

ACKNOWLEDGEMENT



Co-organizer: Dr. Ewa Marszal FDA

Session Chairs: Dr. Rukman De Silva FDA

Dr. Brian Lobo MedImmune/AstraZeneca

Dr. Dean Ripple NIST

Dr. Thomas Spitznagel Macrogenics

Coordination: Ann Anonsen MCERSI/UMD

Website: Malissa Carroll SOP/UMB

Registration: Christopher Klimas SOP/UMB

Financial Support:

Activities



- Research
 - Pharmaceutical and device quality, product bioequivalence, clinical pharmacology, patient preferences, and post-marketing drug utilization
 - CDER, CDRH, CMV, and CBER
 - e.g. Last month, the major epilepsy professional society updated their position statement about generics of anti-epileptic drugs, based on research findings
- Training and Exchange
 - Monthly lectures at FDA
 - Workshops Ideas welcome!
- Education Programs and Events
 - Online MS degree in regulatory science
 - America's Got Regulatory Science Talent Event (Jan 27 2017)
 - Seeking mentors for student teams!





- Organized University Research Center established in 2007
- > Led by School of Pharmacy, with members from Baltimore and College Park Campuses
- > Vision: Develop enabling technologies for industry, regulators, pharmacists, patients...
- > Activities: Research, education, collaboration, service
- Focal areas: biomaterials

 drug delivery and formulation

 computational modeling

 drug transport and pharmacokinetics

 noninvasive analysis of complex drugs (biologics and nano-drugs)

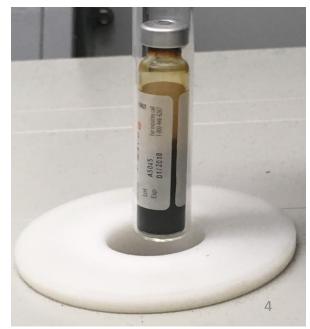
Noninvasive Analysis based on ¹H₂O NMR

- ➤ Water is in all biologic and nano-drug solutions (10³ 106 more concentrated than API)
- → ¹H₂O emits NMR signal (shunned in NMR; embraced in MRI)
- Advantages of ¹H₂O NMR simple cheap fast noninvasive (drug can still be used after analysis)
- \triangleright But is ${}^{1}H_{2}O$ informative?

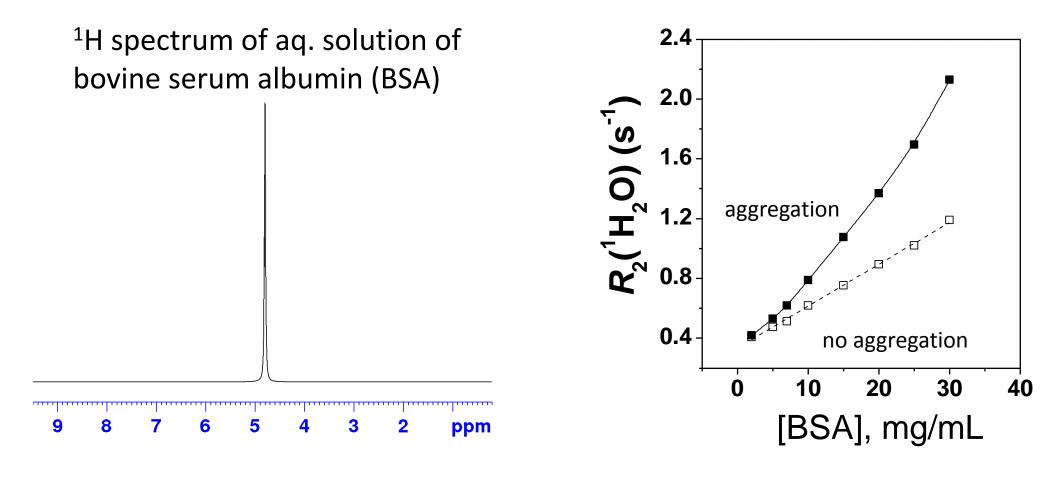
invasive analysis



noninvasive analysis



¹H₂O Responds to Protein Concentration and Aggregation – through its transverse relaxation rate R₂(¹H₂O)



 $R_2(^1H_2O)$: a composite index of complex drugs (like composite index of stocks)

Where ¹H₂O NMR Might Help - pre-release QC

In 2013, EMA recalled 3 million cartridges of insulin Novomix30 Flexpen and Penfill.

EMA press release:

"because of a manufacturing problem during the filling of the cartridges, which resulted in some batches of NovoMix 30 containing too high or too low amounts of insulin units per millilitre"

"only a small percentage of cartridges (0.14%) contain a wrong amount. However, in the affected cartridges the level of insulin may vary between 50% and 150% of the labelled insulin units, which could lead to hypoglycaemia or hyperglycaemia"

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/10/news_detail_001933.jsp&mid=WC0b01ac058004d5c1

MAUDE Adverse Event Report: NOVO NORDISK A/S NOVOPEN INSULIN DELIVERY DEVICE

FDA Home Medical Devices Databases



510(k) | DeNovo | Registration & Listing | Adverse Events | Recalls | PMA | HDE | Classification | Standards CFR Title 21 | Radiation-Emitting Products | X-Ray Assembler | Medsun Reports | CLIA | TPLC

NOVO NORDISK A/S NOVOPEN INSULIN DELIVERY DEVICE

Back to Sea

Catalog Number 185230

Event Date 09/27/2013

Event Type Injury

Event Description

Found collapsed on the floor at home in a hypoglycaemic state [hypoglycaemia], excessive thirst [thirst], collapsed middle lobe of right lung [pneumous suffered two more hypoglycaemic episodes and went into a coma [hypoglycaemia], increased amount and frequency of urination [urine output increased amount and frequency of urination [pollakiuria], suffered two more hypoglycaemic episodes and went into a coma [hypoglycaemic coma], suggested that her insulin dose (via novopen) was incorrect [incorrect dose administered by device], deep and lasting anxiety [anxiety]. Case descripted incident represent a serious public health threat: no. This spontaneous case reported by a consumer from the (b)(6) concerns an (b)(6) female powas treated with novomix 30 penfill (insulin aspart) therapy, and used novopen (insulin delivery device), experienced "found collapsed on the floor and hypoglycaemic state" beginning on (b)(6) 2013 and "collapsed middle lobe of the right lung", "suffered two more hypoglycaemic episodes and went in the coma." "deep and lasting anxiety" "excessive thirst" "increased amount and frequency of urination" and "tests suggested that her insulin dose (via recoma.")

Where ¹H₂O NMR Might Help - post-release QC

- 1. In 2012, EU + Switzerland + Canada temporarily suspended several flu vaccines due to protein aggregates.
 - http://www.euro.who.int/en/health-topics/communicable-diseases/influenza/news/news/2012
- 2. High and variable aggregate content in bevacizumab repackaged by compounding pharmacies in US (Kahook et al., Retina, 30, 887, 2010) and UK (Palmer et al., Eye, 27, 1090, 2013). Eleven patients lost sight after the intraocular injection of improperly handled bevacizumab in Russia (http://www.pharmvestnik.ru/publs/lenta/v-rossii/roszdravnadzor-apteka-prodavshaja-avastin-dlja-kliniki-im-geljmgoljtsa-prekratila-svoe.html#.WERobeYrl2x)
- 3. In 2009, investigation in Thailand found that 27% of Eprex® prefilled syringes in retail pharmacies had protein aggregation levels above EU specification.
 - (attributed to cold chain violation, Fotiou et al., Clin. Therapeutics, 31, 336-346, 2009)

Example of Cold Chain Violation

"VFC (vaccine for children) vaccines stored by 76% of the selected providers were exposed to inappropriate temperatures for at least 5 cumulative hours during that (2-week) period."

"We also found that all 45 providers had recorded temperatures that differed from our independently measured temperatures during the 2-week period"

Office of Inspector General, Department of Health and Human Services, June 2012

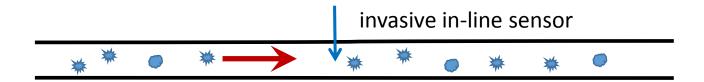
Where ¹H₂O NMR Might Help

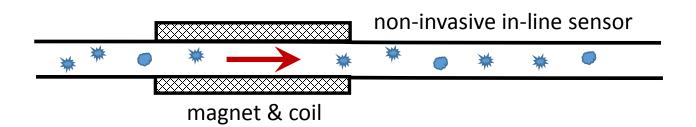
- differentiate innovator & generics

Magnetic field strength (¹H ₂ O resonance frequency)	$R_2(^{1}H_2O)$ (s ⁻¹)		
	innovator iron carbohydrate (62.5 mg Fe/5 mL)	generic iron carbohydrate (62.5 mg Fe/5 mL)	difference%
0.47 T (20 MHz) Benchtop NMR	23.6	16.8	30%
9.4 T (400 MHz) Super-conducting NMR	244.0	100.0	60%

Innovator seems to have more ¹H₂O-accessible irons.

Where ¹H₂O NMR Might Help - continuous (bio)manufacturing

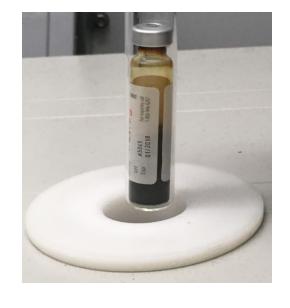




Contract-free in-line sensor; avoids fouling and cleaning

We Need Different Technologies









8:30-9:00 a.m.

WELCOME AND INTRODUCTION

Natalie D. Eddington, PhD, FCP, FAAPS
Dean and Professor
University of Maryland School of Pharmacy

Bruce Yu, PhD
Professor of Pharmaceutical Sciences
Director, Bio- and Nano-Technology Center
University of Maryland School of Pharmacy

Ewa Marszal, PhD
Chemist
Center for Biologics Evaluation and Research
Food and Drug Administration