[Unfulfilled?] Potential of R in Clinical Research

EDUARD PARSADANYAN

Biostatistics & Statistical Programming

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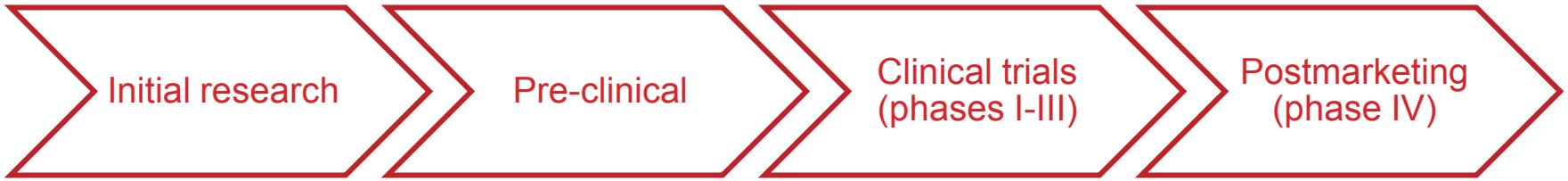
AGENDA

- **What is Clinical Research?** (brief intro and terminology)
- **What is the potential of R?** (in variously regulated environments)
- **What needs to be considered for using R in regulated environments?**
  - Security breaches (case-study with a Shiny App for bioequivalence)
  - Industry standards (for computerized systems and data deliverables)
  - Audits (how to prove that words meet actions)

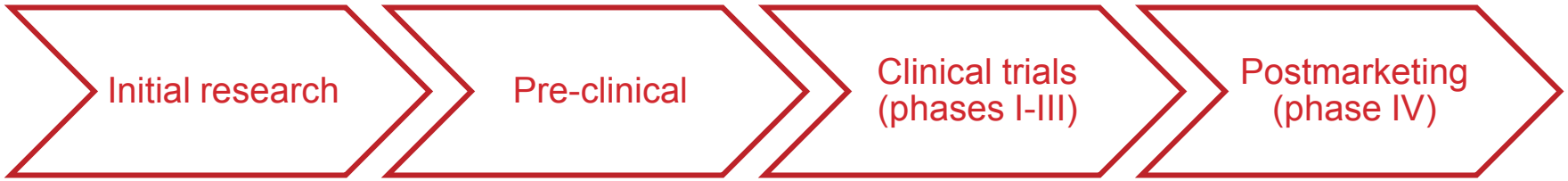
WHAT IS CLINICAL RESEARCH?



Clinical research is a branch of healthcare science that **determines the safety and effectiveness of** drug/device/biologic **products** and treatment regimens **intended for human use.**

These may be **used for prevention, treatment, diagnosis or for relieving symptoms of a disease.**

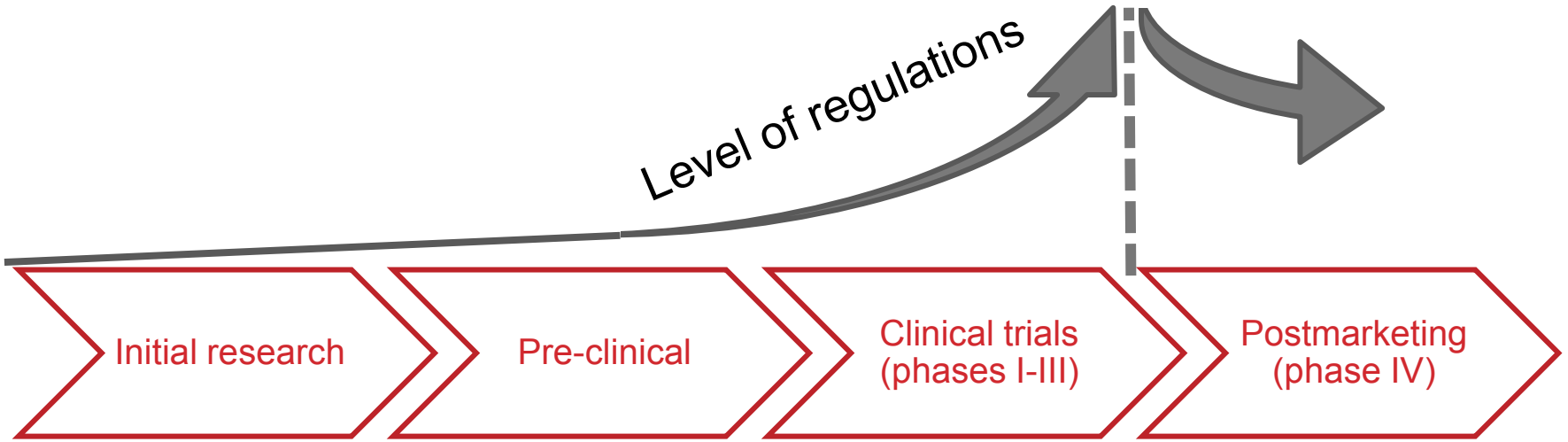
WHAT IS CLINICAL RESEARCH?



Main actor are

- **Sponsors** (e.g. pharma company that own the molecule)
- **Subcontractors** (e.g. contract research organizations – CROs)
- **Regulators** (government agencies like FDA and EMA)

WHAT IS THE POTENTIAL OF R?



NB! Lack of regulations does not mean absence of any standards

Key points: Usage of R is an invers function of regulatory scrutiny

Limitations are confused with prohibition

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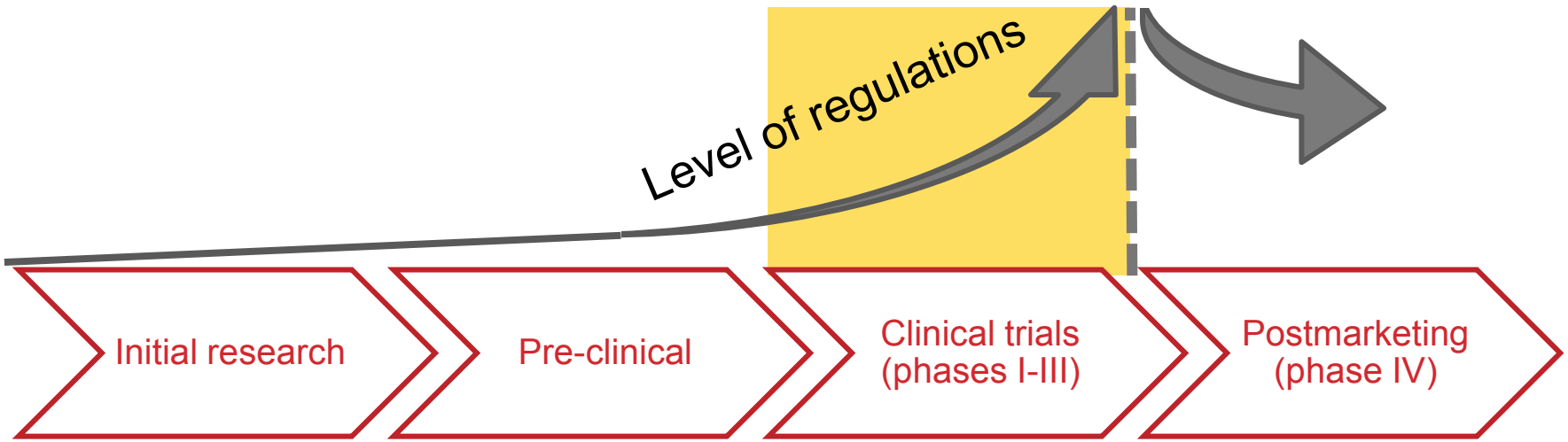

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CONSIDERATIONS FOR USING R IN REGULATED ENVIRONMENT

- **Security breaches**

  In most cases security issues are not directly related to R but sometimes they do.

- **Industry standards**
  - For computerized systems (possibility to use R in principle)
  - For deliverables (electronic submissions to FDA)
- **Audits**

  Sponsors, government agencies, independent parties.

CASE STUDY

Shiny-app for bioequivalence studies by Andrey Ogurtsov:

statist.shinyapps.io/bioeq_en

FDA defines bioequivalence as:

"the absence of a significant difference in the rate and extent to which the active ingredient … in pharmaceutical equivalents [i.e. generics] becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study".

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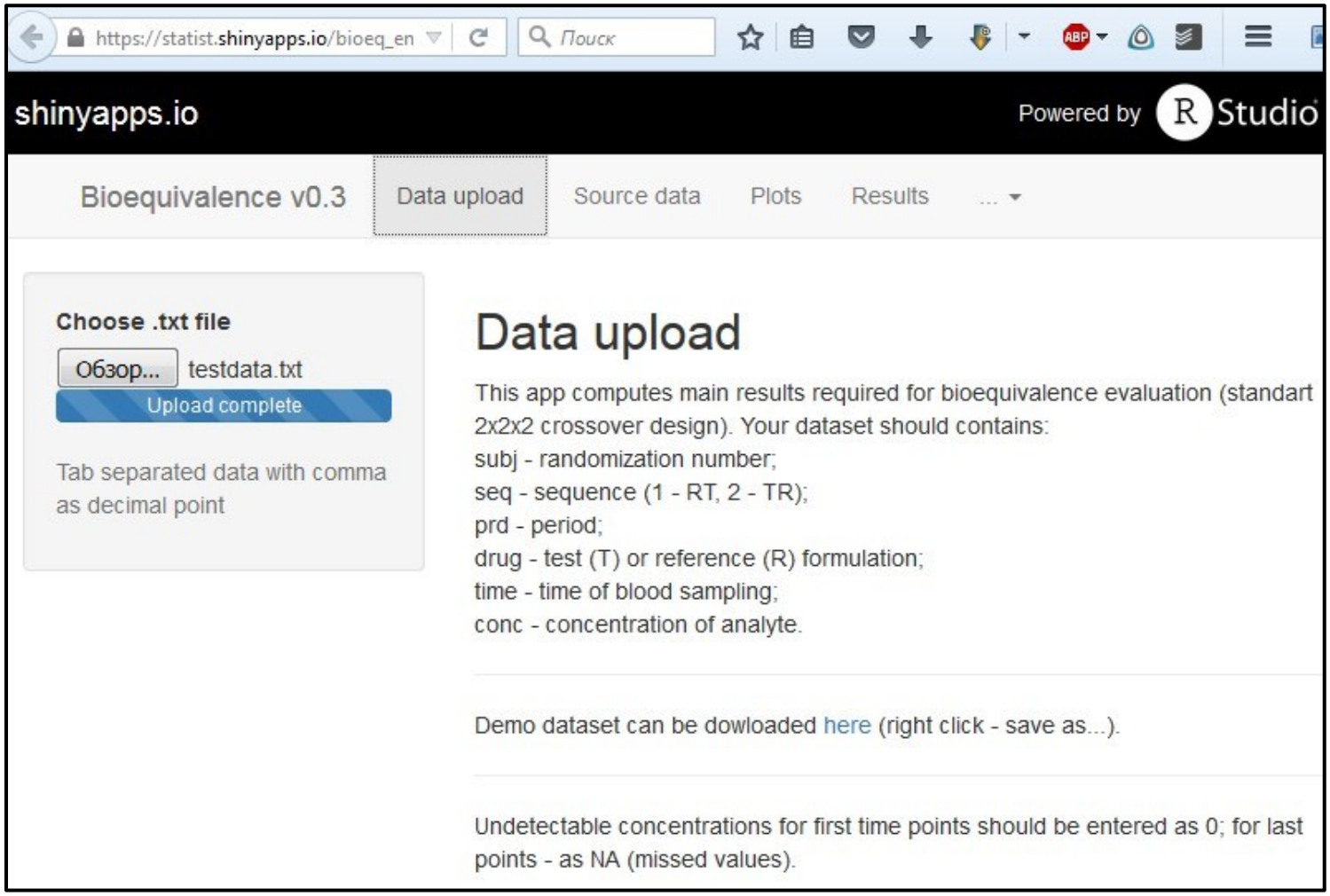

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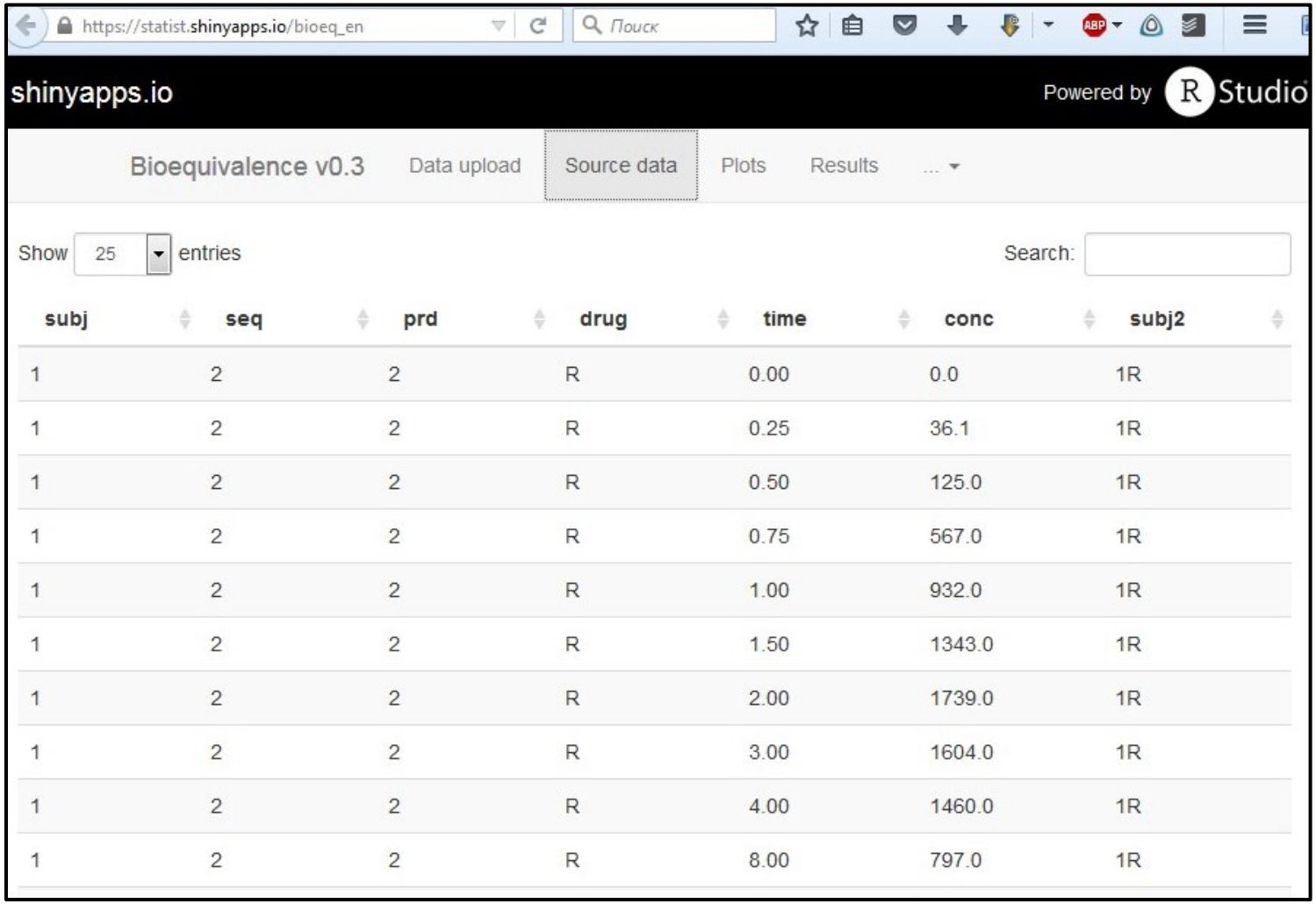

subj	seq	prd	drug	time	conc	subj2
1	2	2	R	0.00	0.0	1R
1	2	2	R	0.25	36.1	1R
1	2	2	R	0.50	125.0	1R
1	2	2	R	0.75	567.0	1R
1	2	2	R	1.00	932.0	1R
1	2	2	R	1.50	1343.0	1R
1	2	2	R	2.00	1739.0	1R
1	2	2	R	3.00	1604.0	1R
1	2	2	R	4.00	1460.0	1R
1	2	2	R	8.00	797.0	1R

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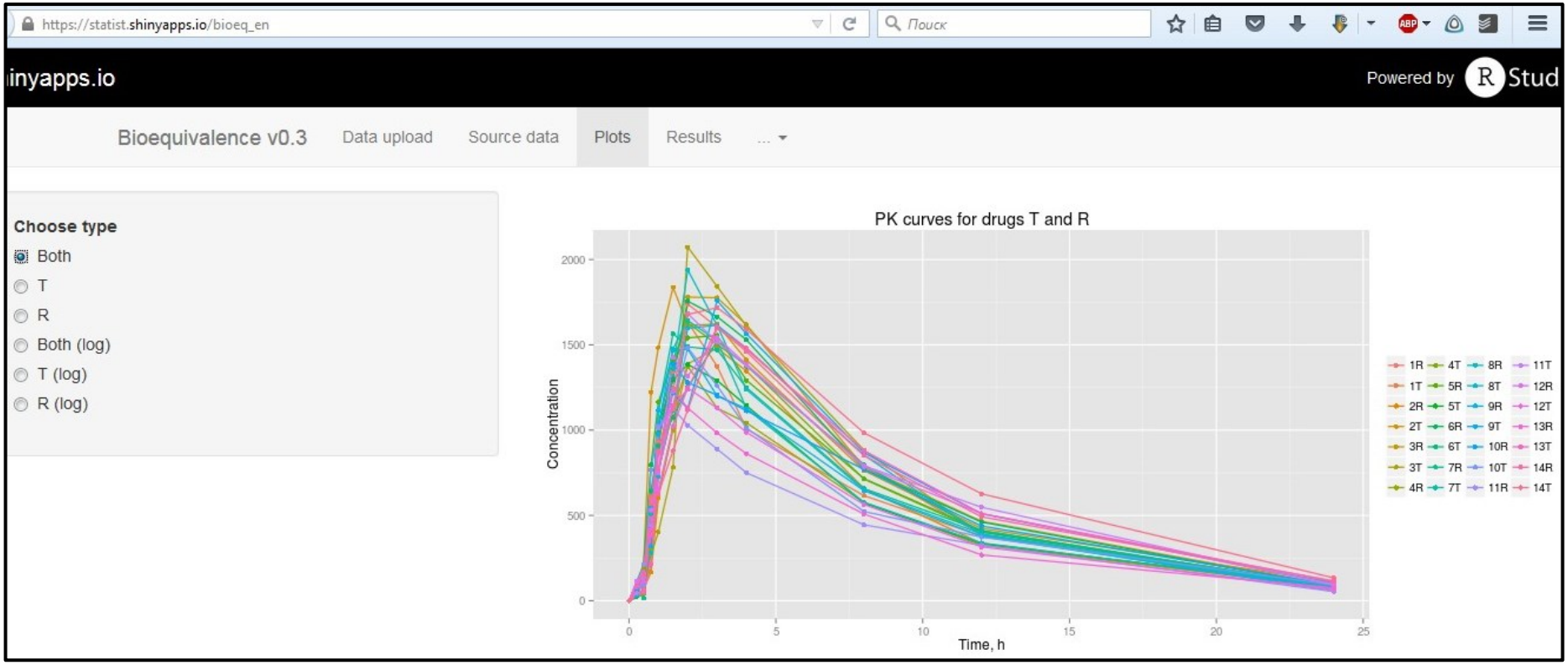

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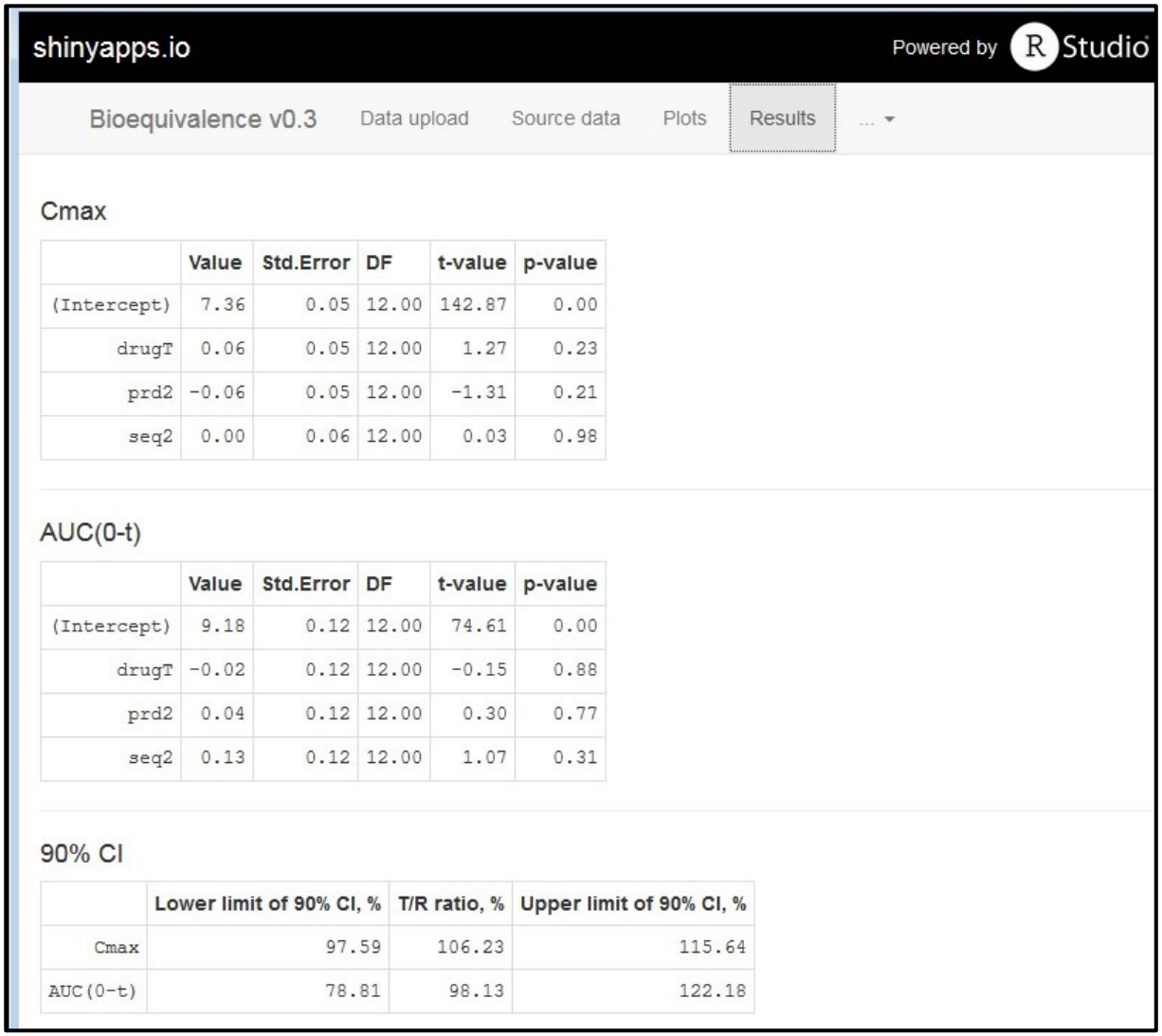

Cmax

	Value	Std.Error	DF	t-value	p-value
(Intercept)	7.36	0.05	12.00	142.87	0.00
drugT	0.06	0.05	12.00	1.27	0.23
prd2	-0.06	0.05	12.00	-1.31	0.21
seq2	0.00	0.06	12.00	0.03	0.98

AUC(0-t)

	Value	Std.Error	DF	t-value	p-value
(Intercept)	9.18	0.12	12.00	74.61	0.00
drugT	-0.02	0.12	12.00	-0.15	0.88
prd2	0.04	0.12	12.00	0.30	0.77
seq2	0.13	0.12	12.00	1.07	0.31

90% CI

	Lower limit of 90% CI, %	T/R ratio, %	Upper limit of 90% CI, %
Cmax	97.59	106.23	115.64
AUC(0-t)	78.81	98.13	122.18

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INDUSTRY STANDARDS

- **Documents collectively referred to as GxP:**
  - 21 CFR Part 11 - Electronic Records; Electronic Signatures
  - Guidance for Industry: Part 11, Electronic Records; Electronic Signatures - Scope and Application
  - 21 CFR Part 58 - Good Laboratory Practice (GLP)
  - 21 CFR Part 312 - Good Clinical Practice (GCP)
  - 21 CFR Part 210 - Current Good Manufacturing Practice (cGMP)
  - ICH E6 - Good Clinical Practice Consolidated Guideline
- **Principal software guidance documents:**
  - Guidance for Industry - Computerized Systems Used in Clinical Investigations (2007)
  - General Principles of Software Validation; Final Guidance for Industry and FDA Staff (2002)
- **Principal statistical guideline documents:**
  - ICH E9 - Statistical Principles for Clinical Trials
  - Guidance for Industry and FDA Staff - Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials (2010)

INDUSTRY STANDARDS

Key points

- Standards do not specify which statistical software can or should be used
- There is a distinct difference between data collection and storage (21 CFR Part 11 - Electronic Records) vs data processing & reporting (General Principles of Software Validation)
- Most standards for computerized systems are already met in established companies
- R installation need to be validated

The R Foundation prepared a document "R: Regulatory Compliance and Validation Issues" in Dec 2014: www.r-project.org/doc/R-FDA.pdf

Revolutionanalytics blog article about R in FDA:
blog.revolutionanalytics.com/2012/06/fda-r-ok.html

INDUSTRY STANDARDS contd.

- **FDA expects data to be submitted in electronic ways**
- **There are standards developed by** CDISC – Clinical Data Interchange Standards Consortium: CDASH, SDTM, ADaM etc., some of them are adopted by FDA.
- **FDA requires datasets to be sent in .xpt** (Transport File) **format** originally developed by SAS Institute. This is an open standard now which is already supported in R.
- **CDISC works towards even more platform independent standards based on XML** (e.g. Define.xml file) – a potential for R to develop new tools.

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RECAP

- **R usage varies across different stages of clinical research**
  (inverse function of regulatory requirements)

- **R community has a great potential for developing new tools**
  (interactive vs static reports, helpful for non-programmers, optimization of processes)

- **R is Okay for electronic submissions to FDA**
  (need to overcome misconceptions and implement accordingly)

- **R can gain reputation by covering existing needs & challenges**
  (e.g. better compliance with CDISC standards for electronic submissions)

Q&A SESSION