

# The Use of LOINC and UCUM in Clinical Research



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**LOINC**<sup>®</sup>  
*from Regenstrief*

# A bit about Jozef ...

- CDISC (Clinical Data Interchange Standards Consortium) volunteer since 2001
- Co-developer of several CDISC Standards
- Software development for use in clinical research in combination with standards
- LOINC and UCUM aficionado
- CEO of XML4Pharma
  - And former Professor in Medical Informatics in Graz (Austria)



# The Use of LOINC and UCUM in CDISC - A bit of history ...

- CDISC was founded around 1998
- Due to a lack of standards for electronic submissions to the FDA
- Started with development of SDM (Submission Dataset Model)
  - And its implementation SDTM (Submission Dataset Tabulation Model)
- Followed by transport standards
  - Lab standard
  - Operational Data Standard (ODM)
- A team was also formed to develop controlled terminology (CDISC-CT)

# The Use of LOINC and UCUM in CDISC - A bit of history ...

- Submission Data Standards
  - Organized as (2D!) dataset tables with classes and domains
- LB domain
  - Usually one of the largest datasets
  - Like all "Findings" class domains, organized as "Entity-Attribute-Value" table:  
test code - test name - attributes - test value - more attributes
  - NOT a relational database table, but more a "VIEW" on a database
    - Redundancy of information all over the place

# The SDTM "LB" domain

File Tools Search Options

STUDYID	DOMAIN	USUBJID	LBSEQ	LBTESTCD	LBTEST	LBCAT	LBLOINC	LBORRES	LBORRESU	LBORNRL0	LBORNRLHI	LBSTRESC	LBSTRESN
CDISCPIL01	LB	01-701-1015	1	ALB	Albumin	CHEMISTRY	1751-7	3.8		3.3	4.9	38	38
CDISCPIL01	LB	01-701-1015	39	ALB	Albumin	CHEMISTRY	1751-7	3.9	g/dL	3.3	4.9	39	39
CDISCPIL01	LB	01-701-1015	74	ALB	Albumin	CHEMISTRY	1751-7	3.8	g/dL	3.3	4.9	38	38
CDISCPIL01	LB	01-701-1015	104	ALB	Albumin	CHEMISTRY	1751-7	3.7	g/dL	3.3	4.9	37	37
CDISCPIL01	LB	01-701-1015	134	ALB	Albumin	CHEMISTRY	1751-7	3.8	g/dL	3.3	4.9	38	38
CDISCPIL01	LB	01-701-1015	164	ALB	Albumin	CHEMISTRY	1751-7	3.8	g/dL	3.3	4.9	38	38
CDISCPIL01	LB	01-701-1015	199	ALB	Albumin	CHEMISTRY	1751-7	3.7	g/dL	3.3	4.9	37	37
CDISCPIL01	LB	01-701-1015	229	ALB	Albumin	CHEMISTRY	1751-7	3.7	g/dL	3.3	4.9	37	37
CDISCPIL01	LB	01-701-1015	259	ALB	Albumin	CHEMISTRY	1751-7	3.8	g/dL	3.3	4.9	38	38
CDISCPIL01	LB	01-701-1015	294	ALB	Albumin	CHEMISTRY	1751-7	3.8	g/dL	3.3	4.9	38	38
CDISCPIL01	LB	01-701-1015	2	ALP	Alkaline Ph...	CHEMISTRY	6768-6	34	U/L	35	115	34	34
CDISCPIL01	LB	01-701-1015	40	ALP	Alkaline Ph...	CHEMISTRY	6768-6	50	U/L	35	115	50	50
CDISCPIL01	LB	01-701-1015	75	ALP	Alkaline Ph...	CHEMISTRY	6768-6	41	U/L	35	115	41	41
CDISCPIL01	LB	01-701-1015	105	ALP	Alkaline Ph...	CHEMISTRY	6768-6	43	U/L	35	115	43	43
CDISCPIL01	LB	01-701-1015	135	ALP	Alkaline Ph...	CHEMISTRY	6768-6	47	U/L	35	115	47	47
CDISCPIL01	LB	01-701-1015	165	ALP	Alkaline Ph...	CHEMISTRY	6768-6	53	U/L	35	115	53	53
CDISCPIL01	LB	01-701-1015	200	ALP	Alkaline Ph...	CHEMISTRY	6768-6	41	U/L	35	115	41	41
CDISCPIL01	LB	01-701-1015	1	ALP	Alkaline Ph...	CHEMISTRY	6768-6	45	U/L	35	115	45	45
CDISCPIL01	LB	01-701-1015	260	ALP	Alkaline Ph...	CHEMISTRY	6768-6	46	U/L	35	115	46	46
CDISCPIL01	LB	01-701-1015	295	ALP	Alkaline Ph...	CHEMISTRY	6768-6	44	U/L	35	115	44	44
CDISCPIL01	LB	01-701-1015	3	ALT	Alanine Am...	CHEMISTRY	1742-6	27	U/L	6	34	27	27
CDISCPIL01	LB	01-701-1015	41	ALT	Alanine Am...	CHEMISTRY	1742-6	41	U/L	6	34	41	41
CDISCPIL01	LB	01-701-1015	76	ALT	Alanine Am...	CHEMISTRY	1742-6	18	U/L	6	34	18	18
CDISCPIL01	LB	01-701-1015	106	ALT	Alanine Am...	CHEMISTRY	1742-6	26	U/L	6	34	26	26
CDISCPIL01	LB	01-701-1015	136	ALT	Alanine Am...	CHEMISTRY	1742-6	22	U/L	6	34	22	22
CDISCPIL01	LB	01-701-1015	166	ALT	Alanine Am...	CHEMISTRY	1742-6	27	U/L	6	34	27	27
CDISCPIL01	LB	01-701-1015	201	ALT	Alanine Am...	CHEMISTRY	1742-6	17	U/L	6	34	17	17
CDISCPIL01	LB	01-701-1015	231	ALT	Alanine Am...	CHEMISTRY	1742-6	21	U/L	6	34	21	21
CDISCPIL01	LB	01-701-1015	261	ALT	Alanine Am...	CHEMISTRY	1742-6	23	U/L	6	34	23	23
CDISCPIL01	LB	01-701-1015	296	ALT	Alanine Am...	CHEMISTRY	1742-6	23	U/L	6	34	23	23
CDISCPIL01	LB	01-701-1015	4	ANISO	Anisocytes	HEMATOL...	38892-6	1	NO UNITS			1	1

# The SDTM "LB" domain

- LBTESTCD is NOT a test code!
  - It is a code for the analyte
    - max. 8 characters, US-ASCII only, may not start with a number
- Postcoordinated identifiers
  - Combination of LBTESTCD, LBSPEC (specimen), LBMETHOD (method) is believed to uniquely identify the test

**It isn't !**

# Why post-coordinated? Why not use pre-coordinated LOINC?

- Arguments we hear:
- We do not know what we will get in advance
  - Protocol states "measure glucose in urine"
- Tests in clinical research are different from those in healthcare
- Laboratories do not use LOINC
- LBLOINC is "permissible"
  - So almost nobody is using it

# CDISC post-coordinated Controlled Terminology for lab tests

- SDTM is about "data categorization" => post-coordination
- CDISC developed own controlled terminology for (among many others):
  - LBTESTCD/LBTEST: the analyte
  - LBSPEC: the specimen
  - LBMETHOD: the method used
- And did not take into account that these already are present in LOINC
  - But with more than 8 characters ...



# CDISC units

- CDISC developed its own **LIST** of units
- A **list**, not a system
- No way to do unit conversions
- Mixes up real units and topic of the unit
  - Examples: "steps/min", "mmHg", "10<sup>7</sup> CFU/mL" ...
- SDTM does not allow to use UCUM notation
  - There is however overlap between UCUM and CDISC "units"

	A	B	C	D	E	F	
	Code	Codelist Code	Codelist Extensible (Yes/No)	Codelist Name	CDISC Submission Value	CDISC Synonym(s)	CDISC
1	C71620		Yes	Unit	UNIT	Unit	Terminology codelist used for units
28304	C25613	C71620		Unit	%	Percentage	One hundred times the quotient of o same units of measurement.
28305	C117963	C71620		Unit	% INHIBITION	Percent Inhibition	The rate of measured normal activity rate of normal activity of a given obje
28306	C48571	C71620		Unit	%(v/v)	Percent Volume per Volume; vol%	A percent ratio of volume to volume, solute (in ml)/ volume of solution (in solutions. (NCI)
28307	C48527	C71620		Unit	%(w/v)	Percent Weight per Volume	A percent ratio of weight to volume, (in gm)/volume of solution (in dl))(10 of this ratio have different units, it is is defined as being 1 gram of solute
28308	C48528	C71620		Unit	%(w/w)	Percent Weight per Weight	A percent ratio of weight to weight, (in gm)/weight of solution (in gm))(10
28309	C114240	C71620		Unit	%/min	Percent per Minute	A unit of frequency expressed as th minute.
28310	C163560	C71620		Unit	%/s	Percent per Second	A unit of frequency expressed as th second.
28311	C102695	C71620		Unit	/100 HPFs	Per 100 High Powered Fields	A unit of measurement of the numbe hundred high powered fields
28312							

# Why does CDISC not use UCUM?

- Arguments heard (and published!):
- Investigators do not know UCUM
- UCUM notation is "unnatural" (e.g. "mm[Hg]")
- UCUM annotations are "weird"
- Topic of unit is already in LBTESTCD
- Essentially ... we do it differently

# Helping CDISC to move to UCUM

- Jozef and Erin Muhlbradt (NCI) developed a mapping from CDISC units to UCUM
- Goal was to help CDISC (and pharma) making the transition to UCUM
- CDISC-CT team argued that the mapping should be used to ... translate UCUM units (e.g. from EHRs) to CDISC units
  - But UCUM is a SYSTEM, not a LIST !
  - So this mapping will only work for a very limited set of UCUM units

# The world is changing - The role of the FDA

- 2017: FDA announces it will require LOINC coding for lab tests for studies starting from 2020
- How did CDISC react?
- A work group was started (CDISC, Regenstrief, NCI, FDA) to develop a mapping between LOINC codes (>2000 most used) and CDISC-SDTM

# The LOINC to CDISC mapping

- 2 years development time
- Now in "internal review" at CDISC
- >2400 mappings
- Published as ... Excel
- LBTESTCD/LBTEST + LBMETHOD + LBSPEC not sufficient to define uniqueness

	A	B	C	D	E	F	G	H	I	J	K
	LOINC Code	Component	Property	Time Aspect	System	Scale	Method	LOINC Short Name		CDISC LBTEST	CDISC LBTSTDTL
1											
2	14682-9	Creatinine	SCnc	Pt	Ser/Plas	Qn		Creat SerPI-sCnc		Creatinine	
3	14682-9	Creatinine	SCnc	Pt	Ser/Plas	Qn		Creat SerPI-sCnc		Creatinine	
4	14682-9	Creatinine	SCnc	Pt	Ser/Plas	Qn		Creat SerPI-sCnc		Creatinine	
5	2823-3	Potassium	SCnc	Pt	Ser/Plas	Qn		Potassium SerPI-sCnc		Potassium	
6	2823-3	Potassium	SCnc	Pt	Ser/Plas	Qn		Potassium SerPI-sCnc		Potassium	
7	2823-3	Potassium	SCnc	Pt	Ser/Plas	Qn		Potassium SerPI-sCnc		Potassium	
8	14749-6	Glucose	SCnc	Pt	Ser/Plas	Qn		Glucose SerPI-sCnc		Glucose	
9	14749-6	Glucose	SCnc	Pt	Ser/Plas	Qn		Glucose SerPI-sCnc		Glucose	
10	14749-6	Glucose	SCnc	Pt	Ser/Plas	Qn		Glucose SerPI-sCnc		Glucose	
11	2951-2	Sodium	SCnc	Pt	Ser/Plas	Qn		Sodium SerPI-sCnc		Sodium	
12	2951-2	Sodium	SCnc	Pt	Ser/Plas	Qn		Sodium SerPI-sCnc		Sodium	
13	2951-2	Sodium	SCnc	Pt	Ser/Plas	Qn		Sodium SerPI-sCnc		Sodium	
14	3094-0	Urea nitrogen	MCnc	Pt	Ser/Plas	Qn		BUN SerPI-mCnc		Urea Nitrogen	
15	3094-0	Urea nitrogen	MCnc	Pt	Ser/Plas	Qn		BUN SerPI-mCnc		Urea Nitrogen	

# The LOINC to CDISC mapping: A RESTful web service

- RESTful web services (RWS) are "sexy" nowadays
- Avoid implementing the wheel over and over again
- Healthcare discovered RWS through **FHIR**
- Several RWS for LOINC exist already
  
- We developed a RWS for LOINC to CDISC mapping
  - As the mapping is still "in review", the API has not made public yet
  - If you would like to use it, just drop me a mail ...

# What's up with UCUM at CDISC?

- There is still a lot of resistance against UCUM at CDISC
- Still not allowed in regulatory submissions
- "Not invented here"
- CDISC-CT does now want to give up their own UNIT-CT
  
- But times are changing ...

# The world is changing - The role of the FDA

## FDA Adopts Units of Measure Standard for Regulatory Submissions

Posted 06 September 2019 | By [Michael Mezher](#)

The US Food and Drug Administration (FDA) on Friday announced its support for the latest set of Unified Code for Units of Measure (UCUM) codes for use in electronic submissions for drugs and biologics.

“UCUM offers a single coding system for units of measure that does not contain ambiguities amongst electronic communication, and assigns a concise semantics to each defined unit,” FDA writes.

With the notice, FDA says it wants drugmakers to use UCUM coding for drug establishment registration, drug listing and in the content of product labeling in regulatory submissions to the Center for Biologics Evaluation and Research (CBER) and Center for Drug Evaluation and Research (CDER).





# FDA embraces UCUM

## What does this mean for CDISC?

- Honestly ... we don't know ...
- Will the FDA allow the use of UCUM in CDISC submissions?
- Will the FDA mandate the use of UCUM in CDISC submissions?

# UCUM Restful Web Services

- A few years ago, one of my students at the University of Applied Sciences FH Joanneum (Graz) developed and programmed an algorithm for UCUM unit conversions, based on the `ucum-essence.xml`



- This algorithm was later extended to work as a RESTful web service
- The code was then donated to the NLM and deployed by the NLM:  
<https://ucum.nlm.nih.gov/ucum-service.html>

# UCUM Restful Web Services at the National Library of Medicine (NLM)

NIH U.S. National Library of Medicine



## Unified Code for Units of Measure (UCUM)

UCUM Resources from the Lister Hill National Center for Biomedical Communications

### UCUM Web Service

This is a set of web services (APIs) for programs to use when working with units from the Unified Code for Units of Measure ([UCUM](#)) system. These are the same APIs as those that are running at [xml4pharmaserver.com](http://xml4pharmaserver.com), and are based on that website's web service code which has been donated to the U.S. National Library of Medicine by FH-Prof. Jozef Aerts and Mr. Milos Ilic MSc, Institute of eHealth, University of Applied Sciences FH Joanneum in Graz Austria.

Currently, three web services are available:

- [UCUM unit Conversion web service](#)
- [UCUM unit validation web service](#)
- [UCUM unit to base units conversion](#)

UCUM Service version: 2.2.0 ([changes](#))

# NLM UCUM Restful Web Service: simple example

- mol/[in\_i]3 to mol/L

```
<?xml version="1.0" encoding="ISO-8859-1"?>
- <UCUMWebServiceResponse ServerDateTime="2019-10-16T08:34:13">
  <WebServiceRequest>http://ucum.nlm.nih.gov/ucum-
    service/v1/ucumtransform/1/from/mol/%5Bin_i%5D3/to/mol/L</WebServiceRequest>
  - <Response>
    <SourceQuantity>1.0</SourceQuantity>
    <SourceUnit>mol/[in_i]3</SourceUnit>
    <TargetUnit>mol/L</TargetUnit>
    <ResultQuantity>61.023744</ResultQuantity>
  </Response>
</UCUMWebServiceResponse>
```

# The SI versus Conventional Units problem

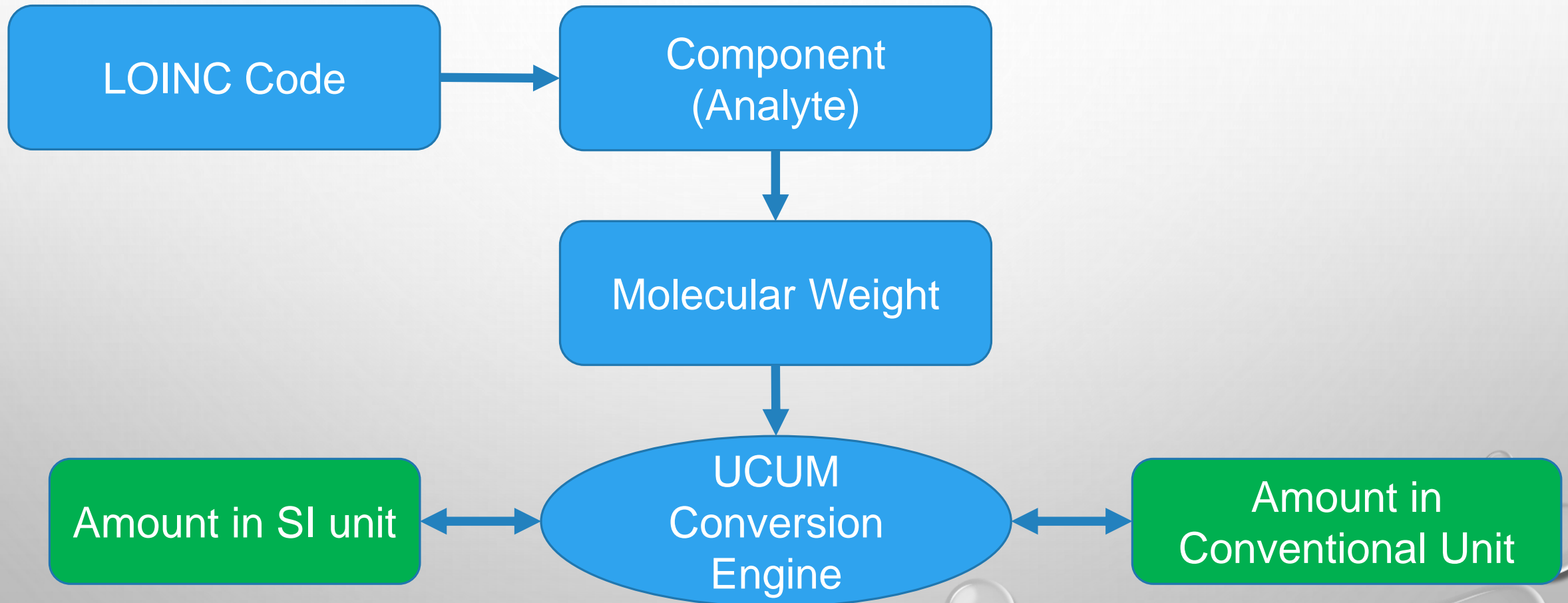
- Pharma companies and the FDA struggle with "the **SI versus Conventional Units** problem"
- Conventional Units: also named "US customary units"
  - Examples: mg/dL, %, ...
- SI units are mostly used everywhere outside the USA
  - Examples: mol/L, proportion of 1.0, ...
- Mostly, conversion tables are used

# The SI versus Conventional Units problem

## Conversion Tables

Agent	Conventional Unit	Conversion Factor	SI Unit
Acetaminophen	µg/mL	6.62	µmol/L
Acetoacetic acid	mg/dL	0.098	mmol/L
Acetone	mg/dL	0.172	mmol/L
Alanine	mg/dL	112.2	µmol/L
Albumin	g/dL	10	g/L
Aldosterone	ng/dL	0.0277	nmol/L
Aluminum	ng/mL	0.0371	µmol/L
Aminobutyric acid	mg/dL	97	µmol/L
Amitriptyline	ng/mL	3.61	nmol/L
Ammonia (as NH <sub>3</sub> )	µg/dL	0.587	µmol/L
Androstenedione	ng/dL	0.0349	nmol/L

Can we automate this?  
Can we provide a RESTful-WS for this?



# The SI versus Conventional Units RESTful Web Service - Examples

- Albumin (in blood/Serum) conventional to SI unit conversion

```
<?xml version="1.0" encoding="ISO-8859-1"?>
<UCUMWebServiceResponse ServerDateTime="2019-10-16T08:51:49">
  <WebServiceRequest>http://xml4pharmaserver.com:8080/UCUMService2/rest/ucumtransform/5.2/from/g/dL/to/mmol/L/LOINC/1751-7</WebServiceRequest>
  - <Response>
    <SourceQuantity>5.2</SourceQuantity>
    <SourceUnit>g/dL</SourceUnit>
    <TargetUnit>mmol/L</TargetUnit>
    <MolecularWeightUsed>66000</MolecularWeightUsed>
    <ResultQuantity>0.78787879</ResultQuantity>
  </Response>
</UCUMWebServiceResponse>
```

- Glucose (in urine) SI to conventional unit conversion

```
<?xml version="1.0" encoding="ISO-8859-1"?>
- <UCUMWebServiceResponse ServerDateTime="2019-10-16T08:57:35">
  <WebServiceRequest>http://xml4pharmaserver.com:8080/UCUMService2/rest/ucumtransform/0.6/from/mmol/L/to/mg/dL/LOINC/15076-3</WebServiceRequest>
  - <Response>
    <SourceQuantity>0.6</SourceQuantity>
    <SourceUnit>mmol/L</SourceUnit>
    <TargetUnit>mg/dL</TargetUnit>
    <MolecularWeightUsed>180.2</MolecularWeightUsed>
    <ResultQuantity>10.812</ResultQuantity>
  </Response>
</UCUMWebServiceResponse>
```



# Status of the SI versus Conventional Units RESTful Web Service

- Currently tested by a number of Pharma companies (Europe, Japan, US)
- Source code donated to the NLM
- Will be tested and deployed by the NLM
- Will allow Pharma and the FDA to execute unit conversions in a highly automated and reliable way
- If you would like to try it out, just drop me a mail ...

# Summary

- LOINC is slowly being accepted within clinical research
  - However only for lab tests
  - Not at all yet for questionnaires, vital signs, microbiology, ...
- UCUM is almost not used in clinical research
  - Many see the advantage, but as long as the FDA does not allow or mandate it ...
- FDA and pharma would enormously benefit when LOINC and UCUM would be used in combination
- Our RESTful web services make the transition easy



LOINC and UCUM:  
also for clinical research and regulatory submissions!