Deficiencies of Deuterium as an Internal Standard in MS
Deficiencies of Deuterium as an Internal Standard in MS Presentation

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About IsoSciences

• Formed in 2002 by Scott Landvatter and David Saunders
• Both were isotope chemists at SmithKline Beecham and have >35 years labeling experience
• Custom Synthesis of Labeled Standards
• Catalog of Labeled Internal Standards
  • Work with NIST on Vitamin Internal Standards
  • Supplier of high purity unlabeled vitamin standards to NIST
  • Worked with International Vitamin D Harmonization group
  • Collaborator with Diagnostic Labs to develop the next generation of internal standards (e.g. steroids)
Which 25-OH D3 Internal Standard Do I Choose?

- D$_3$
- D$_6$
- 13C$_3$
- 13C$_5$
- 13C$_3$ (Not Yet Available)
Which Testosterone Internal Standard Do I Choose?

- \( D_5 \) or \( D_3 \) or \( ^{13}C_3 \)
Selecting a Labeled Internal Standard: What is Typical Now

- ‘Old’ Internal Standards Continued to be Used
  - ‘SOP’s Complete
  - Validation Complete
  - Why Change?
Selecting a Labeled Internal Standard: What is Typical Now

• ‘Old’ Standards Continue to be Used
  • ‘SOP’s complete
  • Validation Complete
  • Why Change?
• What Do ‘Old’ Internal Standards Look Like?
  • Usually Deuterated
  • Usually the Least Expensive
Selecting a Labeled Internal Standard: What about New Internal Standards?

• ‘New’ Standards Rapidly Being Developed

- $^{13}$C
- $^{15}$N
- D in more stable Positions

• Combination of Labels

• Minimize chance of unlabeled material
Selecting a Labeled Internal Standard: What about New Internal Standards?

• ‘New’ Standards Rapidly Being Developed
• ‘New’ Standards Represent a Shift in Approach
  • Minimizing the use of Deuterium
    • $^{13}\text{C}$
    • $^{15}\text{N}$
  • D in more stable Positions
  • Combination of Labels
    • Minimize chance of unlabeled material
Question: Are There Reasons to Switch Standards?
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Answer: In Many Cases the Answer is Yes. But Why?
To understand why we need to look at the factors effecting the synthesis of the labeled standards.
Factors in Isotopic Labeling: Use of Final Compound

Ultimate Use of Labeled Compound

• MS Standard?
  • Chemical Stability
  • Isotope Stability
  • Molecular weight enhancement required
    - At least M+3 is Standard
    - Is Cl present? (Then M+5 Required)
Factors in Isotopic Labeling: Use of Final Compound

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• MS Standard?
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• Biological study?
  • Metabolic Stability Required
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Ultimate Use of Labeled Compound

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• Biological study?
  • *Metabolic Stability Required*

• Human study?
  • *cGMP*
Factors in Isotopic Labeling: Choice of Isotope(s)

$^2$H (Deuterium)

Pros:

• Easy to incorporate
• Inexpensive (usually)
Factors in Isotopic Labeling: Choice of Isotope(s)

\(^2\text{H} \) (Deuterium)

**Pros:**
- Easy to incorporate
- Inexpensive (usually)

**Cons:**
- Prone to exchange/loss of label (chemically and in MS)
- Difficult to get a clean molecular ion
- LC/MS co-elution problems: HPLC can sometimes separate deuterated from non-deuterated compound
Factors in Isotopic Labeling: Choice of Isotope(s)

$^{13}\text{C}$ (Carbon-13)

Pros:

• High isotopic purity/Clean molecular ion
• Chemically stable
• No exchange/loss of label problems in MS
• No LC/MS co-elution problems
Factors in Isotopic Labeling: Choice of Isotope(s)

$^{13}$C (Carbon-13)

Pros:
- High isotopic purity/Clean molecular ion
- Chemically stable
- No exchange/loss of label problems in MS
- No LC/MS co-elution problems

Cons:
- Requires more elaborate syntheses
- More expensive than deuterium (usually)
Factors in Isotopic Labeling: Choice of Isotope(s)

$^{15}$N (Nitrogen-15)

Pros:

• Useful label for compounds containing multiple nitrogens

• No LC/MS co-elution problems
Factors in Isotopic Labeling: Choice of Isotope(s)

$^{15}$N (Nitrogen-15)

**Pros:**
- Useful label for compounds containing multiple nitrogens
- No LC/MS co-elution problems

**Cons:**
- Limited choice of expensive starting materials
- Requires total synthesis
Factors in Isotopic Labeling: Choice of Isotope(s)

$^{18}$O (Oxygen-18)

Pros:

• Molecular weight gain of 2 amu per label
Factors in Isotopic Labeling: Choice of Isotope(s)

$^{18}$O (Oxygen-18)

Pros:
- Molecular weight gain of 2 amu per label

Cons:
- Totally exchangeable in easily accessible functional groups (acids, esters, ketones)
- Only useful in ethers (and those are difficult and expensive to prepare)
Factors in Isotopic Labeling: Choice of Isotope(s)

Multiple Sources of Label ($^{13}$C,$^2$H – $^{13}$C,$^{13}$C – $^{13}$C,$^{15}$N)

Pros:

- Lowest possible amount of unlabeled compound
  
  - 1 source of $^{13}$C$_2$ at 99% $^{13}$C: unlabeled contamination (worst case) = 1%
  
  - 2 sources of $^{13}$C at 99% $^{13}$C: unlabeled contamination (worst case) = $0.01 \times 0.01 = 0.0001 = 0.01\%$
Factors in Isotopic Labeling: Choice of Isotope(s)

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  - 2 sources of $^{13}$C at 99% $^{13}$C: unlabeled contamination (worst case) = 0.01 x 0.01 =0.01%

Cons:

- Requires a total synthesis
- More expensive
Factors in Isotopic Labeling: Route of Synthesis

Three General Routes:

1. Labeling by Exchange
   - Only useful for deuterium
Factors in Isotopic Labeling: Route of Synthesis

Three General Routes:
1. Labeling by Exchange
   • Only useful for deuterium
   • Compound must contain active carbons
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Three General Routes:

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   - Only useful for deuterium
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![Diagram of Testosterone and Testosterone-d<sub>5</sub>]

- Testosterone
  - Converted to Testosterone-d<sub>5</sub>
  - Using MeOD/D<sub>2</sub>O and Base
Factors in Isotopic Labeling:
Route of Synthesis

Three General Routes:

2. Labeling by Deconstruction/Reconstruction
   • Take unlabeled final product (or analog)
Factors in Isotopic Labeling: Route of Synthesis

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   - Take unlabeled final product (or analog)
   - Remove part of the molecule
   - Remake the molecule with label
Factors in Isotopic Labeling: Route of Synthesis

Three General Routes:

2. Labeling by Deconstruction/Reconstruction
   • Take unlabeled final product (or analog)
   • Remove part of the molecule
   • Remake the molecule with label

![Diagram showing the transformation of Boldenone into Testosterone-\(^{13}C_3\).]
Factors in Isotopic Labeling: Route of Synthesis

Three General Routes:
3. Total Synthesis
   - Construct the molecule from basic materials
Factors in Isotopic Labeling: Route of Synthesis

Three General Routes:

3. Total Synthesis
   • Construct the molecule from basic materials
   • Tends to be the most expensive
Factors in Isotopic Labeling: Route of Synthesis

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![Reaction diagram: H₂¹⁵N₁⁵N₂ → Saxitoxin-[¹⁵N₄]](image)
Factors in Isotopic Labeling: Label Stability (Deuterium)

Case Study: Aldosterone
Factors in Isotopic Labeling: Label Stability (Deuterium)

Aldosterone – Which carbons are activated for deuterium labeling by base-catalyzed exchange?
Factors in Isotopic Labeling: Label Stability (Deuterium)

Aldosterone – Which carbons are activated for deuterium labeling by base-catalyzed exchange?
Factors in Isotopic Labeling: Label Stability (Deuterium)

Deuterated Aldosterone – Prepared by H/D exchange under basic conditions.
Factors in Isotopic Labeling: Label Stability (Deuterium)

Aldosterone Standard
Factors in Isotopic Labeling: Label Stability (Deuterium)

Note that a 1:1 mass mix of standard and labeled standard will not give a 1:1 molecular ion intensity
Factors in Isotopic Labeling:
Label Stability (Deuterium)

Aldosterone Standard

Aldosterone-d$_7$
Factors in Isotopic Labeling: Label Stability (Deuterium)

Aldosterone – Label Stability Problems
Factors in Isotopic Labeling: Label Stability (Deuterium)

Aldosterone – Label Stability Problems

Base or Mass Spec

Easy to Incorporate Deuterium Means Easy to Lose Deuterium!
Factors in Isotopic Labeling: Label Stability (Deuterium)

Aldosterone – Label Stability Problems

This exchange process is always occurring, but you only detect it when deuterium is present.
Factors in Isotopic Labeling:
Label Stability (Deuterium)

Aldosterone – Solving the Label Stability Problem
Factors in Isotopic Labeling: Label Stability (Deuterium)

Aldosterone – Solving the Label Stability Problem

- Deuterium from 2 sources
- Deuterium in non-exchangeable positions.
Factors in Isotopic Labeling: Label Stability (Deuterium)

- **Aldosterone**
  - $d_4$: 96.9%
  - $d_3$: 3.1%
Factors in Isotopic Labeling: Label Stability (Deuterium)

Note: All 3 are at exactly the same concentration
Quality Controls Necessitated by Deuterium

Unlabeled standard at m/z 343
Quality Controls Necessitated by Deuterium

D4 label at m/z 347
Quality Controls Necessitated by Deuterium

Select MRMs
Quality Controls Necessitated by Deuterium

Carry Out Analysis with selected MRM
Quality Controls Necessitated by Deuterium

Carry Out Analysis with selected MRM

BUT...How do you know your internal standard is still accurate?
Quality Controls Necessitated by Deuterium

$T=0$
Quality Controls Necessitated by Deuterium

$T=n \text{ hrs}$
Quality Controls Necessitated by Deuterium

\[ T = n \text{ hrs} \]

Deuterium has exchanged and the molecular ion intensity has decreased.
Quantification Complications

• Blank + Internal Standard sample only catches the issue if there is a complete loss of isotope. If a [d4] internal standard begins to lose deuterium and could be detectable at [d3], [d2] and [d1] then the [d4] mass spec internal standard signal is decreased. There is no red flag from the Blank + Internal Standard sample unless it loses all of the deuterium.

• Since the internal standard ratio is used to quantify, if the internal standard signal drifts because of loss of deuterium, then the analyte signal is normalized to the higher internal standards signal, giving erronously higher diagnostic results.
How Much of a Potential Problem is There?
Examples: Androstenedione

Androstenedione- $[^2\text{H}_7]$
- Old Standard Used
- D is Exchangeable

Androstenedione-$[^{13}\text{C}_3]$
- New Standard
- $^{13}\text{C}$ Labeled
Examples: 17α-Hydroxyprogesterone

17α-Hydroxyprogesterone-[^2H_8]  • Old Standard  • D is Exchangeable

17α-Hydroxyprogesterone-[^13C_3]  • New Standard  • ^13C Labeled
Examples: Dehydroepiandrosterone

Dehydroepiandrosterone-$^{[2H_2]}$

- Old Standard
- $D$ is Exchangeable
- Only $M+2$

Dehydroepiandrosterone-$^{[2H_6]}$

- New Standard
- $D$ is non-exchangeable
- $^{13}C_3$ is also available
Examples: Dihydrotestosterone

Dihydrotestosterone-\([^{2}H_4]\)
- Old Standard Used
- D is Exchangeable

Dihydrotestosterone-\([^{13}C_3]\)
- New Standard
- \(^{13}\)C Labeled
Examples: 17β-Estradiol

17β-Estradiol-[²H₅]
- Old Standard Used
- 2 of the D are Exchangeable

17β-Estradiol-[¹³C₃]
- New Standard
- ¹³C Labeled
Examples: Vitamin B3 (Niacin; Nicotinic Acid)

- Nicotinic Acid- $[^2\text{H}_3]$  
  - Old Standard Used  
  - D is Exchangeable  

- Nicotinic Acid-[$^{13}\text{C}_3,^{15}\text{N}$]  
  - New Standard  
  - $^{13}\text{C},^{15}\text{N}$ Labeled
Examples: Vitamin B9 (Folic Acid)

Folic Acid-[^{2}H_{4}]  
- Old Standard Used  
- Potentially Labile D

OR

Folic Acid-[^{13}C_{5}]  
- New Standard  
- \(^{13}\)C Labeled
Examples: Vitamin B12

Old Standard
None

New Standard
Vitamin B12-$^{13}\text{C}_7$ (!!!)
Which Do I Choose?

- Totally Exchangeable Deuterium
- Significant Amount of m0 detected

- Non-Exchangeable Deuterium
- m0 still detected under MS Conditions; MS itself induces some loss of D (up to all 3 D’s)

- No Exchange
- No loss of label in MS
- No m0
Which Do I Choose?

There Can Be No Exchange or Loss of Isotope In MS

There Can Be No Exchange or Loss of Isotope In MS
Which Do I Choose?

If PTAD Derivitization is Used:

![Chemical Structures]
Which Do I Choose?

Label Retained

Label Lost

\[ D_3 \]

\[ D_0 \]
Factors in Isotopic Labeling: Chromatographic Separation of Isotopes

Supelco SPB-5
Fused Silica Capillary Column (30m)
0.25μm film thickness
150 degC held 2 min, ramp 20 degC/min up to 250 degC, held 14 min

EPA Ester and EPA-$d_5$ Ester Co-injection
Factors in Isotopic Labeling: Chromatographic Separation of Isotopes

Analytical Chemistry (1988), 60(19) 2131

Figure 2. Chromatograms demonstrating the separations achieved for the various isotopomers of dopamine. Chromatographic conditions are given in Figure 1.
Factors in Isotopic Labeling: Chromatographic Separation of Isotopes

• Deuterium elutes before hydrogen
• We’ve seen it with 24(R),25-Dihydroxyvitamin D3-d6
• Many other examples in the literature:
  • Benzazepines
  • Dopamines
  • Aminoaromatics
  • Carotenes
  • Fatty Acids
• Issue Will Become More Apparent with Improvements in HPLC
What Does Percent Isotope Incorporation Mean?

Example: Estriol-d₃ (98% D incorporation):
What Does Percent Isotope Incorporation Mean?

Example: Estriol-d$_3$ (98% D incorporation):

What does 98% mean?
What Does Percent Isotope Incorporation Mean?

Isotope Incorporation (technical definition):

“Sum of the isotopic content of all possible isotopomers divided by the theoretical isotope content.”

For Estriol-$d_3$, it would be:

$$d_0 + d_1 + d_2 + d_3 / 3$$
# What Does Percent Isotope Incorporation Mean?

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All are 98% D, but only one is free of d₀!
What Does Percent Isotope Incorporation Mean?

Deuterated aldosterone:

7.50 D/molecule
What Does Percent Isotope Incorporation Mean?

Deuterated aldosterone:

7.50 D/molecule
Is this Aldosterone-d$_7$ or d$_8$?
What Does Percent Isotope Incorporation Mean?

Deuterated aldosterone:

7.50 D/molecule

Is this Aldosterone-d$_7$ or d$_8$?

Is this 93.8% D (for d$_8$) or 107.1% D (for d$_7$)?
Issues if Deuterium is Used

• How Chemically Stable is the Deuterium?
  • Is it stable in your matrix?
  • How long is it stable in your matrix?
  • Is it stable in mobile phase?
  • Stable at t=0 does not mean stable at t=60 min or…
  • Has this validation been run?
  • These answers are unique to each user
Issues if Deuterium is Used

• How Stable is the Deuterium to MS?
  • Is it stable under your MS conditions?
  • As MS becomes more sensitive this will become more of an issue
  • These answers are unique to each instrument

• So There May be No Issue at all with Deuterium
  • But all these Quality Controls Should be Run
Carbon-13 and/or Nitrogen-15 have none of these problems!

Carbon-13
- 1.1%
- 6 protons
- 7 neutrons

Nitrogen-15
- 0.4%
- 7 protons
- 8 neutrons
Can Deuterium Still be Used if There are No Alternatives?

Deuterium 1.56%

- Deuterium is in a non-exchangeable position
- Deuterium MS stability is verified
  - More of a problem with increasing MS sensitivity
- Deuterium in Conjunction with $^{13}\text{C}$ and/or $^{15}\text{N}$
- Deuterium from more than one synthetic source
Summary

• Deuterium has inherent limitations
  –Instability/ Loss of label / False Positives / Co-elution Issues
Summary

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• Next generation of standards must:
  – Incorporate $^{13}$C or
Summary

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  – Instability/ Loss of label / False Positives / Co-elution Issues

• Next generation of standards must:
  – Incorporate $^{13}$C or
  – Incorporate multiple isotopes $^{13}$C, $^2$H ; $^{15}$N, $^2$H or
Summary

• **Deuterium has inherent limitations**
  – Instability/ Loss of label / False Positives / Co-elution Issues

• **Next generation of standards must:**
  – Incorporate $^{13}$C or
  – Incorporate multiple isotopes $^{13}$C, $^2$H ; $^{15}$N, $^2$H or
  – If only deuterium:
    • Synthesized in stable, non-exchangeable positions
    • Synthesized from multiple deuterium sources to minimize unlabeled contaminants
    • Stability Validated
Summary

• The ultimate question is what do you require for the best and most unambiguous results?
  – Interaction with manufacturer in the design phase
  – Selecting the isotope(s)
  – Selecting the number of labels
  – Selecting labeling sites
  – Balancing costs
  – Feedback on performance
Summary

• Don’t know if you have standards with exchangeable deuterium?

• Ask us-
  – call (610-337-3762),
  – Email (info@isosciences.com)

• We’ll tell you
  – This is what we do.
  – We’re synthetic organic isotope chemists, so this is our area of expertise.
Summary

“Tell Us What You Need and We’ll Make It”

info@isosciences.com

scott.landvatter@isosciences.com

610-337-3762