DEVELOPMENT AND APPROVAL OF NARCAN® NASAL SPRAY

ADAPT PHARMA

DDL27

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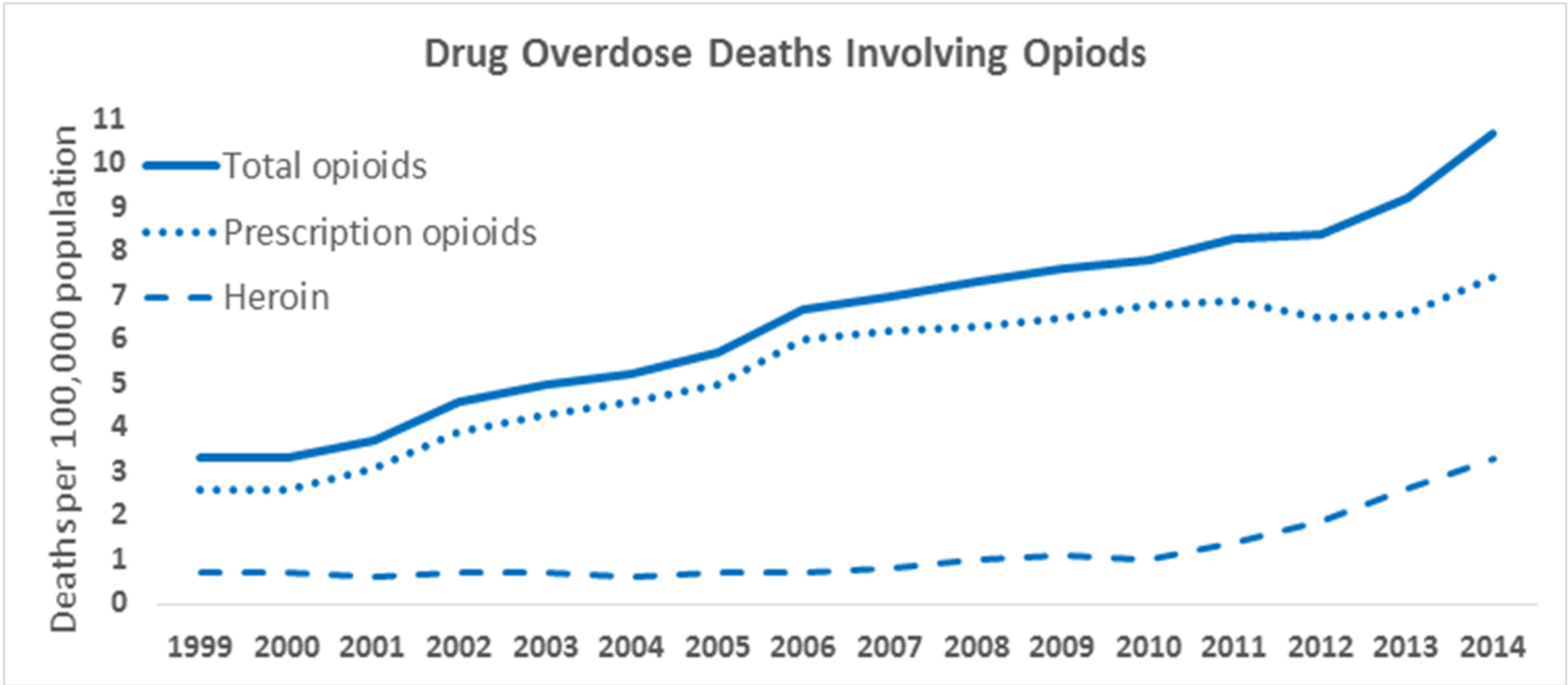
AGENDA

1. Introduction
2. Patient and Product Profile
3. Rationale for Product Design
4. Design History File
5. Human Factor Usability
6. Reliability

Introduction



Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2014 on CDC WONDER Online Database, released 2015.

Introduction

- Naloxone,
  - FDA Approved since 1971[1]
  - Antidote-reverses respiratory depression (OD)
  - Opioid Antagonist
  - Effective if an adequate exposure is achieved in time

- Adequate naloxone reversal depends on often unknown factors: [2]
  - Opioid
  - Patient/Person

[1] Naloxone Hydrochloride Prescribing Information [2] Dahan A et al. Anesthesiology. 2010

Patient and Product Profile

Goal for Community Use/Indication

- Naloxone as a bridge to medical care
- Naloxone Injection or Improvised Nasal Product
- Community based naloxone product should have
  - Onset and Exposure; equivalent up to 2mg Injection
  - Safely, readily and rapidly administered
  - Back-up or additional dose

Patient and Product Profile

Easy-to-use naloxone presentations

Achieve consistently adequate initial exposure in a simple step

- Highest possible naloxone dose
  - Minimum need to re-dose
- Not by parenteral injection route;
- No need to prime
- Simple ease of use
- Robust device
- Willingness of volunteer/first responder to use

Intranasal route

- Good bioavailability
- Fast Onset of action- 2 to 3 minutes
- Reasonable duration of action-90 minutes

Rationale for Product Design

Efficiency in Development

- Quality by Design (QbD)

Medical Devices concepts transfer directly to Drug Device Combination products[1]

CDRH expectation of documentation more prescriptive than QbD

- CMC submissions
- Inspections

Risk Analysis through development

[1]Current Good Manufacturing Practice Requirements for Combination Products. FDA Jan 2015

Rationale for Product Design

Severity Ratings for Product Risk Management Assessment	
Severity	**Description**
Disastrous (D)	Results in patient death
Critical (C)	Results in permanent impairment or life-threatening injury
Important (I)	Results in injury or impairment requiring professional medical intervention
Slight (S)	Results in temporary injury or impairment not requiring professional medical intervention
Negligible (N)	Inconvenience or temporary discomfort

- ISO 14971:2007 Medical Devices –"Application of Risk Management to Medical Devices

Overall Ratings for Severity and Occurrence for Product Risk Assessment					
Severity Occurrence	Negligible (N)	Slight (S)	Important (I)	Critical (C)	Disastrous (D)
Very High (VH)	**ALARP[1]**	**Unacceptable**	**Unacceptable**	**Unacceptable**	**Unacceptable**
High (H)	**Acceptable**	**Unacceptable**	**Unacceptable**	**Unacceptable**	**Unacceptable**
Moderate (M)	**Acceptable**	**Acceptable**	**Acceptable**	**Unacceptable**	**Unacceptable**
Low (L)	**Acceptable**	**Acceptable**	**Acceptable**	**Unacceptable**	**Unacceptable**
Very Low (VL)	**Acceptable**	**Acceptable**	**Acceptable**	**Acceptable**	**ALARP[1]**
[1]NOTE ALARP = As Low as Reasonably Possible					

Rationale for Product Design

Potential Medical Harm List and Overall Assessment of Naloxone Nasal Spray				
Harm	**Severity Rating**	**Occurrence**	**Overall Rating**	**Comments**
Single “No dose” delivered by device	Critical	Low	Unacceptable requires mitigation	Potential life-critical administration; even at 1 in 50,000 defect level assumed to high; requires to be very low
Multiple “No dose” delivered by device	Critical	Negligible	Acceptable	Second device failing at 1 in 50,000-100,000 rate would be 1 in 2,500,000,000 – 10,000,000,000
Single Low dose delivered by device	Important	Very Low	Acceptable	administration of second dose within 60-90 minutes more likely; instructed to seek emergency medical help right away
Multiple High dose delivered by device	Negligible	Very Low	Acceptable	Doses of up to 8 mg used in studies (equal to 2 x 4 mg sprays)
Non insertion into nasal cavity	Critical	Low	Unacceptable requires mitigation	based on HF , subjects, untrained, inserting into mouth or into nostril and not spraying; <10%

Rationale for Product Design

Describes the attributes of the ideal product

- High level assessment of risks of not achieving these product attributes.

Attribute	Rationale	Risk if defective	Mitigate Risk by
Product is easily portable	Must be available for immediate use	Delay in treatment may be harmful or fatal	Small discreet, package which is easily portable
Product is easy to open and make ready for use	Must be available for immediate use	Delay in treatment may be harmful or fatal	Easily opened secondary packaging (still providing adequate protection) Device ready for immediate use, without priming or attaching needles or other preparation steps
Product must be easily non-tamper evident	Must be available for immediate use and be correct quality product	Administration of Incorrect/forged product may be harmful or fatal	Integral seals easily recognised. Quality product easily recognised

Rationale for Product Design

Formulation Consideration

- Early Stage development
  - Concentration/Strength
  - Stability
- Container Closure
  - Stability including extractable and leachable studies
- Spray Characteristics related to Formulation/Device and Pharmacokinetic profile

Product Design Evaluation

Formal Risk Assessment – using Failure Mode and Effects Analysis

Product Design, Materials, Processes, and controls including:

- Device and Formulation
- Process manufacturing
- Shelf life and shipping
- Patient Use

What happens if an attributes fails

Product Design Evaluation

Severity Scale rating of:

Severity Rating	Severity Scale	Outcome
Disastrous (D)	9	Results in patient death
Critical (C)	7	Results in permanent impairment or life-threatening injury
Important (I)	5	Results in injury or impairment requiring professional medical intervention
Slight (S)	3	Results in temporary injury or impairment not requiring professional medical intervention
Negligible (N)	1	Inconvenience or temporary discomfort

Probability of detecting defect rating of:

Detection Ability	Detection Score
Very High	1
Highly Probable	3
Possible to miss	7
Likely to miss	9

Probability of Occurrence rating of

Probability Rating	Probability Scale	Prevalence
Very Low	1	unlikely to occur in life any product unit
Low	3	Unlikely to occur in life of any unit in batch
Probable	7	Likely to occur in batch
Highly Probable	9	Almost certain to occur

Risk Priority Number (RPN) was calculated as the product of Severity x Occurrence X Detection ability and was grouped as:

RPN	Action
up to 34	Current controls adequately manage risk
35 to 60	Mitigation actions need to be defined in detail
61 to 80	Mitigation required
Above 80	Mitigation urgent as high priority

Product Design Evaluation

Major Component Or Process	Risk Item	Impact	Risk to Patient	Current Controls	Probability	Probability Score	Severity	Severity Score	Likliehood of detection	Detection Score	Risk Probable Number	Assessment	Mitigation Actions and Section References
Specific \item **Vial**	Vial dimensions not correct	Seal integrity impacted so leaks	Low Dose as content lost	AQL sampling and checks of each lot of vials and plungers; plunger placement measured in process during filling; multiple filled units visually inspected for defects and tested for function in testing each product lot	Low	3	Slight	3	High	3	27	Current controls adequately manage risk	
		Too tight for plunger to move	No dose	AQL sampling and checks of each lot of vials and plungers; plunger placement measured in process during filling; multiple filled units tested for function in testing each product lot	Low	3	Important	5	High	3	45	Describe controls in more detail as "No dose" risk is high impact	Vial controls and specifications to be detailed and updated to include new incoming and in process AQL sampling and inspection
		Vial does not fit into Holder	Assembly fails so rejected	AQL sampling and checks of each lot; assembly check would show not fully assembled and rejected	Low	3	Slight	3	Very High	1	9	Current controls adequately manage risk	
		Vial does not fit into device	Assembly fails so rejected	AQL sampling and checks of each lot; assembly check would show not fully assembled and rejected	Low	3	Slight	3	Very High	1	9	Current controls adequately manage risk	
		Vial fits but device wont work	No dose	AQL sampling and checks of each lot of vials and plungers; plunger placement measured in process during filling; multiple filled unis tested for function in testing each product lot	Low	3	Important	5	High	3	45	Describe controls in more detail as "No dose" risk is high impact	Vial controls and specifications to be detailed and updated to include new incoming and in process AQL sampling and inspection

Device History File

FDA use both QSR and Drug GMPs for Drug product Device Combination

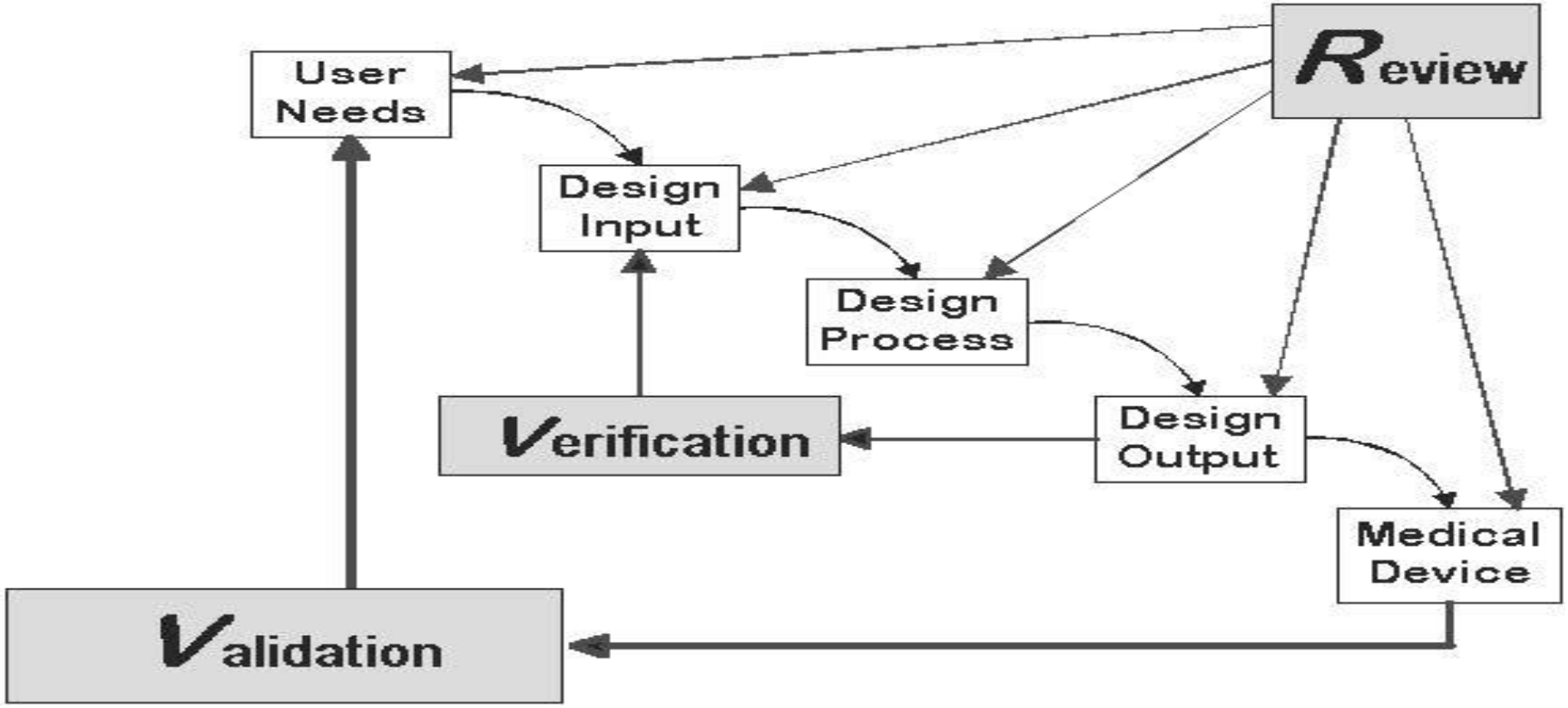
Requirements for a design history file (DHF) are found in 21 CFR 820.30j: *"Each manufacturer shall establish and maintain a DHF for each type of device. The DHF shall contain or reference the records necessary to demonstrate that the design was developed in accordance with the approved design plan and the requirements of this part. "*

Compilation of Records

Compliance with Design Plan and Design Controls

Current Good Manufacturing Practice Requirements for Combination Products. Jan 2015

Device History File



Application of Design Controls to Waterfall Design Process, Health Canada

- The DHF should address all design issues relating to the combined use of the constituent parts.
- Must comply with design control requirements for modifications of any constituent
- Risk assessment, as discussed previously
- DHF Reviewed periodically
- Document maintained as binder (active, change control, Quality group)

Human Factors Studies

Human Factors Usability

- Evaluate Critical task of user interface
- Knowledge Task or Label Comprehension

Qualitative HF

- Help to develop Device/User interface/label

Quantitative HF (Validation)

- Final Proposed Product Presentation
- Agency Agreement
- CRO with IRB

Narcan Nasal Spray Studies

- Subject population including low literacy and teenager
- No training given
- Success Criteria for primary endpoints

Human Factor Studies and Related Clinical Study Considerations In Combination Product Design and Development; FDA Guidance February 2016

Reliability

Reliability must be demonstrated

- Detailed description by fault tree analysis
  - Device, processing and assembly failures lead to a undesired event.
  - starts with a general conclusion broken into specific causes
  - Described by a logic diagram called a fault tree.
  - objective is to identify potential causes of failure or defects
  - FTA mitigations put in place to improve reliability

Reliability

- Not always possible to rely on such statistical tools
  - Life saving medication/Agency don’t agree

- Reliability Simulation Study
  - Worst case conditions
    - Shipping, Vibration, Shock and Aging at elated temperatures
  - Testing condition simulate user worst case e.g. device orientation, temperature of test.
  - Large sample size,
    - AQL/probability based

Development Started 2012

Approved US Nov 2015

Launched Feb 2016

QUESTIONS!