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Center for Drug Evaluation and Research

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Sentinel Postmarketing Surveillance: Safety Signal Identification for Biosimilars

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Danijela Stojanović, PharmD, PhD.
Clinical Analyst, Office of Therapeutic Biologics and Biosimilars
Office of New Drugs | CDER | FDA

Disclaimers/Acknowledgements

- The opinions expressed are those of the presenter, and do not necessarily represent the views of the U.S. Food and Drug Administration (FDA), U.S. Public Health Service, or the U.S. Government
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Overview

Can routinely collected data distinguish biosimilar products and support systematic screening for potential safety differences?

PART I | Product identification

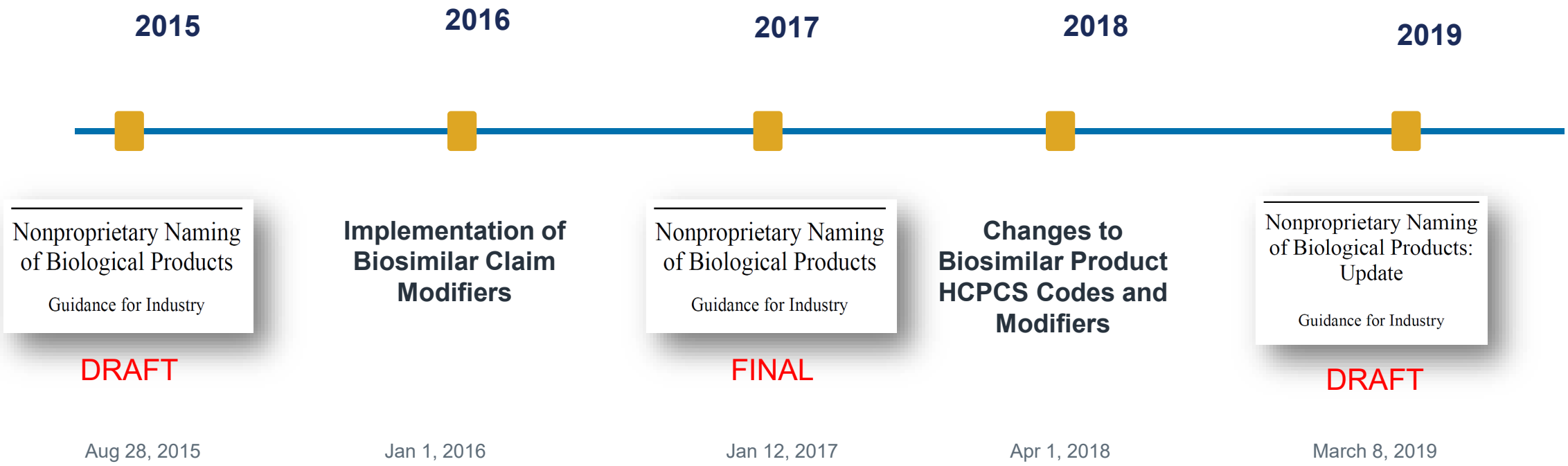
Evolution of CMS Billing-Code Policies

PART II | Safety Signal identification

Safety Signal Identification for Infliximab Biosimilars

Reliable exposure identification is a prerequisite for interpretable postmarketing safety analyses.

Evolution of CMS Billing-Code Policies



Coding policy changes altered how specific biosimilars are distinguished in claims over time.

Centers for Medicare & Medicaid Services. Changes to Biosimilar Biological Product HCPCS Codes and Modifiers: April 2018 OPPS Update. US Dept of Health and Human Services; March 2, 2018. Accessed October 22, 2026. https://www.cms.gov/regulations-and-guidance/guidance/transmittals/2018-transmittals-items/r3988cp

Product-Specific HCPCS Codes Improved Distinguishability

Product	Pre–Apr 1, 2018	Post–Apr 1, 2018
Zarxio (filgrastim-sndz)	Q5101	Q5101
Inflectra (infliximab-dyyb)	Q5102 + Modifier ZB	Q5103
Renflexis (infliximab-abda)	Q5102 + Modifier ZC	Q5104
Avsola (infliximab-axxq)	N/A	Q5121

Centers for Medicare & Medicaid Services. Changes to Biosimilar Biological Product HCPCS Codes and Modifiers: April 2018 OPPS Update. US Dept of Health and Human Services; March 2, 2018. Accessed October 22, 2026. https://www.cms.gov/regulations-and-guidance/guidance/transmittals/2018-transmittals-items/r3988cp

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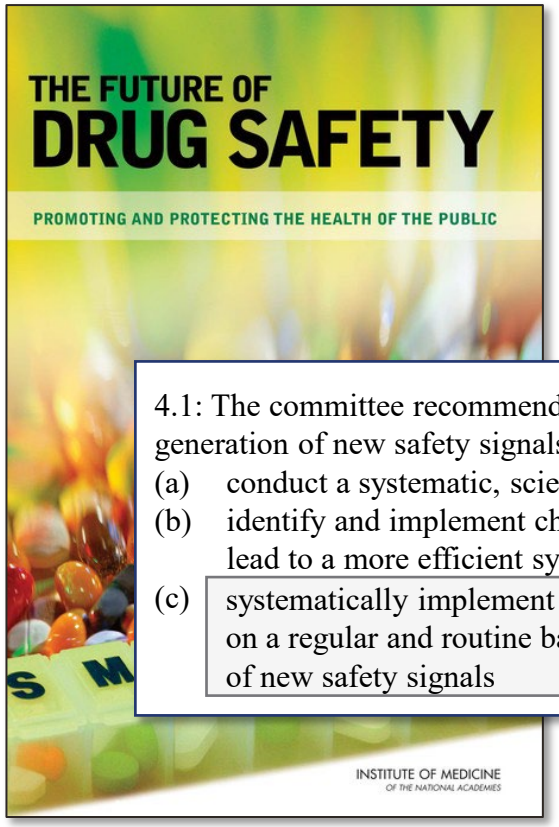
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History of Safety Signal Identification at the U.S. FDA

- In 2006, the U.S. FDA requested the Institute of Medicine to **examine the system of drug safety in the U.S.**



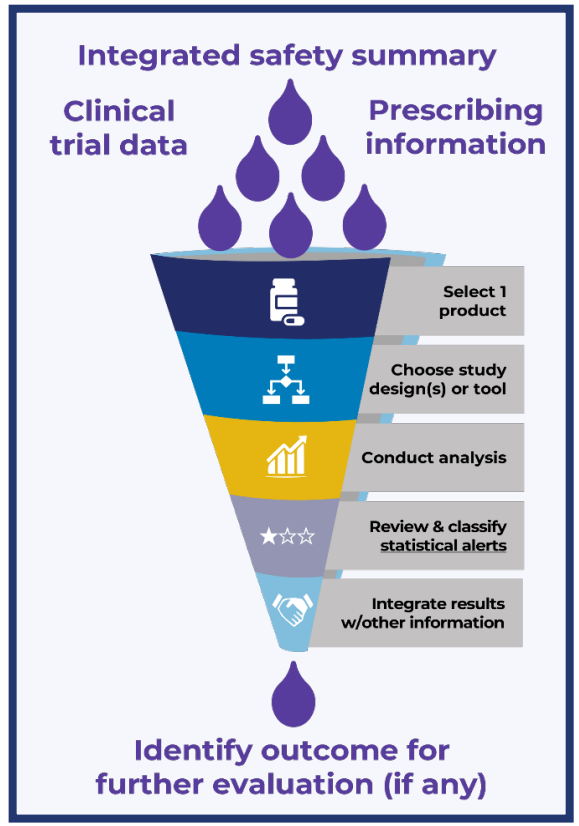
4.1: The committee recommends that in order to improve the generation of new safety signals and hypotheses, CDER

(a) conduct a systematic, scientific review of the AERS system,

(b) identify and implement changes in key factors that could lead to a more efficient system, and

(c) systematically implement statistical-surveillance methods on a regular and routine basis for the automated generation of new safety signals

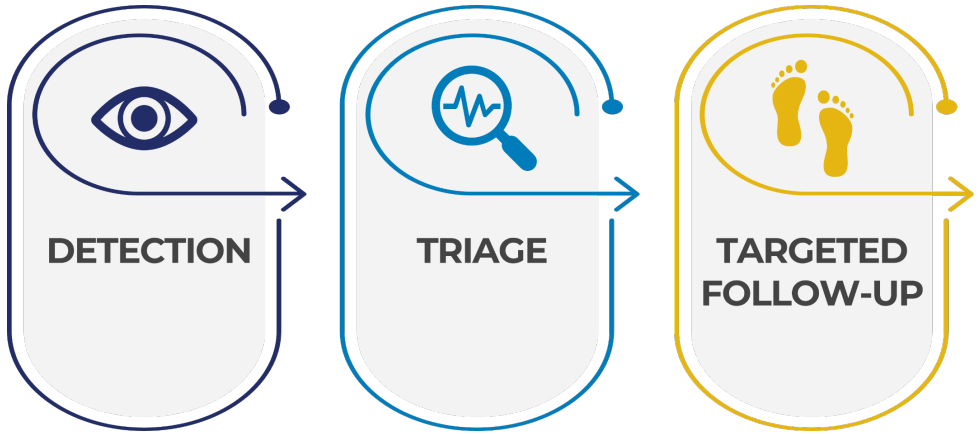
- In 2018, the U.S. FDA proposed a **process for safety signal identification** in Sentinel and integration with other sources of information



Institute of Medicine. The Future of Drug Safety: Promoting and Protecting the Health of the Public; National Academies Press: Washington, D.C., 2007. https://doi.org/10.17226/11750.
Nguyen M. FDA convening presented at: Implementation of Signal Detection Capabilities in the Sentinel System; December 3, 2018; Bethesda, Maryland.

Safety Signal Identification in the Sentinel System

- Process includes **systematically evaluating** potential adverse events related to the use of medical products **without prespecifying an outcome** of interest
  - The Sentinel System uses **tree-based scan statistics (TBSS)**
  - Detect unexpected, higher numbers of health outcomes
  - Clinical review and/or targeted epidemiology safety study follows signal identification



TreeScan

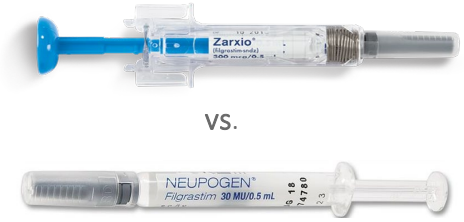
www.treescan.org

Adverse Events after Zarxio (filgrastim-sndz) vs. Neupogen (filgrastim)

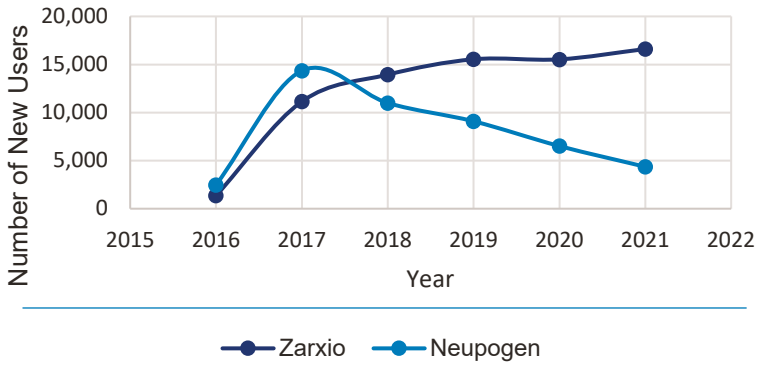
1:1 PROPENSITY SCORE MATCHED SIGNAL IDENTIFICATION STUDY

Is there any difference in medical product safety profiles between the originator product and its biosimilar?

Background



Substitution Effects



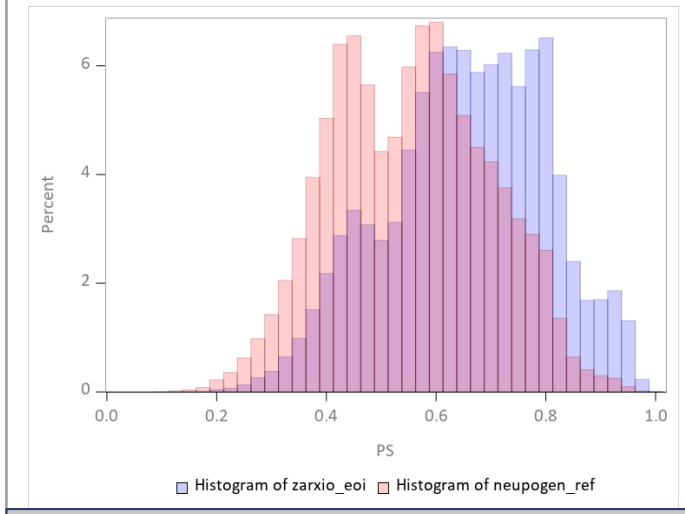
Analysis and Findings

Sentinel Distributed Database

TreeScan

- Scanned ~83,000 non-pregnancy and non-cancer outcomes
- Sensitivities based on encounter setting

Nov. 2016 – Feb. 2022



- 43,009 1:1 Matched Pairs with Conventional PS
- Imbalances on Indication, Year Before Matching
- Significant Alerts: Polyarthritis, Pain in the Leg, Other Disorders of the Peripheral Nervous System

No alerts required further follow-up.

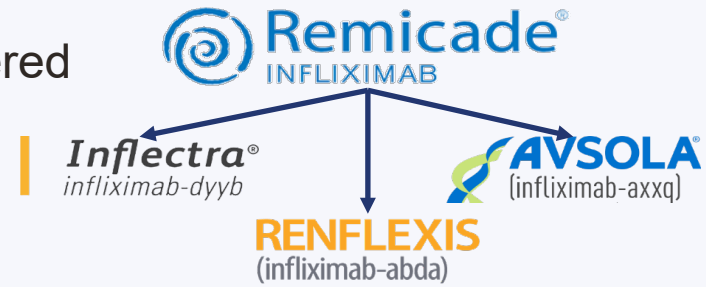
https://www.sentinelinitiative.org/studies/drugs/zarxio-filgrastim-sndz

Infliximab Biosimilars Safety Signal Identification

Background

- Biosimilar products (BPs) are highly similar to and have no clinically meaningful differences from their reference products (RPs).
  - **Post-marketing surveillance is essential to support both BP and RP safety in clinical practice.**

- Infliximab (Remicade®, RP) was approved in 1998. It is used to treat severe, chronic autoimmune conditions (such as Crohn's disease and rheumatoid arthritis).
  - Since late 2016, 3 BPs have entered the market.



Objective

To *address the possibility for differing safety profiles between infliximab RP and its BPs*, use tree-based scan statistics to identify new potential safety signals following infliximab BPs vs. RP initiation.

Data & Population



New users included: non-pregnant adults with continuous medical & drug coverage in the 400 days prior to initiation *without comparator infliximab or another drug in the same class*

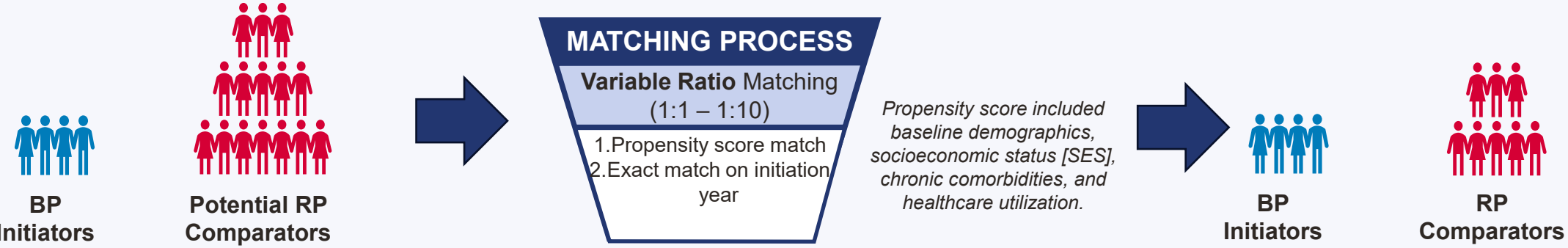
https://bitbucket.sentinel-platform.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcder_sip_wp002
https://www.sentinelinitiative.org/studies/drugs/infliximab-biosimilars

Safety Signal Assessment

Comparisons

1. RP vs. any BP
2. RP vs. Inflectra®
3. RP vs. Renflexis®
4. RP vs. Avsola®

Confounding Adjustment



Identifying Safety Signals



Follow “as treated” matched pairs for 183 days or until either is censored



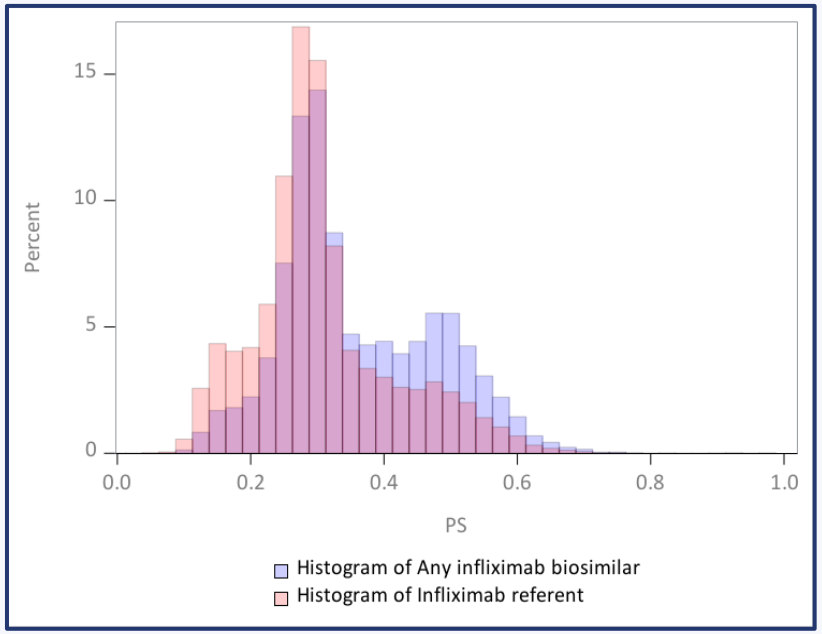
Identify new safety outcomes in 3rd-5th levels of pruned (if sufficient outcome accrual) or designated medical event (DME) ICD-10-CM tree

Variable probability unconditional Bernoulli tree-based scan statistic in 1) acute, and 2) all settings

Safety Signal Identification Results

Analytical Cohort

- Confounding adjustment was successful and resulted in balanced groups
- Average matching ratio was 1:2.2

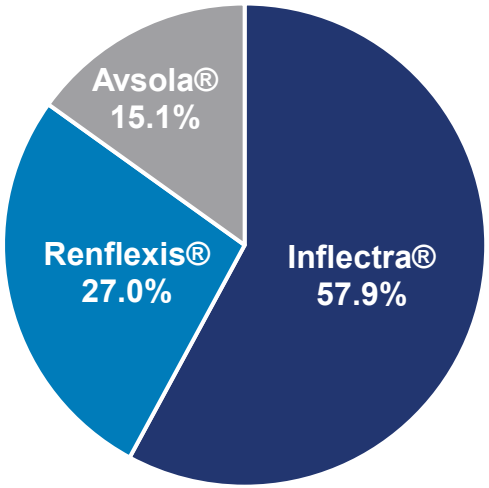


- **Matched 20,564 "Any Infliximab Biosimilar Product (BP)" users to 45,886 Infliximab Originator Product Users**
- Across all comparisons, the most common method of identifying BP use was presence of a procedure code (HCPCS) alone (50-89%).
  - About ¼ of BP new users also had evidence of an NDC, and <10% had only an NDC.

Results

There were no statistically significant elevations in health outcomes in the six months after infliximab BP initiation compared to RP initiation, either as a composite or when individual BPs were assessed.

Biosimilar Products in "Any BP" Comparison



Summary

PART I | Product identification

- Distinct HCPCS coding used for product identification
- BPs and RPs are easily identifiable in active post-marketing safety surveillance databases

PART II | Safety Signal identification

- Infliximab and its BPs had very similar safety profiles
  - Consistent finding with prior research on filgrastim products
- Signal identification is designed for broad screening, and is not built around specific confounding control for targeted outcomes

https://bitbucket.sentinel-platform.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcder_sip_wp002
https://www.sentinelinitiative.org/studies/drugs/infliximab-biosimilars



Questions?