DEVELOPING ALCOHOL-OPIOID ABUSE DETERRANT FORMULATIONS: REGULATORY PERSPECTIVES

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(Towards Alcohol & Abuse Resistant Products)

ROADMAP TO PRESENTATION

- A LOOK AT THE CURRENT STATE OF ALCOHOL-SUSTAINED RELEASE PRODUCT CO-INGESTION INTERACTIONS
- A LOOK AT THE LEADING EDGE OF HOPEFULLY TAMPER RESISTANT SUSTAINED RELEASE PRODUCTS
- A SCENIC DETOUR FOR PERSPECTIVE
- A SHORT SUMMARY

CLASSICAL ORAL SUSTAINED RELEASE MECHANISMS

- **DISSOLUTION CONTROLLED SYSTEMS**
- **DIFFUSIONAL SYSTEMS**
  - **RESERVOIR DEVICES**
  - **MATRIX DEVICES**
- **BIOERODIBLE AND COMBINATION DIFFUSION AND DISSOLUTON SYSTEMS**
- **OSMOTICALLY CONTROLLED SYSTEMS**
- **ION EXCHANGE SYSTEMS**

ALCOHOL CO-INGESTION MEDIATED DOSE DUMPING

PALLADONE

- **HYDROMORPHONE HYDROCHLORIDE EXTENDED RELEASE CAPSULES**
- **FORMULATION - PELLETS MADE WITH MELT EXTRUSION TECHNOLOGY**
- **FDA ALERT OF JULY, 2005 – WITHDRAWN FROM MARKET**

ALCOHOL CO-INGESTION	HYDROMORPHONE C_{MAX}
240 ML OF 40% ALCOHOL	AVG. – 6X INDV. – 16 X
240 ML OF 4% ALCOHOL	INDV. – 2X

ALCOHOL CO-INGESTION MEDIATED DOSE DUMPING

AVINZA

- **MORPHINE SULFATE EXTENDED RELEASE CAPSULES**
- **FORMULATION – PELLETS MADE WITH AMMONIOMETHACRYLATE POLYMERS AND FUMARIC ACID AS OSMOTIC AGENT/LOCAL pH MODIFIER**
- **NOV. 2005 – FDA/LIGAND WARNING**
  - **IN VITRO DISSOLUTION WITH 20% AND 40% ALCOHOL – DOSE OF MORPHINE RELEASED ALCOHOL CONCENTRATION DEPENDENT LEADING TO A MORE RAPID RELEASE OF MORPHINE**
- **CURRENT PI (2006, KING WEBSITE) – RELEVANCE OF IN VITRO RESULTS TO CLINICAL SETTING REMAINS TO BE DETERMINED**

ALCOHOL CO-INGESTION MEDIATED DOSE DUMPING

KADIAN

- **MORPHINE SULFATE EXTENDED RELEASE CAPSULES**
- **FORMULATION – POLYMER COATED PELLETS – HYDROMELLOSE, ETHYLCELLULOSE, METHACRYLIC ACID COPOLYMER**
- **J. PAIN, 2008 APR; 9(4):330-6**

  RELATIVE BIOAVAILABILITY STUDY - WATER VS 240 ML OF 40% ALCOHOL

  NO ALCOHOL-FORMULATION INTERACTION ON AUC OR C_{MAX}

ALCOHOL CO-INGESTION MEDIATED DOSE DUMPING

OXYCONTIN

- **OXYCODONE HCL CONTROLLED RELEASE TABLETS**
- **U.S. FORMULATION – TABLETS CONTAIN AMMONIO METHACRYLATE COPOLYMER, HYPROMELLOSE, LACTOSE**
- **WALDEN, ET. AL; DRUG DEV. AND IND. PHARMACY, 2007; 33:1101-1111**
  - **UK RESEARCHERS – OXYCONTIN 80 MG - (FORMULATION TESTED APPEARS VERY SIMILAR TO U.S. FORMULATION)**
  - **DISSOLUTION VIA MODIFIED USP SGF CONTAINING 4, 16, 24, 32 AND 40% ALCOHOL OVER 2 HOURS – THE PROLONGED RELEASE MECHANISM REMAINED INTACT UNDER THE TESTING CONDITIONS**

ALCOHOL CO-INGESTION MEDIATED DOSE DUMPING

OPANA ER

- **OXYMORPHONE HCL EXTENDED RELEASE TABLETS**
- **APPROVED BY FDA IN JUNE, 2006**
- **FORMULATION – COMPRESSED CONTROLLED RELEASE MATRIX (XANTHAN GUM AND LOCUST BEAN GUM) FORMING A TIGHT GEL UPON HYDRATION WHICH CONTROLS WATER INGRESS AND SUBSEQUENT DIFFUSION OF THE DRUG**

ALCOHOL CO-INGESTION MEDIATED DOSE DUMPING

OPANA ER PACKAGE INSERT

IN VITRO DISSOLUTION (500 ML 0.1N HCL CONTAINING 4, 20,AND 40% ETHANOL) – NO IN VITRO INTERACTION WITH ALCOHOL

- **IN VIVO**

ALCOHOL CO-INGESTION	C_{MAX}
240 ML/40%	AVG. ↑ 70%, IND. ↑ 270%
240 ML/20%	AVG. ↑ 31%, IND. ↑ 260%
240 ML/4%	AVG. ↑ 7%, IND. ↑ 110%

ALCOHOL CO-INGESTION MEDIATED DOSE DUMPING

OPANA ER PACKAGE INSERT

BLACK BOX WARNING

"PATIENTS MUST NOT CONSUME ALCOHOLIC BEVERAGES, OR PRESCRIPTION OR NON-PRESCRIPTION MEDICATIONS CONTAINING ALCOHOL, WHILE ON OPANA ER THERAPY. THE CO-INGESTION OF ALCOHOL WITH OPANA ER MAY RESULT IN INCREASED PLASMA LEVELS AND A POTENTIALLY FATAL OVERDOSE OF OXYMORPHONE."

ALCOHOL CO-INGESTION MEDIATED DOSE DUMPING

ABUSE RESISTANT OXYCONTIN
NDA 22-272

ALSDAC MEETING OF MAY 5, 2008

- **OXYCODONE HCL CONTROLLED RELEASE TABLETS**
- **FORMULATION – HYPROMELLOSE, PEG 400, …….,**
- **SPONSOR INDICATES NO INCREASE IN DISSOLUTION RATE IN ETHANOL CONCENTRATIONS OF UP TO 40% V/V AND THAT THE FORMULATION IS "RUGGED" (AS DESCRIBED IN THE FDA ACPS MEETING OF 0CT. 26, 2005).**

ALCOHOL CO-INGESTION MEDIATED DOSE DUMPING

REMOXY

- **OXYCODONE CONTROLLED RELEASE CAPSULE (NDA SUBMITTED JUNE 10, 2008)**
- **NOV. 13, 2008 ALSDAC MEETING**
- **FORMULATION – HIGH VISCOSITY LIQUID WITH SEVERAL EXCIPIENTS, INCLUDING SUCROSE ACETATE ISOBUTYRATE, IN A HARD GELATIN CAPSULE**
- **ALCOHOL CO-INGESTION** — **C_{MAX} VS WATER**

4% ALCOHOL	**AVG. -1.01**
20% ALCOHOL	**AVG. -1.14**
40% ALCOHOL	**AVG. +1.1 (0.46 TO 2.93)**

ALCOHOL CO-INGESTION MEDIATED DOSE DUMPING

GENERAL REMARKS

- **A NUMBER OF OPIATE FORMULATIONS APPEAR TO BE RESISTANT TO ALCOHOL CO-INGESTION MEDIATED DOSE DUMPING**

- **FDA ACTIONS ON APPLICATIONS MAY PROVIDE INSIGHT REGARDING THE DEGREE OF ALCOHOL RESISTANCE**

  - **CONSIDERED NOT ACCEPTABLE (PALLADONE)**

  - **SUFFCIENTLY ACCEPTABLE AS TO BE ADDRESSED BY LABELING (OPANA ER)**

ALCOHOL CO-INGESTION MEDIATED DOSE DUMPING

GENERAL REMARKS

- **OPANA ER IN VITRO DISSOLUTION VS IN VIVO C_{MAX} SUGGESTS CAUTION IN RELYING ONLY ON DISSOLUTION (OR QUALITY BY DESIGN) TO CHARACTERIZE VULNERABILITY**
  - **WARREN BUFFET TO CHARLIE ROSE CONCERNING THE COMPUTER DRIVEN MODELING SYSTEMS THE FINANCE INDUSTRY HAS RELIED ON TO MINIMIZE RISK**

"ALL I CAN SAY IS, BEWARE OF GEEKS… BEARING FORMULAS."

ABUSE DETERRANT FORMULATIONS

OXYCONTIN: THE LATEST PROBLEM
WITH R_X OPIATE DRUG ABUSE

- **DEC. 12, 1995: FDA APPROVAL**

  - **PACKAGE INSERT:** ***INDICATION OF LOWER ABUSE POTENTIAL DUE TO CONTROLLED RELEASE***

    INDICATION THAT CRUSHING OF TABLET WILL DISRUPT THE CONTROLLED RELEASE PROPERTIES

- **NOV. 2000: FDA BECAME AWARE OF PROBLEM WITH ABUSE AND MISUSE**

ABUSE DETERRANT FORMULATIONS
LEADING EDGE

NEW ABUSE RESISTANT(?) OXYCONTIN
NDA 21-272/MAY 5, 2008 ALSDAC MEETING

- **PURPORTED TAMPER RESISTANT PROPERTIES AS COMPARED TO ORIGINAL FORMULATION**

  - **MORE RESISTANT TO CRUSHING & MILLING**
  - **MORE RESISTANT TO CHEMICAL EXTRACTION**
  - **NO ACCELERATED DISSOLUTION IN ETHANOL**
  - **GEL FORMATION UPON WATER EXPOSURE TO INHIBIT IV INJECTION**

ABUSE DETERRANT FORMULATIONS
LEADING EDGE

NEW ABUSE RESISTANT(?) OXYCONTIN NDA 21-272
MAY 5, 2008 ALSDAC MEETING

A SELECTION OF TAMPER RESISTANCE TEST RESULTS

	% RELEASE	
	NEW	ORIGINAL
CRUSH/DISSOLUTON	20-49%	≥ 91%
MILL/DISSOLUTION	36-52%	≥ 91%
MILL/CRUSH R.T. EXTRACTION	max. 75%	max. 101%
MILL/CRUSH THERMAL EXTRACTION	max. 103%	max. 107%
INSULIN SYRINGE UPTAKE	≤ 4%	49-58%

ABUSE DETERRANT FORMULATIONS
LEADING EDGE

NEW ABUSE RESISTANT(?) OXYCONTIN NDA 21-272
MAY 5, 2008 ALSDAC MEETING

- **PROPOSED LABELING**

  "DURING *IN VITRO* TESTING, TABLETS WERE MANIPULATED TO RECOVER OXYCODONE BY CRUSHING, MILLING, HEATING, AND CRUSHING FOLLOWED BY BOILING AND FILTERING FRAGMENTS, AND CRUSHING FOLLOWED BY EXTRACTING WITH VARIOUS SOLVENTS, INCLUDING ETHANOL. THE TABLETS EITHER DID NOT BREAK OR BROKE INTO FRAGMENTS THAT RETAINED SOME OF THE CONTROLLED RELEASE CHARACTERISTICS. WHEN IN CONTACT WITH AQUEOUS MEDIA, THE TABLETS OR THE FRAGMENTS FORMED A GELATINOUS MASS."

- **INTENT OF PROPOSED LABELING**

  - **NOT MAKING CLAIMS OR ABUSE RESISTANCE**
  - **NOT PROVIDING CLEAR INSTRUCTIONS ON HOW TO TAMPER**

ABUSE DETERRANT FORMULATIONS
LEADING EDGE

NEW ABUSE RESISTANT(?) OXYCONTIN NDA 21-272
MAY 5, 2008 ALSDAC MEETING

- **SELECTED ADVISORY COMMITTEE FEEDBACK**

  - **AVAILABLE DATA NOT ADEQUATE TO EVALUATE WHETHER THE REFORMULATION IS LIKELY TO REDUCE ABUSE, MISUSE, AND DIVERSION**

  - **MOST MEMBERS STATED THAT THE LABEL SHOULD NOT BE CHANGED TO ALLOW THE SPONSOR TO MAKE A CLAIM OF TAMPER-RESISTANCE W/O FURTHER EVIDENCE TO SUPPORT THE CLAIM**

  - **THE COMMITTEE FELT THE INCLUSION OF PHYSICOCHEMICAL ATTRIBUTES INTO THE LABELING COULD BE MISLEADING AS INDICATING LESS LIKLIHOOD FOR ABUSE AND ADDICTION**

  - **COMMITTEE DID NOT FEEL THAT THE LABEL SHOULD BE PERMITTED TO MAKE CLAIMS OF TAMPER-RESISTANCE GIVEN THE AVAILABLE DATA**

ABUSE DETERRANT FORMULATIONS
LEADING EDGE

REMOXY XRT

NEW ABUSE RESISTANT (?) OXYCODONE

- **SCHEDULED FOR NOV. 13, 2008 ALSDAC MEETING**
- **HIGH VISCOSITY LIQUID FORMULATION IN A HARD GELATIN CAPSULE**
  - **DESIGNED TO RESIST COMMON METHODS OF ABUSE SUCH AS CRUSHING, SNORTING, HEATING, FREEZING, DISSOLUTION IN ALCOHOL, ETC.**

ABUSE DETERRANT FORMULATIONS
LEADING EDGE

REMOXY XRT

NEW ABUSE RESISTANT (?) OXYCODONE

A SELECTION OF IN VITRO TAMPER RESISTANCE TEST RESULTS

EXTRACTION CONDITION	% RELEASED	
	REMOXY	OXYCONTIN
BEVERAGES (60 MIN.)	MAX. 15%	MAX. 92%
BUFFERS PH 1-12 (60 MIN.)	MAX. 12%	MAX. 92%
DISRUPTION, 4 SOLVENTS (60 MIN.)	MAX. 35%	MAX. 93%

COULD NOT BE DRAWN INTO LARGE NEEDLES

ABUSE DETERRANT FORMULATIONS
LEADING EDGE

REMOXY XRT
NEW ABUSE RESISTANT (?) OXYCODONE

A SELECTION OF IN VIVO TAMPER RESISTANCE TEST RESULTS

ABUSE CONDITION	APROX. AUC (0 to 2 HOURS) NG/ML		
	REM WHOLE	REM. ABUSED	OXYCONTIN ABUSED
CRUSHED/40% ALCOHOL		52	110
RIGOROUS MASTICATION	5	65	
BUCCAL	10	50	

ABUSE DETERRANT FORMULATIONS
LEADING EDGE

EMBEDA

MORPHINE SULFATE EXTENDED RELEASE

WITH SEQUESTERED NALOXONE HYDROCHLORIDE CAPSULES

- **SCHEDULED FOR NOV. 14, 2008 ALSDAC MEETING**

- **TAKEN AS DIRECTED NALTREXONE REMAINS SEQUESTED AND PASSES THROUGH THE BODY**

- **TAMPERING (E.G., DISSOLUTION IN ETHANOL) CAUSES RELEASE OF BOTH MORPHINE AND NALTREXONE**

A SCENIC DETOUR FOR PERSPECTIVE: 30 YEARS OF FDA REGULATION OF CHLOROFLUROCARBONS

1974 – RECOGNITION THAT OZONE DEPLETION IS CAUSED BY DEGRADED CFCs

1978 – 21 CFR 2.125 BANNED USE OF CFCs IN FDA REGULATED PRODUCTS (ESSENTIAL EXEMPTIONS FOR METERED DOSE INHALERS)

- **NO TECHNICALLY FEASIBLE ALTERNATIVE**
- **PROVIDES SUBSTANTIAL (HEALTH, PUBLIC, ENVIRONMENTAL) BENEFIT**
- **RELEASE OF CFC IS SMALL OR JUSTIFIED BY GIVEN BENEFIT**

1987- MONTREAL PROTOCOL ON SUBSTANCES THAT DEPLETE THE OZONE LAYER

1996- FDA ADVANCED NOTICE OF PROPOSED RULEMAKING PROPOSING REVISION OF 21 CFR 2.125 TO PROVIDE MECHANISM FOR DELISTING NON-ESSENTIAL DRUGS

A SCENIC DETOUR FOR PERSPECTIVE: 30 YEARS OF FDA REGULATION OF CHLOROFLUROCARBONS

2003 - AMENDMENT OF 21 CFR 2.125 PROVIDING FOR NONESSENTIALITY CRITERIA

2007 - PROPOSED RULE TO REMOVE ESSENTIAL-USE DESIGNATION FOR 7 CFC MDI DRUGS SINCE THERAPEUTIC ALTERATIVES THAT DO NOT CONTAIN CFCs ARE NOW AVAILABLE

DEC. 31, 2008 - CFC PROPELLED ALBUTEROL INHALERS WILL NO LONGER BE AVAILABLE

A SCENIC DETOUR FOR PERSPECTIVE: 30 YEARS OF FDA REGULATION OF CHLOROFLUROCARBONS

LESSONS LEARNED

- **MANDATED CHANGE IN PHARMACEUTICAL REQUIREMENTS IS TECHNICALLY CHALLENGING**

- **TRANSPARENCY OF PROCESS – MAINTAINS CREDIBILITY WITH STAKEHOLDERS**

- **PRIORITY GIVEN TO PATIENT PROTECTION/BENEFIT THROUGHOUT THE PROCESS**

- **PROCESS TAKES TIME – PATIENCE IS REQUIRED**

- **ULTIMATELY SUCESSFUL – COMBINATION OF MARKET INCENTIVES AND GOVERNMENT REGULATION**

SUMMARY

NEW PHARMACEUTICAL DESIGN CRITERIA FOR SUSTAINED RELEASE OPIATES

- **RESISTANCE TO ALCOHOL MEDIATED DOSE DUMPING**

  DATA INDICATE THIS IS READILY OBTAINABLE NOW

- **TAMPER RESISTANT/ABUSE DETERRANT FORMULATIONS**

  THIS LOOKS TO BE THE FUTURE – POTENTIAL VALUE TO PUBLIC HEALTH REMAINS TO BE ELUCIDATED IN THE NEXT FEW DECADES