
Should You Start a CRO?

Ways to Get Science Done in Future Pharma

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Brief Outline

- What is Averica?
- Value propositions - benefits of outsourcing
- Starting a CRO - Bootstrapping 101

America Discovery

- Contract Research Organization (CRO) specializing in separations/purification/characterization
- Discovery focused - responsive, flexible, fast, non-GLP/GMP
- Specialized separations technology:
 - SFC
 - Bulk purification: chiral compounds, difficult separations, natural products
- Analytical characterization
 - Impurity profiling, enantiomeric excess, reference standards

Services

Post-chemistry

- Final purification
- Difficult or unique separations
- Chiral separations
- Scales from 5 mg to 500 g
- Salt exchange
- Solvent removal

Compound management

- Aliquoting
- Custom labeling, barcoding
- Characterization, analysis
- Water and residual solvent analysis
- Optical purity, EE
- Certificate of analysis, QC
- Consultation with project team and downstream CROs

Compound integrity

- HPLC, SFC, LCMS, NMR
- Method development
- Preliminary stability

Case Study: Discovery Chiral Separations

- High value to 15-25% of Discovery teams
 - Lead optimization, nomination, pre-CMC planning
 - Frequently outsourced
- Small to medium scale: supporting *in vitro* assay to *in vivo* efficacy studies
 - 5 mg to 500 g projects
 - Non-GMP, GLP
- Downstream (Development) strategies include co-crystallization, asymmetric synthesis, catalysis, bulk separations

FDA Guidance on Chirality

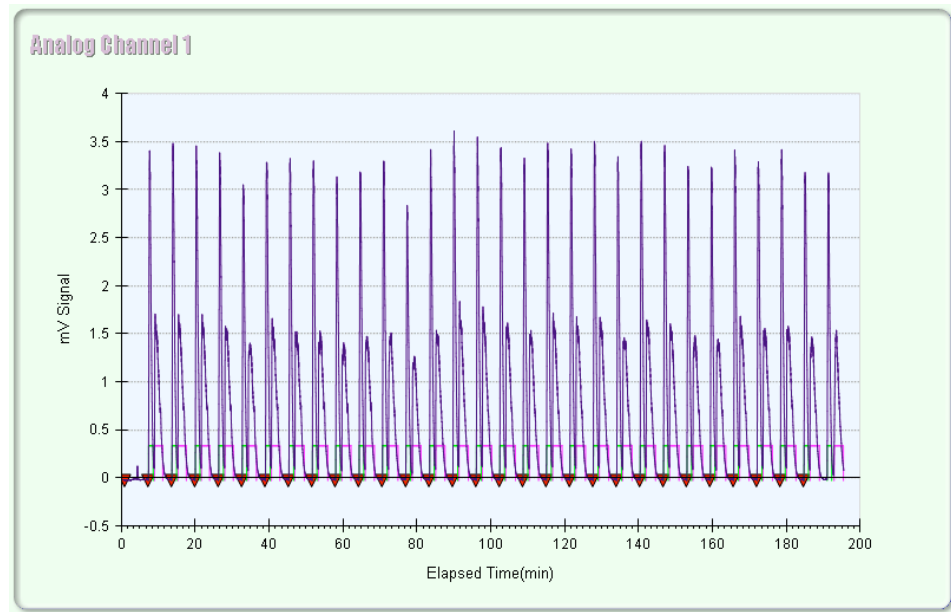
- *“Unless it proves particularly difficult, the main pharmacologic activities of the isomers should be compared in in vitro systems, in animals and/or in humans.”*
- CMC
 - Stereoselective specific identity tests for DS, DP
 - Differential characterization of isomers if DS is racemate
- Compare single enantiomer vs. racemate in longest repeat-dose preclinical tox study

Averica's SFC Technology

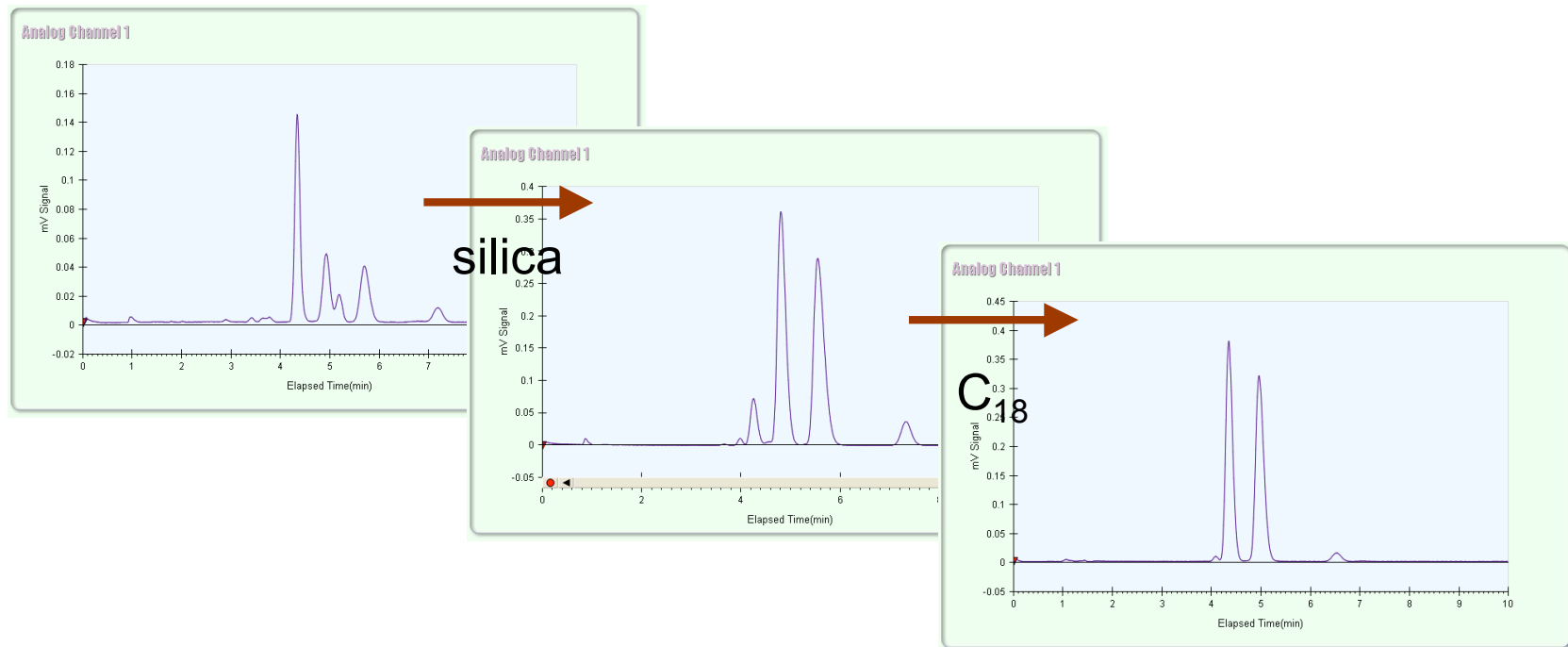
- Supercritical CO₂ is an amazing fluidity enhancer, offering a chromatography edge
 - High coefficient of mass transfer, narrow bands
 - Rapid chromatographic development
- Isocratic SFC separations on chiral solid phases are 3-10x more efficient than HPLC
- *Green chemistry* technology - minimal solvent waste, re-use industrial CO₂
- Averica is the only full analytical services lab offering SFC

Chiral Bulk Purification

- Efficiency from rapid isocratic methods + injection stacking
- Averica “typical” prep system” : 3.0 x 25 cm column at 80g/min
 - Best: 225 mg every 1.5 minutes, 9 g/hr, 2.25 kkd
 - Worst: 20 mg every 5 min, 0.24 g/hr, 0.06 kkd



Purification as a Process Component



- Using RP-HPLC: 5 FTE-wks to pure racemate
- Using SFC: 3.5 FTE-wks to pure enantiomers
- Cost savings \$50-\$80K

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Value Proposition

- Limit expensive in-house investment
 - Capital + dedicated manpower
 - Chiral columns, CO₂ delivery
 - Time investment to build experience, expertise
- Access quality through a dedicated & experienced outsource
- Access capacity to give flexibility, scalability

Industry Dilemma

Tim Olah, Director Metabolism & PK, BMS

- Be “innovative” in a time of resource “constraint”
 - Multiple R&D impacts
 - Scientific, Regulatory, Financial, Generics
 - More complex and unique partnerships
 - Joint ventures, Co-development, Sales / Marketing
 - Finite amount of talent, IP, technologies
 - Priorities and issues arise and change rapidly
- Strategic Sourcing offers the following options:
 - Selectively increase internal capabilities
 - Buy down risk; ensure flexibility
 - Free up the internal staff for proprietary innovation

Drivers for Outsourcing

Tim Olah, Director Metabolism & PK, BMS

- Capacity: manage peak demand periods
- Convenience: local support, timelines
- Capabilities: specialty, technical, regulatory
- Commodity work: scalability, flexibility
- Quality: dedicated specialists, centralization
- Cost: savings associated with lost overhead
- Innovation: free up time for research

Outsourcing: Failed Approaches

Roderic Cole, Director DMPK Abbott

- Put the samples in a box and mail
- Put the compound in a box and mail
- Let the CRO process the data and then send it to the teams
- Rely on tele- and/or videoconferences as primary communications
- Assume the CRO will self regulate given sufficient \$\$\$
- Larger CROs are better
- One qualified CRO is enough

CRO Relationships

Roderic Cole, Director DMPK Abbott

- Establish and manage the *relationship*
 - Know the key leadership and project managers
 - Know the people doing the work
 - Go see the labs you use regularly!
 - Make sure everyone meets!
- Manage the *work*
 - Scientists own the process
 - Review raw data files and process
 - Troubleshoot method issues directly

Deciding to Start a CRO

- “I want to see the direct impact of our scientific contribution”
- “We break everything down to processes now. My part is important, and I can do it well”
- “If I were running my own shop, I could really focus on quality”
- “I’ve always wanted to take a risk and try it on my own”
- “A small company is more productive (agile, innovative...) than a big company”
- “Everyone says we’re going to outsource more and more”

Lessons from a (Partial) Success

- Averica is a bootstrapped, debt-laden, one-owner company
 - \$750K capital equipment using \$50K owner capital
 - <4% interest on long-term debt
 - 36 clients in 20 operational months
 - Two fiscal years of operating income
 - Growth plans slowed by recession, but business model still very solid

Questions to Ask Frequently

- Have you tested your ideas?
- Do you know your competitors AND their pricing methods?
- Can you make deals with vendors, lenders, customers?
- How's your network?
- Does asking stupid questions bother you?
- Do you like the job of CEO?
- Do you know accounting?
- Are you prepared to take no salary, have no insurance?
- How do you deal with not working?

Idea Testing

- Learn to enjoy being picked on
- Recognize confirmation bias
- Get a team if you can, but choose carefully
- Pre-selling is essential
- The Market is everything
 - How much can you sell, at what price
 - What is your value to your customer

Deal Making

- You need:
 - Better deals on instrumentation than your present employer can make
 - Ready-to-go contract(s) - on paper!
 - A great lender - interview several
 - Personal guarantees
- No one wants to talk to anyone but the Principal

Networking

- Talk to scientists, peers, potential customers, other business owners
- Talk to everyone they suggest you talk to
- Call people you don't know
- Get numbers. Hear horror stories. Find the successful people. Find people you admire and tell them so
- Join a CEO network
- Introduce others to your contacts

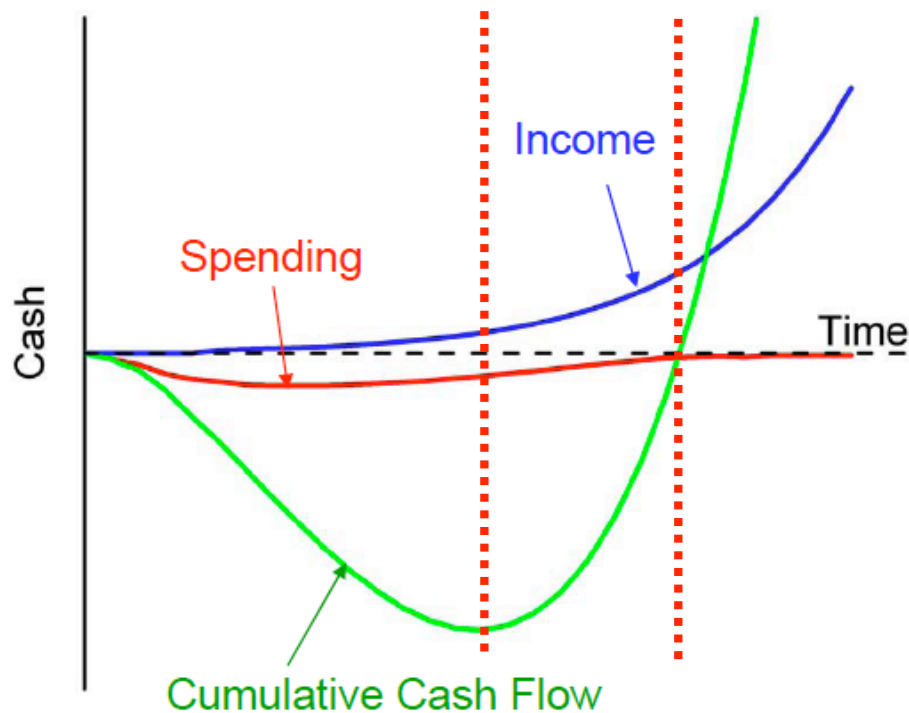
CEO Role

- Operations
 - Management, definition of process
 - HR: hiring/firing, benefits, negotiation, payroll, records
 - Bookkeeping, invoicing, purchasing, vendor management
 - Consultants (accounting, legal, HR, benefits)
 - Regulatory filings, insurance
 - Landlord/tenant
 - CRM, contracts, documentation, agreements
- Financing
 - Bank, investors, family/friends, customers
- Investing
 - Vendors, leasing agencies, used equipment
 - Tax preparation

Reasons to Learn Accounting

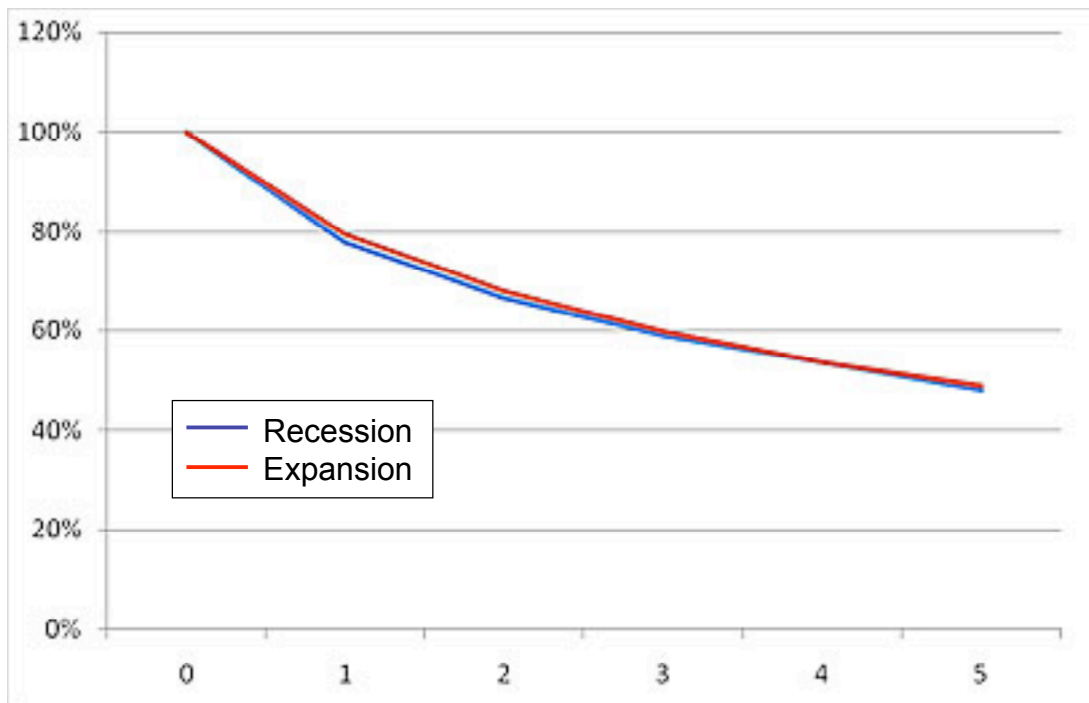
- Somewhere between “highly invested” and “cash is king” is a sweet spot
- Your accountant should be an advisor, not just a tax accountant
- Growth & exit strategies for CROs are fuzzy, but are the genesis of planning
- Small business lives and dies on cash flow & balance sheet. **Stop thinking in P&L terms!**

Why Cash Flow is Everything



- Get to revenue ASAP
- When revenue = spending, you are at the bottom of the hole
- Getting out of the hole is a process of improving balance sheet
- You'll only get credit when you have money

Small Business Survival



- Failure rate is 50% after 5 years
- Equivalent for corporations and sole proprietorships
- Constant over 1977-2000

Source: *Longitudinal Business Database, U.S. Census*

Resources

- Traditional
 - Entrepreneurship programs, MBA programs, workshops
 - “Venture Forums”
 - State and pseudo-governmental agencies
 - Tech transfer agencies
- Valuable
 - Network: other entrepreneurs, esp. bootstrappers, their networks
 - CEO networking groups
 - Consultants (with obvious caveats)
 - Key customers

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