xuriden® (uridine triacetate) – treatment of hereditary orotic aciduria
- 505 b(2) approval in 2015
- Small efficacy trial supported with literature data
- NME and orphan exclusivity

Ref: Uridine triacetate approval data
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/208169Orig1s000SumR.pdf
YOSPRALA® (ASPIRIN-OMEPRAZOLE DELAYED RELEASE TABLETS)

- Delayed release aspirin (81 mg and 325 mg) combined with omeprazole (40 mg), approved in 2016
- 505 b(2) approved in 2016 for patients who require aspirin for secondary prevention of cardiovascular and cerebrovascular events and who are at risk of developing aspirin associated gastric ulcers
- Product was studied in 2 randomized clinical trials for safety and efficacy, PK/PD studies conducted
- 3 year exclusivity

Ref:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/205103s000lbl.pdf
FINAL THOUGHTS..

- 505 b(2) applications are a unique development strategy that can add high value products to patients.
  - Lower risk, lower cost development pathway by leveraging available information.

- Emerging knowledge in systems biology that expands understanding of biology behind disease pathways can lead to many more opportunities for repurposing and repositioning of existing drugs.