Real-World Data Approaches for Early Detection of Potential Safety and Effectiveness Signals for Generic Substitution: A Metoprolol Extended-Release Case Study

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Outline

- Introduction
  - Regulatory oversight of generic drug manufacturing
  - Current uses of “real-world data” for generic drugs
  - History of generic drug “failures,” specifically metoprolol ER
- Study objectives
  - Collaborations between pharmacometrics and pharmacoepidemiology
  - Modernizing manufacturing surveillance using RWD
- Methods/Results
- Implications

Generic drugs provide an economic benefit to the U.S. Healthcare System

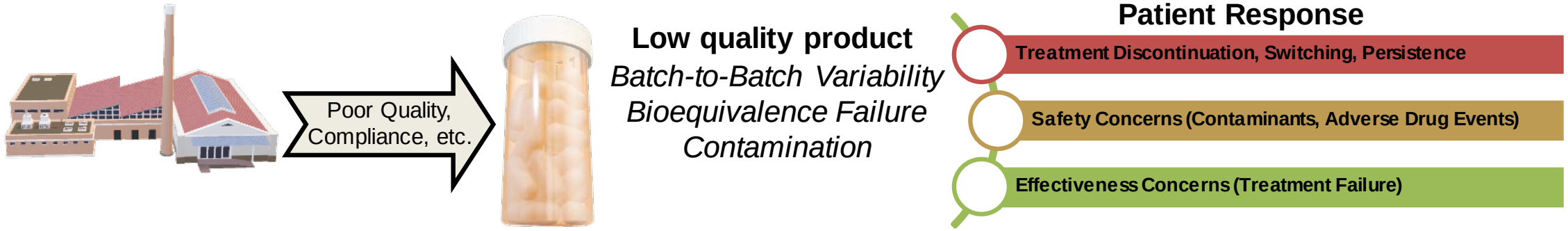
- Account for ~90% of all prescriptions
- Estimated $253 billion savings in 2016
- Increase patient access, adherence

Generic Approval Process (the abridged version)

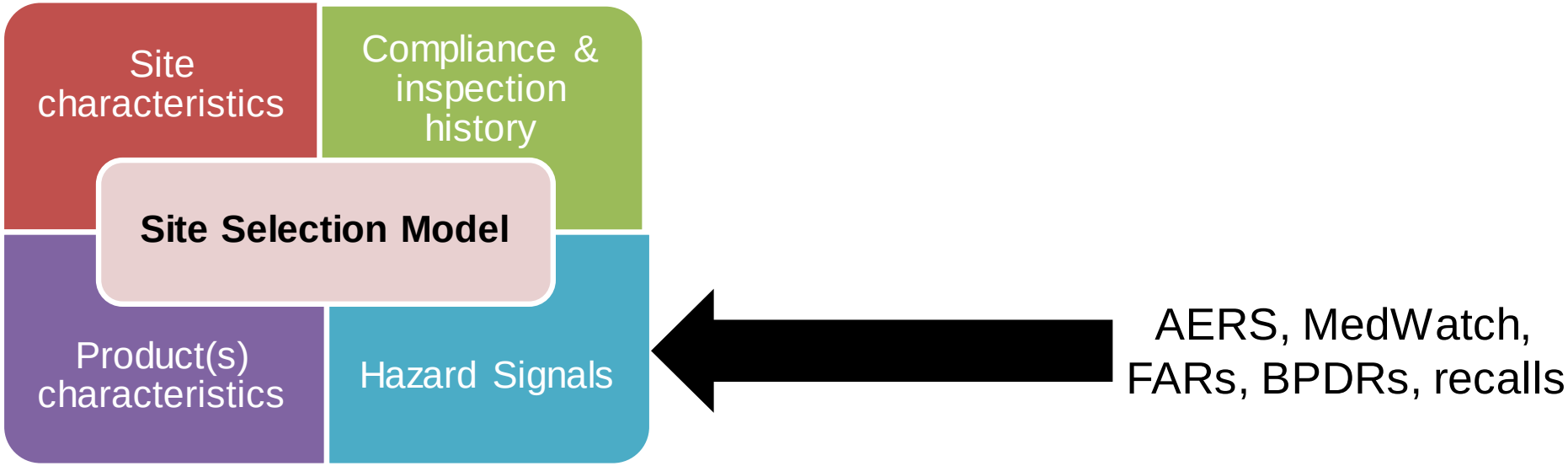
- FDA requires pharmacokinetic (PK) bioequivalence of generics compared to reference product
  - Assumed to lead to same physiological response

Generic manufacturing

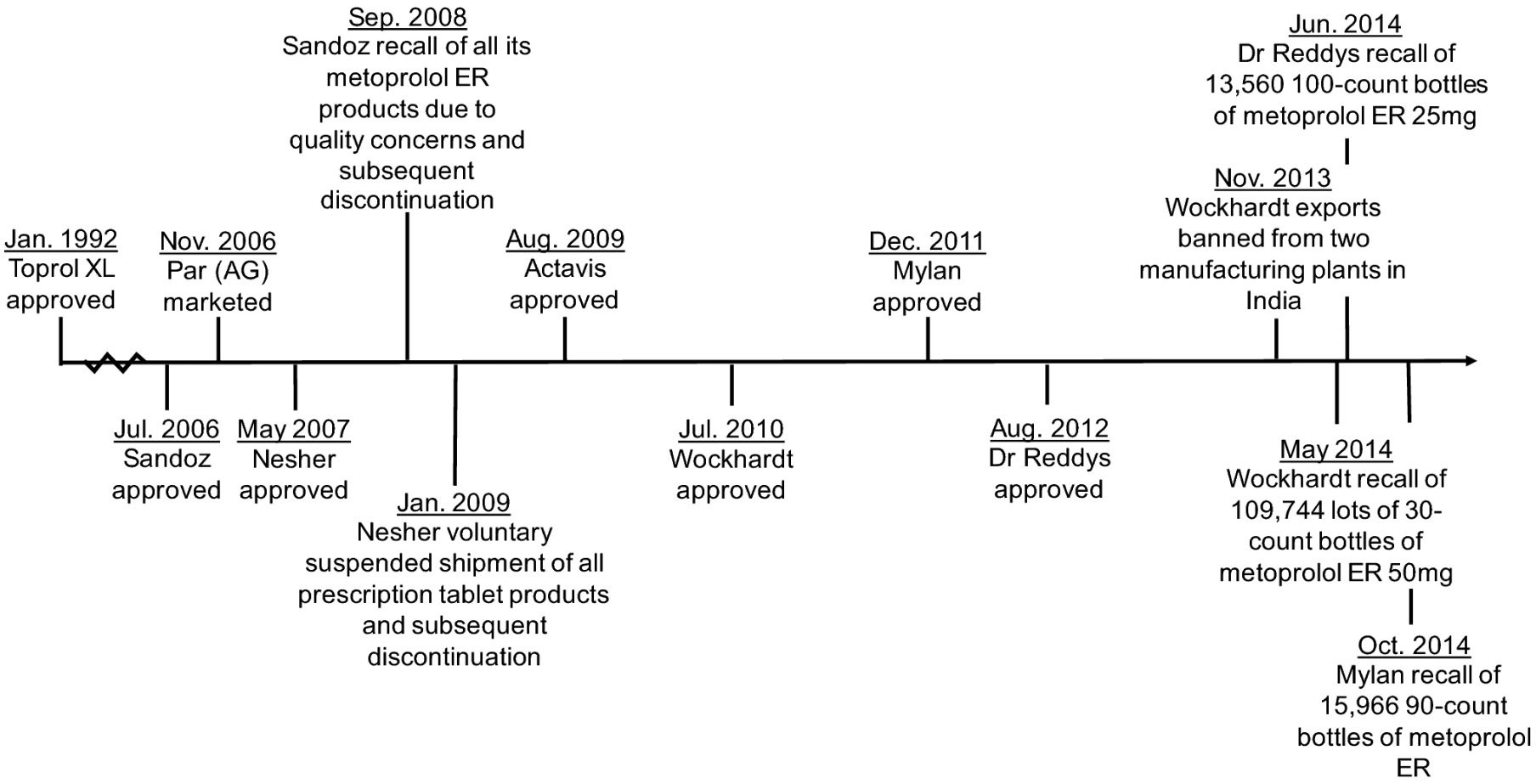
- Imperfect compliance and poor quality is still possible



High risk facilities/products monitoring



The history lesson



The historic headlines

Another Metoprolol Recall Reveals the Dark Side of Generic Drugs

Here we go again: another generic metoprolol recall from an Indian drug company. The FDA announced problems with Dr. Reddy's metoprolol succinate 25 mg extended release tablets and the company is in the process of recalling 1,356,000 pills.

FDA Finds Fault with Generic Toprol XL which is Metoprolol Succinate ER

Beta-Blocker Pulled

November 02, 2018

Teva Pharmaceuticals USA is recalling 53,451 bottles of metoprolol succinate extended-release tablets USP, 50 mg, after an out-of-specification dissolution result occurred during routine stability testing. The recall was included in the October 31, 2018, US Food and Drug Administration (FDA) Enforcement Report.

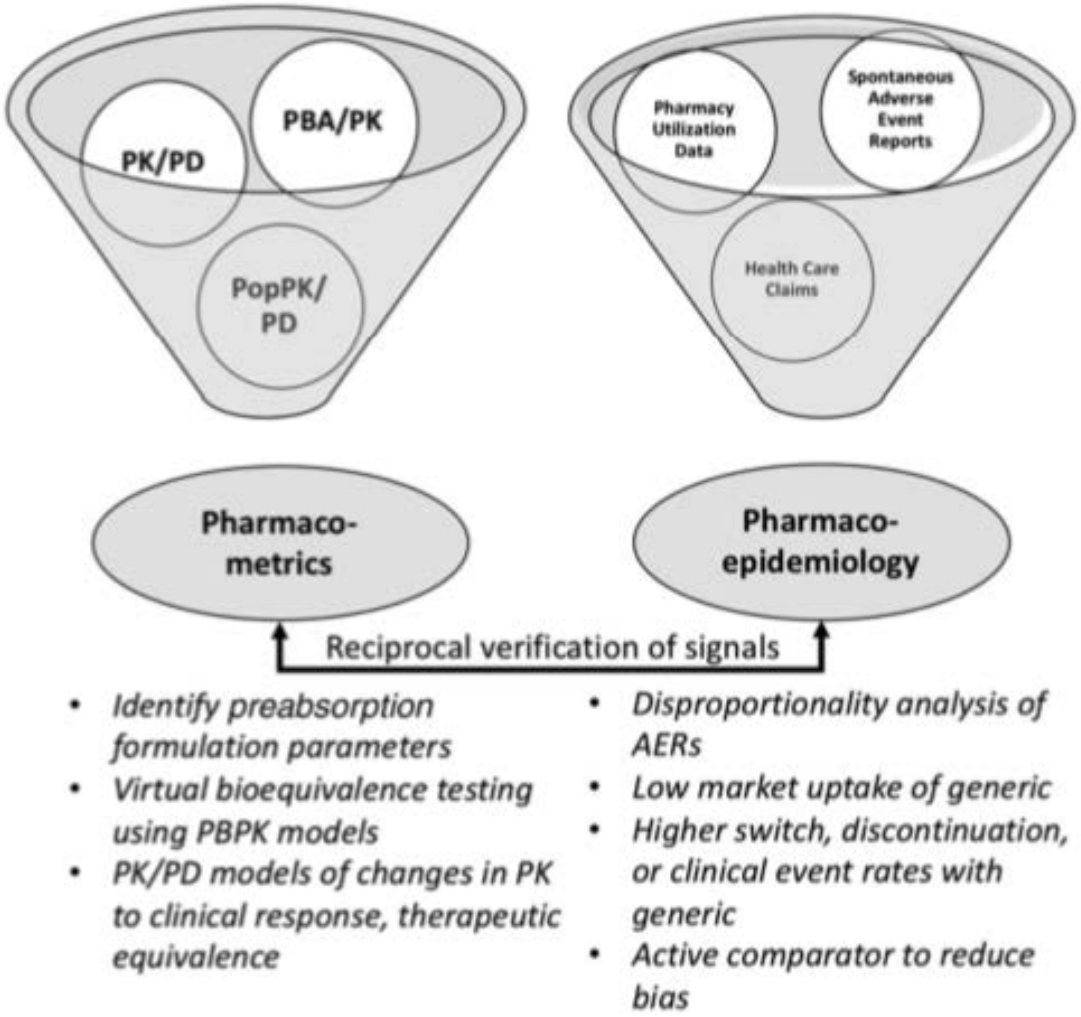
Collaborations between pharmaceutics and pharmacoepidemiology

Reciprocal validation: Strengthen **causality** with mechanistic pathway / exposure:outcome relationship

Design enhancement: **Focus** relevant questions based on mechanistic / utilization / outcome results

Extrapolation: **Calibrate** effects based on demonstrated drug / biomarker / outcome effect modifiers

Advance precision medicine: **Model** outcomes in a learning health system that integrates clinical and mechanistic information



Goals of research

Project goal – Understand problems with a specific product(s) – metoprolol succinate ER – as an historic prototype use case

- Can we capture "signals" in claims data for metoprolol?

Global goal - Evaluate whether real-world data (i.e. claims) can be used for active surveillance of generic quality

Approach

- Use traditional surveillance methods
  - FDA Adverse Event Reporting System (FAERS)
  - Capture outcomes that are representative of ADEs
- Evaluate “historic” claims data to capture measures indicative of generic issues

FAERS analysis

- Extracted all FAERS data from 1997 through Q1/2017
- Assessed medication names by brand or generic*
- Disproportionality analysis of MedDRA terms for reactions

Claims analysis –data source

- IBM Marketscan Databases between July 2007 and June 2008
  - Emulates the period of generic release and public knowledge of generic issues
  - Focuses on a short time period for regulatory action

Claims analysis – outcome measures

- Generic market share (or market uptake) would be lower
- Discontinuation or switch (back) would be higher
- Event rates for indications or adverse effects would be higher

Claims analysis – selection of comparator

- An active comparator can help control for biases in trends and patient factors
- Generic formulation of amlodipine-benazepril
  - Approved in same year
  - Once daily dosing
  - Cardiovascular indications

Claims analysis – Generic uptake

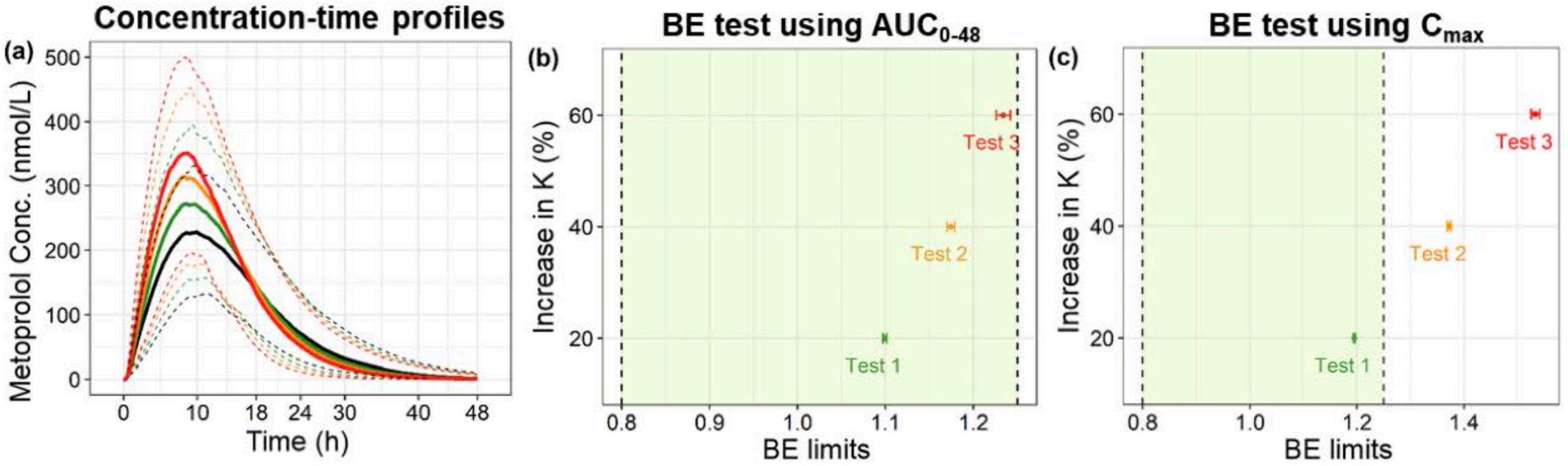
- # of metoprolol ER generic users per month over the total metoprolol ER users (generic+trade)
- Compared to amlodipine-benazepril
- Plotted by month

Claims analysis – D/C or switch

- Switch – switch from generic to trade
- Discontinuation – gap of 30 days in generic use without a switch
- Tracked whether people were new users or prevalent users prior to generic entry

Snippets from the PK studies

200 mg



Claims analysis – event rates

- Events were identified by ICD-9 codes
- Included events associated with super- and sub-therapeutic doses
  - Myocardial infarction, heart failure, hypertension, hypotension, syncope, angina, dysrhythmias
- Identified on hospitalization and ER visits only

Statistical analyses

- Uptake – Chi-squared analysis
- D/C or switch – Cox PH model with 3-way interaction of medication, prior use, and dose
- Event rates – Poisson regression model
- Models were stratified into full study period and a 90-day period to test rapidity of detection

Results -FAERS analysis

- 7,860 total reports
  - 6,562 brand; 1,374 generic
- Top 25 MedDRA terms included…
  - "Product quality issue" 12.2%
  - Dizziness (10.8%), blood pressure increase (9.5%), palpitations (7.9%)

Table 1. Food and Drug Administration Adverse Event Reporting System (FAERS) Case Analysis for Brand versus Generic Metoprolol Succinate

Reported Adverse Event (MedDRA Preferred Terms)[a]	Metoprolol Succinate: Generic			Metoprolol Succinate: Brand			Generic vs Brand LCI[b]	
	Prev.	ROR-LCI	PRR-LCI	Prev.	ROR-LCI	PRR-LCI	ROR Ratio	PRR Ratio
Product quality issue	**12.2%**	**9**	**8.17**	0.9%	0.51	0.51	17.65	14.48
Dizziness	**10.8%**	**3.73**	**3.48**	6.1%	2.14	2.08	1.74	2.00
Blood pressure increased	**9.5%**	**10.52**	**9.77**	6.3%	7.38	7.01	1.43	1.68
Palpitations	**7.9%**	**9.52**	**8.97**	3.9%	4.89	4.76	1.95	2.25
Product substitution issue	**7.6%**	**26.92**	**25.31**	0.4%	1.22	1.22	22.07	15.86
Bradycardia	**5.9%**	**13.83**	**13.23**	2.6%	6.24	6.13	2.22	2.55
Nausea	5.1%	0.93	0.93	3.4%	0.68	0.69	1.37	1.69
Hypotension	**5.0%**	**3.45**	3.35	2.4%	1.73	1.71	1.99	2.36
Therapeutic response unexpected	**4.4%**	**12.14**	11.78	0.6%	1.55	1.54	7.83	7.08
Chest pain	**4.0%**	**2.25**	2.21	3.0%	1.9	1.87	1.18	1.53
Syncope	**3.5%**	**3.99**	3.92	1.6%	1.91	1.9	2.09	2.51
Malaise	3.4%	1.09	1.09	6.8%	2.75	2.64	0.40	0.59
Heart rate decreased	**3.4%**	**14.77**	**14.43**	1.9%	9.19	9.06	1.61	2.02

Results – Generic uptake

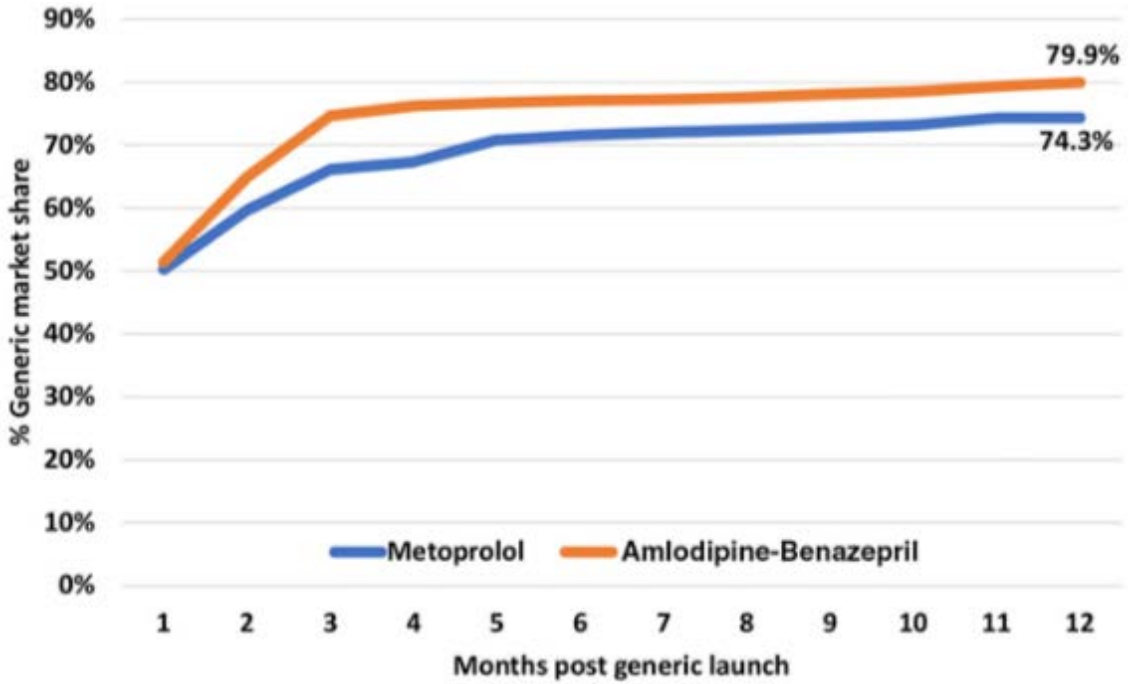


Figure 2. Generic market share of metoprolol succinate extended release versus amlodipine-benazepril in the months immediately after generic availability. Chi-squared test $P < .0001$.

Results – D/C or switching

- N=653,502 metoprolol ER users;
  - 3.6% switch back to trade
  - 53.9% discontinued
- N=243,388 amlo-benz users
  - 3.2% switch back to trade
  - 58.7% discontinued

Results- D/C or switching

Table 2. Cox Proportional Hazard Regression Results for Time to Discontinuation and Switching to Brand Products Among Individuals With Generic Formulation Use for Metoprolol Succinate and Amlodipine-Benazepril Stratified by Prior Use and Dose Strength

	Discontinuation (Full Study Period)		Switch to Brand (Full Study Period)	
METO vs AM-BE Stratified By:	HR	99.375%CI	HR	99.375%CI
New users taking low dose	1.23[a]	(1.12-1.34)	4.57[a]	(2.36-8.85)
New users taking moderate dose	1.06[a]	(1.03-1.09)	2.61[a]	(2.22-3.07)
New users taking high dose	1.00	(0.98-1.03)	0.78[a]	(0.70-0.86)
New users taking highest dose	0.87[a]	(0.84-0.91)	0.72[a]	(0.59-0.88)
Prior users taking low dose	1.10[a]	(1.03-1.19)	1.49[a]	(1.05-2.10)
Prior users taking moderate dose	1.01	(0.99-1.03)	1.78[a]	(1.62-1.96)
Prior users taking high dose	0.97[a]	(0.95-0.99)	1.09[a]	(1.01-1.17)
Prior users taking highest dose	0.93[a]	(0.91-0.96)	0.96	(0.85-1.08)

Results- D/C or switching (90-days)

Table 2. Cox Proportional Hazard Regression Results for Time to Discontinuation and Switching to Brand Products Among Individuals With Generic Formulation Use for Metoprolol Succinate and Amlodipine-Benazepril Stratified by Prior Use and Dose Strength

	Discontinuation (≤90 days)		Switch to Brand (≤90 Days)	
METO vs AM-BE Stratified By:	HR		99.375%CI	
New users taking low dose	1.22[a]	(1.12-1.34)	5.28[a]	(2.54-10.99)
New users taking moderate dose	1.04[a]	(1.01-1.07)	2.80[a]	(2.35-3.33)
New users taking high dose	0.96[a]	(0.94-0.99)	0.82[a]	(0.74-0.92)
New users taking highest dose	0.84[a]	(0.81-0.88)	0.79[a]	(0.64-0.97)
Prior users taking low dose	1.07	(0.99-1.15)	1.68[a]	(1.12-2.52)
Prior users taking moderate dose	0.97[a]	(0.95-0.99)	1.90[a]	(1.70-2.12)
Prior users taking high dose	0.95[a]	(0.93-0.97)	1.33[a]	(1.23-1.45)
Prior users taking highest dose	0.91[a]	(0.88-0.94)	1.21[a]	(1.06-1.38)

Results – Event rates

Table 5. Incident Rate Ratios of Clinical Events in Emergency Room and Hospitalizations for Generic versus Brand Users of Metoprolol Succinate Extended Release and Amlodipine-Benazepril[a]

		MI	
		IRR	95%CI
Metoprolol Succinate			
Generic vs Trade			
ER visits	Primary	2.06[b]	(1.46-2.90)
	All	2.42[b]	(1.75-3.35)
Hospitalizations	Primary	1.00	(0.93-1.09)
	All	1.11[b]	(1.04-1.18)
Amlodipine-Benazepril			
Generic vs Trade			
ER visits	Primary	0.8	(0.42-1.63)
	All	0.89	(0.46-1.78)
Hospitalizations	Primary	0.91	(0.75-1.09)
	All	0.88	(0.76-1.02)

Results – Event rates

Table 5. Incident Rate Ratios of Clinical Events in Emergency Room and Hospitalizations for Generic versus Brand Users of Metoprolol Succinate Extended Release and Amlodipine-Benazepril[a]

		MI		HF		Hypertension		Hypotension		Syncope		Angina		Arrhythmia	
		IRR	95%CI	IRR	95%CI	IRR	95%CI	IRR	95%CI	IRR	95%CI	IRR	95%CI	IRR	95%CI
Metoprolol Succinate Generic vs Trade															
ER visits	Primary	2.06[b]	(1.46-2.90)	1.31[b]	(1.15-1.48)	1.18[b]	(1.10-1.27)	1.33[b]	(1.05-1.68)	1.43[b]	(1.31-1.56)	1.51[b]	(1.16-1.95)	1.29[b]	(1.21-1.39)
	All	2.42[b]	(1.75-3.35)	1.20[b]	(1.08-1.33)	1.31[b]	(1.27-1.35)	1.22[b]	(1.01-1.47)	1.39[b]	(1.28-1.52)	1.49[b]	(1.20-1.85)	1.21[b]	(1.14-1.28)
Hospitalizations	Primary	1.00	(0.93-1.09)	1.00	(0.94-1.06)	1.08	(0.96-1.20)	0.92	(0.77-1.09)	0.99	(0.88-1.12)	1.22	(0.86-1.74)	1.12[b]	(1.07-1.19)
	All	1.11[b]	(1.04-1.18)	1.08[b]	(1.04-1.12)	1.44[b]	(1.41-1.48)	1.25[b]	(1.15-1.35)	0.95	(0.89-1.01)	1.39[b]	(1.30-1.49)	1.12[b]	(1.09-1.15)
Amlodipine-Benazepril Generic vs Trade															
ER visits	Primary	0.8	(0.42-1.63)	0.71	(0.51-1.00)	0.63[b]	(0.56-0.71)	0.78	(0.49-1.23)	0.78[b]	(0.67-0.93)	1.00	(0.53-1.87)	0.85	(0.69-1.04)
	All	0.89	(0.46-1.78)	0.77	(0.57-1.03)	0.76[b]	(0.72-0.80)	0.76	(0.52-1.11)	0.79[b]	(0.68-0.93)	0.88	(0.53-1.47)	0.82[b]	(0.69-0.97)
Hospitalizations	Primary	0.91	(0.75-1.09)	0.73[b]	(0.62-0.86)	0.52[b]	(0.42-0.65)	1.03	(0.67-1.60)	0.95	(0.74-1.23)	0.48	(0.22-1.04)	0.91	(0.78-1.06)
	All	0.88	(0.76-1.02)	0.84[b]	(0.76-0.92)	0.86[b]	(0.83-0.90)	0.95	(0.79-1.14)	1.01	(0.88-1.16)	0.82[b]	(0.70-0.97)	0.86[b]	(0.80-0.93)

Discussion – Capturing events in claims data

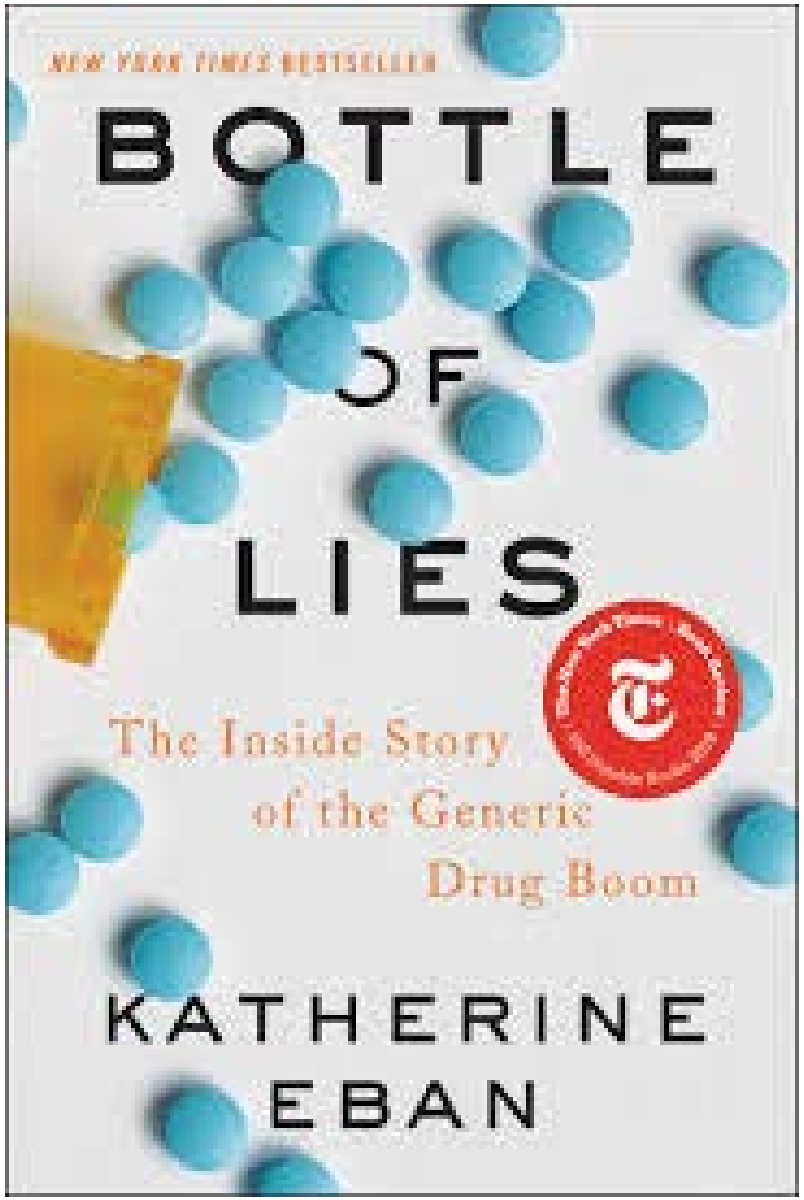
- D/C and switching are a potential universal outcome
- Capture patient behaviors as a proxy
- Less sensitive to exposures, i.e. need at least 2 exposures to measure
- Larger signals detected in 90-day period

Discussion – Capturing events in claims data

- Event rates related to adverse effects or failed efficacy appear to be more sensitive measures!
- Not universal and would have to be tailored to each intervention
- More sensitive as events can be detected with a single day's exposure

Conclusions

- This analysis shows a historic generic formulation failure captured in real-world data
- Serves as a prototype analysis that could be implemented in automated claims-based systems, e.g. FDA Sentinel
- Could modernize Office of Pharmaceutical Quality approaches to high risk facility/product monitoring
- Answers a call given public awareness of drug safety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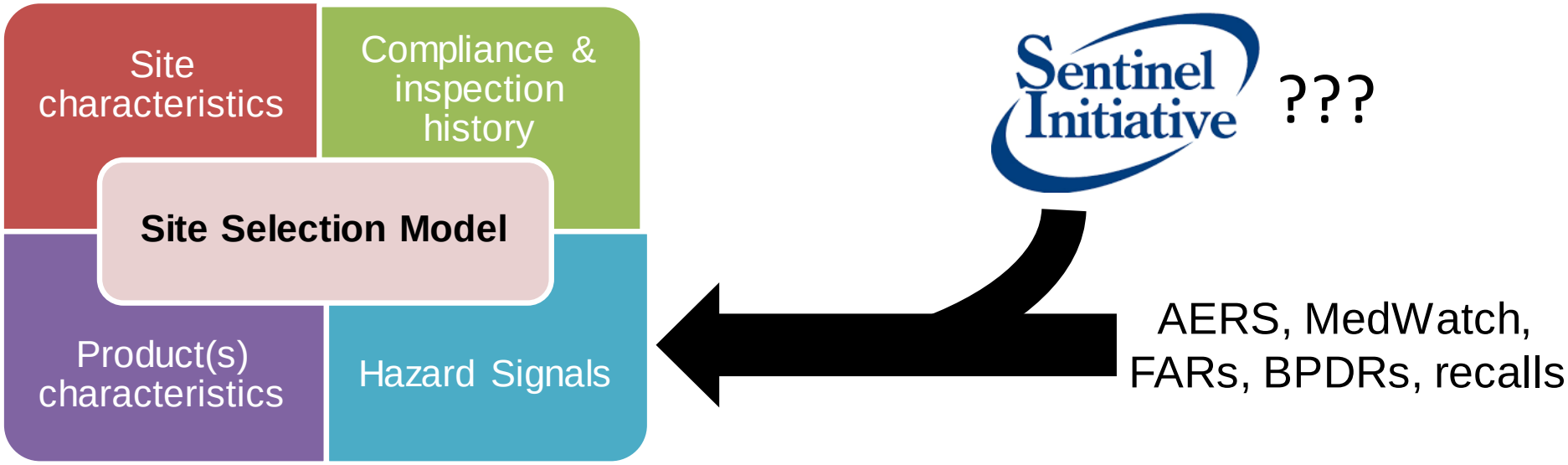


Potential Challenges for Implementation

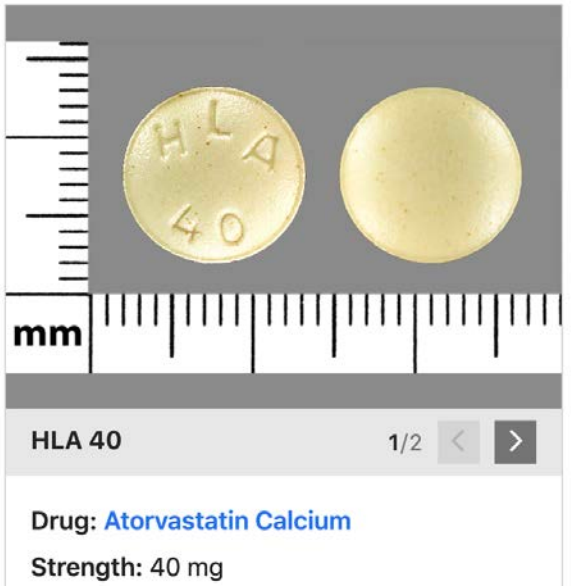
- Automation of non-universal outcomes vs. sensitivity of universal outcomes
- Further validation on historic examples with more subtle outcomes?
- Linkage between NDC and facility?
- Rapidity (Lag) of claims data
- Unique designs to control for confounding factors

Thought experiment

Brand

Authorized generic

Generic



Thanks for listening

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