

Dietary Supplements at Lightning Speed:

From Identity Requirements to Contaminant Screens

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Issues Facing DS Industry

- Now under new cGMP's (21 CFR part 111)
- FDA FSMA gives FDA direct recall authority/expanded detention authority
- FDA expanding staff and intensifying enforcement
- Companies need new and faster ways to test product lots
- Scientifically valid lot sampling plans required meaning many samples per lot need analysis
- API Contaminants and identity main concerns at FDA



Tainted Dietary Supplements and Foods: Responsibilities of Retailers and Distributors

Be proactive — Products with the following characteristics warrant further investigation ...

1. Product Categories:
 - Sexual Enhancement • Weight Loss • Bodybuilding • Diabetes
2. Labeling claims like:
 - “Alternative to [approved drug product]” or “legal alternative to [anabolic steroid]”
 - Sexual enhancement products claiming immediate effects
 - Directions and warnings that resemble FDA approved drug products
 - “May cause positive result in performance enhancing drug test”
3. Labels primarily in a foreign language
4. Beware of mass solicitations (particularly emails) from suppliers and wholesalers offering products in the above categories.



What are Tainted Supplements/Foods?

In recent years, FDA has identified hundreds of products marketed as dietary supplements or conventional foods with hidden drugs and chemicals. The products are typically promoted for sexual enhancement, weight loss, bodybuilding, and diabetes. FDA lab analyses have found products that have been laced with a wide variety of potentially dangerous ingredients that include:

- Approved prescription drug ingredients and their analogues
- Drugs banned by FDA for safety reasons
- Controlled substances such as anabolic steroids and stimulant diet drugs
- New active drug ingredients that are untested and unstudied

Health Risks

Tainted products place consumers at risk of injury and death, especially those consumers with underlying health conditions. These products can also interact in life threatening ways with other medications a consumer may be taking.

Know What’s in Your Products

FDA is becoming more active in pursuing criminal convictions for sellers of tainted supplements. For example, in 2010, VMG Global was convicted of a felony and fined for selling supplements laced with anabolic steroids; in recent months, FDA has brought misdemeanor charges against several persons for selling sexual enhancement supplements with hidden active pharmaceutical ingredients.

Requirements Under the Law

Firms that sell dietary supplement products play an integral role in preventing tainted supplements from harming consumers and have a legal responsibility to ensure that the products they sell are not tainted.

Anyone who sells or distributes these illegal products may be subject to:

- Criminal liability – misdemeanors and felonies
- Seizure of your products
- Injunction of the responsible party or company
- Disgorgement of profits and restitution. [FDA](#)

API Adulteration

- Active Pharmaceutical Ingredients (API)
- Many drugs are novel analogues not previously known
- Emergence of old abandoned pharmaceuticals
- Often multiple complex mixtures of pharmaceuticals buried in botanical matrix
- Industry needs rapid methods for pass/fail testing of targeted compounds
- Ability to run many replicates from one lot quickly vital to industry survival

DART (Direct Analysis in Real Time)

- DART allows for rapid analysis of samples in seconds
- Sample preparation is virtually eliminated
- Uses power of mass spectroscopy to resolve compounds from matrix
- Gives versatility in settings and sample introduction options for faster & easier assays
- Samples testing positive can be further analyzed while clean samples clear hold in minutes

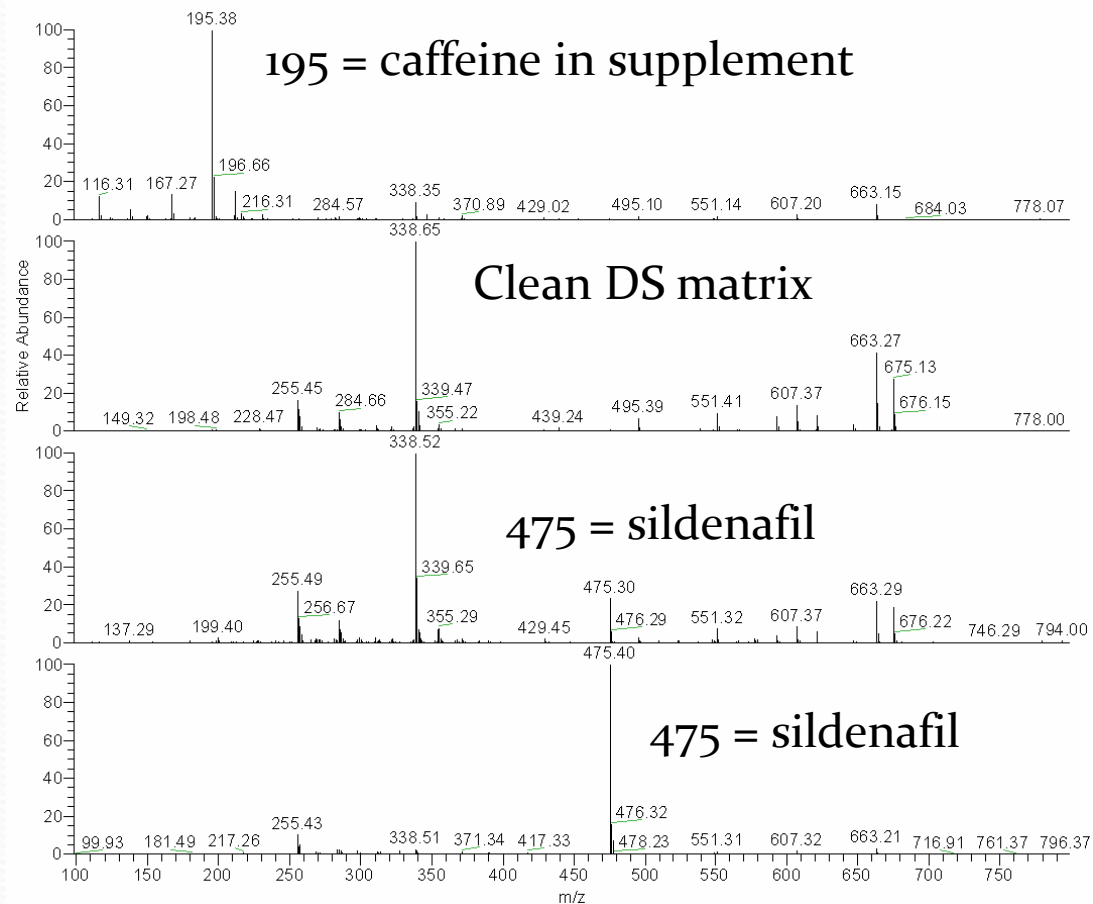
PDE-5 Inhibitors (Viagra etc.)

- First detected in herbal supplements shortly after launch of Viagra (sildenafil citrate)
- Following launch of Cialis (tadalafil) and Levitra (vardenafil), these too show up in herbals
- Clandestine synthetic organic chemists begin tweaking molecules to create analogues
- Hongdenafil (acetyldenafil) first analogue identified
- Numerous others follow including analogues of all 3 approved ED drugs (now close to 40+)
- Latest approach is to add thione groups & create prodrugs

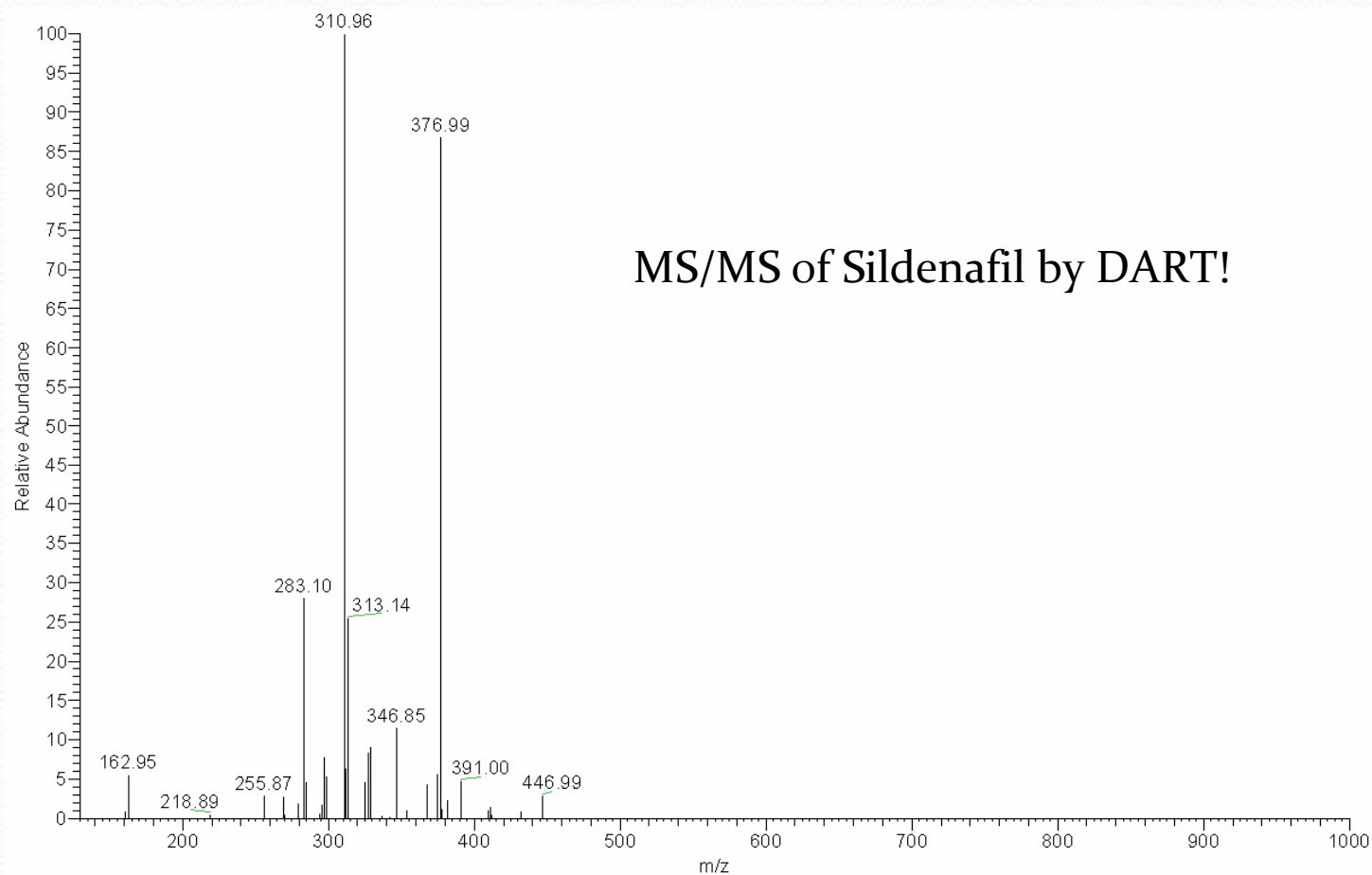
Analysis of ED Drugs by DART

- Experiments were performed using a DART SVP interfaced to a Thermo Finnigan LCQ Deca ion trap
- All samples were analyzed neat; the closed end of a melting point capillary was dipped into the powder, excess sample was shaken off, and the capillary was manually placed in the ionization region.
- All samples were analyzed using helium as the ionization gas. The ion polarity and gas temperature were varied for each sample.
- Analysis of each sample took approximately 5 seconds.

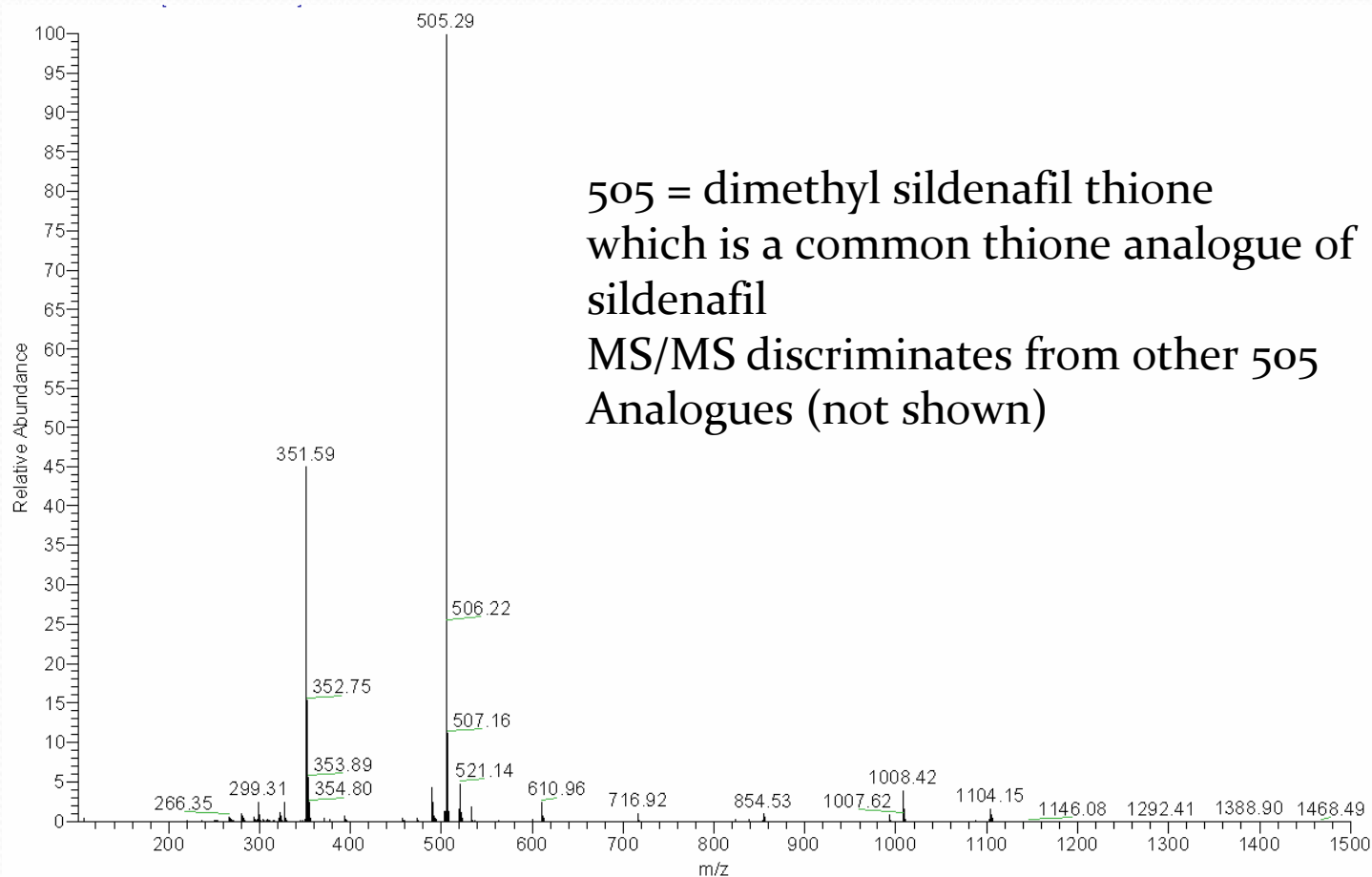
Analysis of ED Drugs by DART



Analysis of ED Drugs by DART



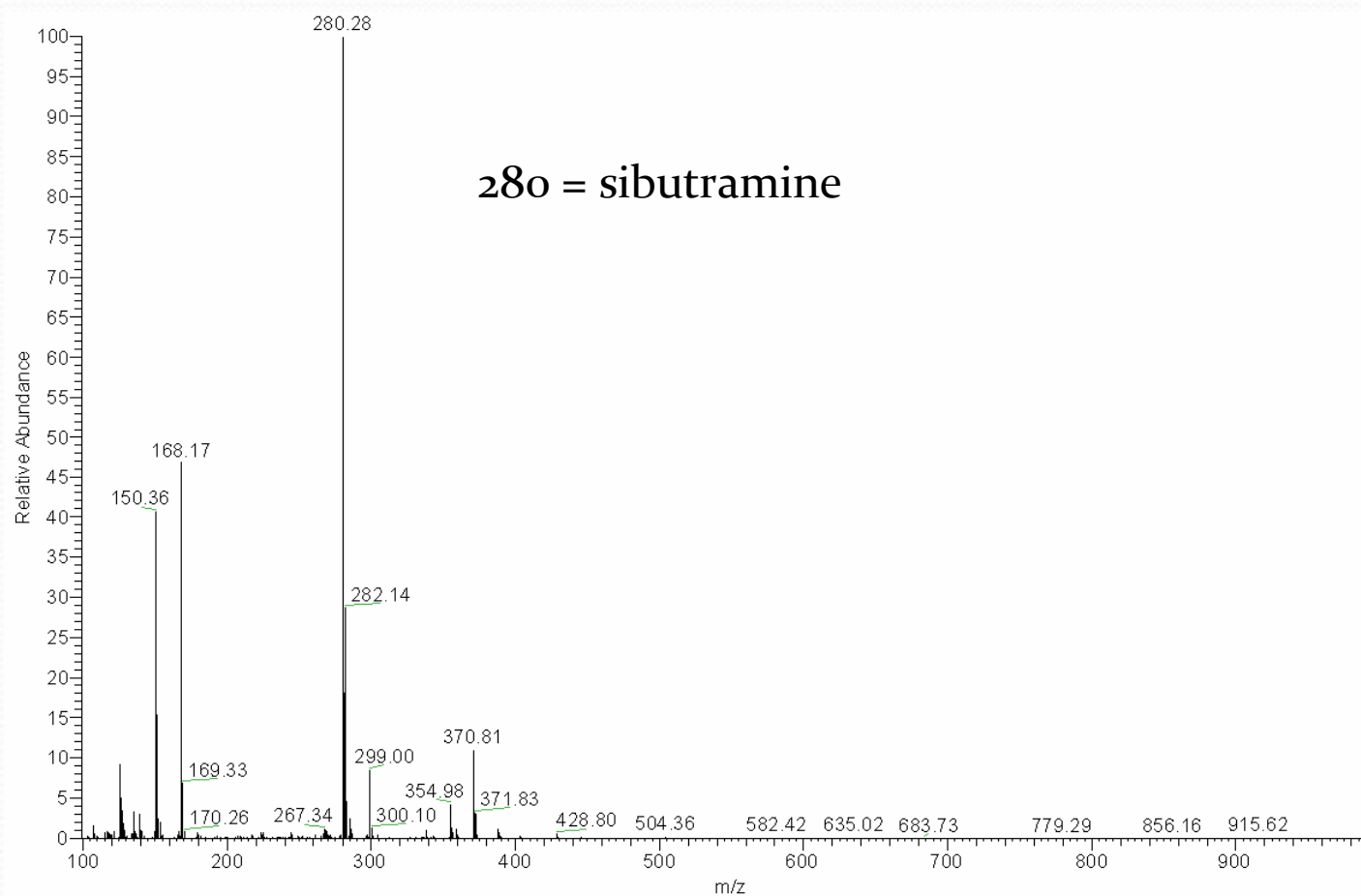
Analysis of ED Drugs by DART



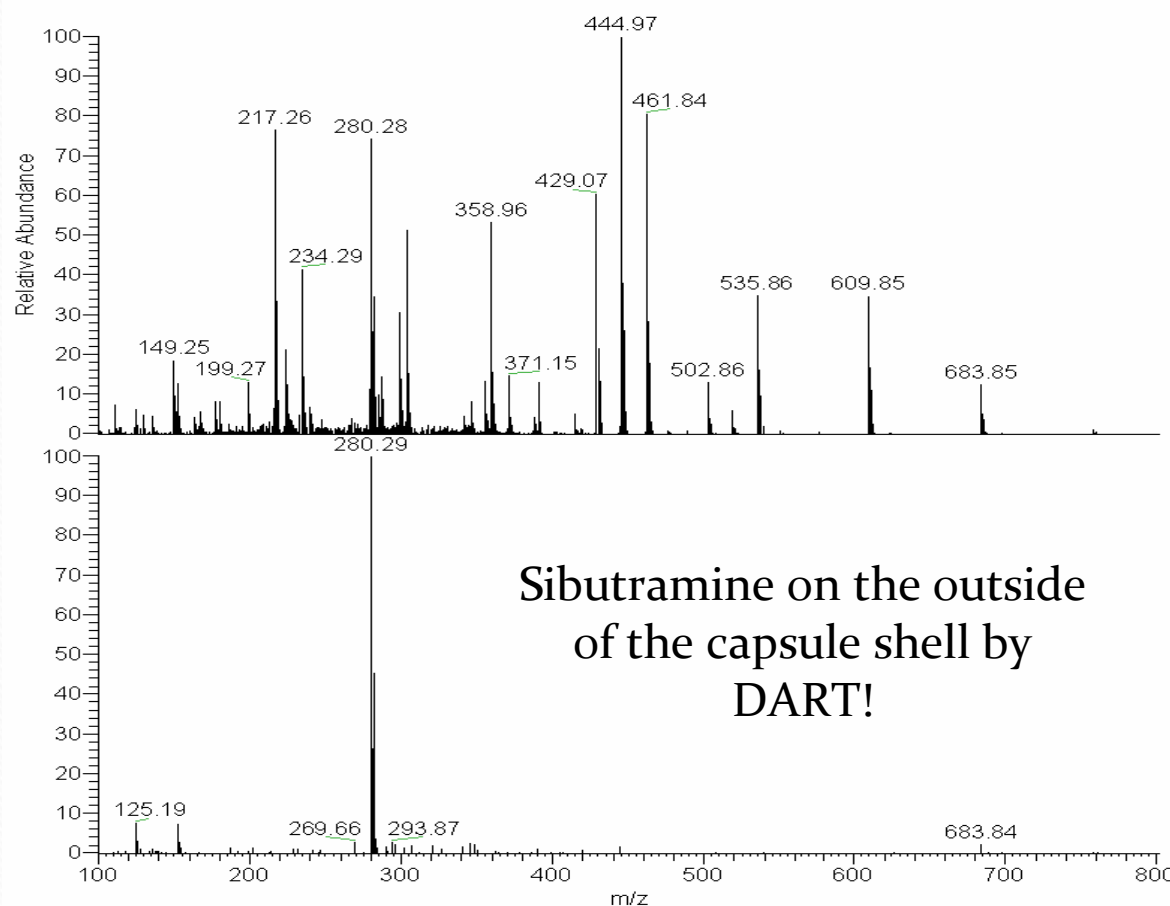
APIWL – Weight Loss API's by DART

- Sibutramine is an anorectic DEA Schedule III controlled substance
- Removed in 2010 by Abbott due to post market AER's
- Product appeared in DS products several years ago
- New analogues and metabolites appearing as well
- Despite withdrawal from market, sibutramine in DS products is on the rise!
- Other compounds include diuretics, laxatives, stimulants, benzodiazepines and more!

Sibutramine in DS by DART



On-the-shell DART!



NL: 4.22E5
FLORA_IS-
001_Green_Capsule_Shell_Run01_
POS_20110526#35-43 RT:
0.78-0.97 AV: 9 T: + c ESI Full ms
[100.00-1300.00]

NL: 2.80E5
FLORA_IS-
001_Green_Capsule_Shell_Run01_
POS_20110526#35-43 RT:
0.78-0.97 AV: 9 SB: 16 1.77-2.11
T: + c ESI Full ms [100.00-1300.00]

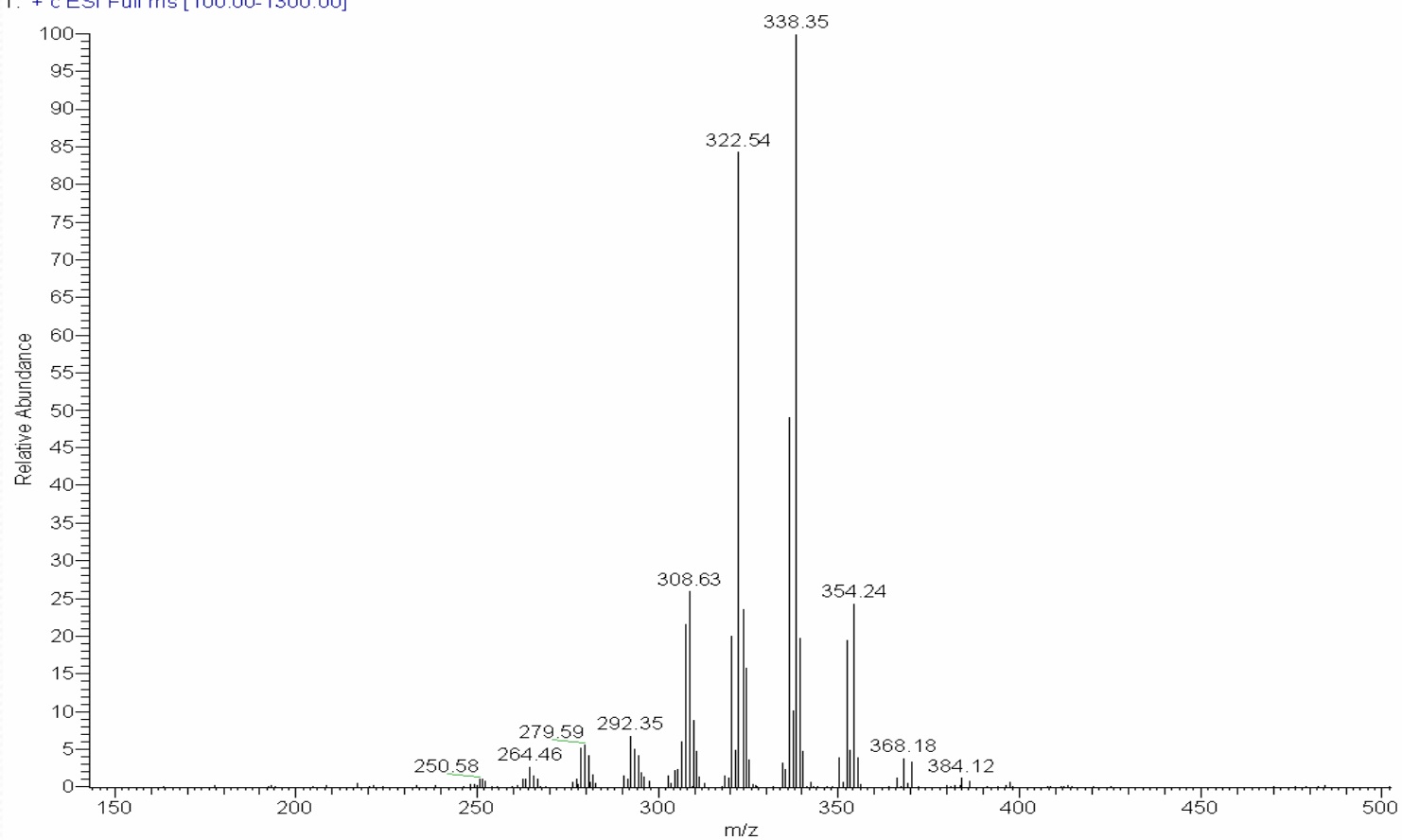
Sibutramine on the outside
of the capsule shell by
DART!

Botanical Identity by DART

- Many botanicals have common major markers
- Coptis and Goldenseal alkaloid profile mostly berberine & minor alkaloids
- Coptis is cheap and Goldenseal is expensive
- Berberine is not a marker suitable for differentiation
- HPTLC (3 hr + long process) can differentiate them
- Look at what we see with DART analysis of the roots

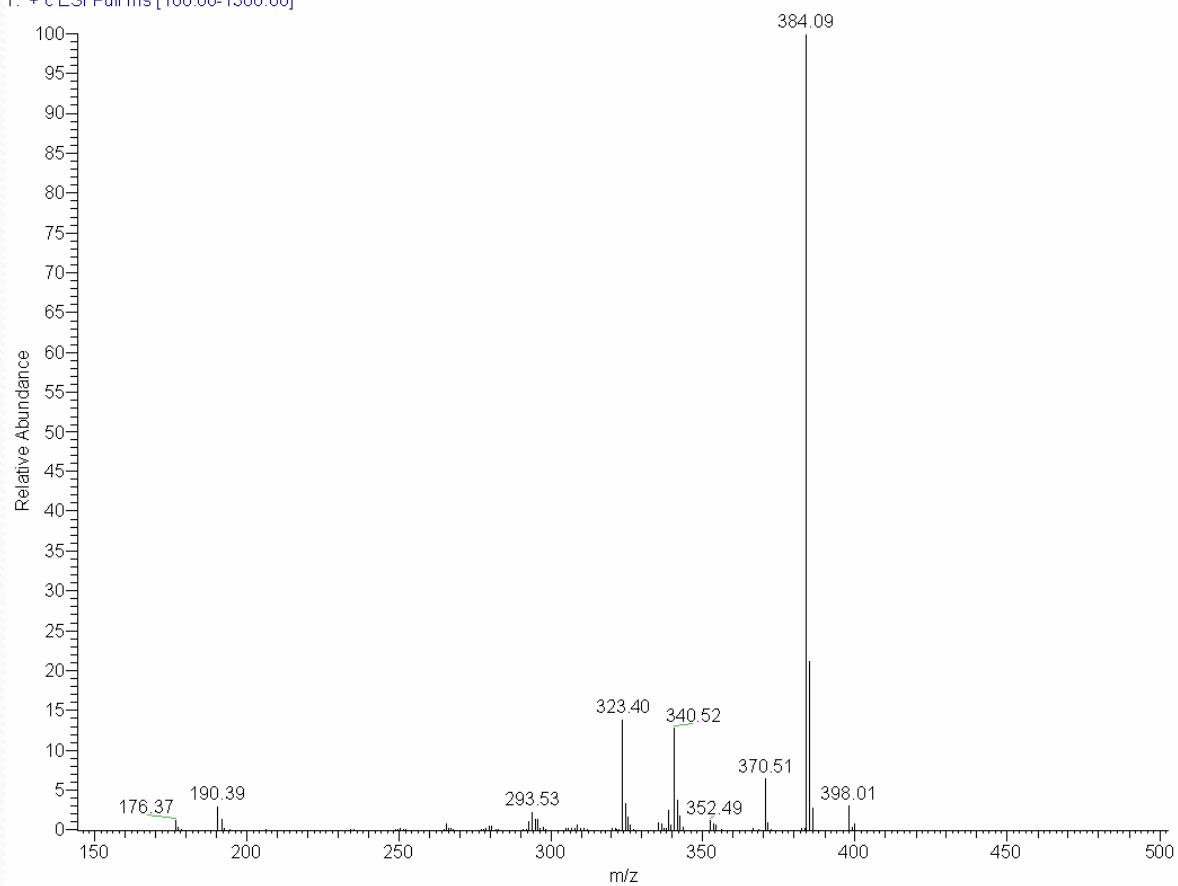
Coptis

FLORA_IS-002_CoptischinensisRoot_Run01_POS_HEATED_1%AAinACN_20110525 #59-64 RT: 1.27-1.36 AV: 6 SB: 9 0.94-1.12 NL:
T: + c ESI Full ms [100.00-1300.00]



Goldenseal

FLORA_HydrastisCanadensisRoot_Run04_POS_Thin_BulkRoot_20110525 #41-46 RT: 0.87-0.96 AV: 6 SB: 6 1.06-1.17 NL: 6.59E7
T: + c ESI Full ms [100.00-1300.00]



Next Steps in FRL DART Project

- DART for multi-compound simultaneous screen
- DART for ID testing of dietary ingredient singles
- DART for ID testing of complex botanicals
- DART for orthogonal analysis of HPTLC plates for critical diagnostic pairs in botanical ID (HPTLC-DART-MS)
- DART for ... (you will just have to come back next year and see for yourselves)

Thank You

Watch out new ED
analogue because DART
is going to get you!

MS Data Review Active Chromatogram and Spectrum Plots - 5/20/2011 3:58 PM

