

Natural Stable-Isotopic Records of Pharmaceutical Compounds: Anticounterfeiting and Process Patent Protection

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*Product
Authentication*

Quality Control

*Process
Authentication*

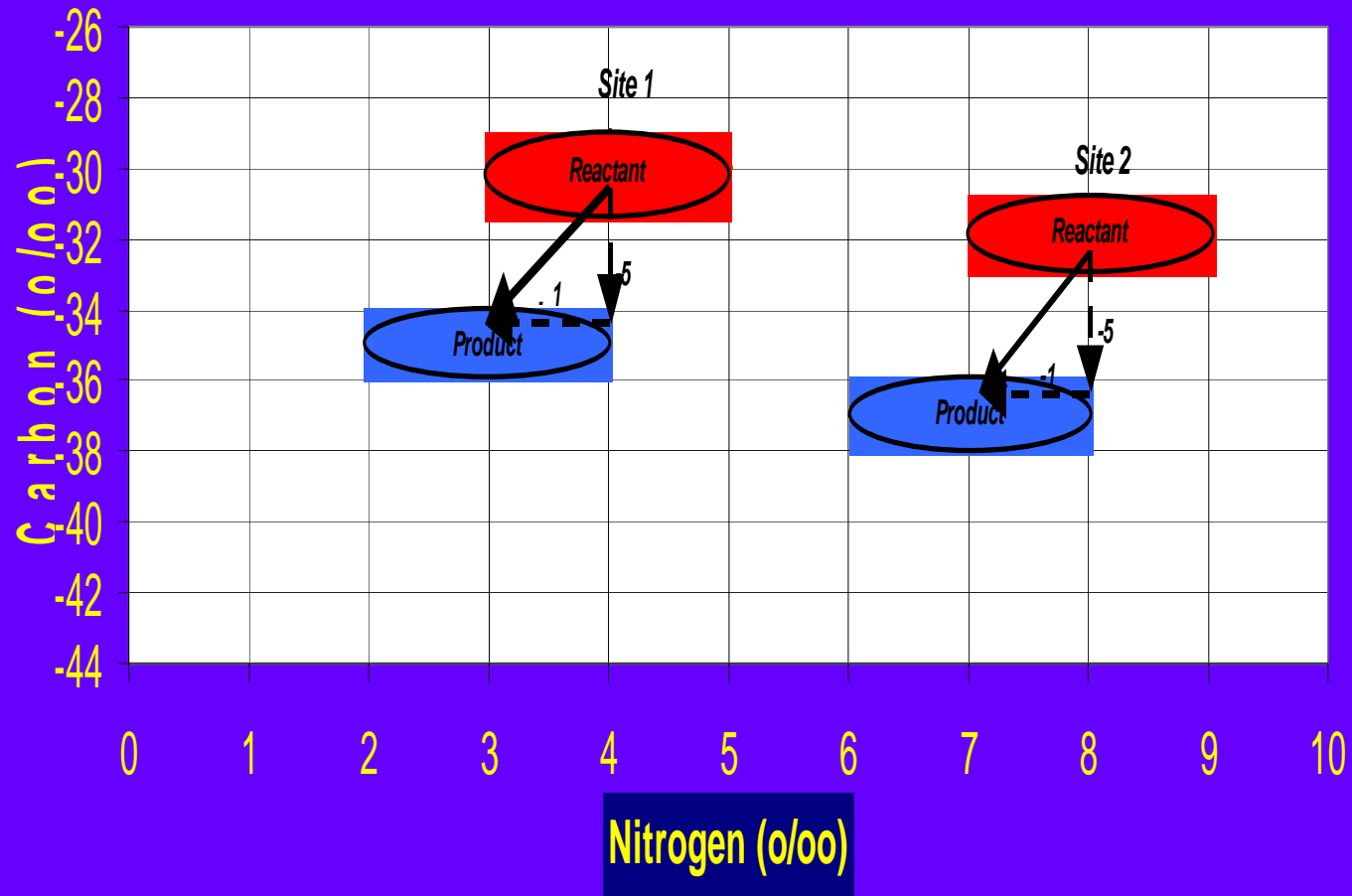
Batch Identification

- Qualification of Raw Materials
- Anticounterfeiting

Process Analytical Chemistry (PAC)

- Uniformity of Manufacturing
- Patent Protection

Product and Process Authentication



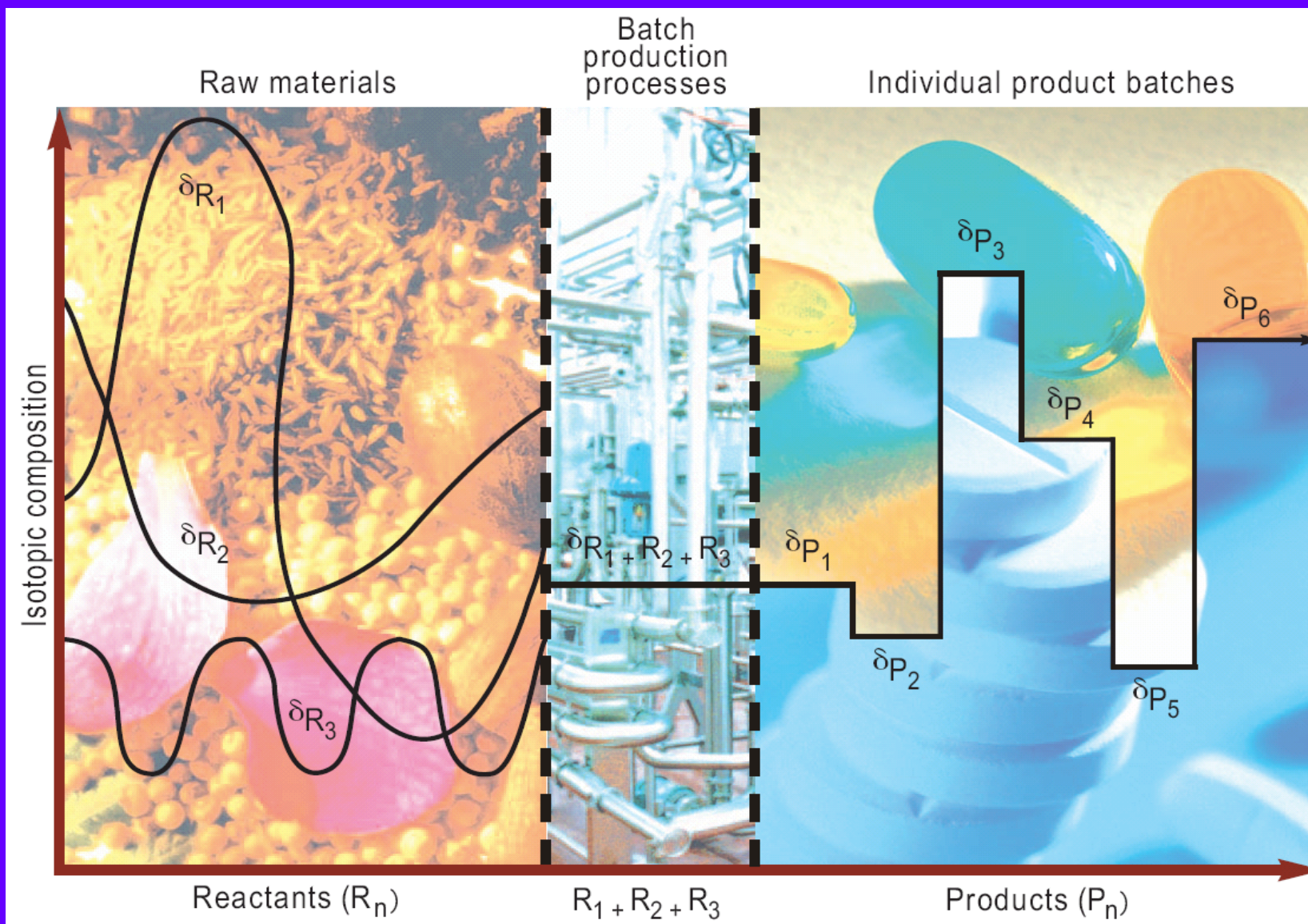
Outline

1. Product Authentication
 - a. *Qualification of Raw Materials*
 - b. *Batch Auditing*

2. Process Authentication
 - a. *Process Understanding*
 - b. *Process Patent Protection (PPP)*

3. PPP Summary Presentation

Product Authentication by Isotopes



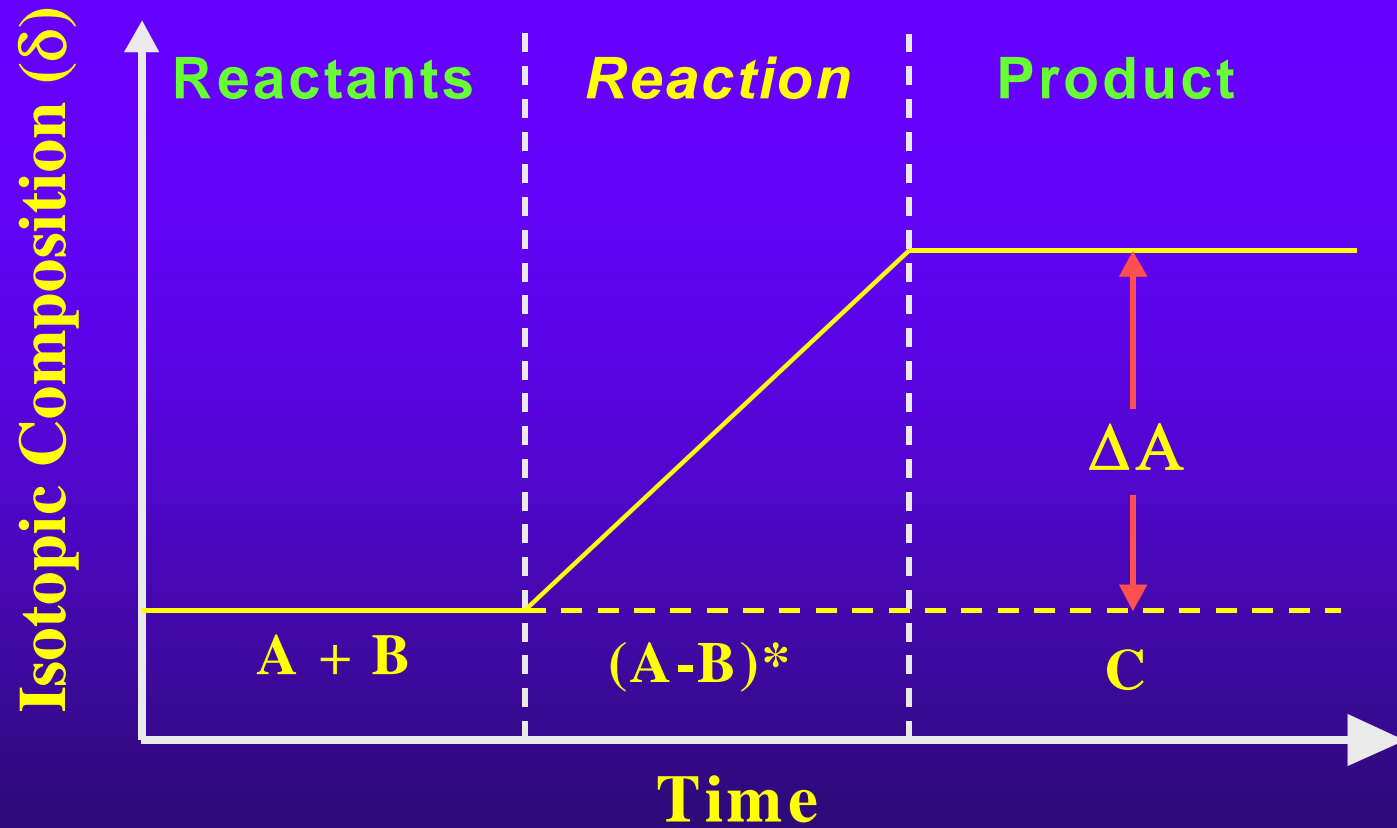
[Jasper, 2004, *Tablets & Capsules* 2(3):37-42]

Isotopic Provenance

= $f(\text{reactants, synthetic process})$



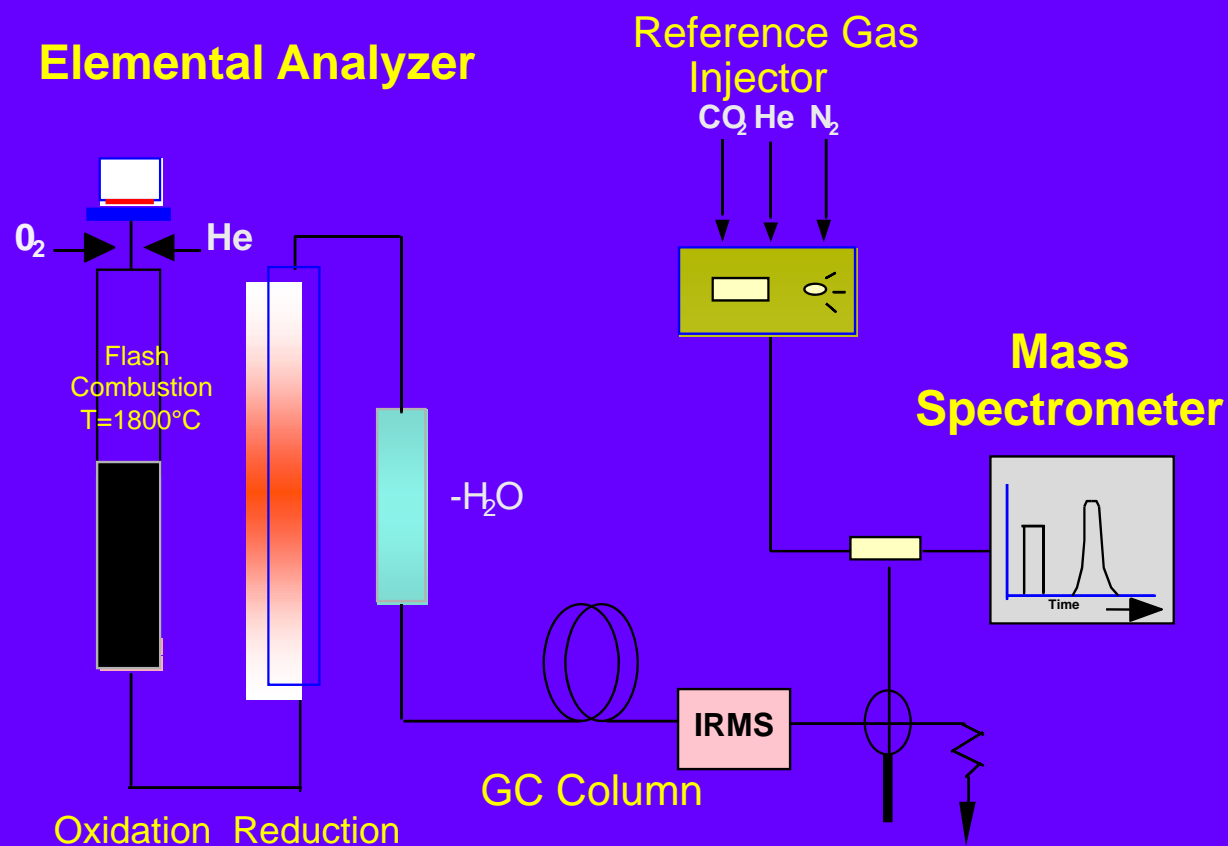
Key Mechanism: Isotope Fractionation



Pharmaceutical Materials

- 1. Active Pharmaceutical Ingredients (APIs)**
- 2. Excipients**
- 3. Drug Products (APIs + Excipients)**

Elemental Analyzer/Mass Spectrometer (EAMS)



Part 1. Product Authentication*

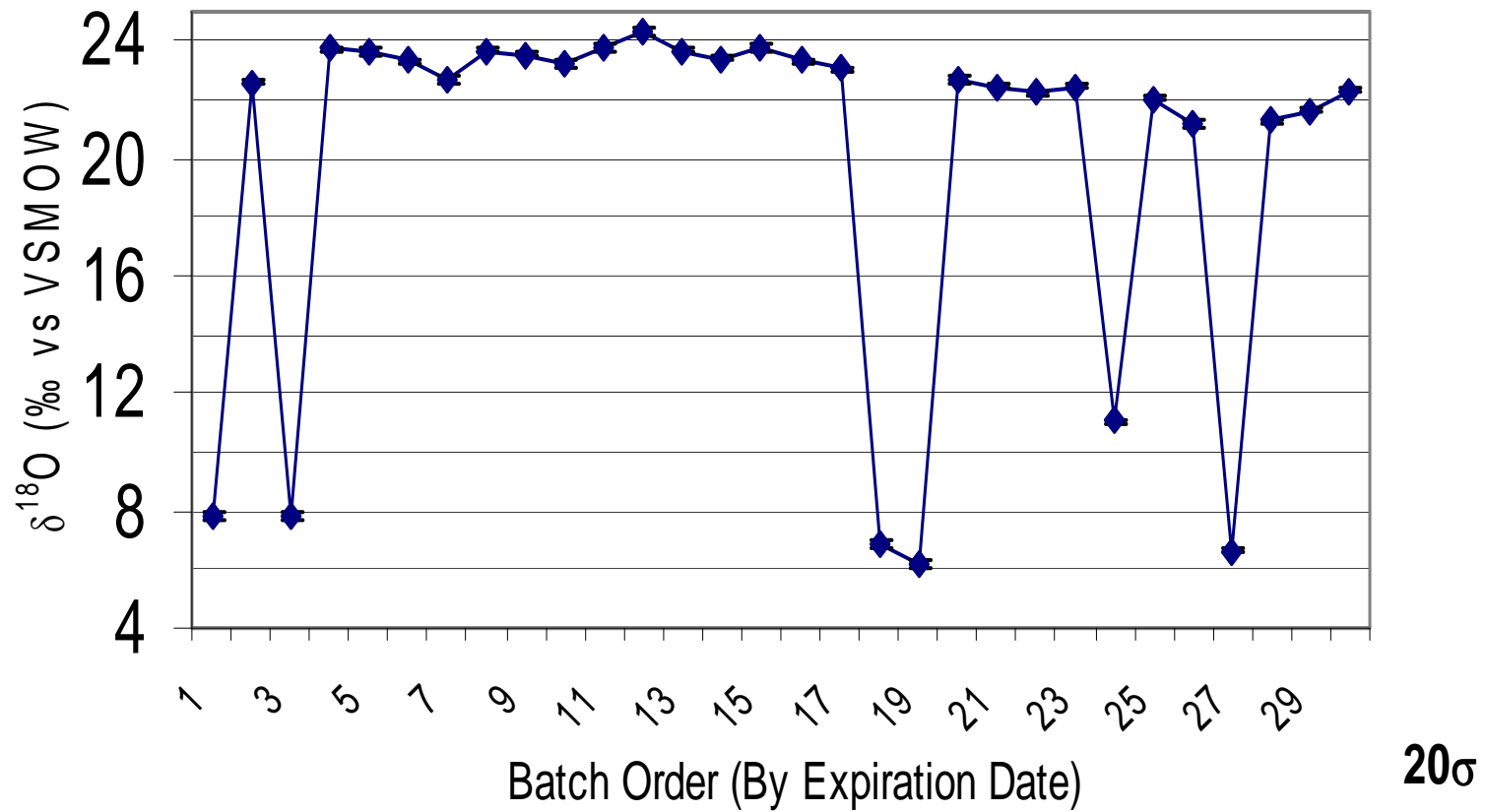
- Batch Processes
- Anticounterfeiting

*US Patent Issued to MIT LLC on Jan. 29, 2008.

1A. OTC Analgesic Drug Products: Batch-to-Batch Variation

- **One Drug Product**
- **One Manufacturer**
 - **Thirty Batches**

$\delta^{18}\text{O}$ Records by Batch Order: Acetaminophen



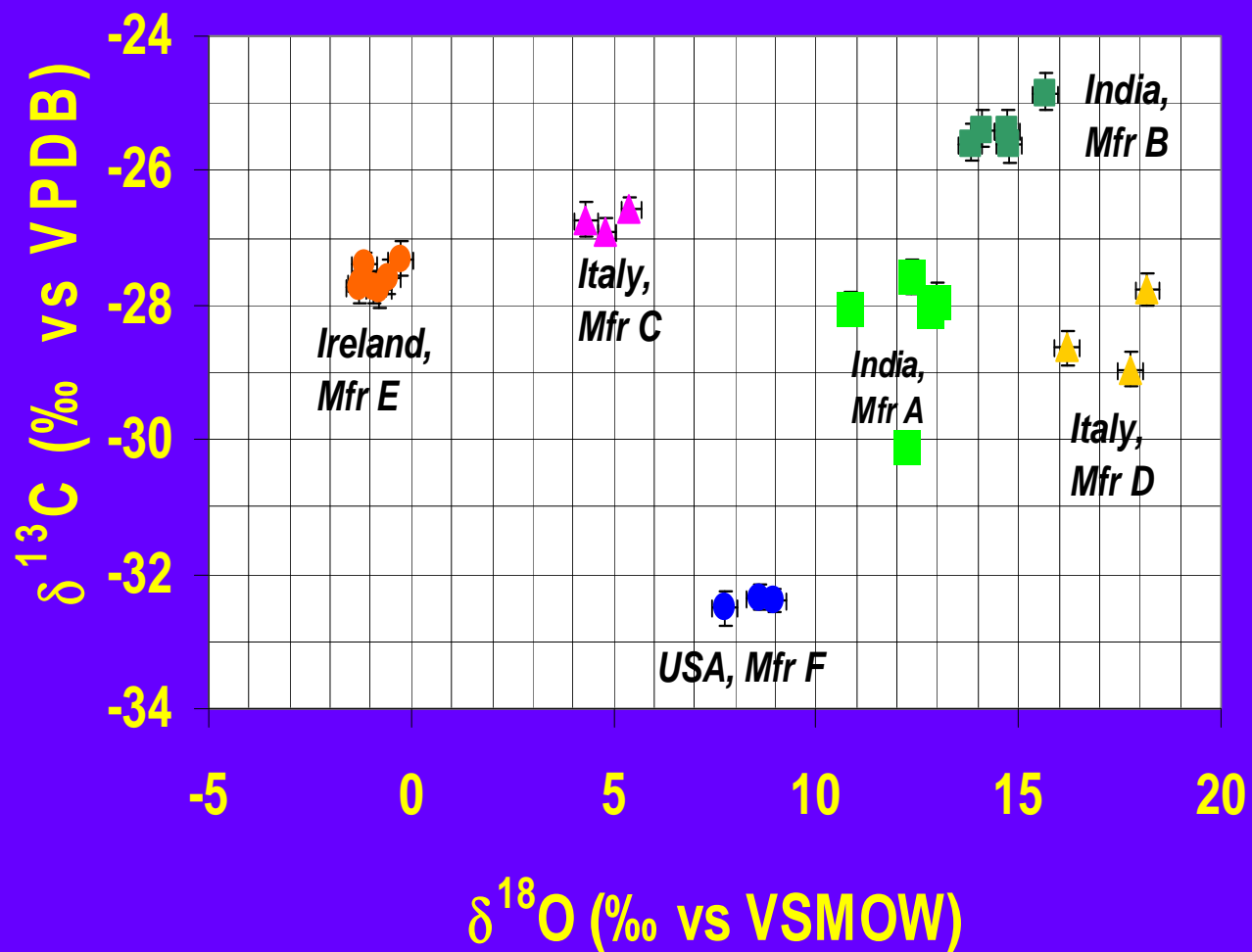
[*Pharm. Tech.* 2004, 28(8):60-67]

1.B.1. APIs:

Differentiating Manufacturers:

- **One API**
- **Six Manufacturers**
- **Four Countries**

Naproxen: $\delta^{13}\text{C}$ vs. $\delta^{18}\text{O}$



(Wokovich et al., 2004, *JPBA* 38:781-784)

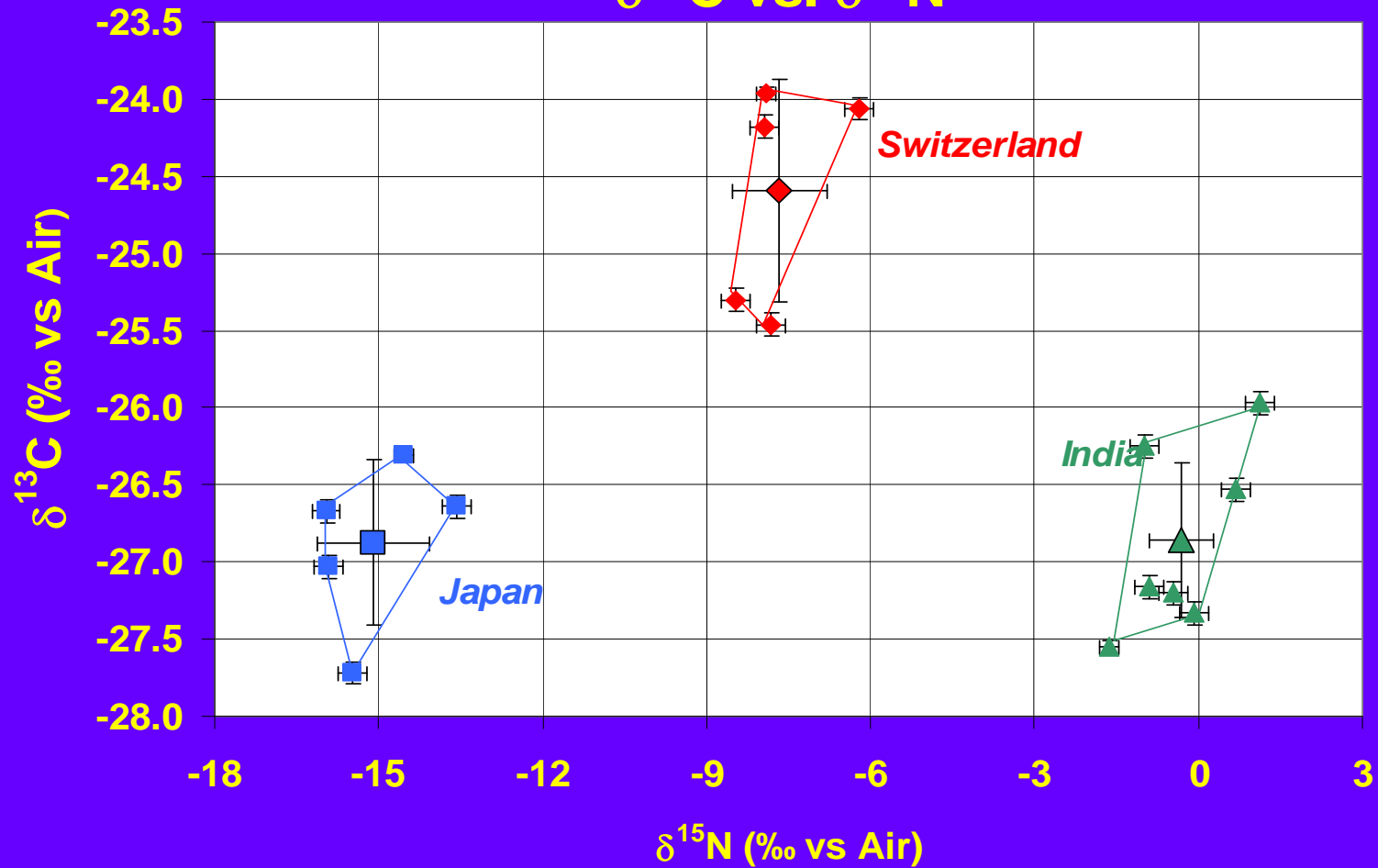
1.B.2 APIs:

Differentiating Manufacturers:

- **One API**
- **Three Manufacturers**
- **Three Countries**

Folic Acid From 3 Pharmaceutical Companies:

$\delta^{13}\text{C}$ vs. $\delta^{15}\text{N}$



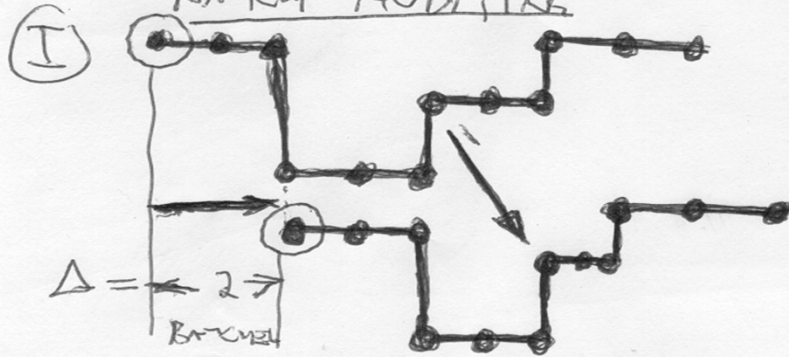
1.C. Batch Auditing / Batch Smearing

- Batches Shifted
- Batches Mixed

BATCH AUDITING // BATCH SMEARING

PARK HYATT HOTELS®

(BA/BS)

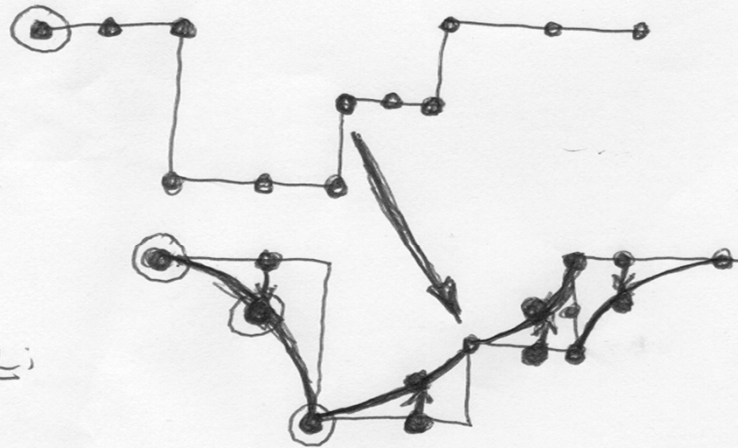


~~BATCH AUDITING~~

SHIFTED BY 2 BATCHES

(II) BATCH ~~SMOOTHING~~ SMEARING

IDEAL:



ACTUAL:

30% CARRY OVER OF
STARTING MATERIALS
TO NEXT BATCH'S
EXPONENTIAL SMEAR

(JPJ: 7/25/07)

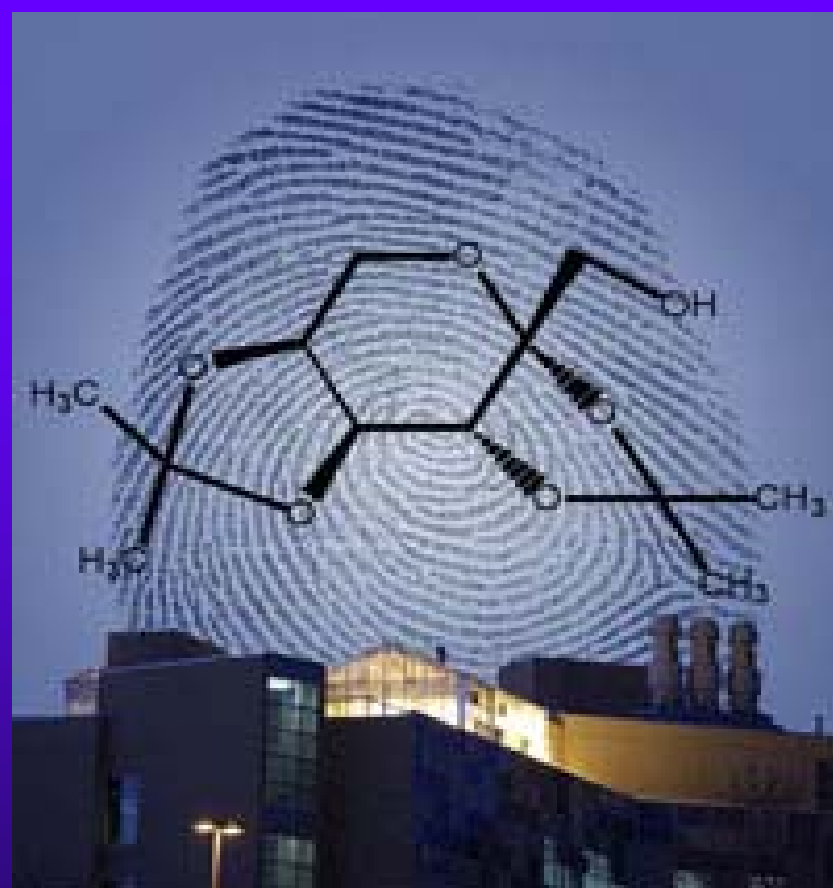
Part 2. Process Understanding*:

- *PAC*

- *Process Patent Protection*

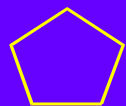
*US Patent Pending to MIT LLC.

“Characterizing Synthetic Pathways By Stable-Isotopic Measurements”

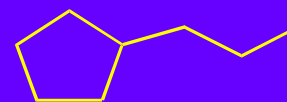
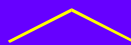


(Jasper, Weaner, & Hayes,
Pharm. Tech., March, 2007)

Complete Record of Stable-Isotopic Synthesis



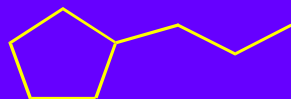
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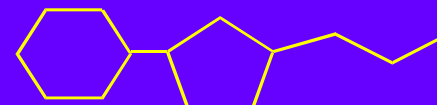
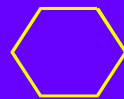
A: -30.0‰, 0.25, -10‰

B: -15‰, 0.05, -30‰

C: -25.5‰, [-24.4‰]



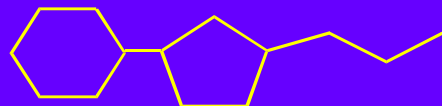
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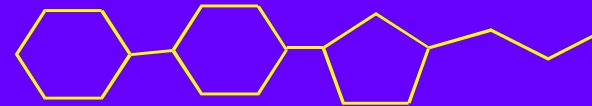
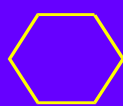
C: -25.5, 0.50, -30‰

D: -10‰, 0.05, -30‰

E: -20.4‰, [-18.2‰]



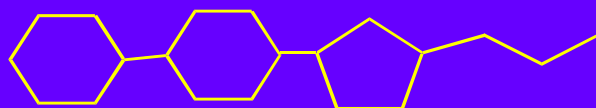
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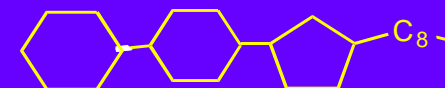
E: -20.4‰, 0.10, -15‰

F: -15‰, 0.30, -5‰

G: -19.1‰, [-17.2‰]



+

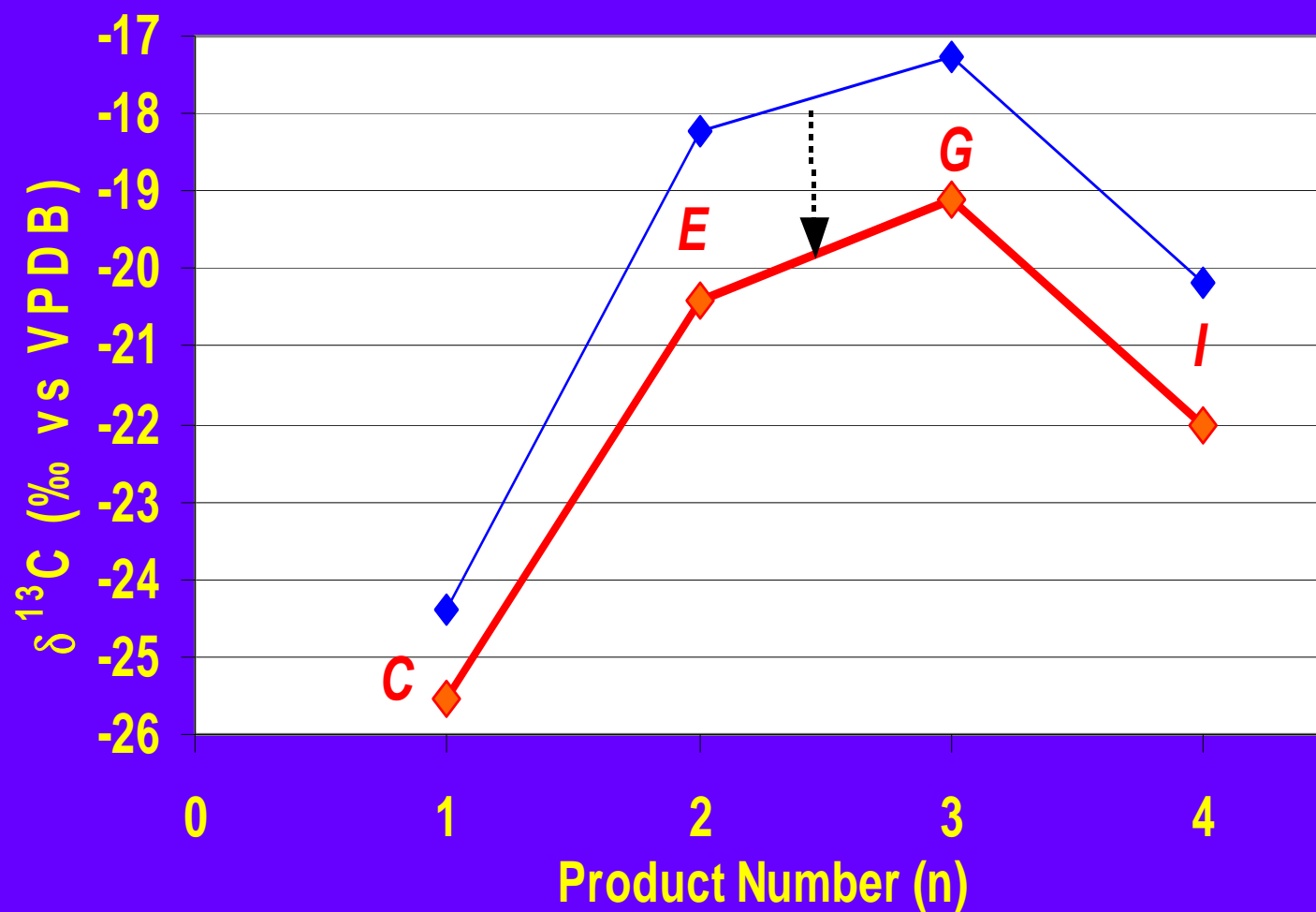


G: -19.1‰, 0.20, -15‰

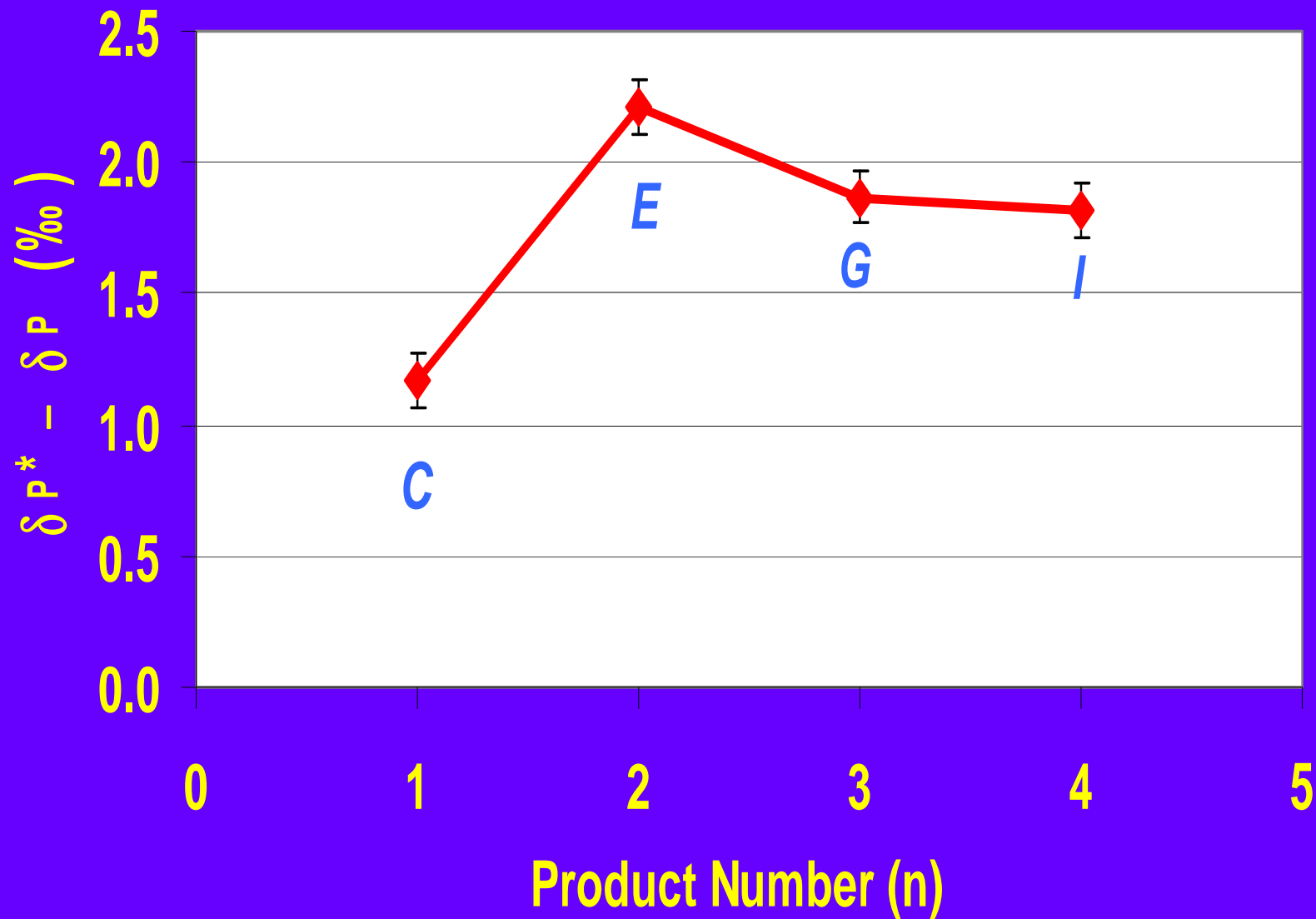
H: -30.0‰, 0.10, -15‰

I: -22.0‰, [-20.2]

Isotopic Records of Products With and Without Isotopic Fractionation



Isotopic Differences Caused by Fractionation



Carbon-Isotopic Fingerprints of Three Synthetic Pathways

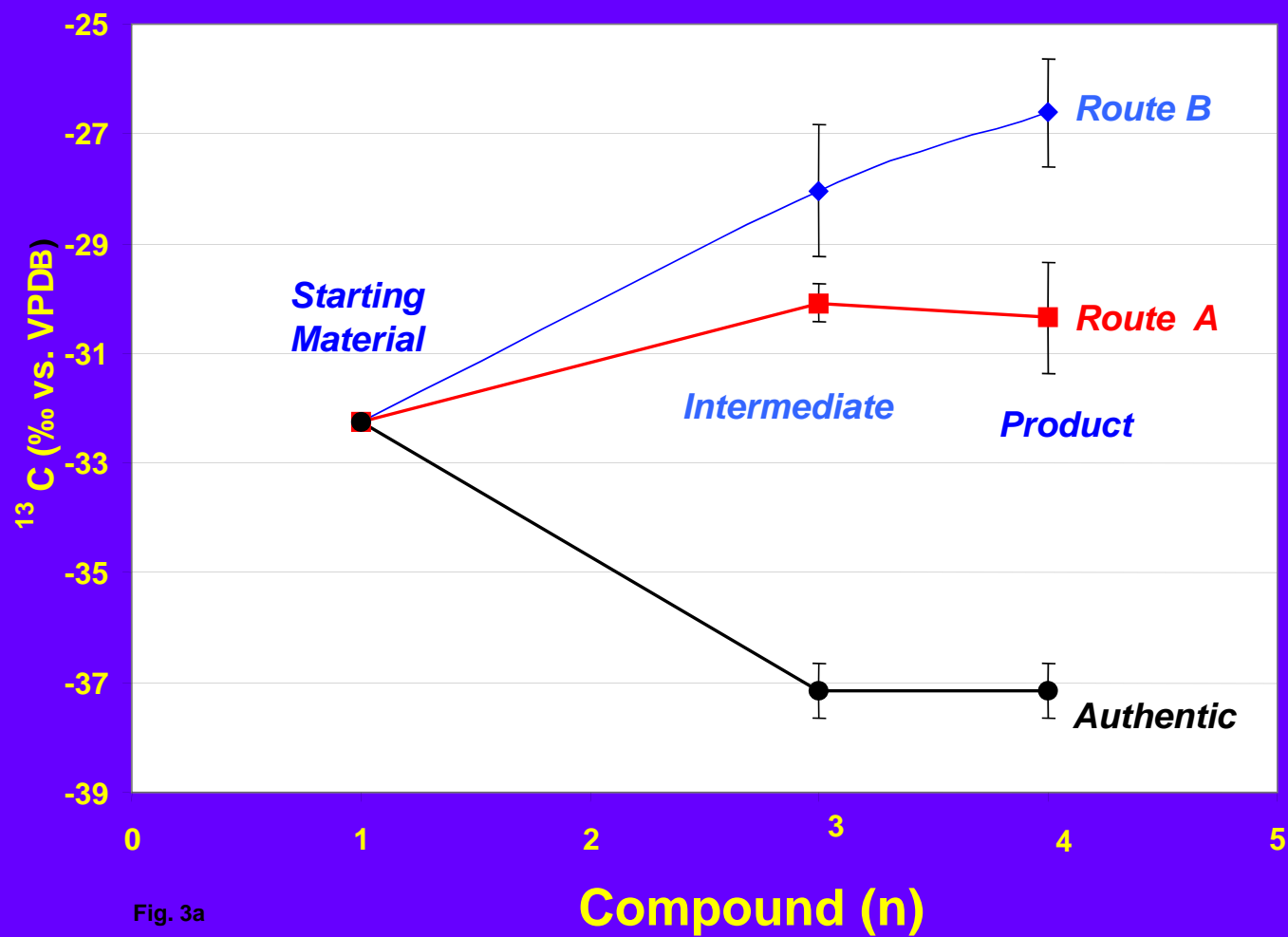
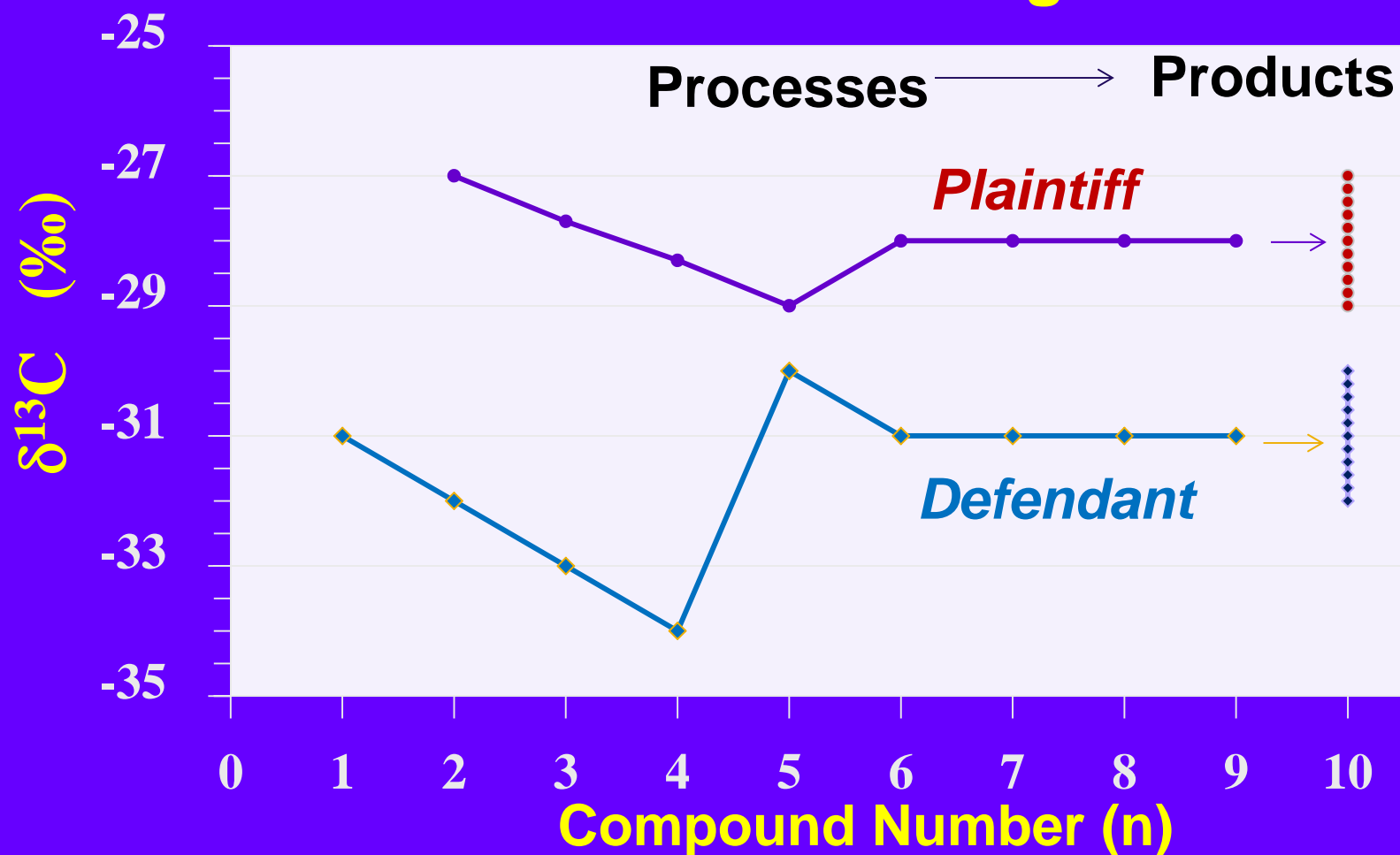


Fig. 3a

Process Patent Protection

Schematized Patent Infringement Case



The Isotopic Record of Pharmaceutical Synthesis

-----Precursors -----

Starting Materials

Synthetic Intermediates

Product



Int./Products

 δ_C
 δ_E
 δ_G

Precursors

 δ_A, δ_B
 δ_C, δ_D
 δ_E, δ_F

Fraxn Rmng.

 f_A, f_B
 f_C, f_D
 f_E, f_F

Isotopic Frxtn.

 ε_C
 ε_E
 ε_F

Three Levels of Understanding

1. **Isotope Mass Balance.**
2. **Isotope Mass Balance with 1 Excess Component.**
3. **Isotope Mass Balance with 2 Excess Components.**

The Basic Format: Isotope Mass Balance

Excess
Components

$$0: \quad m_A \delta_A + m_B \delta_B = m_C \delta_C$$

$$1: \quad m_A (\delta_A - \Delta_A) + m_B \delta_B = m_C \delta_C$$

$$2: \quad m_A (\delta_A - \Delta_A) + m_B (\delta_B - \Delta_B) = m_C \delta_C$$

Overall...

- Isotopic compositions are controlled by reactants and processes.
- Variations from mass balance are due to isotope effects of specific processes.

Part 3.

Summary of Process Fingerprinting via Stable Isotopes

Product Fingerprint for Authentic API:
Manufacturing Site 1

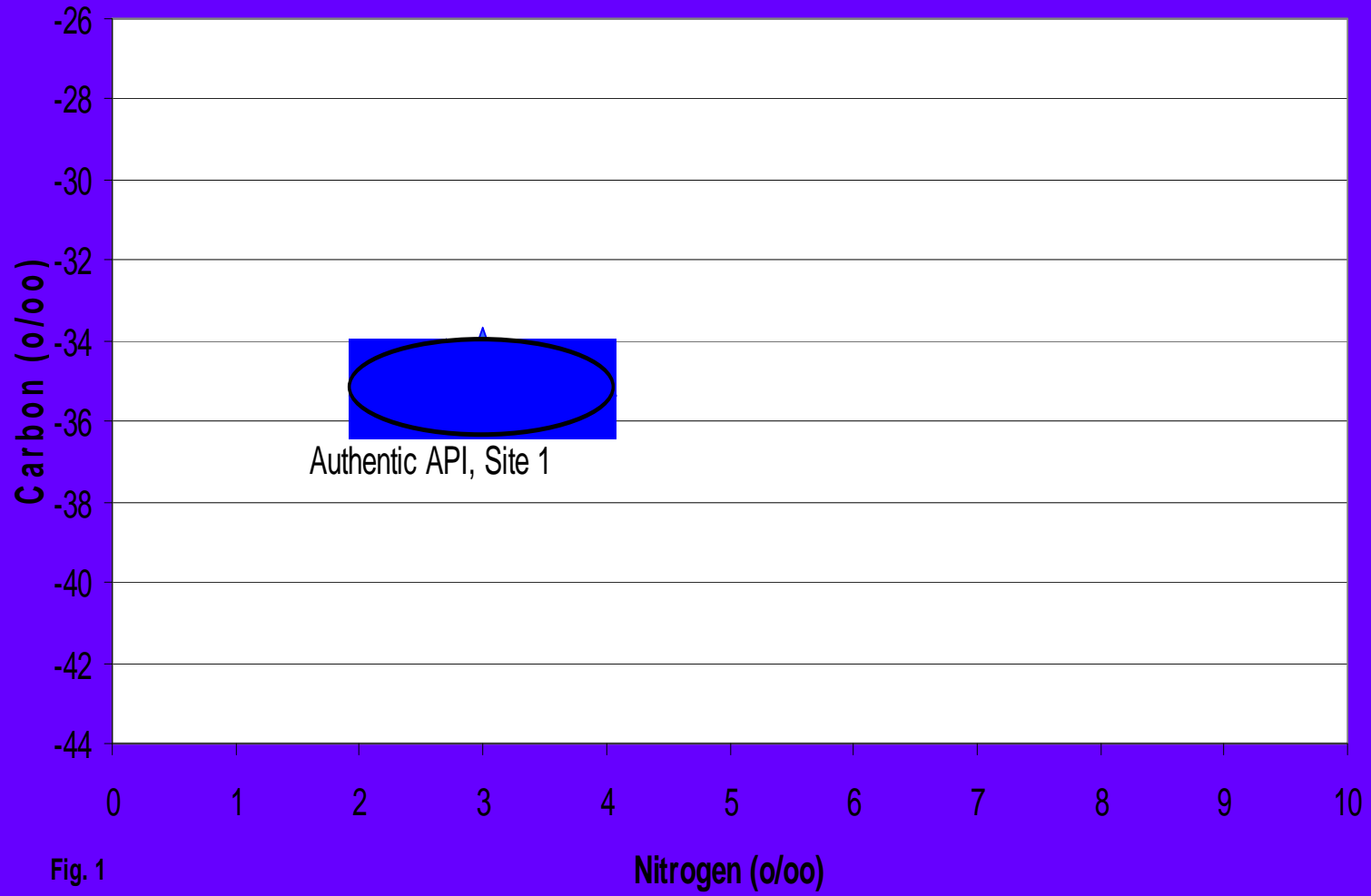


Fig. 1

**Starting Material and Authentic API:
Overall Reaction (5 Steps Not Shown Here)**

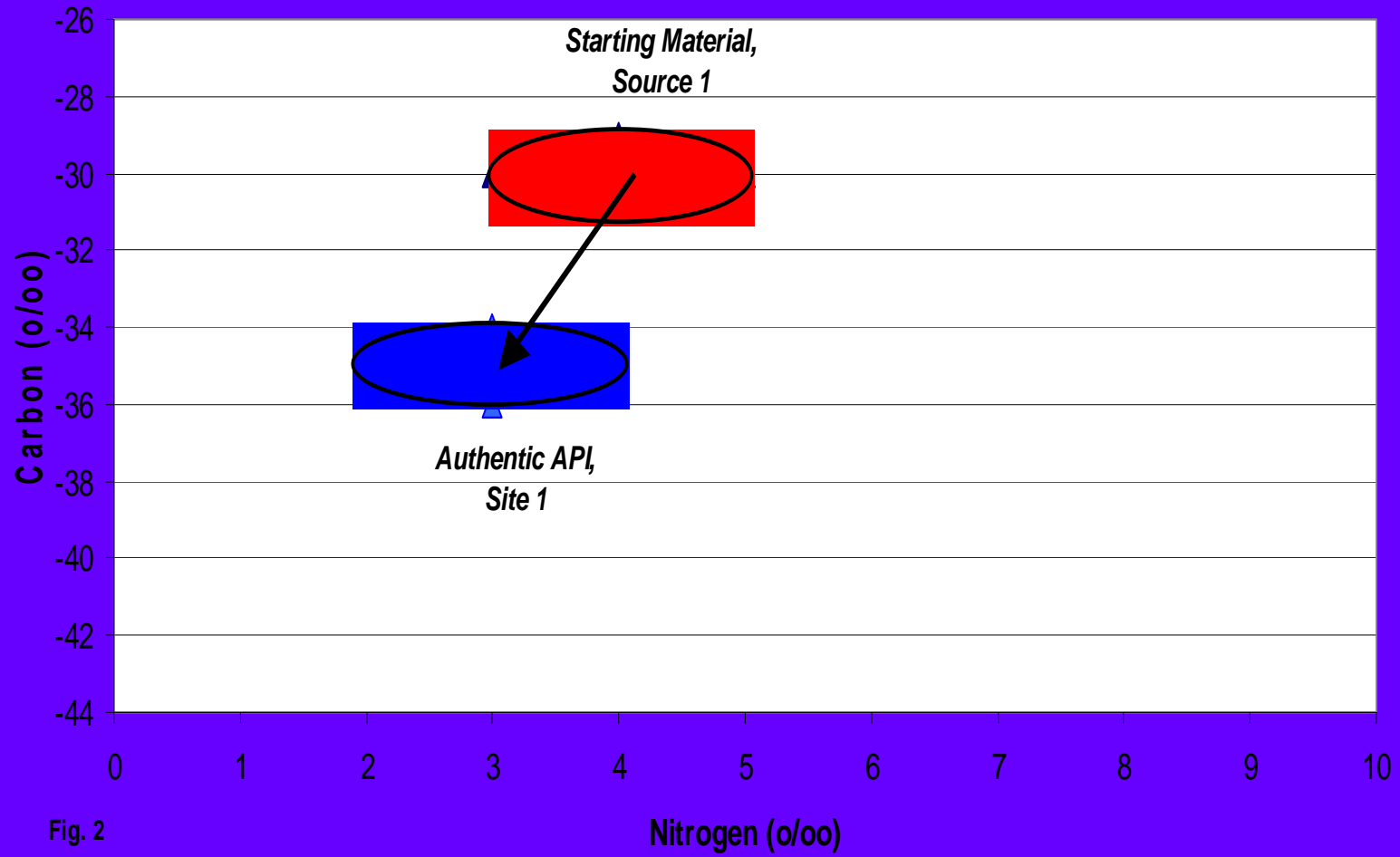
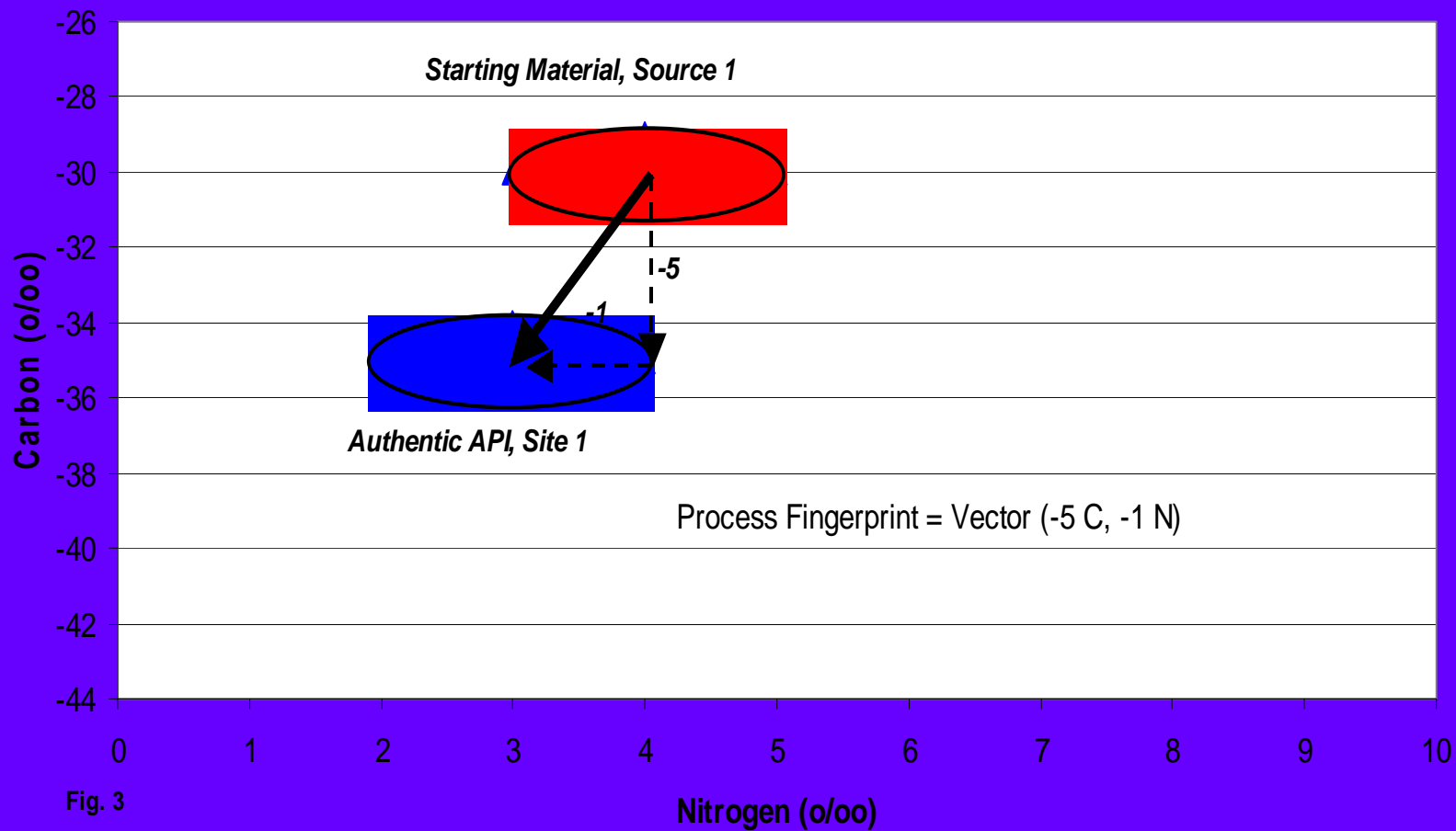


Fig. 2

Process Fingerprint: Isotopic Pedigree^R for Authentic API



**Product Fingerprint for Authentic API:
Manufacturing Site 2**

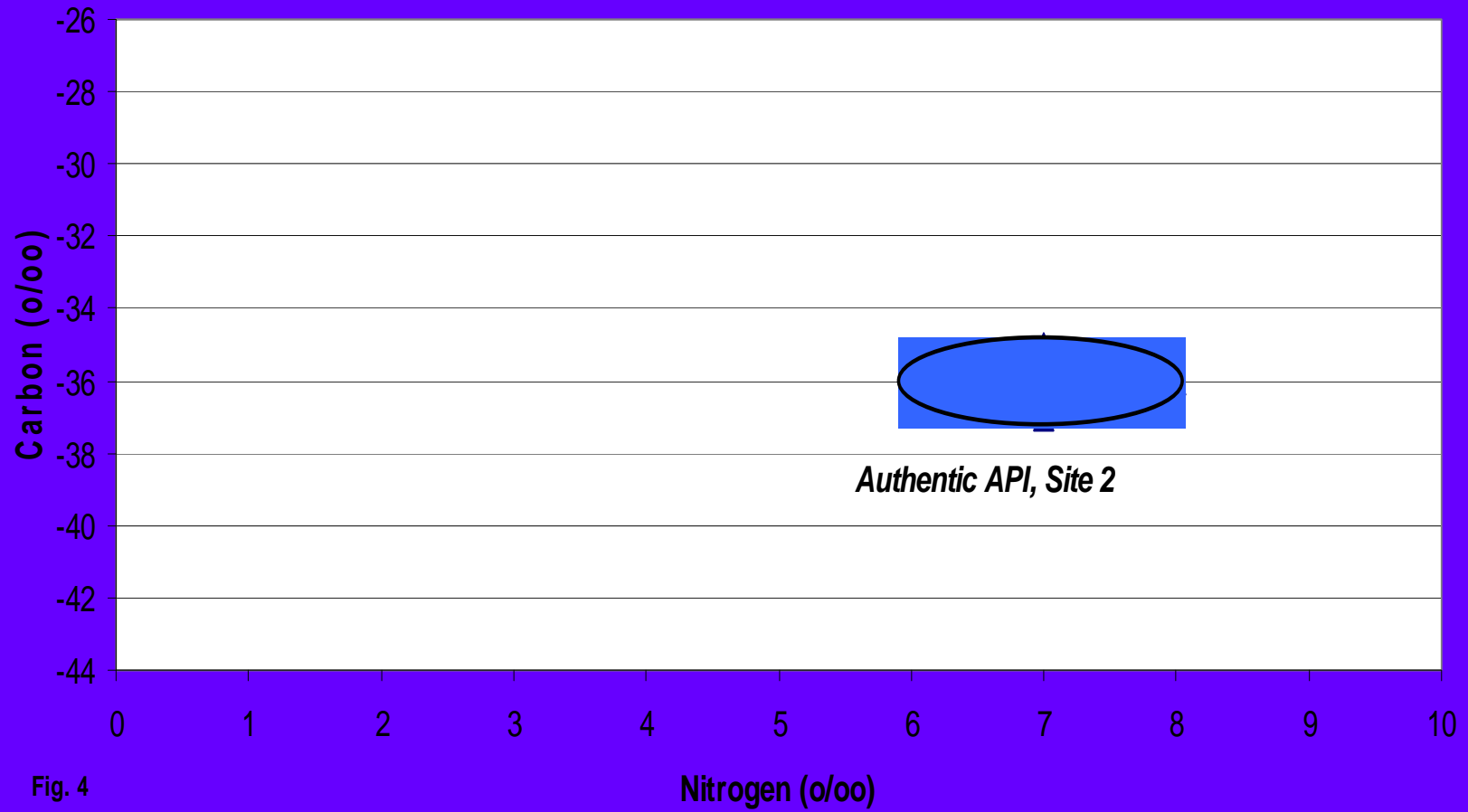


Fig. 4

**Starting Material and Authentic Product:
Manufacturing Site 2**

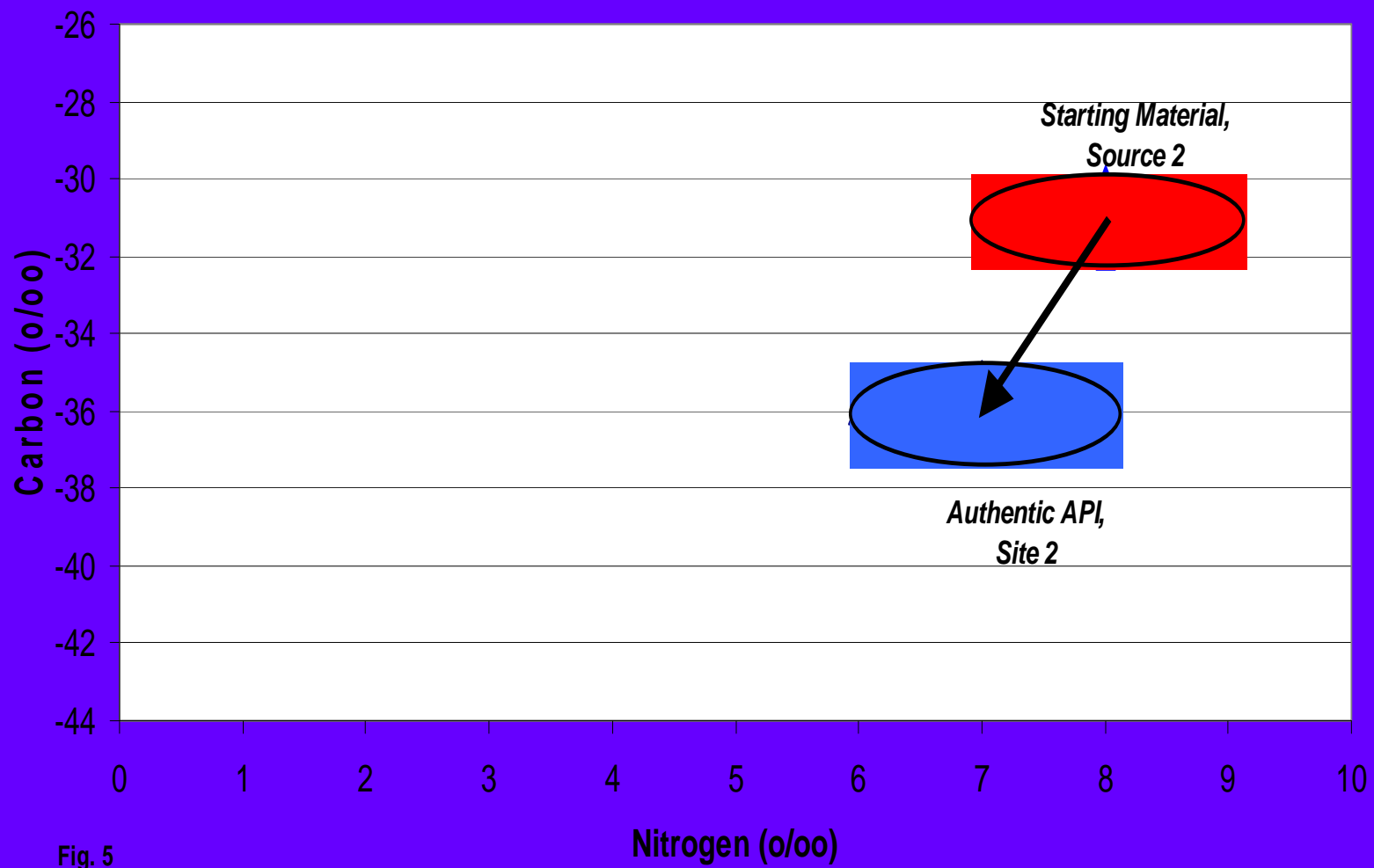


Fig. 5

Process Fingerprint: Same Isotopic Pedigree^R
Generated at Two Sites

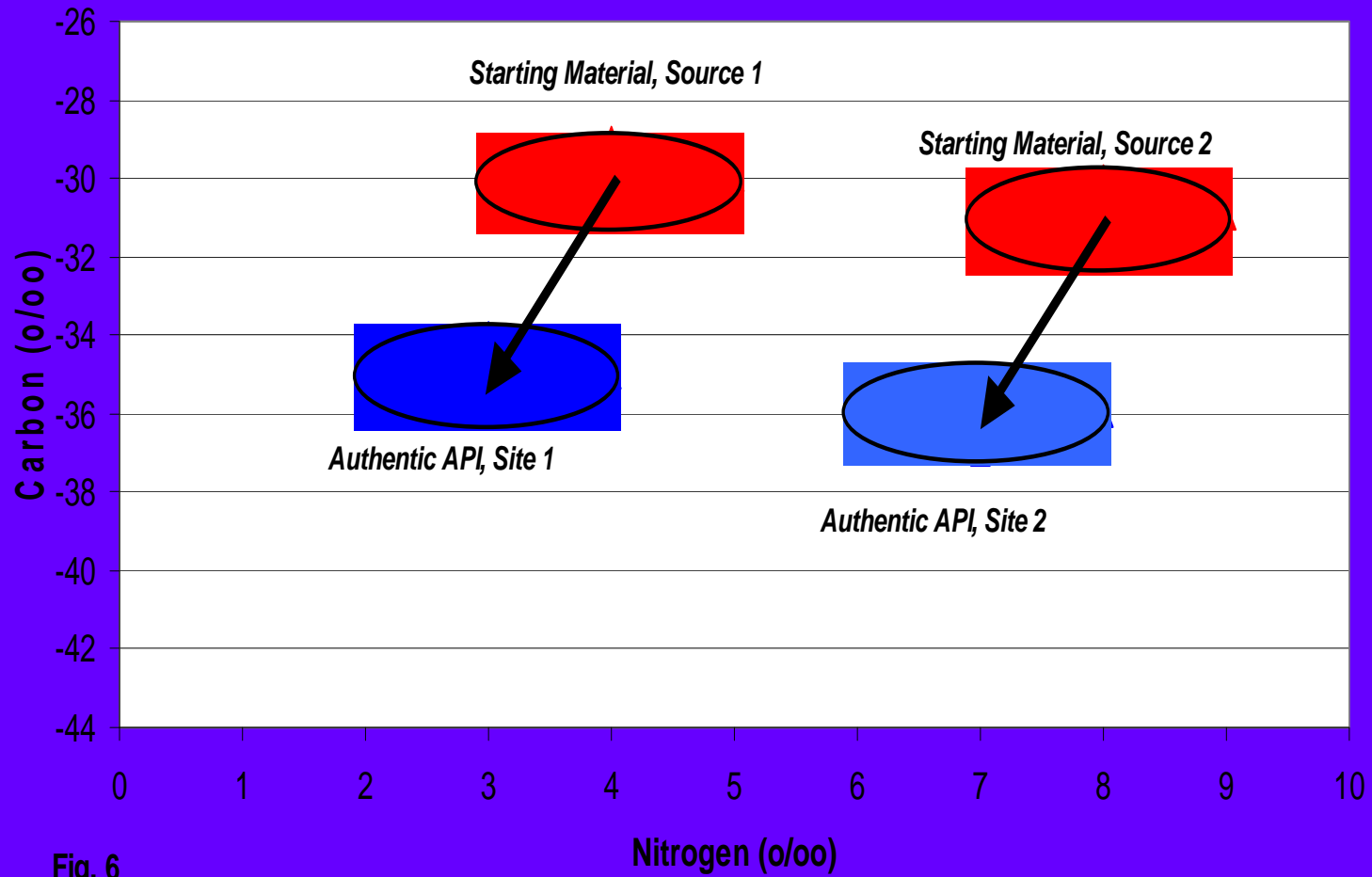


Fig. 6

Alternative Manufacturing Process: Non-Infringing

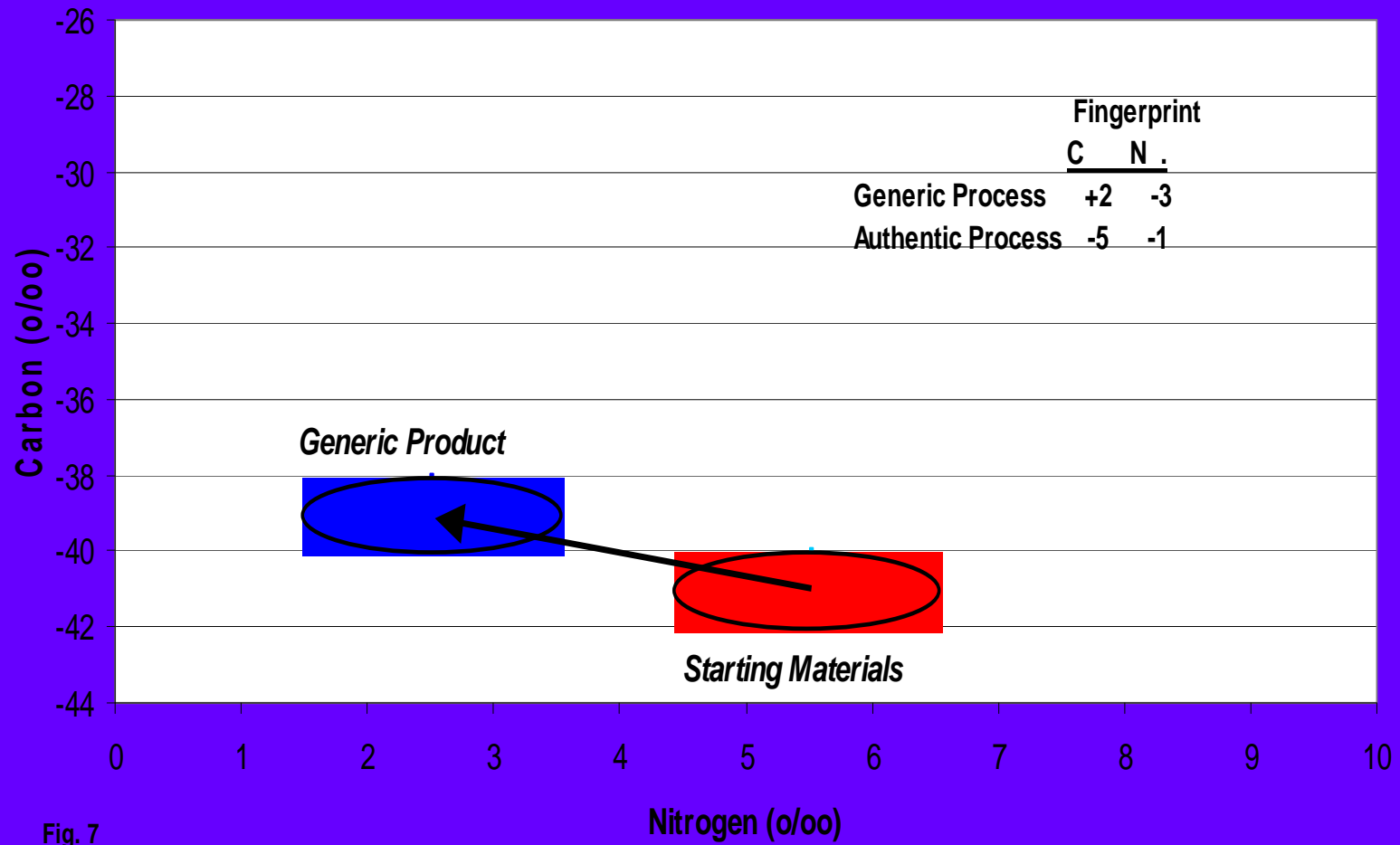


Fig. 7

**Alternative Manufacturing Process:
Non-Infringing**

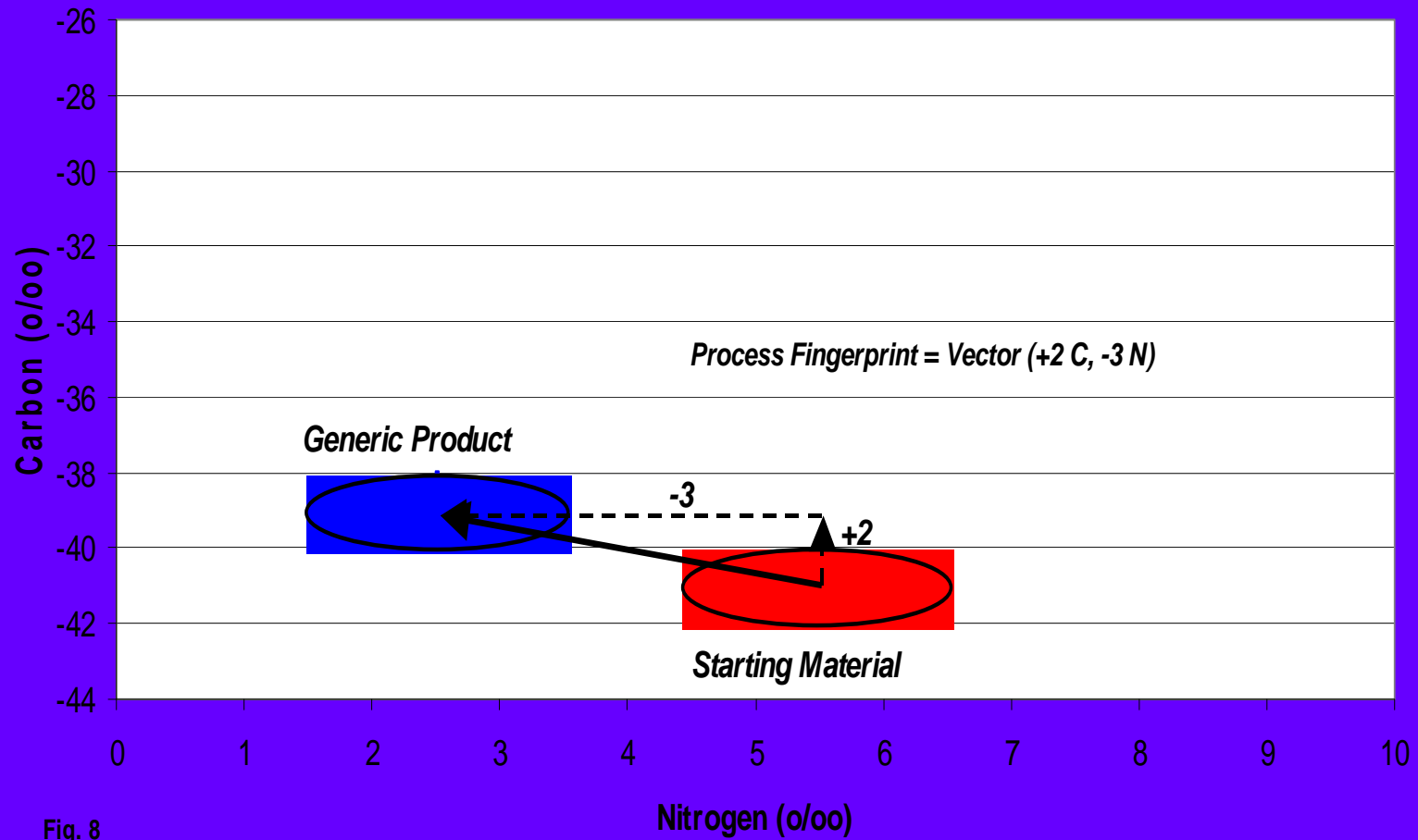


Fig. 8

Alternative Manufacturing Process:
Non-Infringing

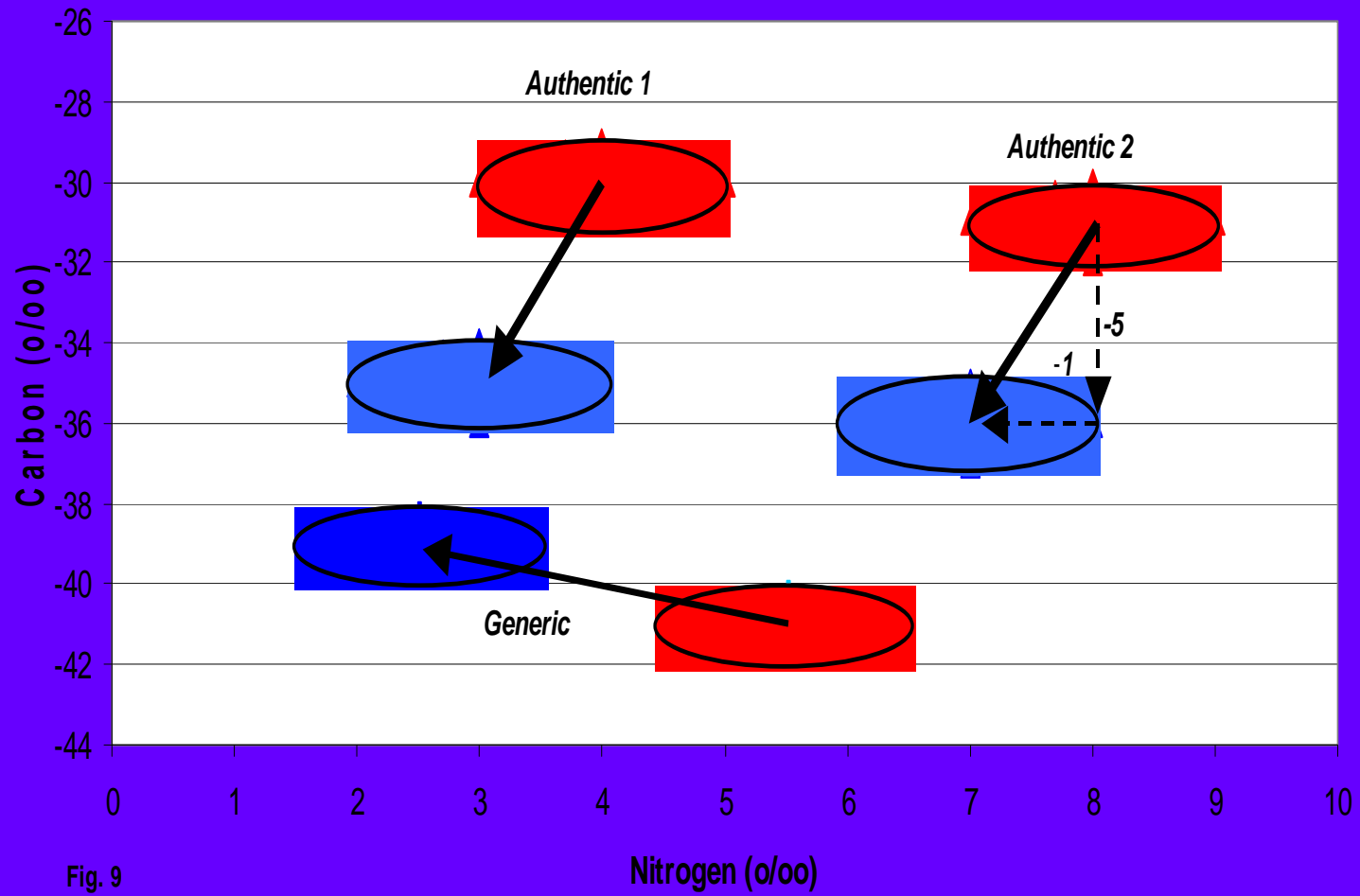


Fig. 9

Generic Sample Likely Infringing Authentic Process

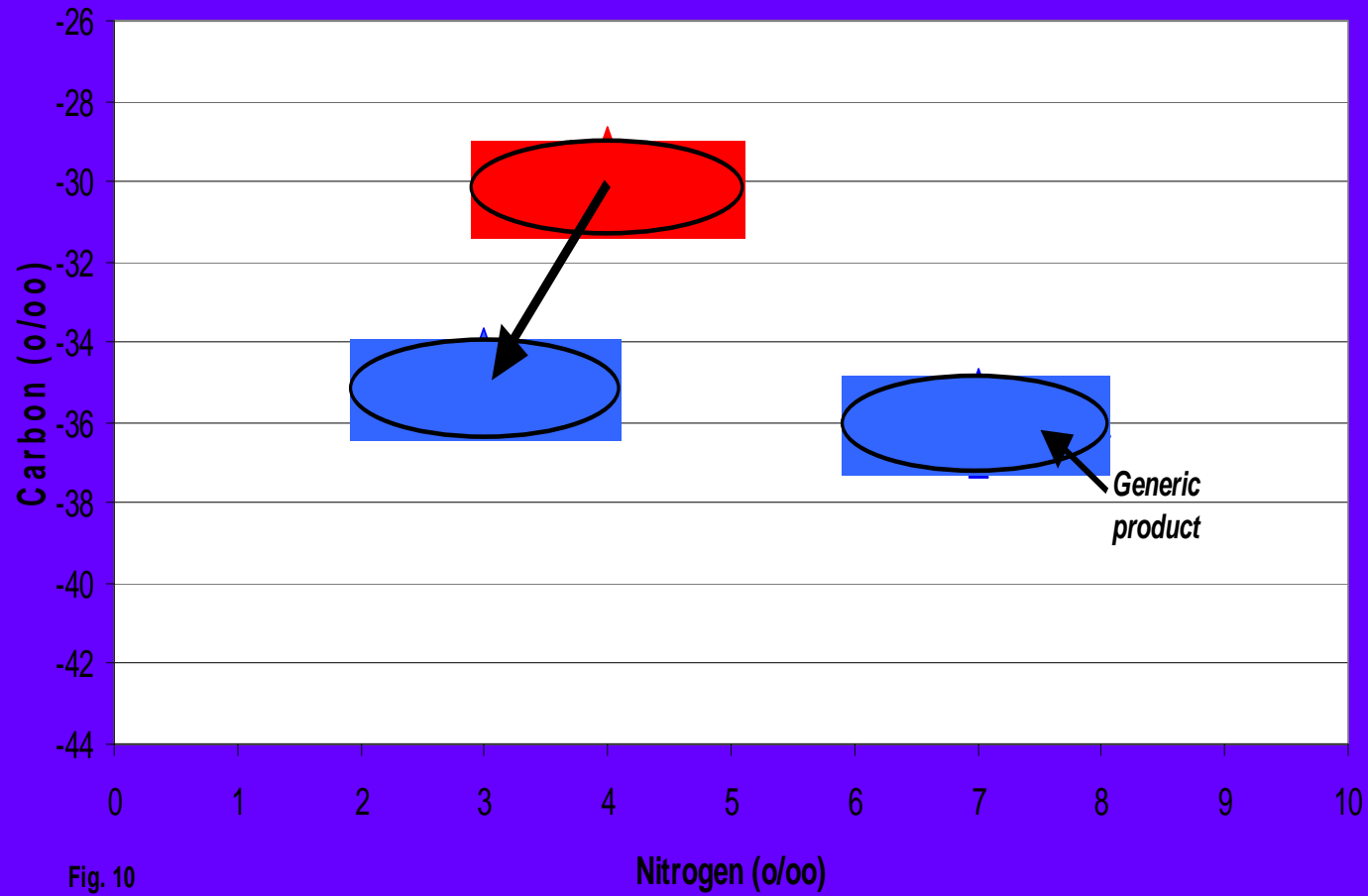


Fig. 10

Generic Sample Likely Infringing Authentic Process

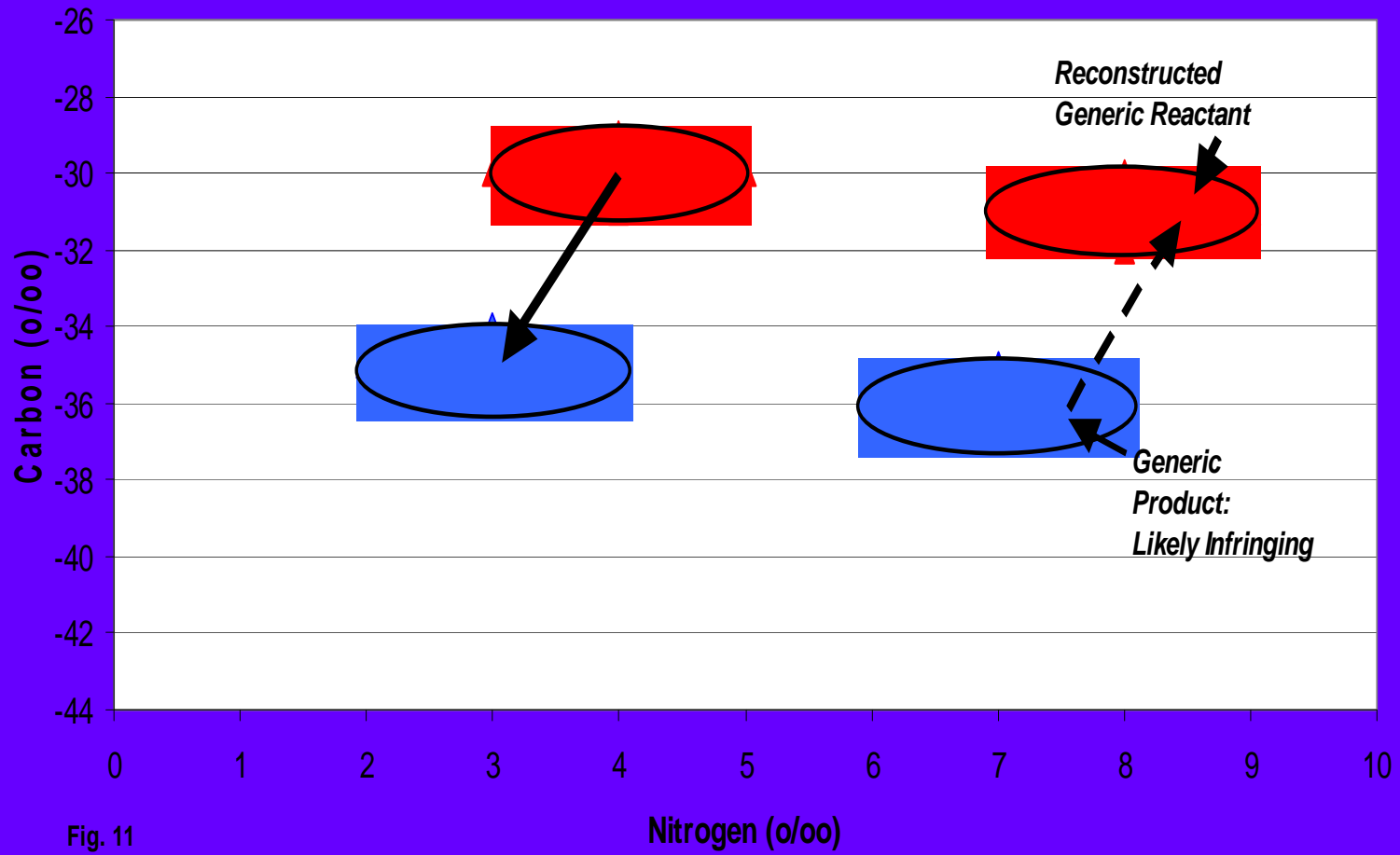


Fig. 11

Generic Sample Infringing Authentic Process

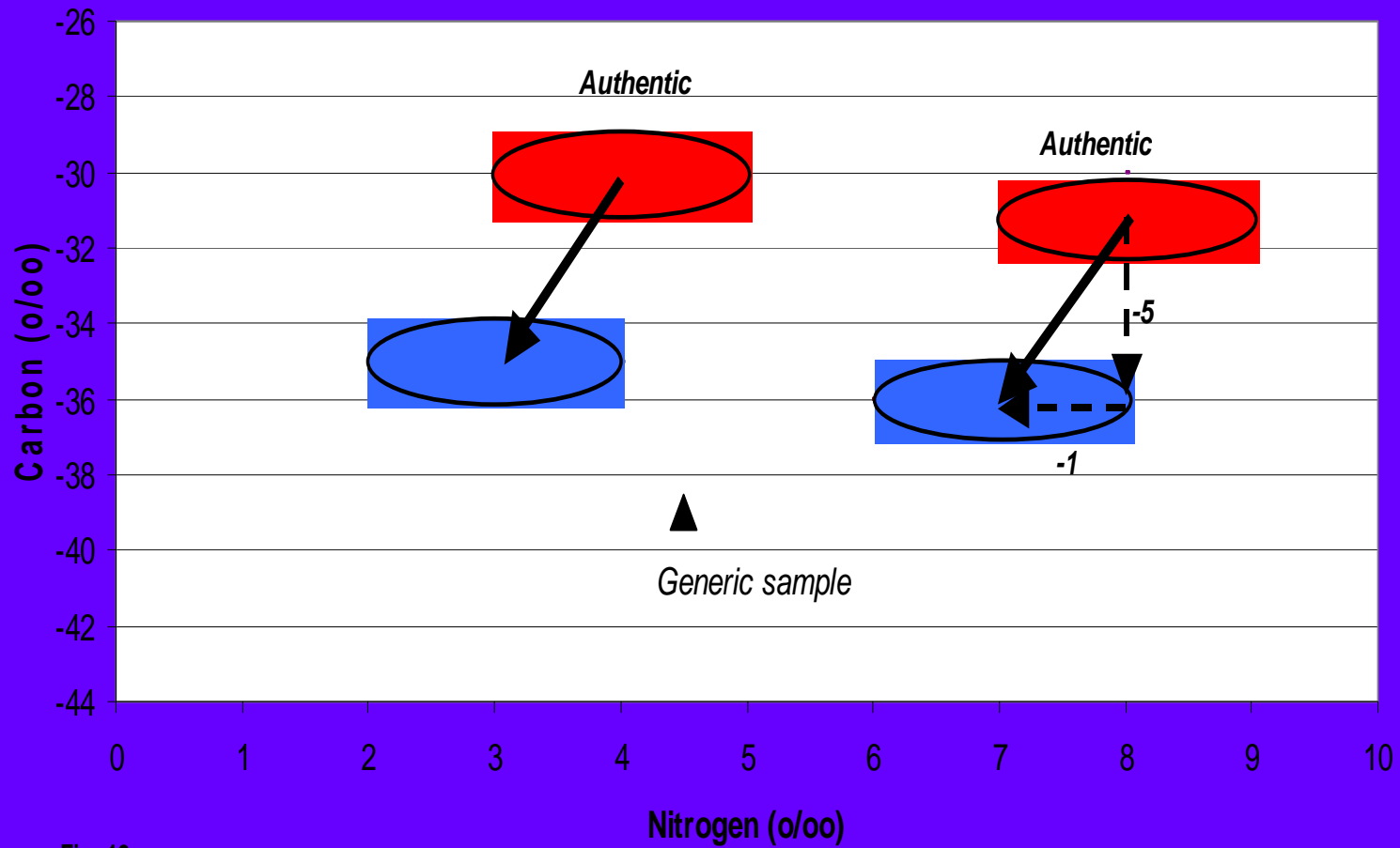


Fig. 12

Generic Sample Infringing Authentic Process

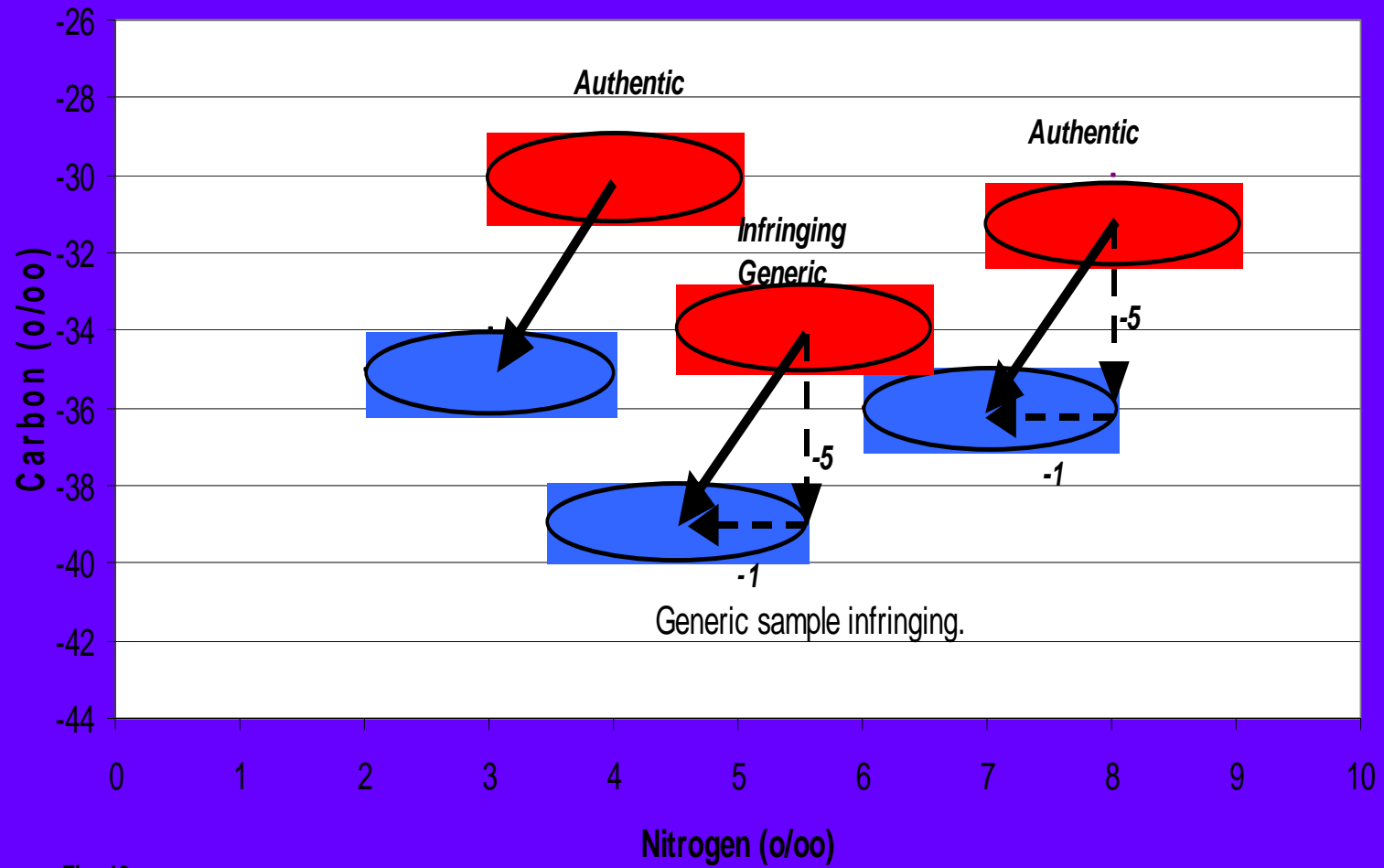


Fig. 13

Generic Sample Infringing Authentic Process

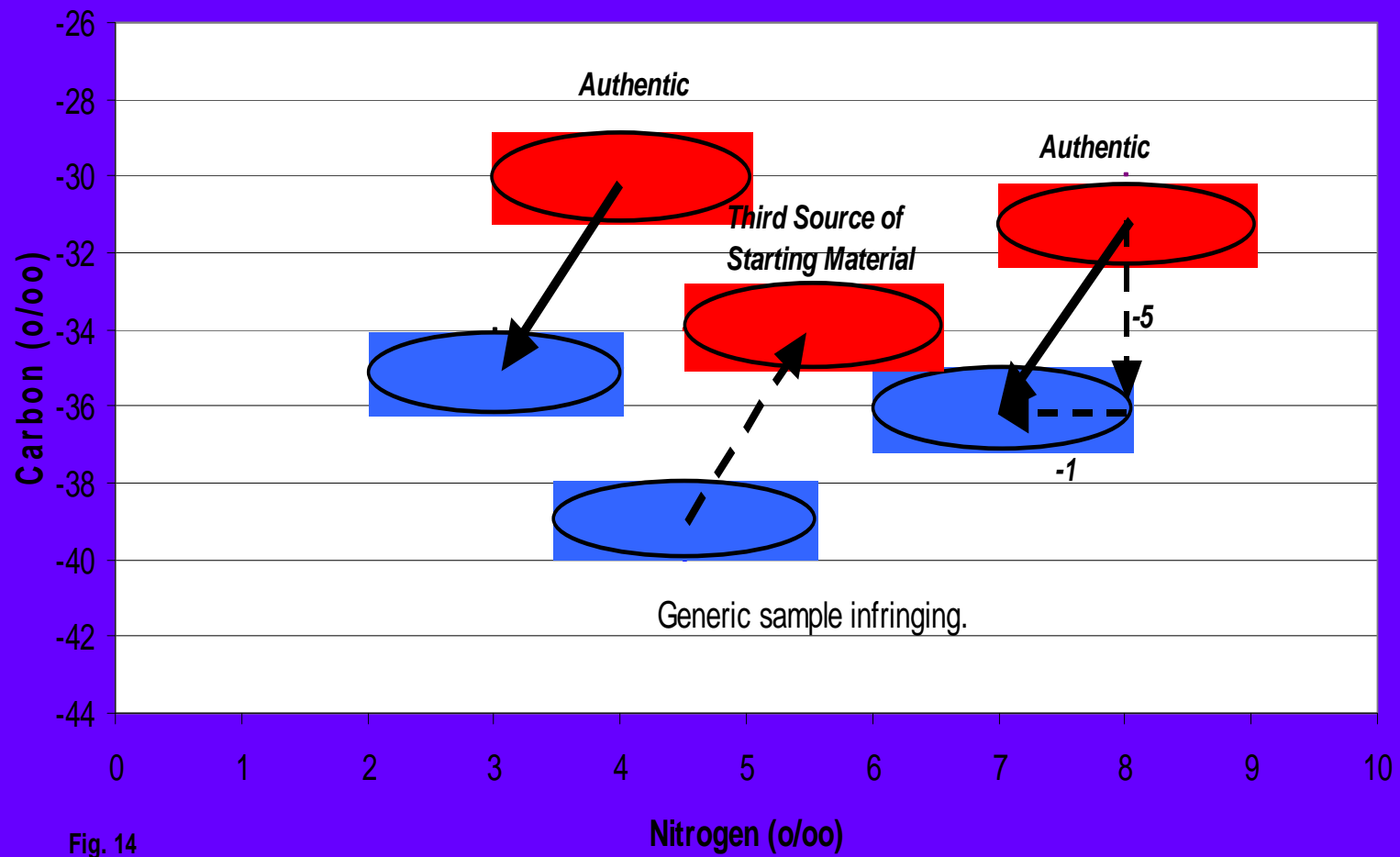


Fig. 14

Summary:

Major Applications for Pharmaceutical Isotope Analysis

1. Product Authentication

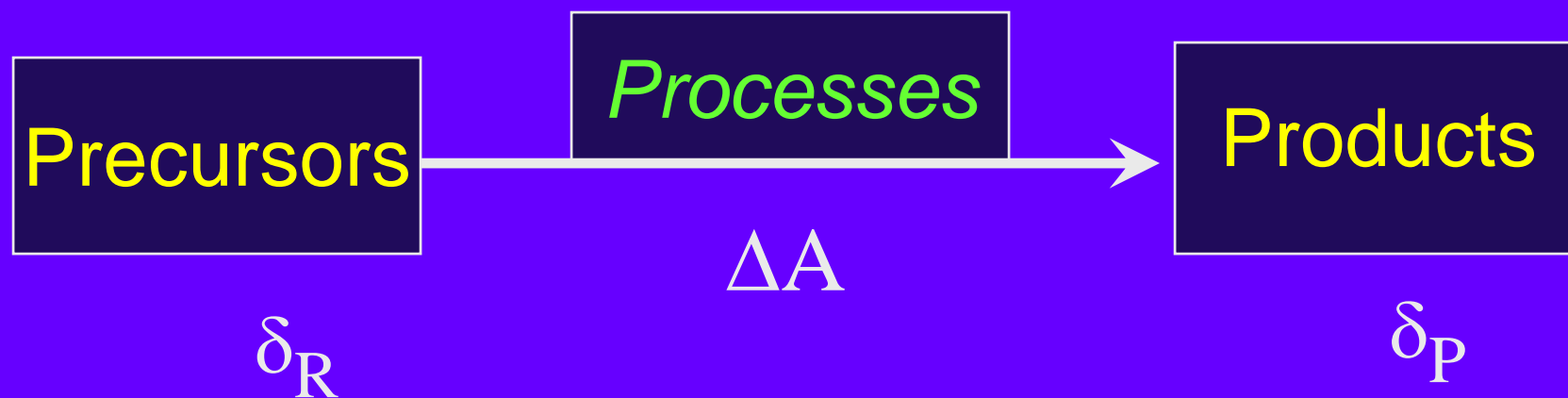
- a. Qualification of Raw Materials*
- b. Batch Auditing*

2. Process Authentication

- a. Process Understanding*
- b. Process Patent Protection (PPP)*



Isotopic Processes and Products



- Product Identification
- Process Consistency and Patent Protection



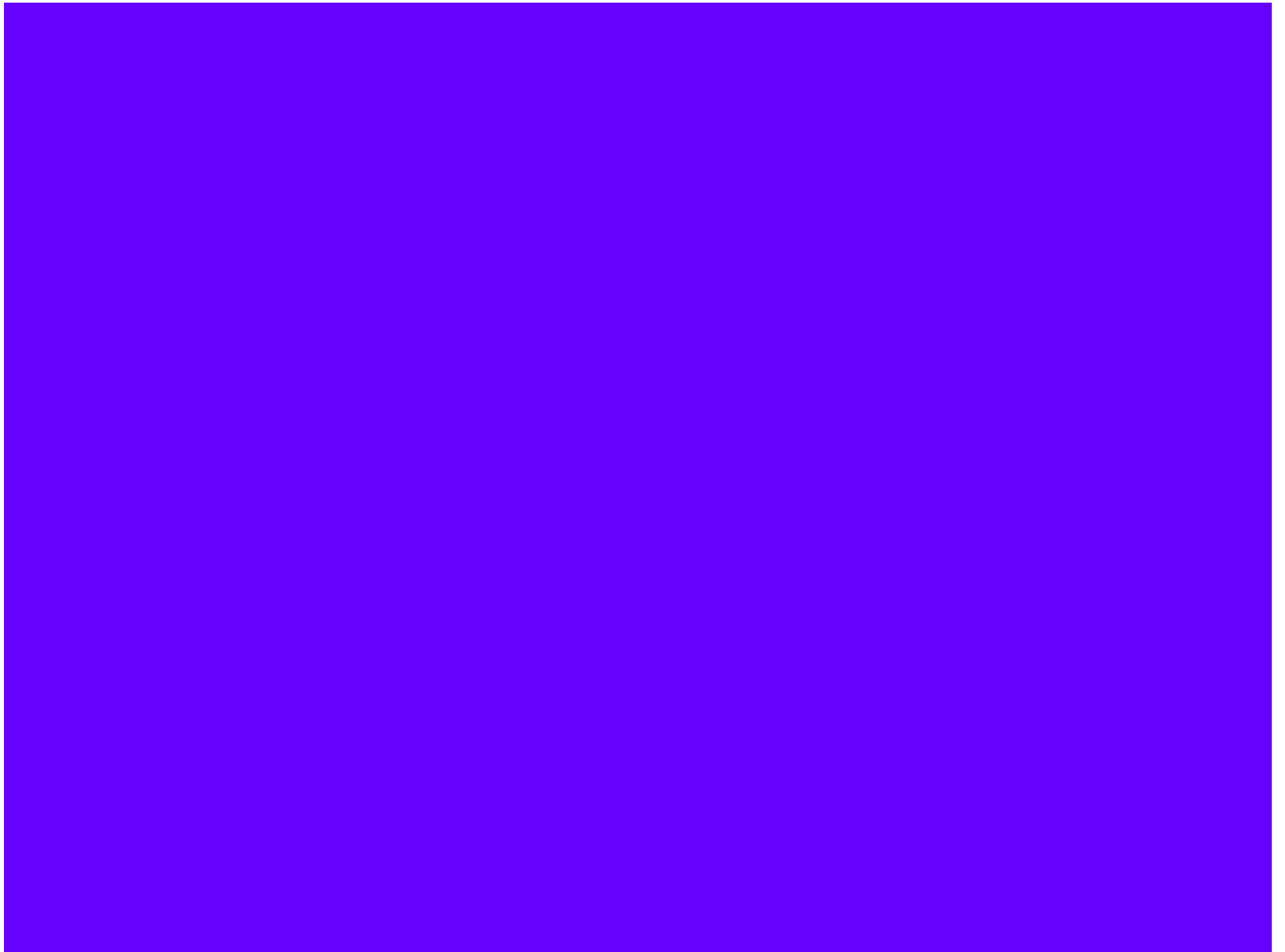
Patents Granted and Pending

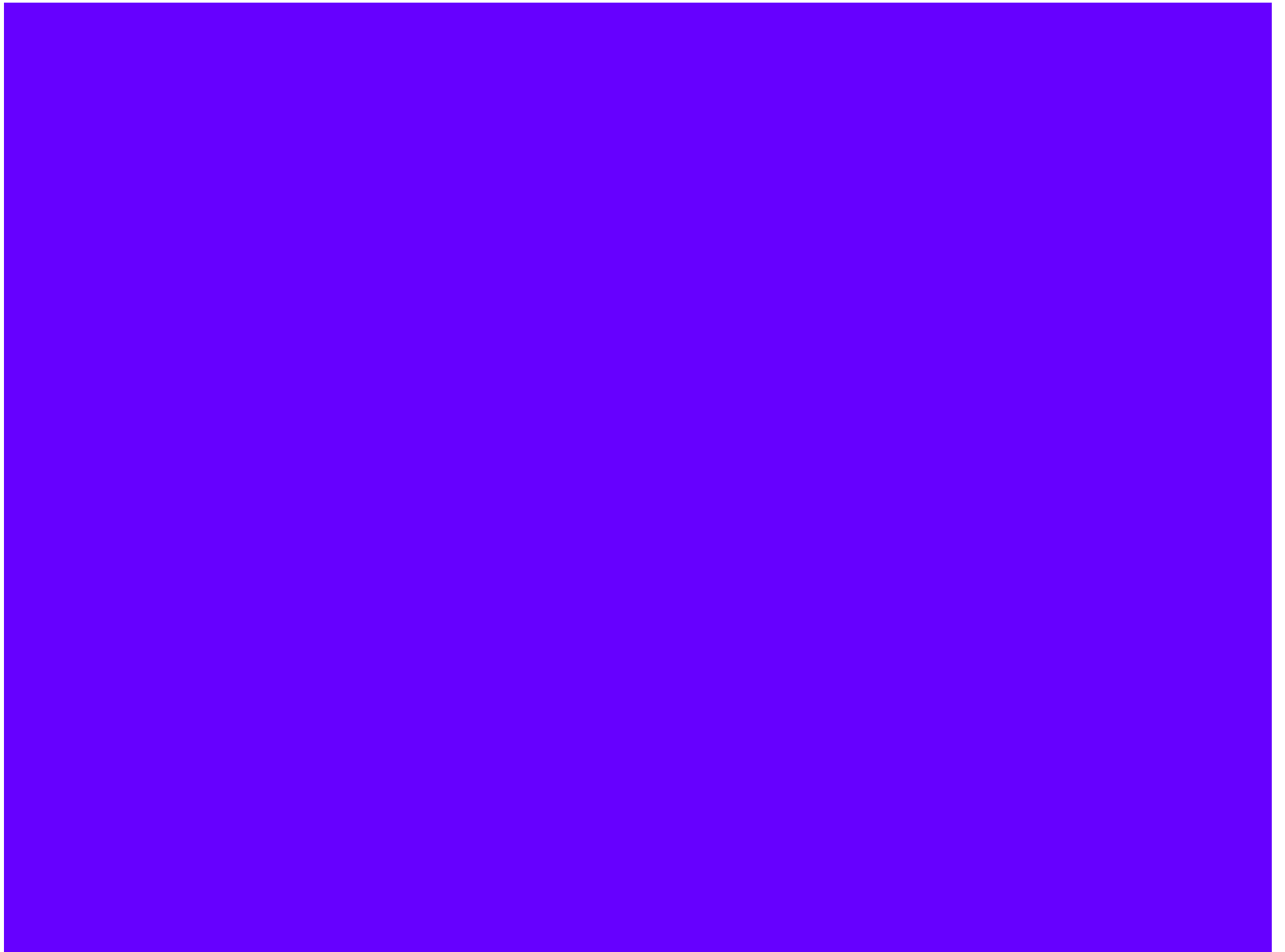
- ***Product Authentication (Anticounterfeiting)***
- ***Process Authentication (Patent Protection, PAC)***

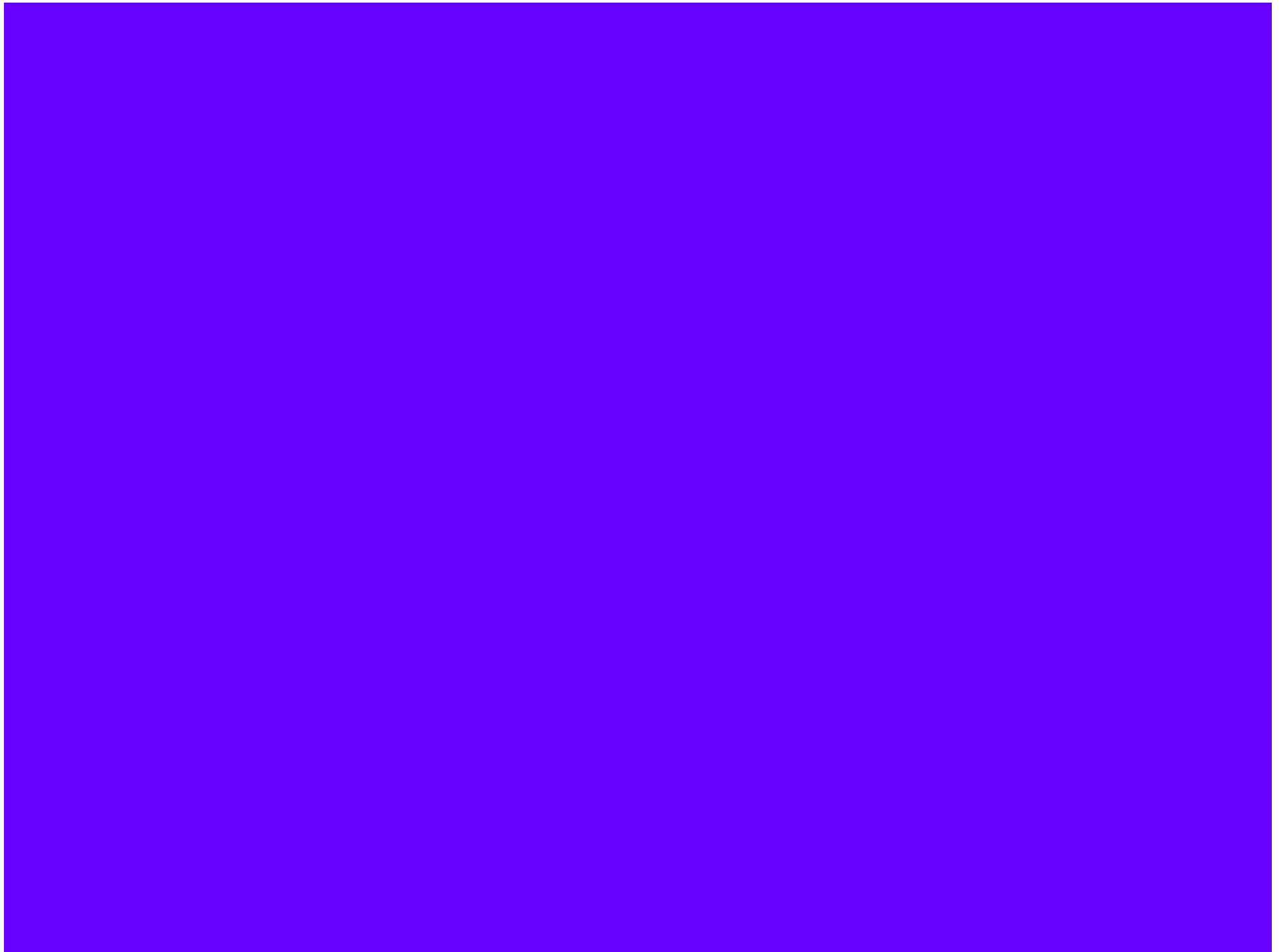
FDA Disclaimer

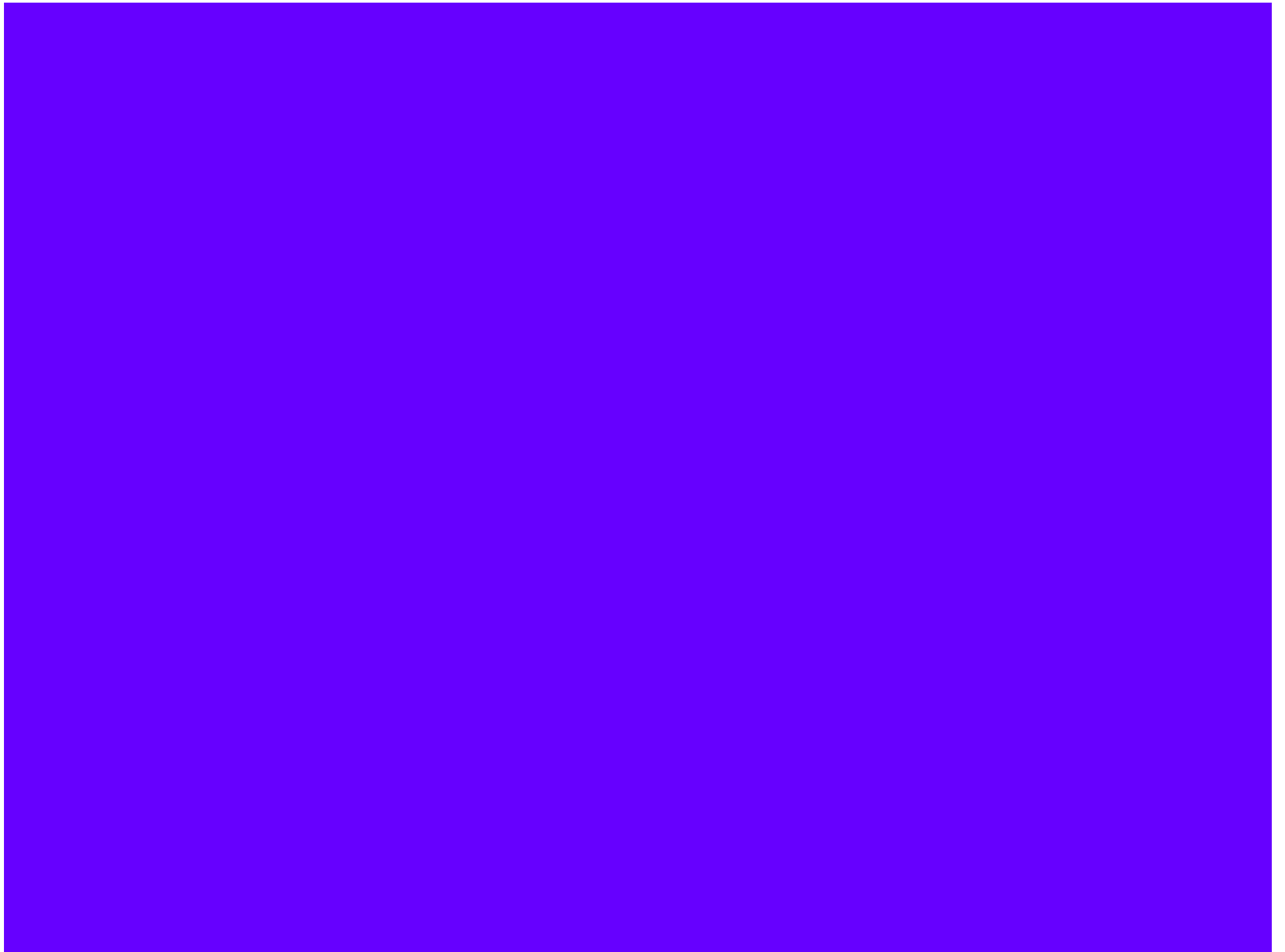
***The views presented here
do not necessarily reflect those of the
Food and Drug Administration.***

www.NaturesFingerprint.com









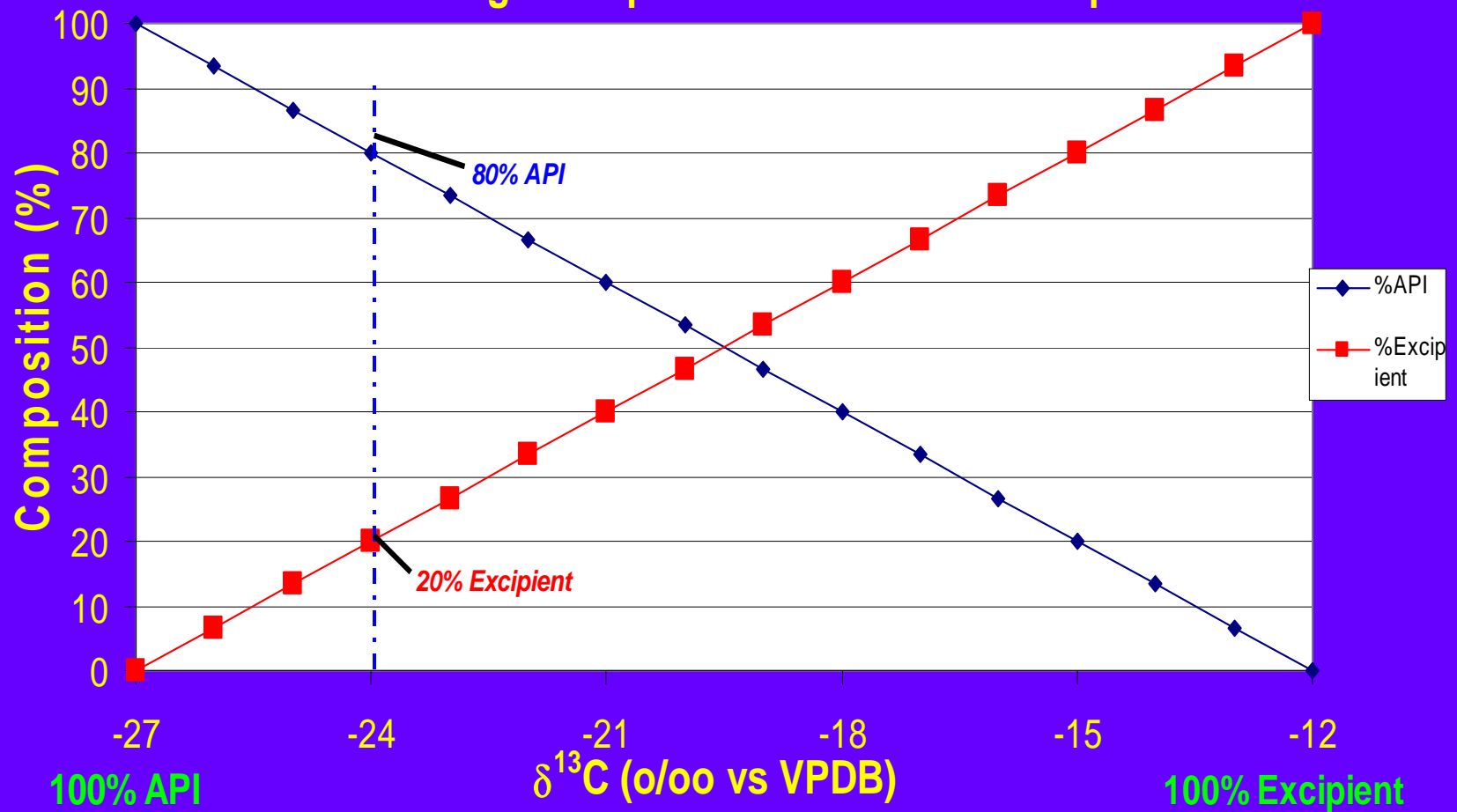
Part 3.

Summary of Process Fingerprinting via Stable Isotopes

1.D Monitoring Proportions of API and Excipient

- **One API**
- **One Excipient**
- **Continuum of Mixtures**

Carbon-Isotopic Composition Reflects the Percentage Compositions of API and Excipient



1.E. Monitoring Fractional Composition **of a Four-Step Process**

- **Four Components**
- **Four-Step Process**
- **Incremental Compositional QC**

Carbon-Isotopic Composition at Four Steps of a Blending Process

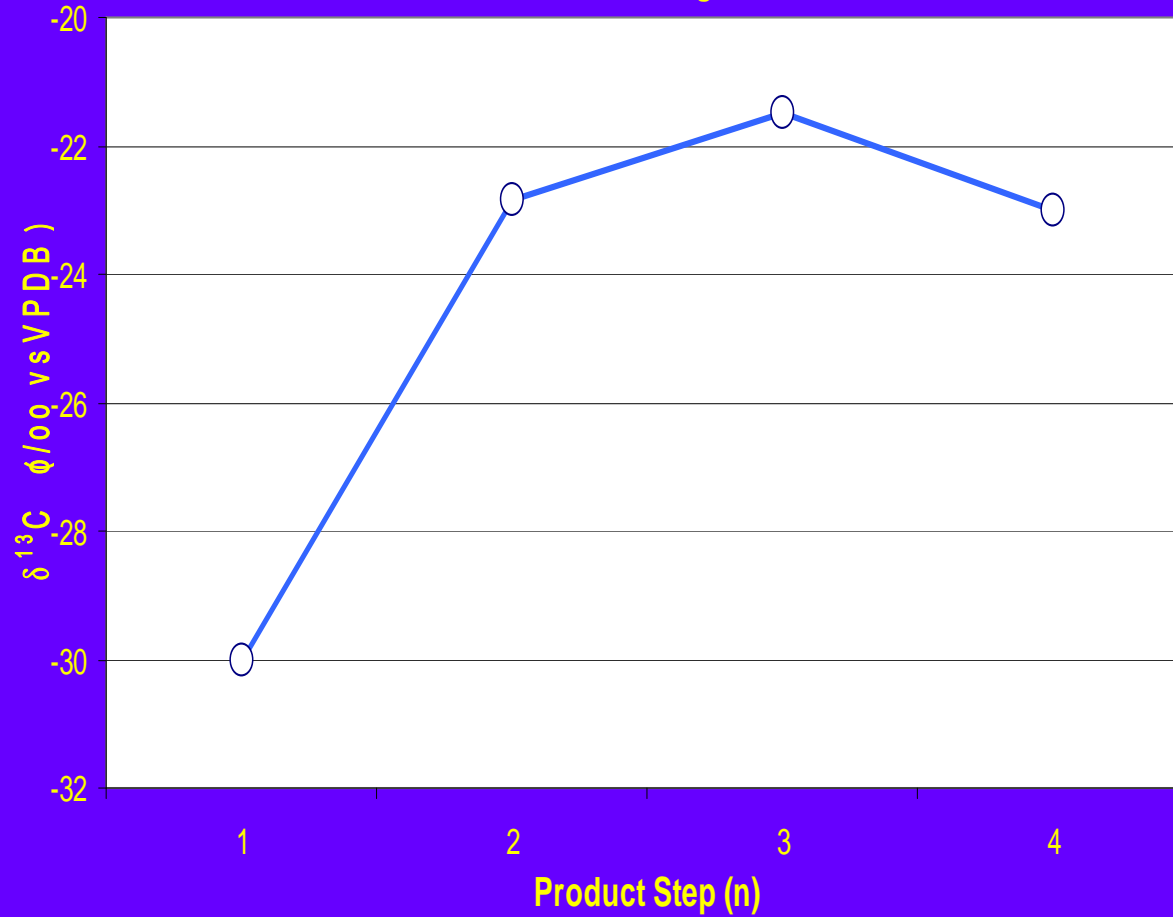


Table 4. $\delta^{13}\text{C}$ of a Series of Products along a Production Pathway									
Step	mA	dA	mB	dB	mC	dC	mD	dD	dT
1	1.00	-30.00							-30.00
2			2.50	-20.00					-22.86
3					0.50	-12.00			-21.50
4							1.50	-27.00	-23.00