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# Leveraging RxNorm and drug classifications for analyzing prescription datasets



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# Disclaimer

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# Outline

## ◆ Drug ontologies

- RxNorm
- Drug classification systems

## ◆ RxNorm in action – 3 use cases

- Comparing prescribed vs. defined daily dose
- Identifying potentially inappropriate medications for elderly patients
- Identifying potential risk in drug prescriptions during pregnancy

## ◆ Discussion



# Relevance to AMIA's informatics areas

- ◆ Translational Bioinformatics
  - Interoperability between drugs in research and healthcare
- ◆ Clinical Research Informatics
  - Analysis of observational datasets (e.g., OHDSI, PCORnet)
- ◆ Clinical Informatics
  - E-prescribing
  - Information exchange
  - Reference for drugs for clinical decision systems (drug allergies, drug-drug interactions)
- ◆ Consumer Health Informatics
  - Facilitating access to Medline Plus
- ◆ Public Health Informatics
  - Drug value sets (e.g., for opioid addiction)



# Drug ontologies

# RxNorm

- ◆ Terminology integration system
  - Structured Product Labels, First DataBank, Micromedex, Multum, MeSH, SNOMED CT, NDF-RT, ATC, ...
- ◆ Scope
  - Drug names and codes
  - Drugs available on the U.S. market
- ◆ Developer: National Library of Medicine
- ◆ Publicly available\*
- ◆ Monthly updates
- ◆ Size: > 10k ingredients; 19k clinical drugs
- ◆ Uses: e-prescription, information exchange, analytics



# Normalization Lexical level

Source	Code	String
MMSL	5977	azithromycin 250 mg oral tablet
RXNORM	308460	Azithromycin 250 MG Oral Tablet
MTHSPL	54868-5478	AZITHROMYCIN 250 mg ORAL TABLET, FILM COATED
MMX	124911	Azithromycin 250 MG Oral Tablet_#1
NDDF	26721	AZITHROMYCIN 250 mg ORAL TABLET_#1
GS	22681	Azithromycin 250mg Oral tablet_#2
NDFRT	N0000158080	AZITHROMYCIN 250MG TAB
MTHSPL	21695-012	AZITHROMYCIN ANHYDROUS 250 mg ORAL TABLET, FILM COATED AZITHROMYCIN DIHYDRATE 250 mg ORAL TABLET, FILM COATED
MTHSPL	60505-2581	[Azithromycin Dihydrate]
SNOMEDCT_US	375555002	Azithromycin dihydrate 250mg tablet
MTHSPL	66116-418	AZITHROMYCIN MONOHYDRATE 250 mg ORAL TABLET, FILM COATED
MTHSPL	0093-7146	AZITHROMYCIN MONOHYDRATE 250 mg ORAL TABLET, FILM COATED_#1
...	...	...



308460 Azithromycin 250 MG Oral Tablet



# Normalized form

**Strength**

250 MG

**Ingredient**

Azithromycin

**Dose form**

Oral Tablet

**Strength**

Semantic clinical drug component

**Ingredient**

**Ingredient**

**Dose form**

Semantic clinical drug form

**Strength**

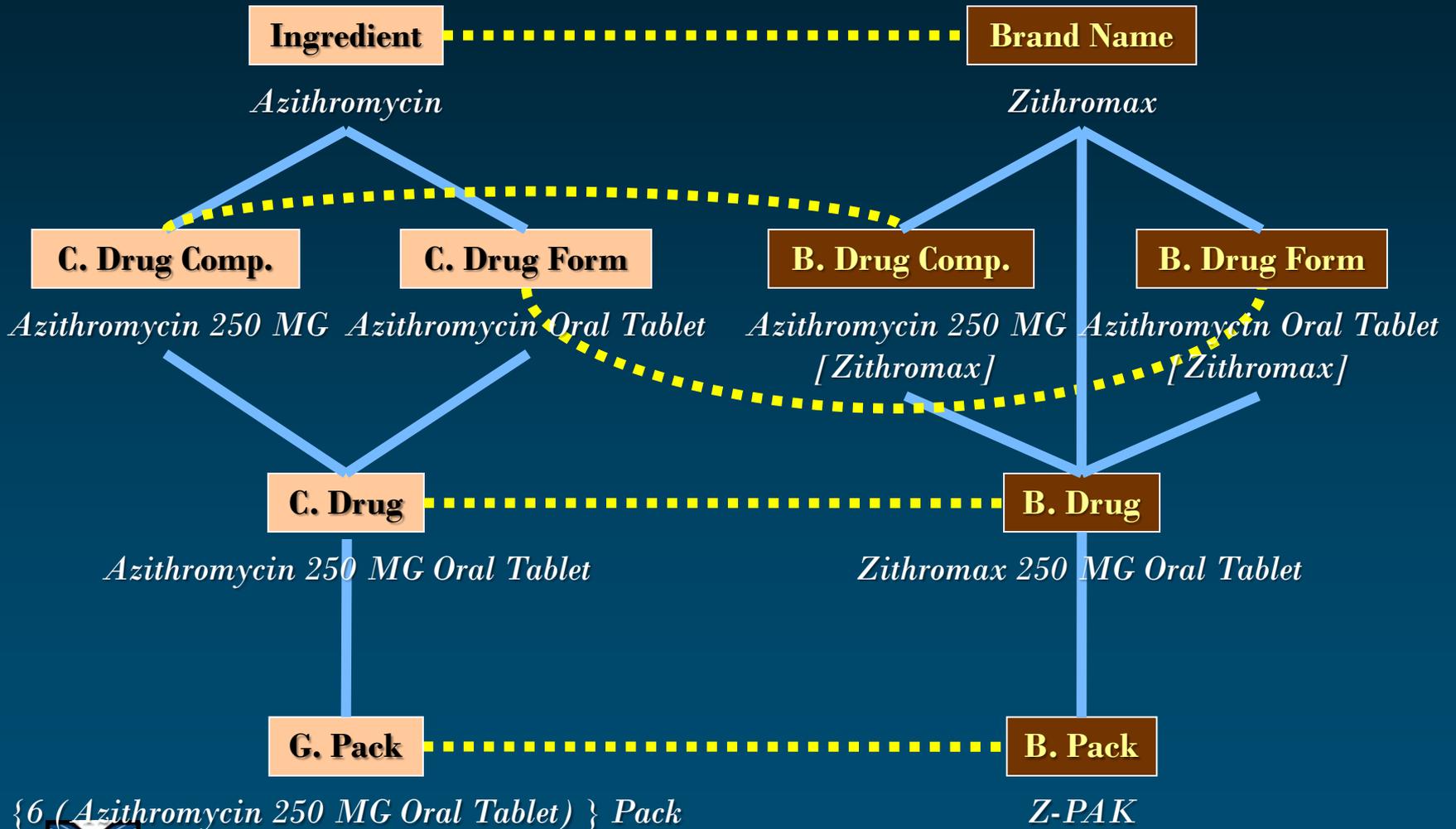
Semantic clinical drug

**Ingredient**

**Dose form**



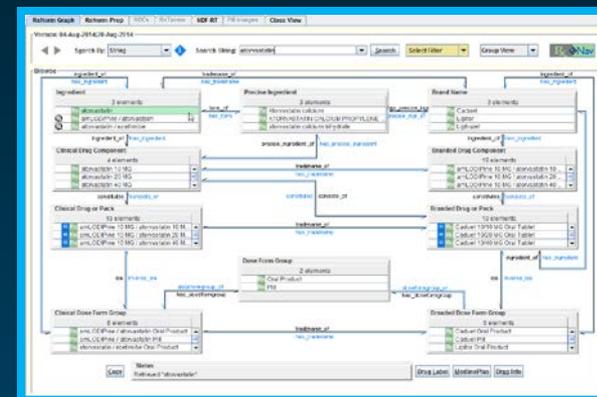
# Normalized relations



# Applications

## ◆ RxNav

- Drug-centric browser
- Links among drug entities (graph)
- Links to other sources of information
  - Drug classes
  - Drug-drug interactions from DrugBank



## ◆ RxClass

- Drug class-centric browser
  - ATC, NDF-RT, DailyMed (SPL), MeSH
- All classes for a given drug
- All drug members for a given class
- Class-class similarity

The screenshot shows the RxClass interface with a search for 'HMG CoA reductase inhibitors / ATC10AA / class type: ATC1.4 / show context'. Below the search results, there is a table titled '7 RxNorm generic drugs in ATC'.

Type	WCCS	Belongs Term	Source ID	Source Name	Relation	Full context
R	83267	atorvastatin	CT10A05	atorvastatin	DIRECT	Show
R	41727	rosuvastatin	CT10A04	rosuvastatin	DIRECT	Show
R	6272	lovastatin	CT10A02	lovastatin	DIRECT	Show
R	86104	pitavastatin	CT10A06	pitavastatin	DIRECT	Show
R	42863	pravastatin	CT10A03	pravastatin	DIRECT	Show
R	30162	mevastatin	CT10A07	mevastatin	DIRECT	Show
R	36567	simvastatin	CT10A01	simvastatin	DIRECT	Show



# Application Programming Interfaces (APIs)

## ◆ RxNorm

- Map drug names and codes to RxNorm
  - Including approximate matches and spelling suggestions
- Navigate among drug entities (e.g., brand to generic)

## ◆ RxClass

- Map drug class names and codes to classification systems
  - ATC, NDF-RT, DailyMed (SPL), MeSH
- Link between drug classes and their drug members
- Similarity between drug classes

## ◆ Related APIs

- RxTerms, NDF-RT, Interactions

## ◆ Usage

- 30,000 unique users per month
- 1B calls in 2015

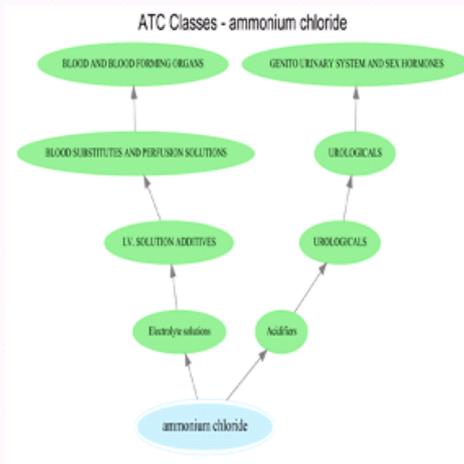


# RxNav

RxNav is a browser for several drug information sources, including RxNorm, RxTerms and NDF-RT. RxNav finds drugs in RxNorm from the names and codes in its constituent vocabularies.



**Launch RxNav**



**RxNav**

**APIs**

**RxMix**

**RxClass**

<https://rxnav.nlm.nih.gov/>

News

Statistics

## RxNav brand names

Recent brand names added

Alecensa	Aspercreme with Lidocaine
Bendeka	Bridion
Broncovac Sore Throat	Canker Cover
Clear Eyes Pure Relief	Empliciti
FLUAD 2015-2016	Hydase
Hypertet	Kanuma

## DailyMed API in RxMix

Functionality of the [DailyMed API](#) has been added to RxMix. Included are functions to retrieve drug classes, manufacturer drug names, National Drug Codes (NDCs), packaging information and drug class members. See RxMix for more details including runnable examples.

## Video Tutorials

### RxMix

[Using RxMix to Retrieve NDCs for an](#)

## NDC Properties Function

A new function to retrieve National Drug Code (NDC) properties for an NDC, a Structured Product Label (SPL) or an RxNorm concept is now available. See [getNDCProperties](#) (SOAP) or [/ndcproperties](#) (REST).

## NDC History Function

A function to retrieve National Drug Code (NDC) history for any RxNorm concept is now available. The function provides past

# Use case #1

*Comparing prescribed vs. defined daily dose*

[Bodenreider, AMIA, 2014]

# Prescribed vs. defined daily dose

## ◆ Dataset

- Surescripts feed
- All prescriptions to ER patients
- For 3 months in 2011 in a Bethesda hospital

## ◆ Reference for defined daily dose: ATC

## ◆ Methods

- RxNorm clinical drug  $\rightarrow$  RxNorm ingredient  $\leftrightarrow$  ATC ingredient  $\rightarrow$  ATC defined daily dose  $\leftrightarrow$  prescribed daily dose
- Restricted to systemic drugs (based on dose form)

## ◆ Findings

- Confirmed feasibility
- 25% of the prescriptions exactly match the ATC DDD
- 50% of the prescriptions within 66-150% of the ATC DDD
- 75% of the prescriptions within 50-200% of the ATC DDD



# ATC/DDD Index

## ◆ Origin

- World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology (Norway)
- For drug utilization research / pharmaco-epidemiology
  - Not for clinical purposes

## ◆ Organization

- Drug classification on 4 levels
  - Anatomical
  - Therapeutic
  - Chemical

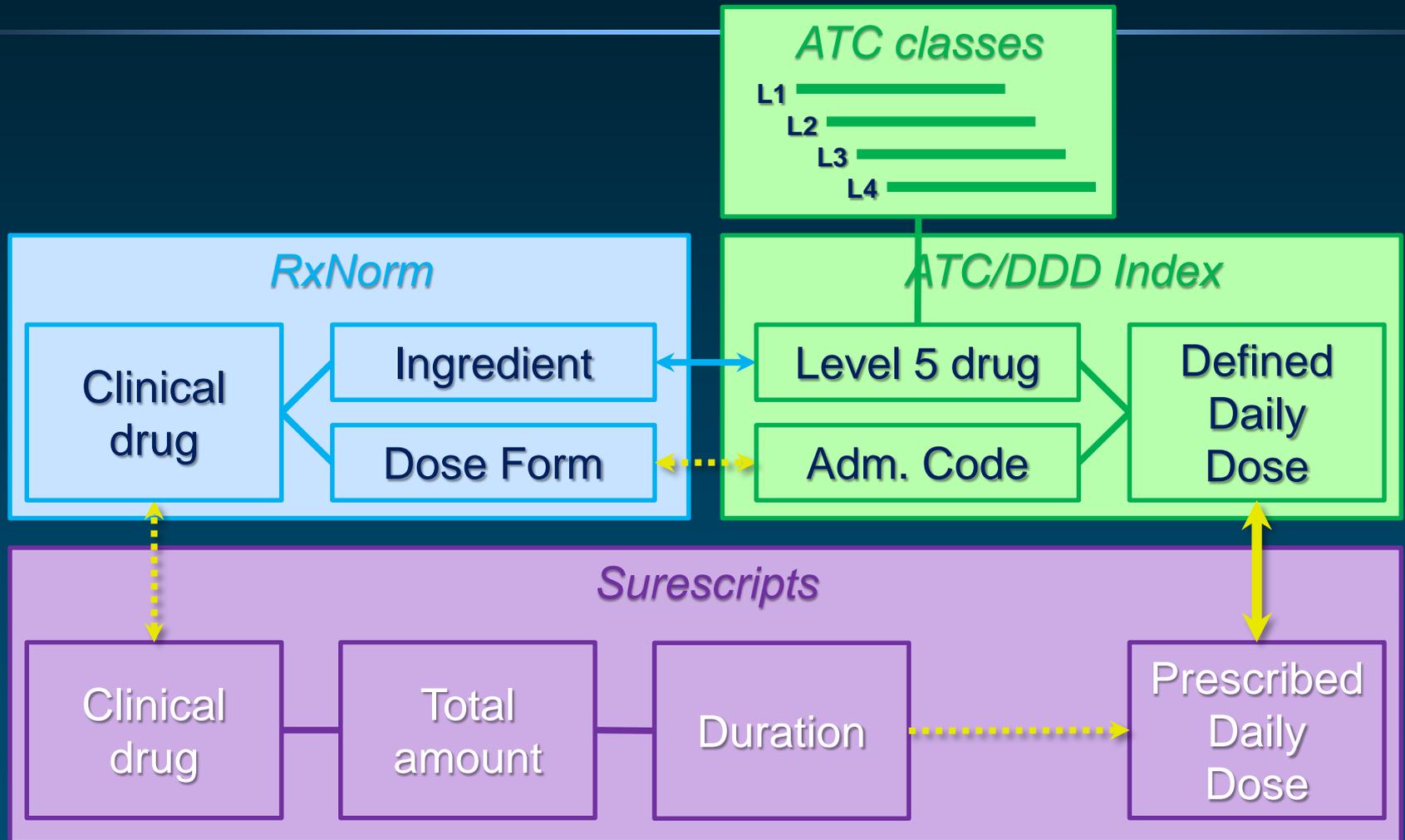
- Drugs (5<sup>th</sup> level)
- Daily dose
  - For a given route

**J ANTIINFECTIVES FOR SYSTEMIC USE**  
**J01 ANTIBACTERIALS FOR SYSTEMIC USE**  
**J01C BETA-LACTAM ANTIBACTERIALS, PENICILLINS**  
**J01CA Penicillins with extended spectrum**

ATC code	Name	DDD	U	Adm.R	Note
J01CA04	<u>amoxicillin</u>	1	g	O	
		1	g	P	



# Methods Overview



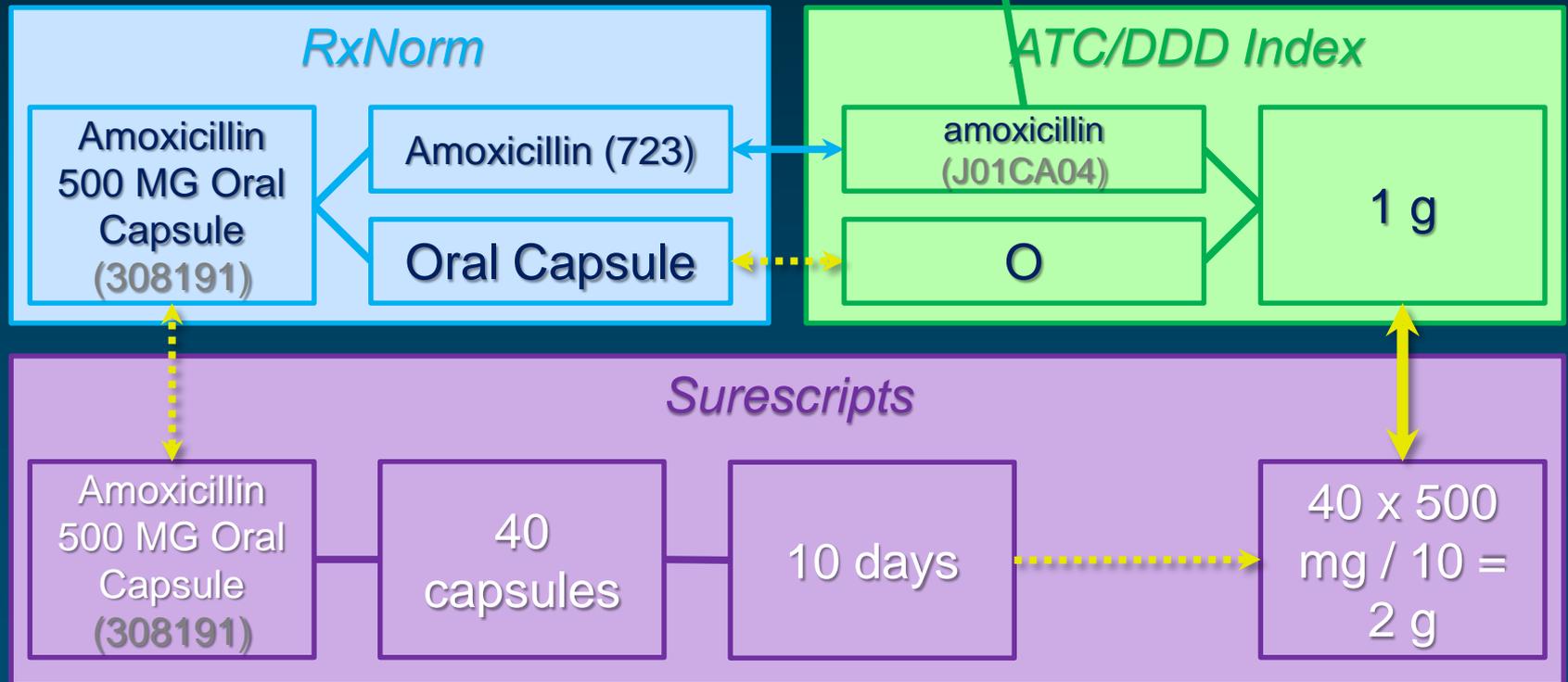
# Methods Example

J **ANTIINFECTIVES FOR SYSTEMIC USE**

J01 **ANTIBACTERIALS FOR SYSTEMIC USE**

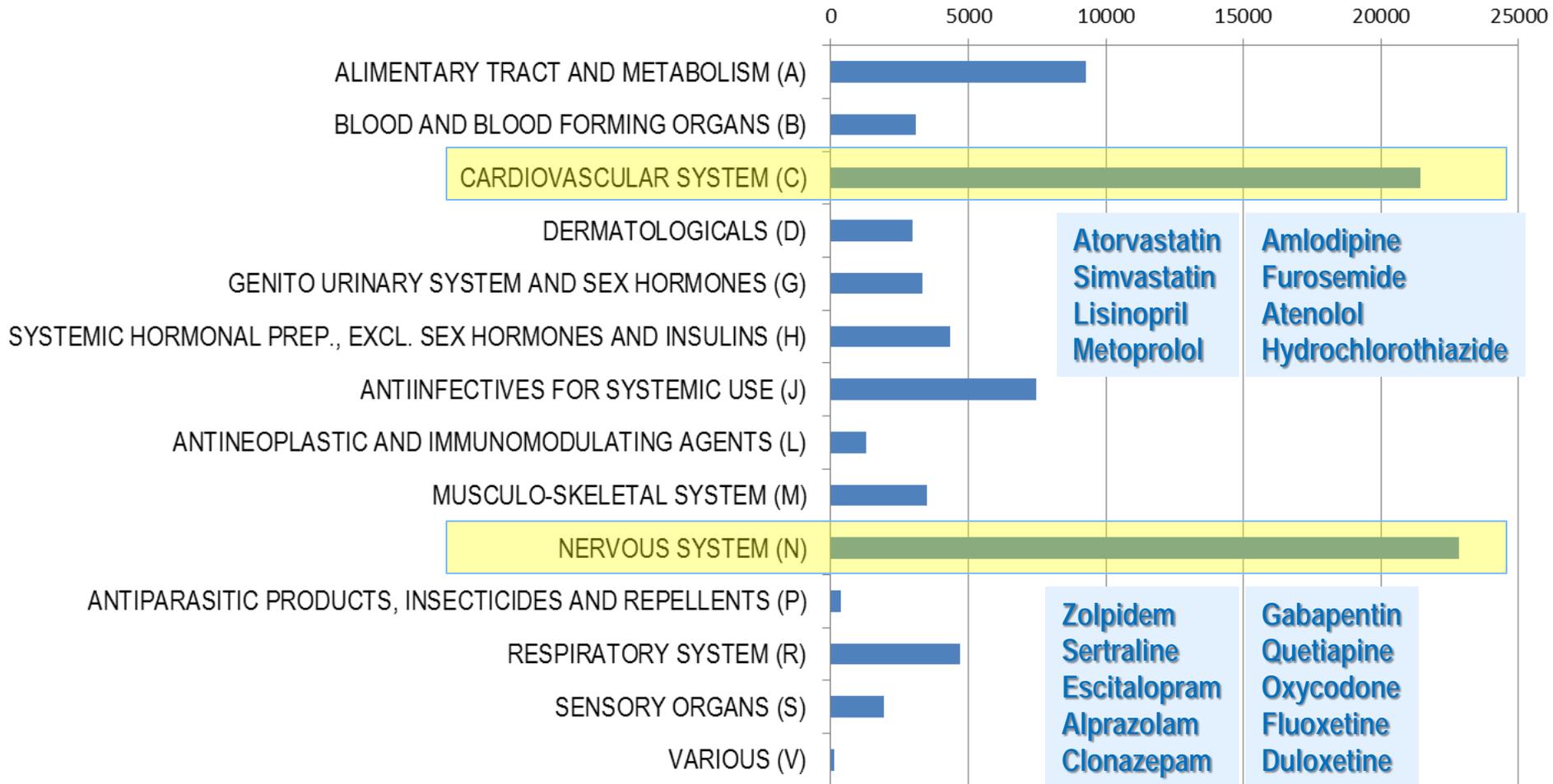
J01C **BETA-LACTAM ANTIBACTERIALS, PENICILLINS**

J01CA **Penicillins with extended spectrum**

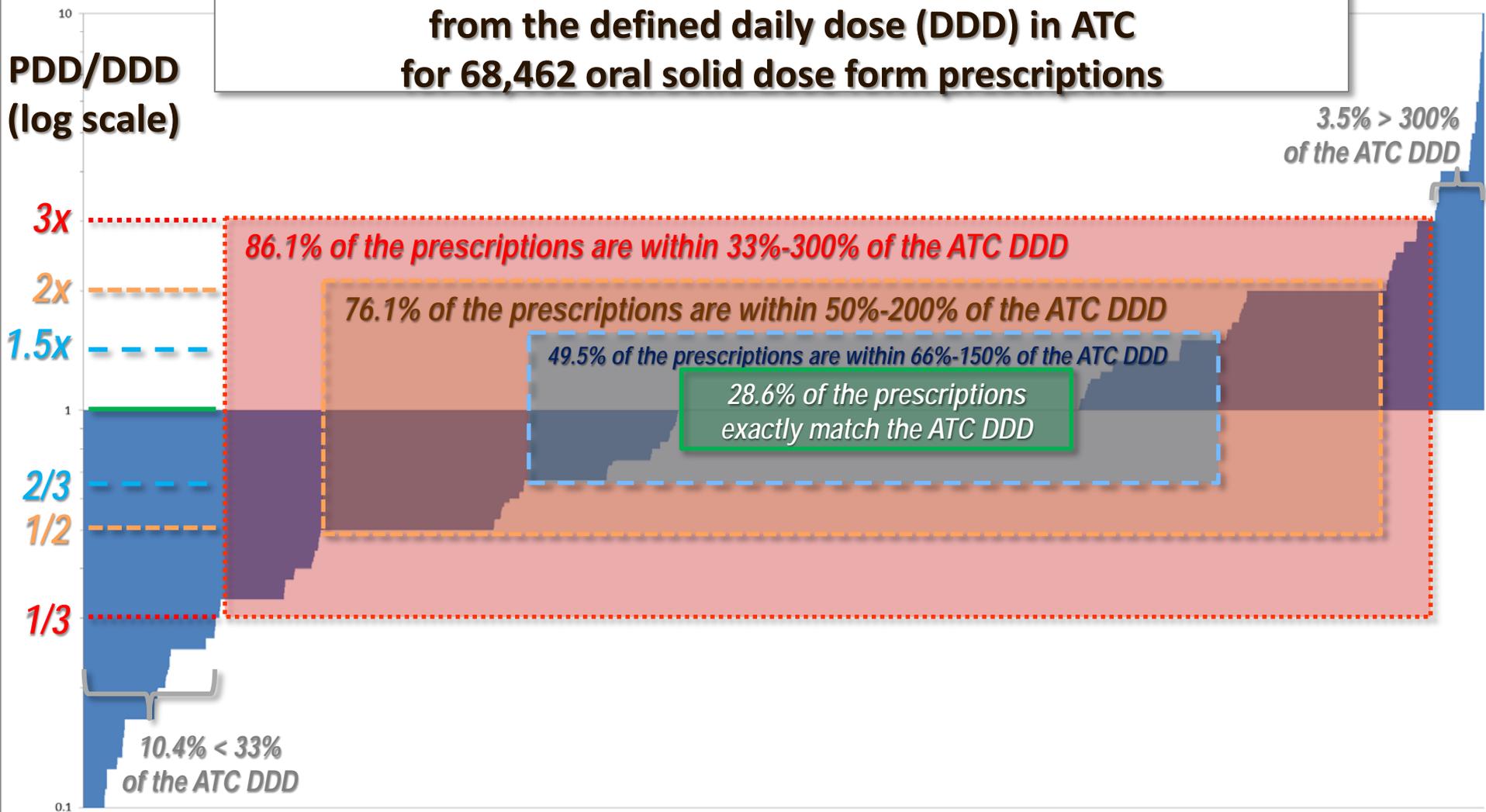


# Results Prescription classification

Frequency of drugs by level-1 ATC group in the Surescripts prescription dataset **N=86,578**



# Deviation of the prescribed daily dose (PDD) in Surescripts from the defined daily dose (DDD) in ATC for 68,462 oral solid dose form prescriptions



## Use case #2

*Identifying potentially inappropriate medications for elderly patients*

# PIMs for elderly patients

## ◆ Dataset

- Medicare Part D
- 1M beneficiaries  $\geq 65$
- All prescriptions for one year (2009)

## ◆ Reference list of PIMs: Beers list

## ◆ Methods

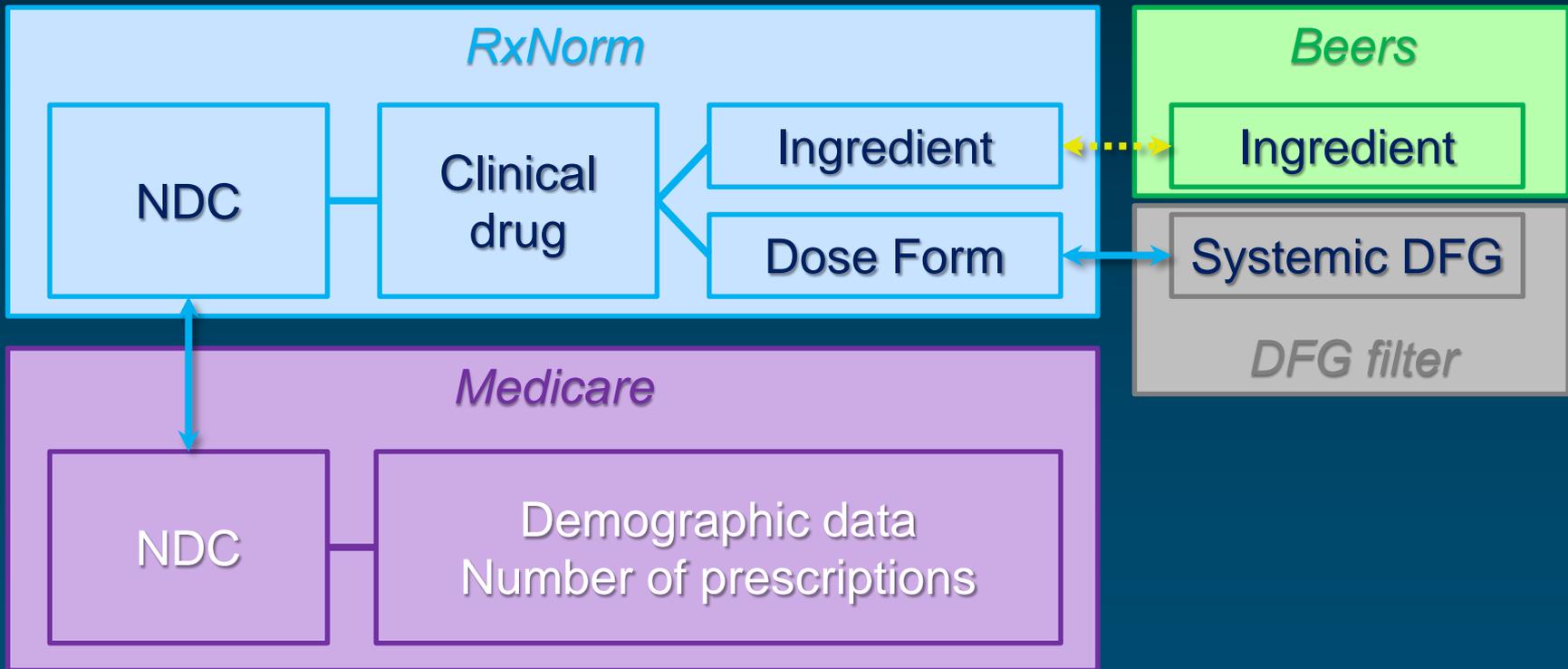
- NDC  $\rightarrow$  RxNorm clinical drug  $\rightarrow$  ingredient  $\leftrightarrow$  Beers
- Restricted to systemic drugs (based on dose form)

## ◆ Findings

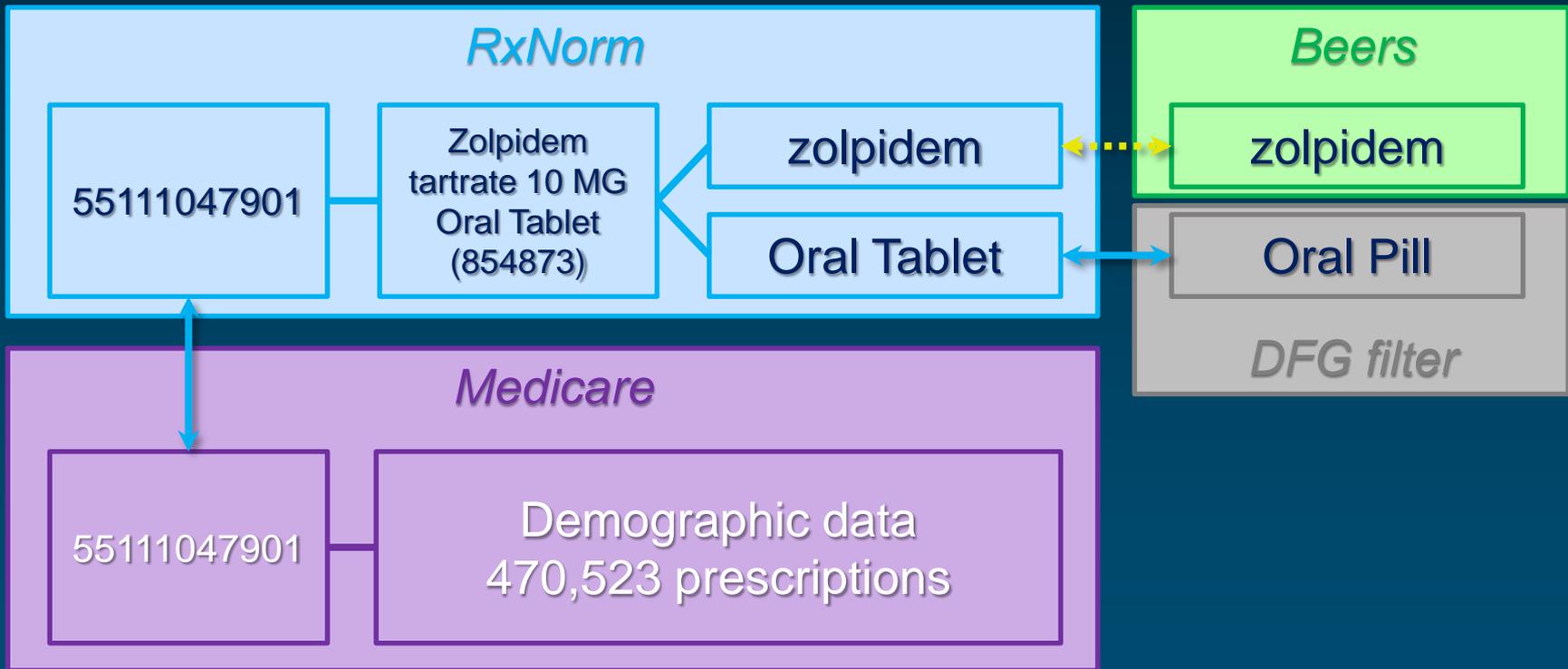
- 47% of all beneficiaries were prescribed at least 1 PIM
- Top PIMs: *zolpidem* (6.3%), *nitrofurantoin* (4.5%)



# Methods Overview



# Methods Example



# Specific challenge

## ◆ Obsolete identifiers

- NDC = drug + manufacturer + packaging information
  - 200,000 active NDCs
  - 400,000 obsolete NDCs in the past 10 years
- Obsolete NDCs
  - Removed from RxNorm (e-prescribing use case)
  - Needed for analytics (longitudinal datasets)
- RxNorm API provides access to obsolete NDCs
  - Mapping obsolete NDCs to active drugs
  - List of all NDCs – active or obsolete – for a given drug



## Use case #3

*Identifying potential risk in drug prescriptions  
during pregnancy*

# Potential risk during pregnancy

## ◆ Dataset

- Large prescription dataset from private insurer (150M patients)
- 3.7M pregnant women; 19M prescriptions (2003-2014)
- OMOP common data model

## ◆ Reference list for risk during pregnancy: Briggs textbook

## ◆ Methods

- RxNorm clinical drug → ingredient ↔ Briggs drug → fetal risk
- Restricted to systemic drugs (based on dose form)

## ◆ Findings

- 41.2% compatible with pregnancy or probably compatible
- 55.6% potential risk
- 3.29% high risk or contraindicated



# Discussion

# RxNorm supports interoperability

- ◆ Need to map across
  - Identifiers (e.g., NDC to RxNorm; RxNorm to ATC)
    - Facilitated by RxNorm concepts
      - Coming soon: DrugBank codes in RxNorm
  - Levels of granularity (e.g., NDC to clinical drug; clinical drug to ingredient; ingredient to class)
    - Facilitated by RxNorm relations
  - Reference datasets (e.g., Beers, Briggs) and standard terminologies (RxNorm)
    - Facilitated by the RxNorm API mapping functions
  - Obsolete and active identifiers (e.g., NDCs)
    - Facilitated by the RxNorm API status functions



# Remaining challenges

- ◆ Obsolete identifiers
  - Needed for analytics
- ◆ Reuse of identifiers
  - NDCs (time-indexed)
- ◆ Insufficient coverage in RxNorm
  - International drugs
  - Over-the-counter drugs
- ◆ Granularity of knowledge
  - Ingredient-class vs. clinical drug-class
- ◆ Heterogeneity of drug classification
  - Different use cases



# NLM drug resources

- ◆ RxNav, RxClass, Drug APIs
  - <https://rxnav.nlm.nih.gov/>
- ◆ RxNorm
  - <https://www.nlm.nih.gov/research/umls/rxnorm/>
- ◆ RxTerms (interface terminology for RxNorm)
  - <https://wwwcf.nlm.nih.gov/umlslicense/rxtermApp/rxTerm.cfm>
- ◆ DailyMed (Structured Product Labels)
  - <https://dailymed.nlm.nih.gov/dailymed/>
- ◆ Druginfo
  - <http://druginfo.nlm.nih.gov/>



# References

- ◆ American Geriatrics Society Beers Criteria Update Expert Panel. *American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults*. *J Am Geriatr Soc* 2015;63(11):2227-46.
- ◆ Briggs, G.G., R.K. Freeman, and S.J. Yaffe, *Drugs in pregnancy and lactation : a reference guide to fetal and neonatal risk*. Tenth edition. ed. 2015, Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins Health. xix, 1579 pages.





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<https://rxnav.nlm.nih.gov/>



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