Development of Novel Controlled Release Formulations
Mitigating Dose Dumping and Misuse
By Shams Rustom
Today’s operating environment

- The patent cliff is here
- Regulatory hurdles rising
- Drug development costs rising and margins decreasing
- Ever earlier paragraph IV applications

- The need to extend the value of existing product assets via drug delivery technologies has never been greater for pharmaceutical companies -
  
  - Such strategies are now considered early in the commercial development cycles of many drugs
Today’s operating environment

- If such strategies are to be successful technologies employed must be able to demonstrate value in the market place over and above the original presentation and over notional convenience and compliance.
- Preferably any technology employed should improve the patient experience and generate new label claims that are difficult to ‘carve out’.
- New technologies should be backed by solid intellectual property
- New technologies must acknowledge the price-pressures experienced today and must allow differentiation via simple, rapid and robust development strategies.
Dose Dumping
The risks to patients
an Unmet Need
What is Dose Dumping?

- The uncontrolled release of drug from a modified release formulation
- Relates primarily to Controlled Release (CR) Formulations
- CR products can contain the full daily dose of drug.
  - If damaged or misused, CR products can liberate their entire contents rapidly into the blood (Dose Dump)
  - Problem for All Drugs. With some, Dose Dumping leads to serious health risks.
FDA’s view on dose-dumping - a major concern

**Rx Products**

- e.g. Palladone - RX opioid
  Withdrawn due to problems with dose dumping

**OTC Products**

- e.g. Guaifenex Crantex and Wellbid - OTC products
  Withdrawn due to dose dumping issues;
  
  ‘*Dose dumping is a major concern with these products*’,

Deborah M. Autor: Director of the office of compliance (CDER),
Why Does Dose Dumping Occur?

- Dose dumping occurs when the controlled release mechanism of a formulation is defeated e.g. by:

  Physicochemical
  - Alcohol Interactions
  - pH Interactions

  Product Tampering/Medication Error
  - Patients breaking the tablets (due to confusion, to self titrate, to economise, to aid swallowing)
  - Patients or care givers crushing the tablet (due to confusion, to aid/disguise administration)
Commercial Once-a-Day Tramadol Formulation
In vitro performance of split tablets
The Unmet Need

• Patients Require Safer Formulations that Mitigate the Risk of Dose Dumping through interaction, breakage or crushing
  
  - In a pilot study performed by RADARS® commissioned by Labopharm, tampering occurred in c.30% of the cases reported to Poison Centers where extended release opioids were prescribed.

• Such formulations should also protect from recreational misuse (injection, insufflation).

* RADARS = Researched, Abuse, Diversion and Addiction Related Surveillance System
• **Primary Aims:**
  - Develop controlled release products that offer maximum benefit to the patient.

  - Develop controlled release products with technologies that minimize risk to the legitimate patient of Dose Dumping through accidental misuse.

  - Only use technologies that in themselves are safe and pose no additional risk to the legitimate patient.

    - No antagonists
    - No deterrence agents

  - Only use technologies that are simple, compliant and robust allowing low cost reliable manufacturing.
FLEX DOSE

Fully bisectable controlled release tablets.
Case Study: Once-a-Day Trazodone Tablets for MDD

• Required Product Characteristics:
  - Robust matrix tablet with low CoGs
  - Once-a-day administration
    • difficult with a pH sensitive drug insoluble at neutral pH
  - 300mg and 150mg dosage strengths
    • Bio-equivalent ($AUC_{0-\infty}$) to 100mg/50mg given TID
  - Scored to allow ‘start low, go slow’ titration schedule from 75mg to 375mg.
    • Never previously achieved with a robust matrix tablet
Human Pharmacokinetics: 26 subject cross over study

Plasma concentration of trazodone

- 300 mg OAD given at bedtime (23:30)
- 100mg IR given at 10:00, 14:00 and 18:00
Flex-Dose: Effect of Bisecting the Tablet

Intact and bisected tablets were dose proportional. Approved tablet labelling states: ‘tablets may be broken along the score’
unique self-forming surface membrane allows sustained release (SR) to be maintained even after tablets are bisected:

Flex Dose - mechanism of action mediated by Contramid

1. Dry granular core
2. Transition layer
3. SR membrane

Solid State NMR of Tablet in Water

Amylose chains form interlocking helices

0-15 min
Wetting allows Contramid surface chains to move and combine

30 min
Combined chains self-form porous SR membrane on tablet surface

30 min - 12 hr
SR membrane releases drug from core at constant rate.

SR membrane will form on any new surface exposed to liquid e.g. new surface of half tablet
Model validation: Model predictions of the mean concentration profiles of our product were confirmed in phase I clinical trials, for both single dose and multiple dosing regimen [1].
Conclusions

• Once-a-Day Formulation of pH sensitive drug developed and commercialised.
  - Formulation development: 6 months
  - Direct Compression Manufacturing
  - Blister and bottle stability intact and bisected (in-use)

• Formulation met PK requirements Fed and Fasted.

• Formulation performed as predicted by Labopharm’s proprietary SIMPHARM in silico iv/ivc platform.

• Bisected tablets demonstrated full bio-equivalence with intact tablets.

• Commercial product achieved differentiating labelling based on low cost PK studies.

• Now this product is approved for USA in 2010 & for Canadian market in 2011

• New Patent Application under prosecution
Intellitab: a safer solution to today’s commercial challenges

Case Study: DDS-08B
• **Required Product Characteristics;**

- 12 hr controlled release versions of oxycodone-acetaminophen (650mg and 325mg acetaminophen)
- Bio-equivalent AUC and Cmax to IR tablets taken Q6h
- Controlled release if bisected
- Controlled Release if crushed
- Simple Robust Manufacturing (Bilayer tablet)
- Platform Validation for 505(b)(2) Applications
- New and differentiated labelling
- New IP
Target In Vivo Plasma Profiles

- **Rapid rise to plateau \( \approx C_{\text{max}} \) of IR**
- **Tmax c. 6-7 Hr**
- **\( C_{\text{max}} \) between \( C_{\text{max}} \) of IR’s**
- **Plateau with clearance c. 6hr**
Data: Oxycontin BID
Model
In Vitro Performance of the Tablets

Performance of Intact Tablets

Misuse Resistance Properties in Comparison to the Intact Tablet
Tablet Performance - Intact and Bisected Tablets: Oxycodone

Comparaison between half and intact tablet

TIMES (hours)

% RELEASE OXYCODONE

0 2 4 6 8 10 12

0 10 20 30 40 50 60 70 80 90 100

08B13508 intact tablet
08B13508 half tablet
Tablet Performance -
Intact Tablets and Bisected Tablets - Acetaminophen

Comparison between half and intact tablet

% RELEASE ACETAMINOPHEN

TIMES (hours)
Effect of Alcohol

effect of alcohol on drug release from intact tablets

**Oxycodone**
- Alcohol Concentration
  - 0%
  - 20%
  - 40%

**Acetaminophen**
- Alcohol (%)
  - 0%
  - 20%
  - 40%
Tablet strength - resists misuse

tablet has a hardness of over 300N; resists breaking (except via score) resists crushing
deters chewing (adults jaw strength less than 300N)

can only be ground in a mill coffee grinder etc.
when ground forms a hard matrix on contact with liquid that maintains sustained release*

*also prevents injection and snorting
Tablet performance v.s. oxycodone sustained release tablets

Effect of Crushing, pH and Alcohol

% Drug Released in 60 min

Formulation and diluent

- Oxycodone CR
- Intact
- Crushed pH 1.2
- Crushed pH 6.8
- Crushed pH 10
- Crushed Water
- Crushed 40% EtOH

no dose dumping even after crushing provides labelling opportunities
DDS-08B
in vivo performance
Human pharmacokinetic data
Acetaminophen

Rapid absorption to effective concentration
sustained absorption

Bio-equivalent AUC

Plasma Concentration (mg/L)

Time (hr)

Intellitab 12hr APAP
IR Q6 APAP
Human pharmacokinetic data
Oxycodone

Plasma Concentration (mg/L)

Time (hr)

C_max equivalent

[Plasma] equivalent at 12hr

T_max highly delayed (6hr)

IR Q6 Oxy
Intellitab 12hr Oxy
Human pharmacokinetic data DDS-08B - Oxycodone performance intact and crushed versus IR tablet

- No Dose dumping
- Tmax crushed: 4.5hr
- All 3 Cmax equivalent
- Significant concentrations at 12hr

Full sustained release and bioequivalent Cmax maintained despite crushing the tablet
Summary

- Controlled release 12hr oxycodone/acetaminophen formulations successfully developed meeting required in vivo performance.
- Formulations allow scoring (bio-equivalence maintained) and does not dose dump in alcohol or various pH solvents.
- Formulations resist crushing but if crushed do not dose dump in vivo.
- Platform validated
- Opportunities for 505(b)(2) validated
- Opportunities for new labelling demonstrated
  - e.g. no clinically significant increase in Cmax was observed after crushing and administering to subjects
Intellitab Additional Opportunities
Branded/Super Generics
Branded/Super Generic Strategies

- Life cycle management strategies may be extended by employing improved or ‘super-generic’ strategies

- Super generic formulations match the pharmacokinetics of the original CR formulation but display additional performance features and labelling (e.g. safety features scoring, crush resistance) - The Flex Dose and Intellitab platforms offer this opportunity
• The generic market place is becoming increasingly crowded
• The ability to produce differentiated products, at generic pricing, allows competitiveness within the generics space.

• The Flex Dose and Intellitab platforms offer this opportunity
Human PK Results - Fed

- **Commercial Comparator tablet**
- **Tramadol Intellitab**

**Tramadol Concentration (ng/mL)**

**Time (h)**

0 4 8 12 16 20 24 28 32 36 40 44 48
Branded/super generic opportunities
Intellitab version of Commercial Tramadol Once-a-Day Tablet

Human PK Results - Fasted

- Commercial Comparator tablet
- Tramadol Intellitab

Tramadol Concentration (ng/mL)

Time (h)
Overall Conclusions

- Dose Dumping has potentially harmful effects for patients. There is presently an unmet need in the market place for technologies that mitigate this effect.
- In today’s environment maximum value must be extracted from existing assets
- Early development of life cycle management strategies is key
- LCM strategies must allow differentiation in the market-place, must be cost-effective and robust to deal effectively with generic competition
- The Flex-Dose and Intellitab platforms, offering greater patient safety, robust IP and rapid low risk low cost PK-based differentiation are well positioned to address these unmet commercial needs
Thank You