Partnerships for Life

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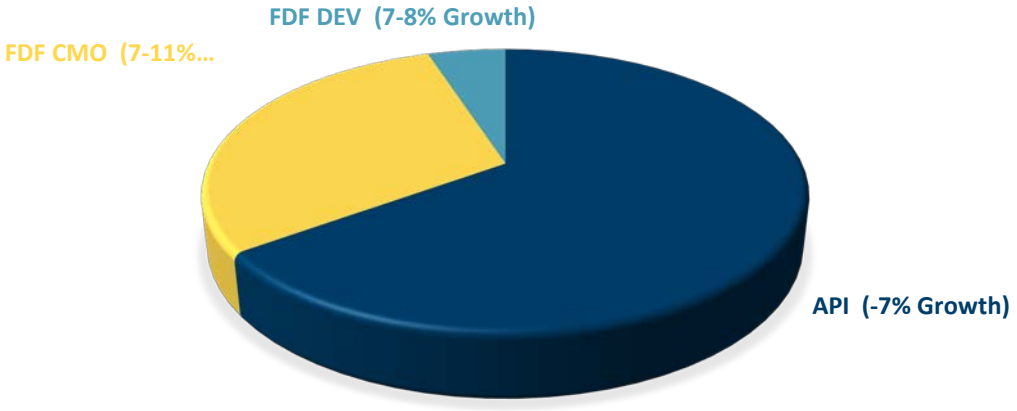
CDMO/CMO Landscape

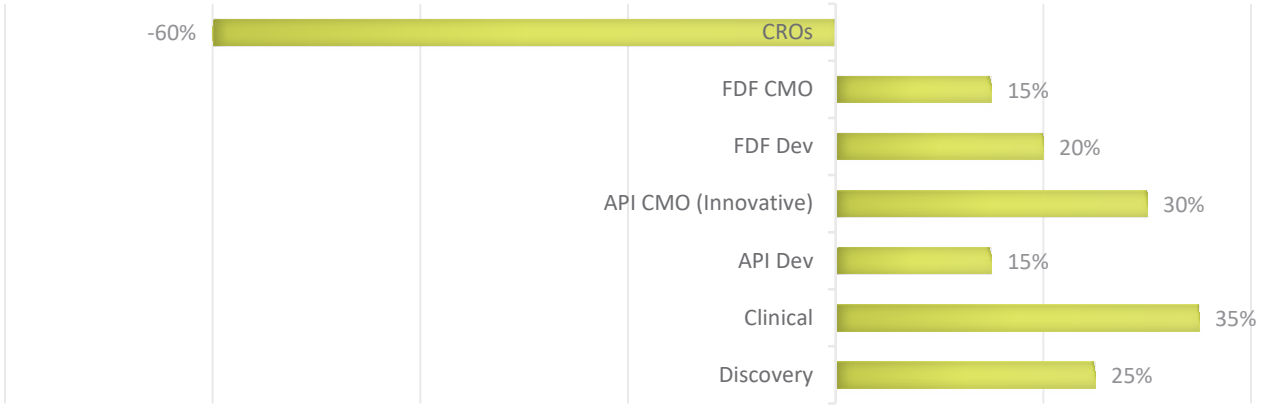
Sector Size and Growth

Highly fragmented CDMO sector: among the more attractive sectors in healthcare

Global API and FDF Market - $40B



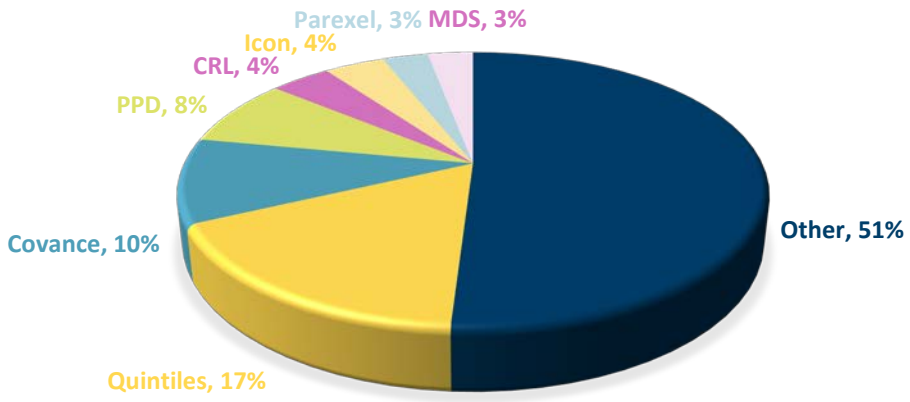
Outsourcing Penetration Rates (%)



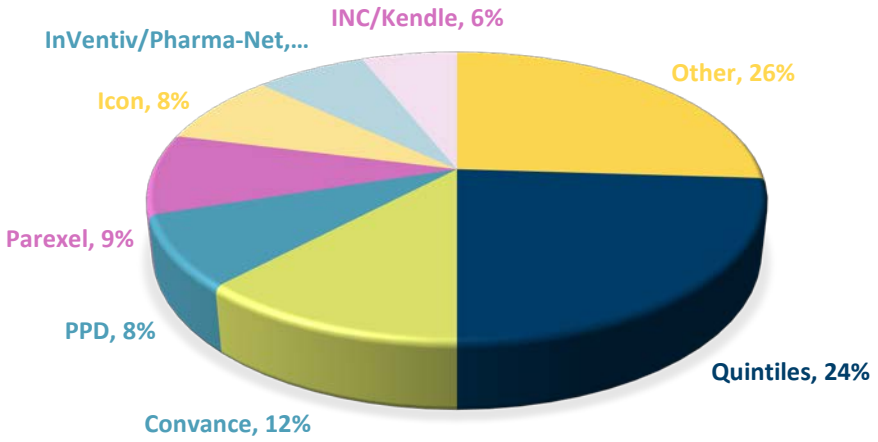
CRO ≠ CDMO

CRO Market Evolution[1]

Top 7 CROs = 49% of Market in 2007

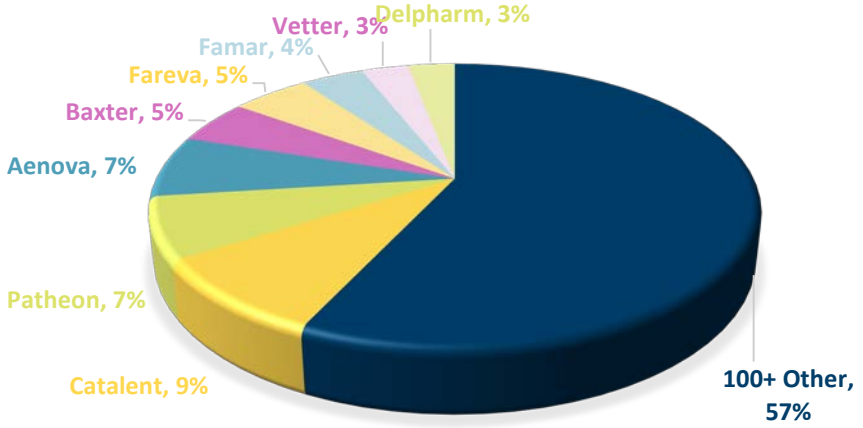


Top 7 CROs = 74% of Market in 2013



CMO Market Evolution[2]

Top 8 CMOs = 43% of Market in 2014



[1]Clinical CRO Market only; excludes pre-clinical
[2]CMO Market PharmSource

CDMOs are Growing in Sophistication

AM-17-2554

Evaluation of Mini-Tablet Drug Delivery System for Pediatric Dosage Form (PDF)

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PURPOSE

The development of pediatric dosage forms (PDF) is challenging, mainly due to the differences in swallowing abilities, taste preferences, and the dosage requirements of children. The most commonly prescribed dosage form for pediatric patients is a liquid dosage form due to its ease of administration. However, liquid dosage forms may have stability issues, have limits on dose accuracy and as a result lead to dispensing errors. The traditional solid dosage forms (tablets & capsules) may be difficult to swallow in young children. With the aim to improve drug delivery for pediatric patients, the development of a mini-tablet may prove beneficial. Mini-tablets represent a new trend in solid dosage form design and can employ a flexible drug delivery tool for single API or a composite of multiple API in low dose pediatric products. Moreover, mini-tablets with well controlled quality attributes, could be a practical choice for administering solid dosage forms in capsules or stick packs. The goal of this study was to assess size of granules, flowability, and weight variability with a mini-tablet formulation. The physical characteristics of granules prepared by roller compaction was assessed as to the impact on mini-tablets weight

OBJECTIVE(S)

The objective of this study was to investigate the properties of granules and conventional dry blend tablets to support the manufacturing of a mini-tablet as dosage form for a pediatric product.

METHOD(S)

Formulation A: Drug X (ASD), Mannitol, Croscarmellose sodium, Colloidal silicone dioxide, Microcrystalline Cellulose and Magnesium Stearate.
Formulation B: Roller compaction product of Formulation A.

Blending:
All excipients were passed through a #30 mesh screen, added to a 1 cu. ft. V-blender, and mixed together for ~ 360 revolutions (pre-lubrication). The magnesium stearate was added to above mixture and mixed for additional ~ 80 revolutions (Post-lubrication).

PSD and Flow Measurement: PSD – As per USP 40 <786>, Flow – Sotax FT300

Roller Compaction (Gerteis Mini-Pactor):
Roller Type: Knurled; Compaction force: 5 kN/cm;
Roller Gap: 2.0 mm; Screen: 0.5 mm and Roller Speed: 4 rpm

Compression:
Mini-tablets were produced by directly compressing the final blends on a Killian TX32 press fitted with 2 mm diameter, deep concave and 12-tip tooling

RESULT(S)

The particle size distribution (PSD) data for Formulation A and Formulation B is shown in **Figure 1**. The PSD data of Formulation A revealed that more than 90% of particles are less than 90 µm in size and because of such fine particles final blend have significantly lower flowability (1.28 g/sec) **(Figure 1A & 2A)**.

Figure 1A

Figure 1B

In order to improve flowability of final blend, Formulation B was developed using roller compaction. The granules of Formulation B are homogenous with more than 60% of particles are in the range of 250 µm and 425 µm and shows higher flowability (8.17 g/sec) than the corresponding counterpart Formulation A **(Figure 1B & 2B)**.

Figure 2A

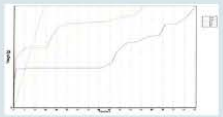

Figure 2B

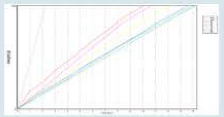

Figure 3 shows plot for weight variation during compression of three (3) different target weights (6.5 mg, 7.5 mg and 8.5 mg) mini-tablets. The weight variability was seen higher with low target weight mini-tablets (6.5 mg) as compared to higher target tablet weight (8.5 mg). Overall, weight variability was in the order of 6.5 mg > 7.5 mg > 8.5 mg.

Figure 3A – 6.5 mg

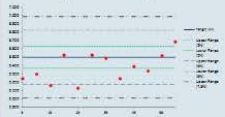

Figure 3B – 7.5 mg

Figure 3C – 8.5 mg

Figure 4 Illustrates mini-tablets and their different packaging configurations.

CONCLUSION(S)

Mini-tablets are an excellent choice for pediatric dosage forms. We evaluated the effect of particle size on tablet weight variability in mini-tablets. A large proportion of particles larger than the optimum ratio in final blend subsequently led to an increase in tablet weight variability during compression. The tolerance for weight variability in mini-tablets is smaller than for larger tablets since small absolute weight variations will lead to more significant relative variations in potency. Despite potential challenges (e.g. blend physical attributes, weight variability, size of mini-tab), this study clearly demonstrates the feasibility of mini-tablets as a drug delivery tool for low potency drug substances where to achieve high drug load per dosage is needed.

Why do companies use CDMOs?

- Specific capabilities
  - wurster-solvent coating, softgels, topicals, suppositories, controlled substances, other unique equipment trains
- Access to a particular geography
  - avoid 2nd QP/QC test when going to EU
  - avoid customs/import-export issues
- Virtual companies need development and manufacturing infrastructure
- Back up supply
  - high-value products may require risk mitigation (NCEs and sterile products)
- Technology
  - opioid abuse deterrent and solid dispersion capabilities
- Scale
  - Many commercial CMOs can offer large scale batch size options to keep COGS down
- Scale (the other way)
  - Small volume products (e.g. pediatrics) are disruptive to larger sponsor plants and are more likely to be outsourced
- Consolidation in generics
  - Plant closures may lead to an increase in outsourcing (asset “lite” models)

Confidential

Lifecycle of a Typical CDMO-Generic Company Relationship

Contract Phase	Development Phase	Approval Phase
RFI/RFQ Responses Proposals MSAs COGS Legal Project Plan Definition	Prototype Development Excipient Compatibility Accelerated Stability DOE BE Batch(s) Registration Batches and Stability	CMC CRL Responses Scale-up PPQ Design and Execution PAI Hosting and Responses Launch

Keys to a Successful CDMO Partnership

- Be Transparent
  - CDMOs are sophisticated enough to understand the market for a particular product. Larger CDMOs have access to IMS and can interpret the information.
- Be Creative
  - CDMOs will work on a key-milestones basis and share some risk. Try to structure flexibility into the relationship to drive win-win.
- Be Aggressive
  - CDMOs have the ability to handle more than one project at a time under very tight timelines. CDMOs are used to working in a fast paced tight timeline environment. The market is changing and being an “early filer” may ensure better economics.
- Communicate
  - There will always be technical challenges during development. Constant communication is critical.

Q&A