

- ■ Evolution and current trends in nasal drug delivery devices with an emphasis on systems for pain management.

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Background

- Nasal aerosol products have been around for a number of years
- Estimated market for nasally administered systemic drugs, >2Bn\$ in 2009 & growing (source IMS & Espicom), >1B\$ for nasal pain management products
- Main factors driving market changes:
 - Severe pressure on health care costs ↘
 - Increasing generics sector ↗
 - Fast growing emerging markets sector ↗
 - Drugs coming off patent → differentiation & life cycle management ↗
 - Increased and ageing population ↗
 - Unmet medical needs ↗
 - More emphasis on patient compliance and convenience ↗

Advantages of nasal route of administration

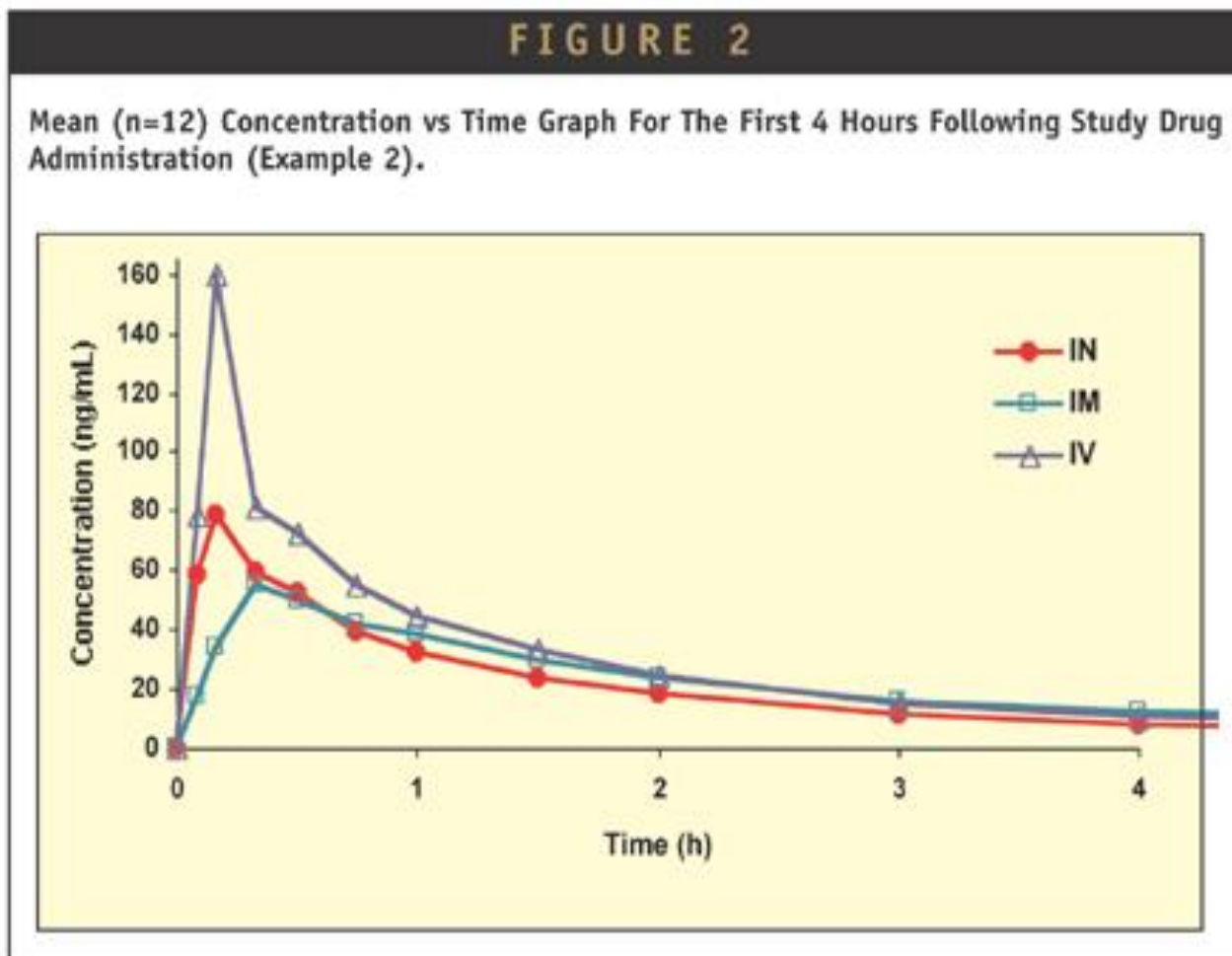
- ■ Non-invasive (eliminate pain & anxiety of injections)
- ■ Rapid onset of action
- ■ Good bioavailability
- ■ Acceptability, improved comfort / compliance
- ■ Self-medication
 - Reduced medical staff supervision/intervention
 - Significant cost savings (vs injections)
- ■ Avoidance of 1st pass metabolism (vs oral)

Advantages of nasal route of administration

	Tmax, min.	Bioavailability, %
Opioids	<25	>50*
Benzodiazapines	10 to 25	38 to 98
Anti-migraine agents	25 to 90	5 to 40

* As compared to intravenous

Advantages of nasal route of administration



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Potential applications of nasal route of administration

■ In-hospital

- Post-operative pain management
- Burns pain management
- Breakthrough cancer pain management etc

■ Out of hospital

- Palliative care
- Paramedic retrieval medical services
- Post-operative pain management
- Anti-migraine treatments
- Drug overdosing emergency etc

Early generation of anti-migraine nasal spray devices

❖ Diergospray®/Migranal®

- Adaptation of a standard nasal spray pump
- With glass ampoule containing anti-migraine product
- Open ampoule, put dip tube (& spray pump) in ampoule
- Prime the nasal spray device
- Deliver dose into nasal cavities



Early generation of anti-migraine nasal spray devices

■ Imigran®/Imitrex®

- Specifically developed unidose system
- No need to prime before use



■ Zomig®

- Customized unidose system
- No need to prime before use



Nasal multidose systems for pain management

■ Stadol®

- Active ingredient , Butorphanol
- Prime pump before use
- Can deliver 14 or 15 doses



Recent additions to the marketplace

■ PecFent®

- Active ingredient , Fentanyl
- Prime pump before use
- Can deliver multiple doses
- Can be self-administered



Recent additions to the marketplace

■ Instanyl®

- Active ingredient , Fentanyl
- Prime pump before use
- Can deliver multiple doses
- Can be self-administered



Coming to market soon

■ Sprix™

- First systemic non-opioid nasal spray for pain management in the US market
- Developed by Roxro Pharma
- Active ingredient , Ketorolac tromethamine
- Can deliver multiple doses
- Can be self-administered



Coming to market soon?

❑ Optinose

- For single or multiple dosing of liquid/powder formulations
- Airflow initiated by patient's exhale air or external flow-source
- Bi-directional airflow to improve deposition
- Currently in clinical studies for anti-migraine treatments (sumatriptan) amongst others



Also happening in inhalation.....

■ Taifun®

- Reservoir DPI
- Active ingredient , Fentanyl citrate
- « for breakthrough cancer pain management »
- « Clinical results deliver rapid onset of action and increased bioavailability... »



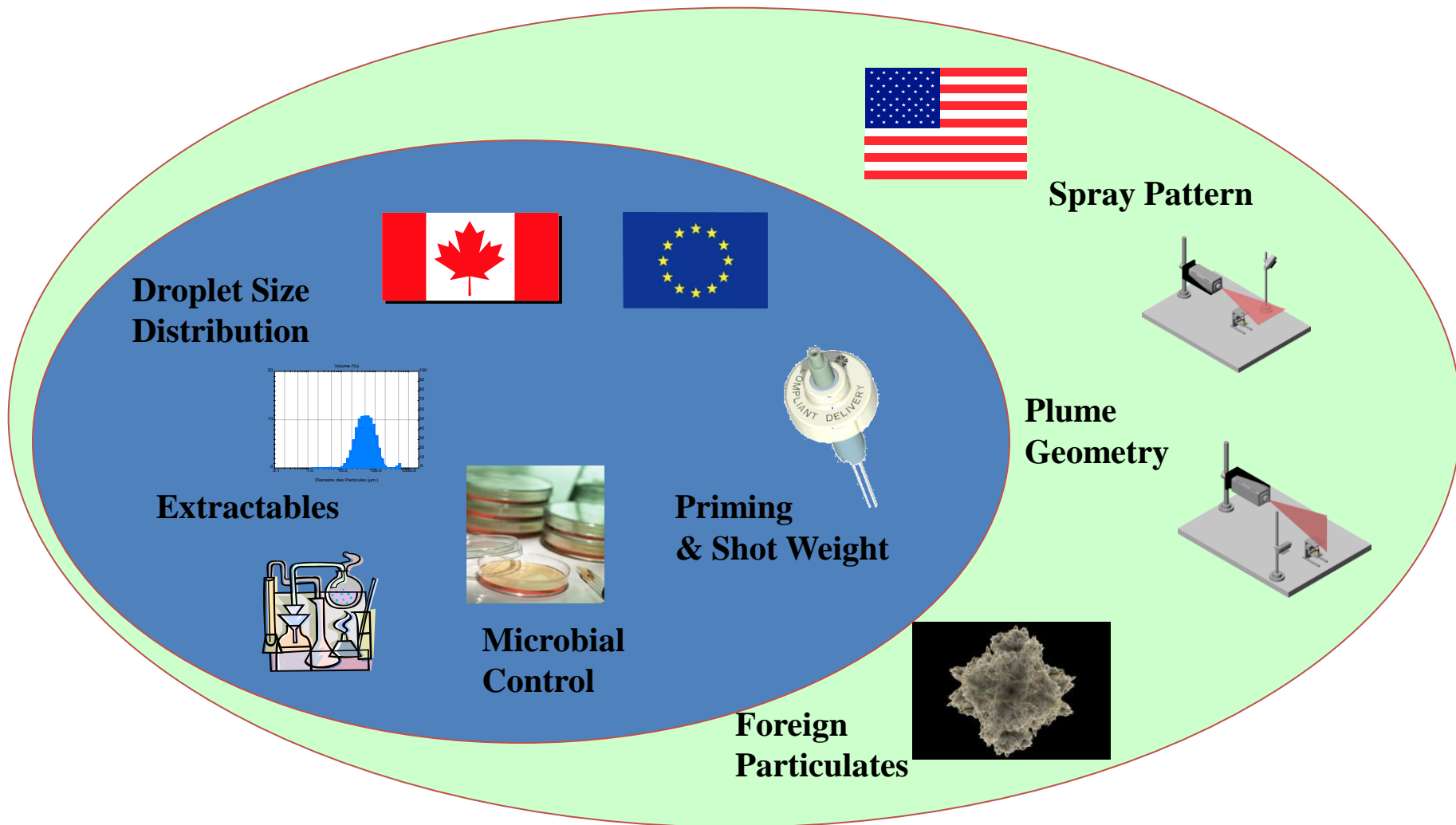
Challenges and future opportunities

❑ Evolving regulatory landscape, examples

- **Europe** - EMEA-Heath Canada: Joint Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products EMEA/CHMP/QWP/49313/2005
- **USA** - Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products Chemistry, Manufacturing and Controls Documentation, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), May 1999
- **Brazil** - Guidance for Pharmaceutical Equivalence and the Bioequivalence of Nasal Sprays and Aerosols, Agência Nacional de Vigilância Sanitária [National Health Surveillance Agency], Brasil, 2008



Evolving regulatory landscape, examples



Future challenges and opportunities

- ■ Powerful pain management treatments, potent molecules, controlled substances

- ■ Potential issues
 - Overdosing
 - Side effects
 - Diversion, misuse

- ■ Can be dealt with by
 - Dose counters
 - Lockout systems
 - Tamper or child resistance packaging solutions



Future challenges and opportunities

- Patient compliance and convenience
- Significant waste of medicines
 - Not taking the right dose
 - At the right time
 - According to the prescription
 - Several Bn\$/yr related costs, due to lack of compliance



- Can be dealt with by
 - Mechanical or electronically based device solutions
 - Dose counters
 - Lockout systems
 - Tele-medicine, healthcare monitoring of device (medicine) use, adjustments to make maximum efficacy & efficiency, reduced healthcare costs

Potential e-device solutions

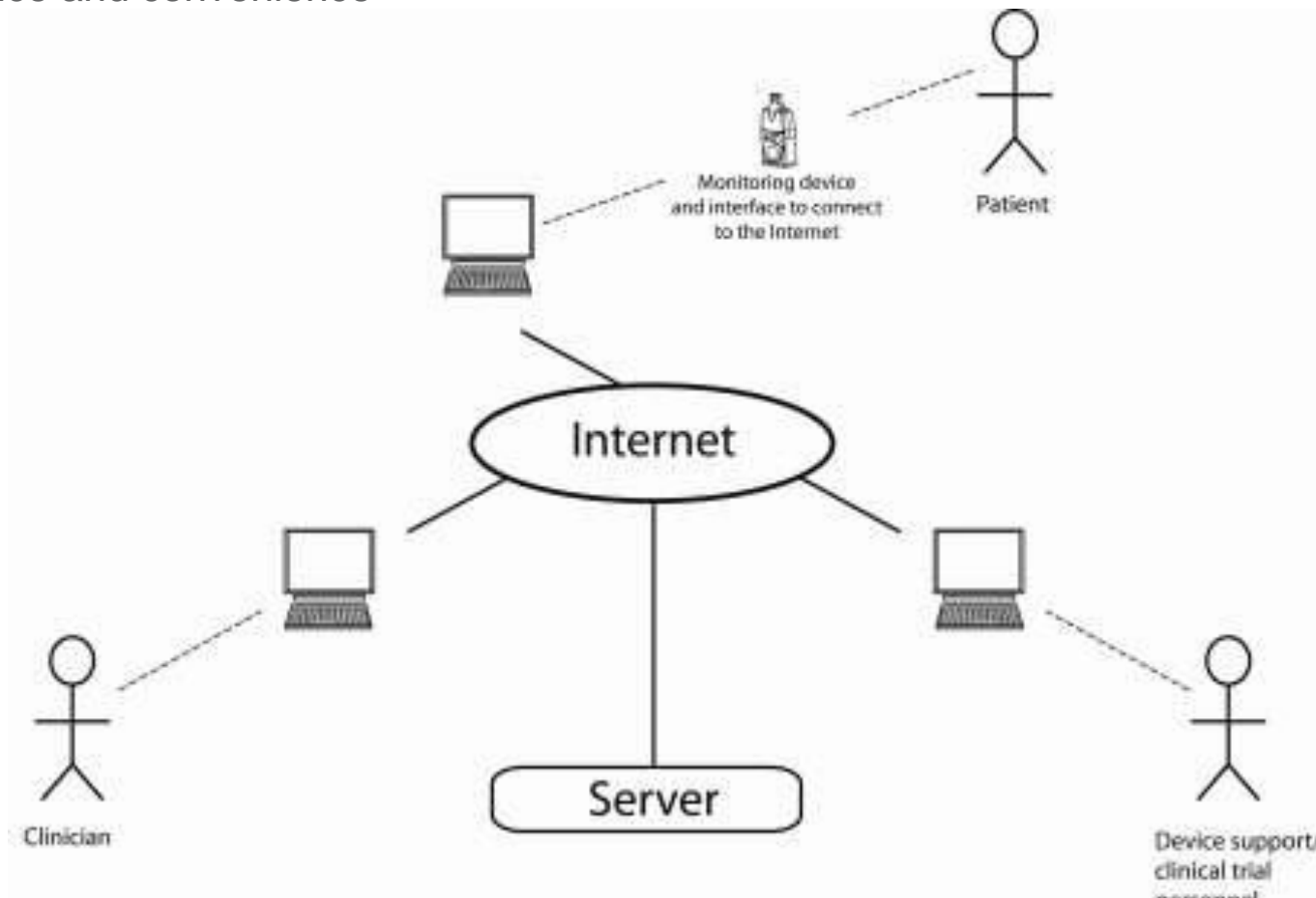
- Dose counting
- Lock-out systems
- Monitoring (home tele-medicine)
- Can prevent theft & diversion (RFID..)
- Costs of electronics are reducing
- Self-titration, reduced healthcare costs
- Improved compliance

- Regulatory acceptance?



Future challenges and opportunities

- Patient compliance and convenience
- Tele-medicines?



Summary

- ■ Nasally administered aerosols have many advantages
- ■ Managing pain by the nasal route is a growing market
- ■ Devices have evolved over the years to meet market and regulatory needs
- ■ Many opportunities and challenges exist
- ■ These can be met by mechanical or electronically based device solutions
- ■ This nasal drug delivery mode has a bright future