DRUG ENFORCEMENT ADMINISTRATION

Supply Chain Conference 2024

Aggregate Production and Individual Quotas
UN Reporting and Quota Section
Diversion Control Division

April 30 - May 2, 2024

Little Rock, Arkansas

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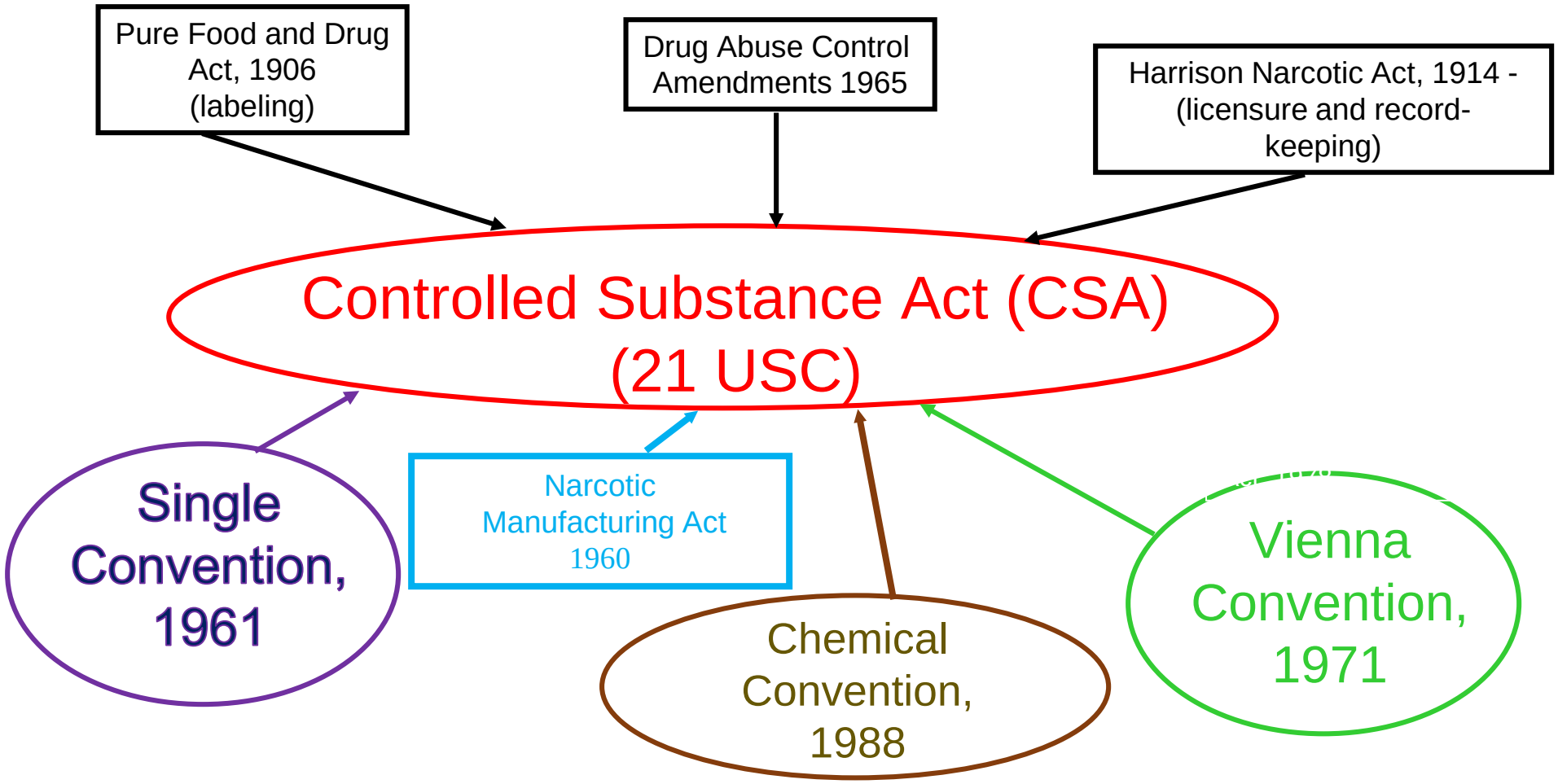
CSA - Historical Perspective



Levels of Drug Control under the CSA

Schedule I (CI) - NEED QUOTA (MFG)

Substances with **high** abuse potential and **no** currently accepted medical use (most restrictive): *e.g., GHB, MDMA, Heroin*

Schedule II (CII) - NEED QUOTA (MFG)

Substances with **high** abuse potential but has a currently accepted medical use in treatment: *e.g., Fentanyl, Hydrocodone, Morphine, Oxycodone.*

Schedule III, IV and V – no quota needed

Substances with accepted medical use in treatment in the U.S. and high (CIII) to progressively lower levels of abuse potential, dependence profile and regulatory controls: *e.g., NaGHB (sodium oxybate), Ketamine, Buprenorphine, Benzodiazepines.*

CMEA* List I chemicals - NEED QUOTA (MFG/IMPORT)

ephedrine (EPH), pseudoephedrine (PSE) & phenylpropanolamine (PPA)

Substances used for manufacture of cough & cold medicines and veterinary products, but can also be used for illicit manufacture of methamphetamine & amphetamine

*Combat Methamphetamine Epidemic Act

Purpose of Quotas

- **Limit the quantity of importation of CMEA List I chemicals, as well as manufacturing and procurement of CMEA List I chemicals and CI and CII**
- **Restrict the above import, manufacture and procurement to DEA registered manufacturers**
- **Provide for legitimate need – medical, scientific, research, industrial, export**
- **Provide adequate inventories to support legitimate needs**

New Quota Rules

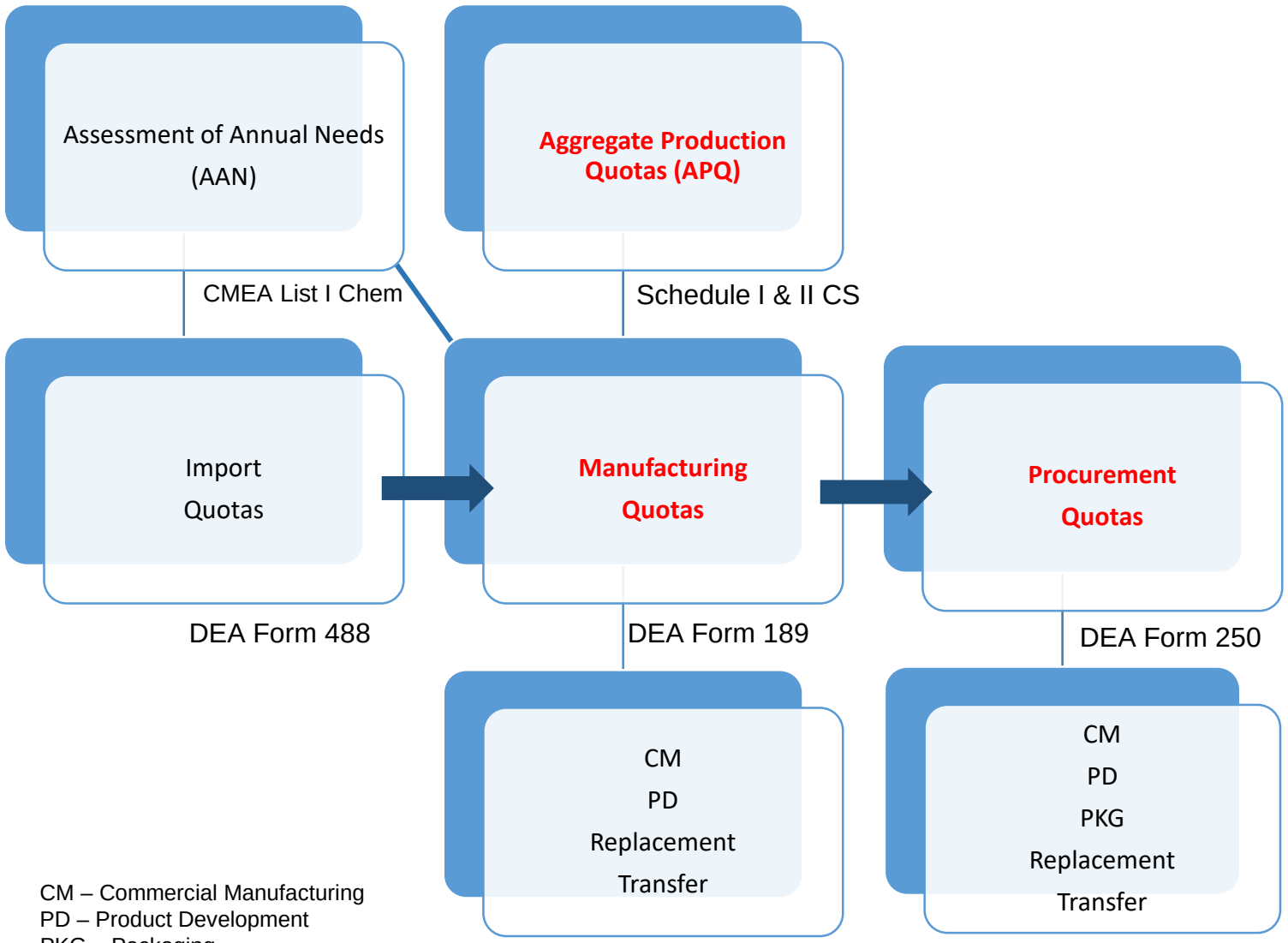
Management of Quotas for Controlled Substances and List I Chemicals

- Effective on November 29, 2023
- 88 FR 60117, published on August 31, 2023

Overview of changes

- Formalization of subcategories for manufacturing and procurement quotas
  - Commercial sales, transfer, product development, replacement, packaging/repackaging and labeling/relabeling
- Changes to regulatory deadlines
  - Establishment of APQ and the AAN: September 1
  - Issue procurement, import and manufacturing quota: December 1
  - Adjust individual manufacturing quota: July 1
- Reduction of manufacturer's inventory allowances (discussed in later slides)
- Procurement quota certification requirements for manufacturers
  - Requiring both manufacturers and distributors to obtain certification of a buyer's quota for the requested schedule I and II controlled substances, as well as list I chemicals when the buyer is a manufacturer.

AAN vs APQ: Quotas with subcategories



CM – Commercial Manufacturing
PD – Product Development
PKG – Packaging

Schedule I and II CS Quota Requirements

Pursuant to 21 CFR Part 1303

- **Aggregate Production Quotas (APQ)**
  21 CFR 1303.11 and 1303.13

- **Individual Manufacturing Quotas (MQ)**
  21 CFR 1303.21 through 1303.27

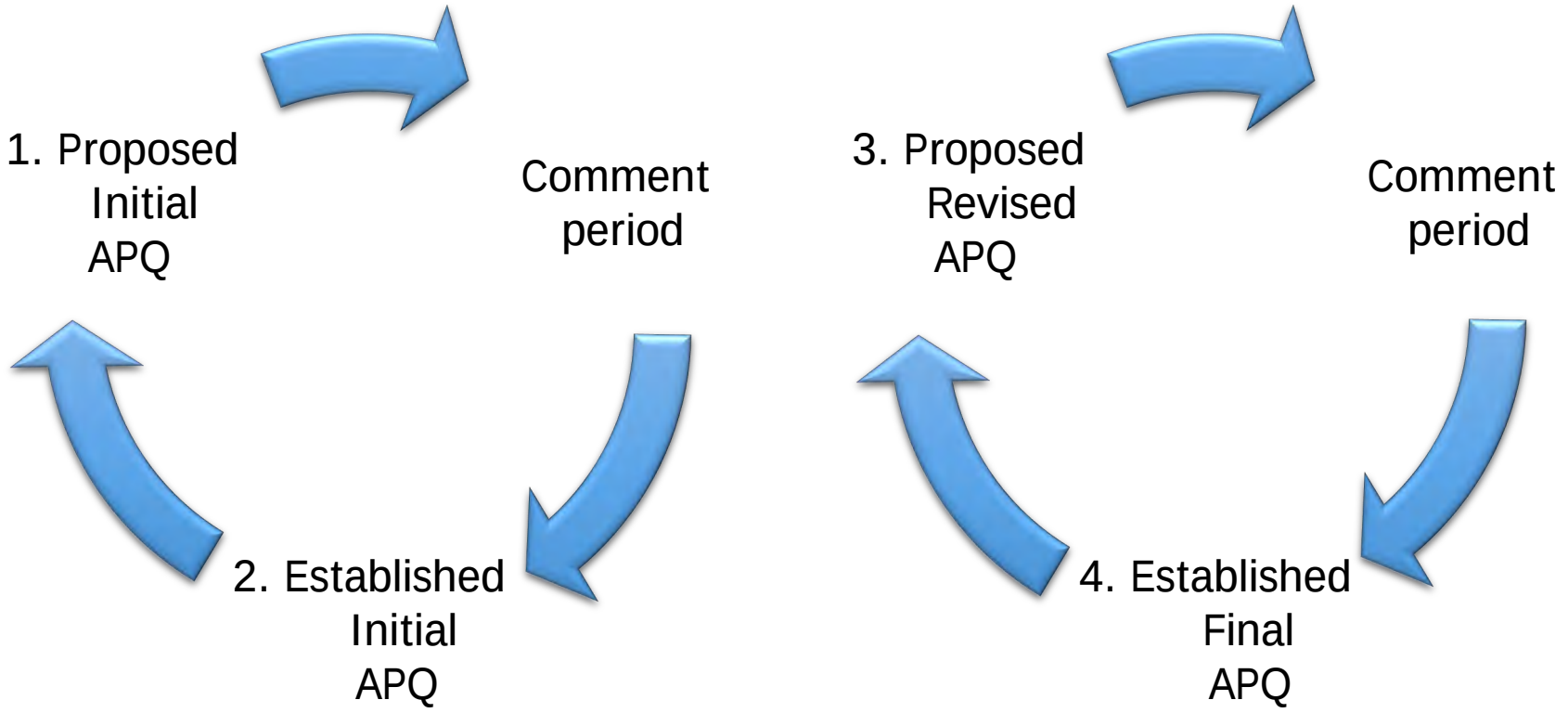
- **Procurement Quotas (PQ)**
  21 CFR 1303.15 through 1303.17

- **Import Quotas (IQ)**
  IQ only needed for CMEA List I chemicals

Aggregate Production Quotas

- Only applies to Schedules I and II controlled substances (as the basic class i.e. anhydrous base)
- Sets the upper limit of national manufacturing
- Historically established annually with one revision
- Federal Register notices required

Aggregate Production Quotas (APQ) Federal Registers



APQ Determined By Considering

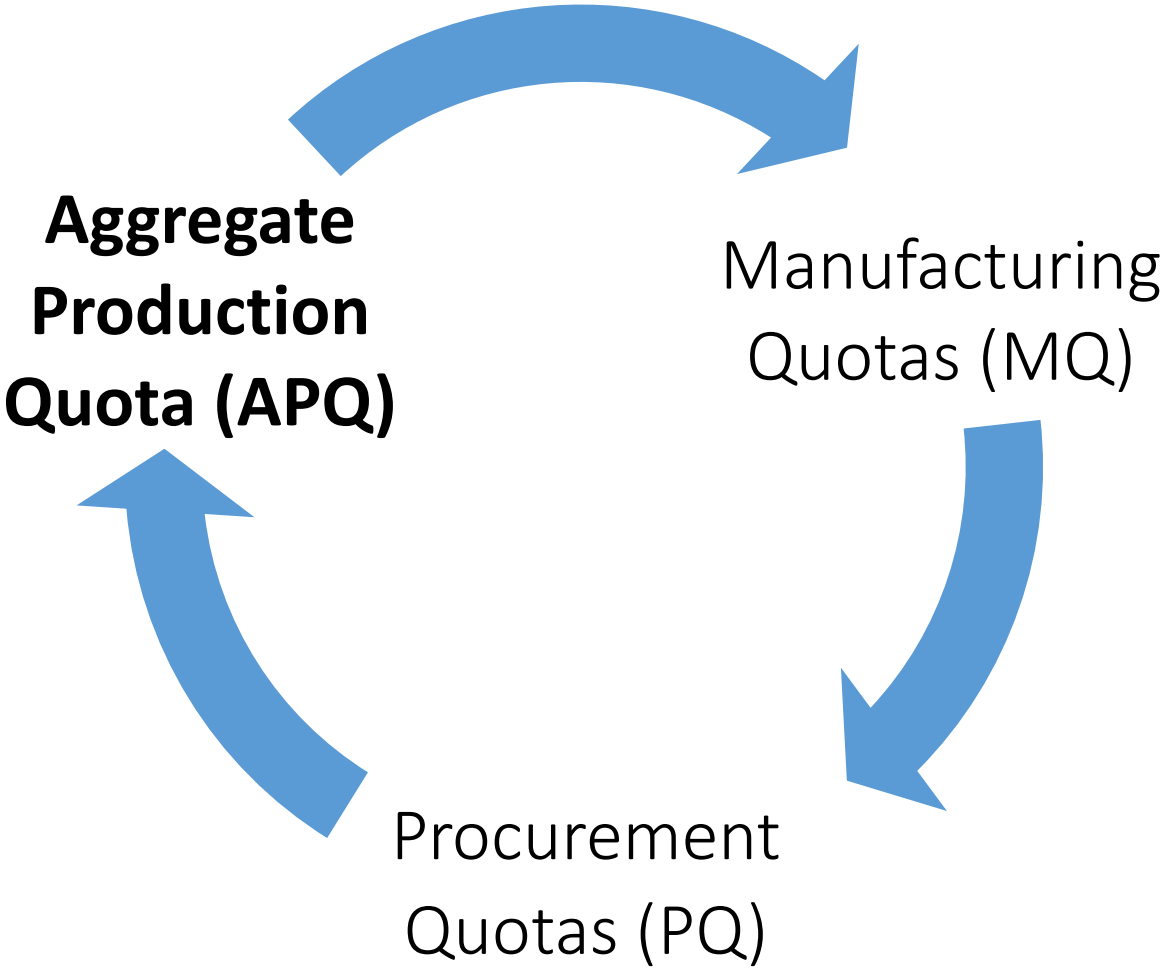
- **Data from Procurement Quotas applications**
  - Dispositions – domestic and export
  - Product development, yields, etc.
  - Inventory data

- **Data from Manufacturing Quotas**
  - Procurement quotas
  - Historical share of the market
  - Product development, yields, etc.
  - Inventory data

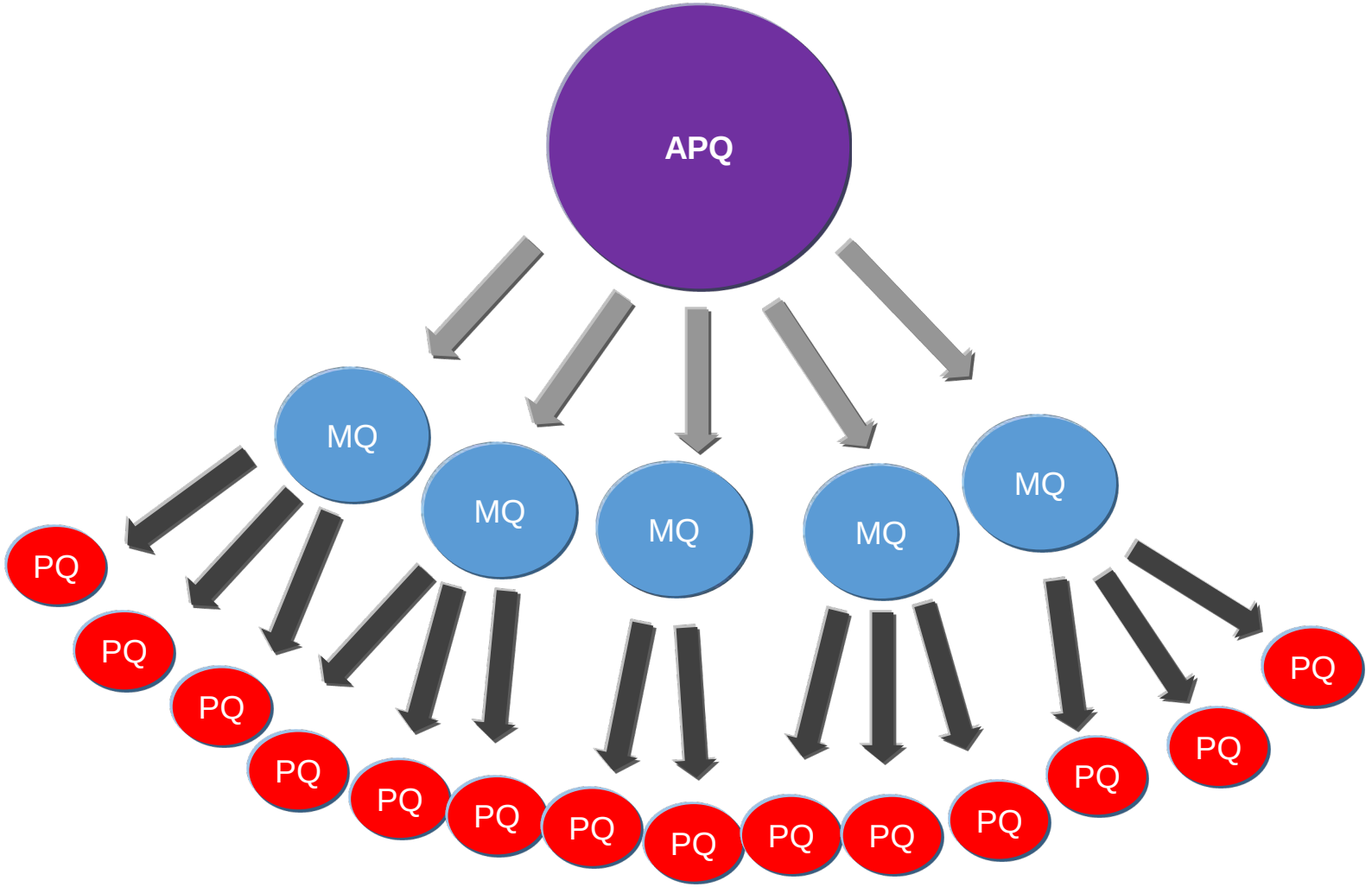
- **FDA Estimates of legitimate domestic medical need**

- **Diversion, abuse, consumption, trafficking data**
  - SUPPORT Act
  - CDC overdose data
  - State PDMP data
  - DEA Drug Theft Loss Data

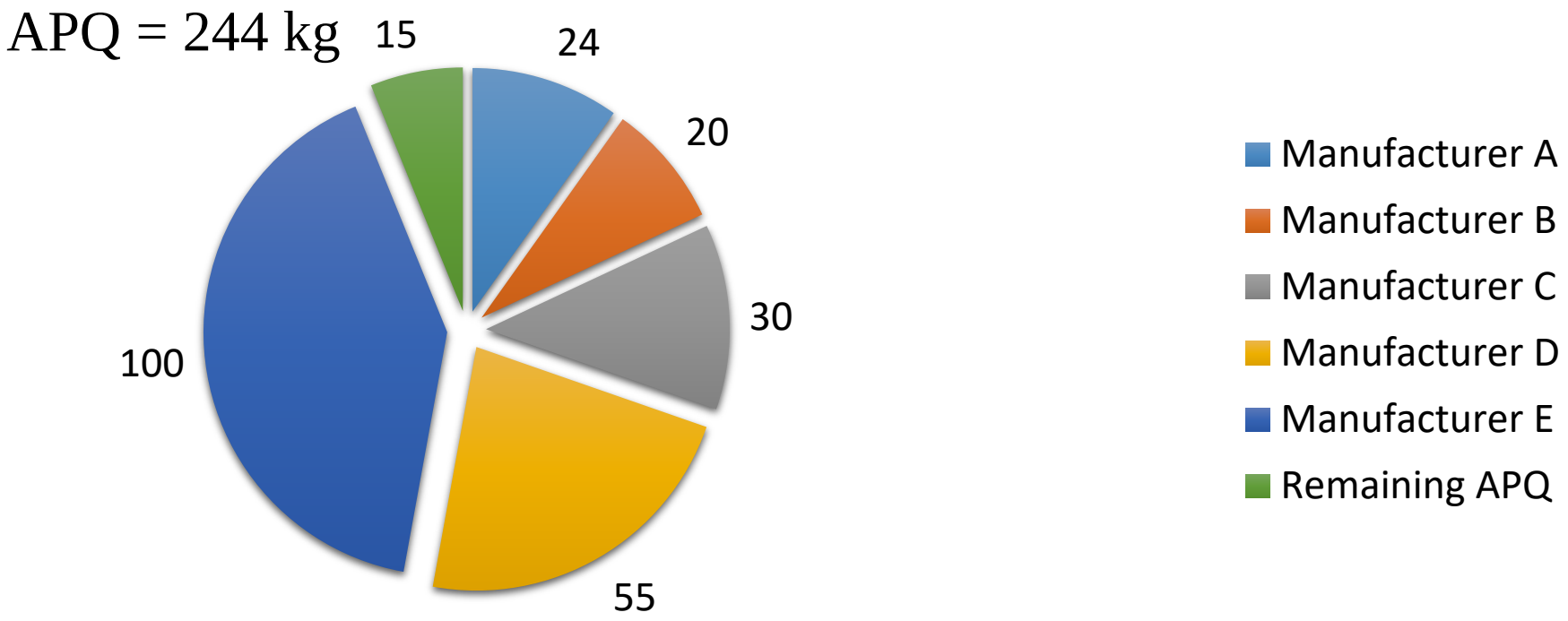
Quota – APQ Relationship



APQ – MQ – PQ



Relationship Between APQ and Manufacturing Quotas



APQ Time Machine

Basic class	Proposed 1995 quotas
Schedule I	
Acetylmethadol	2
Aminorex	2
Bufotenine	10
Cathinone	4
Difenoxin	14,000
2, 5-Dimethoxyamphetamine	15,650,000
Dimethylamphetamine	2
N-Ethylamphetamine	4
Lysergic acid diethylamide	41
Mescaline	2
4-Methoxyamphetamine	12
4-Methylaminorex	2
3-Methylfentanyl	12
Methaqualone	2
Methcathinone	9
3, 4-Methylenedioxyamphetamine	12
3, 4-Methylenedioxy-N-ethylamphetamine	2
3, 4-Methylenedioxymethamphetamine	12
Normorphine	2
Tetrahydrocannibinols	35,000
Thiophene Analog of Phencyclidine	10

1995 APQ:
21 Schedule I Substances

2024 APQ:
262 Schedule I Substances

APQ Time Machine

Schedule II

Alfentanil	7,000
Amobarbital	5
Amphetamine	635,000
Cocaine	550,000
Codeine (for sale)	67,312,000
Codeine (for conversion)	16,181,000
Dextropropoxyphene	124,012,000
Dihydrocodeine	202,000
Diphenoxylate	688,000
Ecgonine (for conversion)	650,000
Fentanyl	76,000
Hydrocodone	8,474,000
Hydromorphone	393,000
Levo-alpha-acetylmethadol	200,000
Levorphanol	8,000
Meperidine	8,637,000
Methadone	3,779,000
Methadone (for conversion)	364,000
Methadone Intermediate (for sale)	300,000
Methadone Intermediate (for conversion)	4,393,000
Methylphenidate	7,935,000
Morphine (for sale)	7,612,000
Morphine (for conversion)	78,105,000
Noroxymorphone (for sale)	21,000
Noroxymorphone (for conversion)	3,500,000
Opium	1,118,000
Oxycodone (for sale)	3,613,000
Oxycodone (for conversion)	6,200
Oxymorphone	2,500
Pentobarbital	15,706,000
Phencyclidine	52
Phenylacetone (for conversion)	3,528,000

1995 APQ:
36 Schedule II Substances

2024 APQ:
77 Schedule II Substances

Manufacturing Quotas

Bulk manufacturers (also known as API manufacturers) of Schedules I and II controlled substances and/or CMEA List I chemicals whose methods include:

- **Extraction from plant material**

  - coca leaf, opium, concentrated poppy straw

- **Synthetic routes**

  - converting morphine into hydromorphone

  - controlled substances derived from non-controlled starting materials

*API Manufacturers = Active Pharmaceutical Ingredient Manufacturers

Manufacturing Quotas

- Only DEA registered manufacturers with the specific CI or CII drug codes receive MQ
- Establish maximum amount which the individual API manufacturer may *manufacture* in a calendar year
- Manufacturers cannot exceed manufacturing quota
- Establish guidelines for inventory allowances

Manufacturing Quotas Inventory Allowance

21 CFR 1303.24 and 1315.24

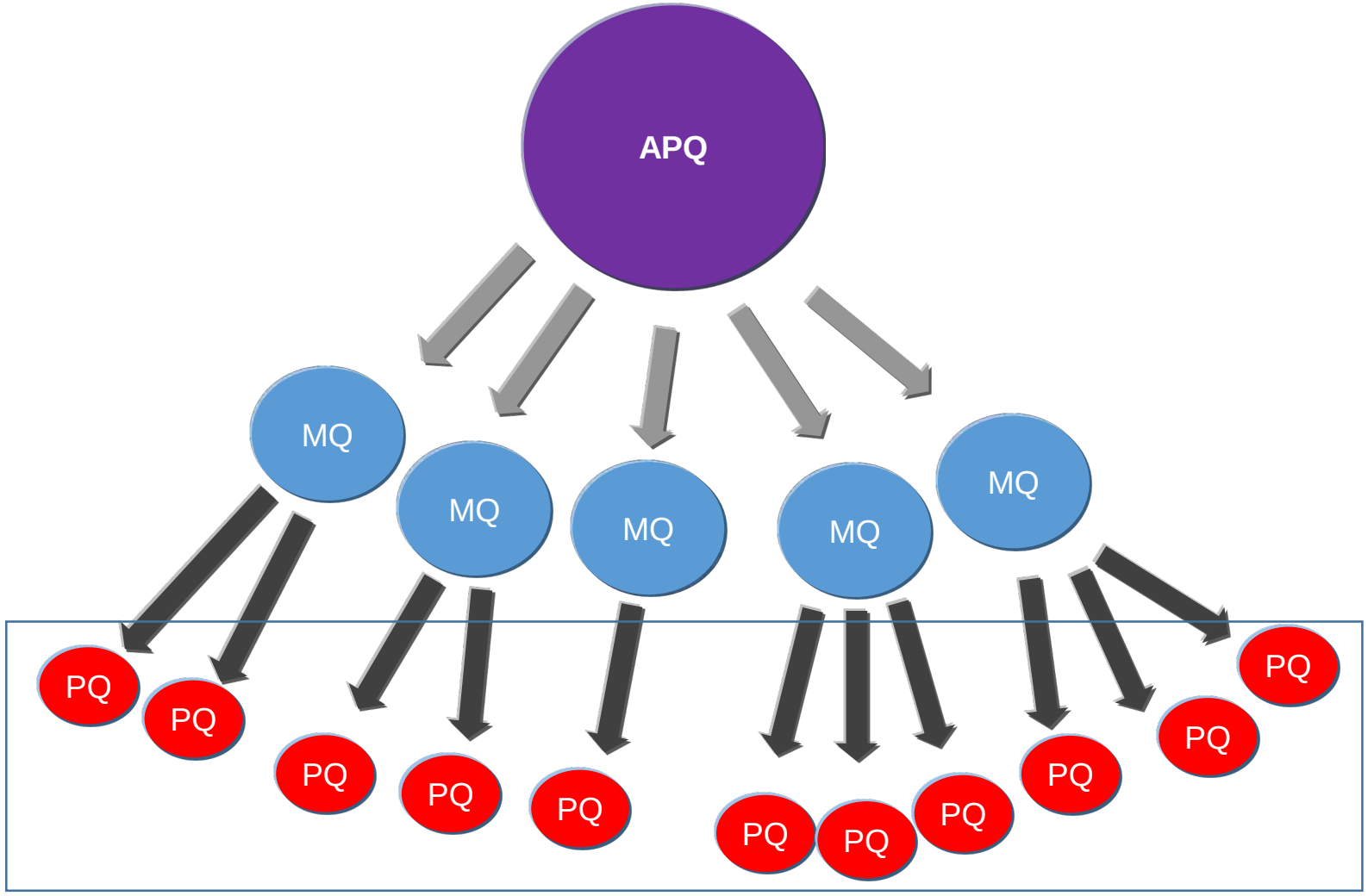
- Normally 40% of average net disposals for current and last preceding year
- During the calendar year, inventory may not exceed 55% of estimated net disposal
- Exceeding 55% will suspend quota until inventory is less than 50% of net disposals

Manufacturing Quotas

Granted to DEA registrants based on:

- **Procurement Quotas**
- **Historical share of the market**
- **Inventory (saleable; bulk, in-process and finished dosage forms)**
- **Product development efforts**
- **Limited by the APQ (CI and CII), AAN (CMEA List I chemicals)**

APQ – MQ – PQ



Procurement Quotas

Manufacturers who procure a Schedule I or II controlled substances, or CMEA List I chemicals for the purposes of:

- **Converting bulk API into finished dosage forms**
- **Formulating products such as exempt chemical preparations or reference standards**
- **Packaging, repackaging, labeling or re-labeling a commercial container or dosage form**
- **Performing product development activities**

Procurement Quotas Inventory Allowance

21 CFR 1303.16 and 1315.31

Solid dosage form manufacturers:

- Normally 35% of average net disposals for current and last preceding year
- During the calendar year, inventory may not exceed 50% of estimated net disposal
- Exceeding 50% will suspend quota until inventory is less than 45% of net disposals

Liquid injectable dosage form manufacturers:

- Normally 50% of average net disposals for current and last preceding year
- During the calendar year, inventory may not exceed 65% of estimated net disposal
- Exceeding 65% will suspend quota until inventory is less than 60% of net disposals

Procurement Quotas

- **Only DEA registered manufacturers with the specific CI or CII drug code can receive**
- **Establish maximum amount which the individual manufacturer may *acquire* in a calendar year**
- **Manufacturers cannot procure amounts exceeding the procurement quotas**
- **Certification of adequate quota needed to place order**
  - 21 CFR 1303.15(f) and 1315.32(h)
  - Manufacturers must provide written certification to their supplier(s) before procuring schedule I & II controlled substances and CMEA List I chemicals ephedrine, pseudoephedrine and phenylpropanolamine

Procurement Quotas

Granted to DEA registrants based on:

- **Dispositions (domestic sales and exports)**
- **Manufacturing loss and destruction**
- **Inventory of saleable material**
- **Acquisitions from both domestic manufacturers and importers**
- **Product development, packaging and repackaging activities**
- **Customer data**

Procurement Quota - FAQ

- Analytical exempted Standards

  - No quota is needed as per 21 CFR 1303.15 (e)(2)

- Research

  - No quota needed for research registration per 21 CFR 1303.15 (e)(3)

  - Be aware of what is considered research versus manufacturing

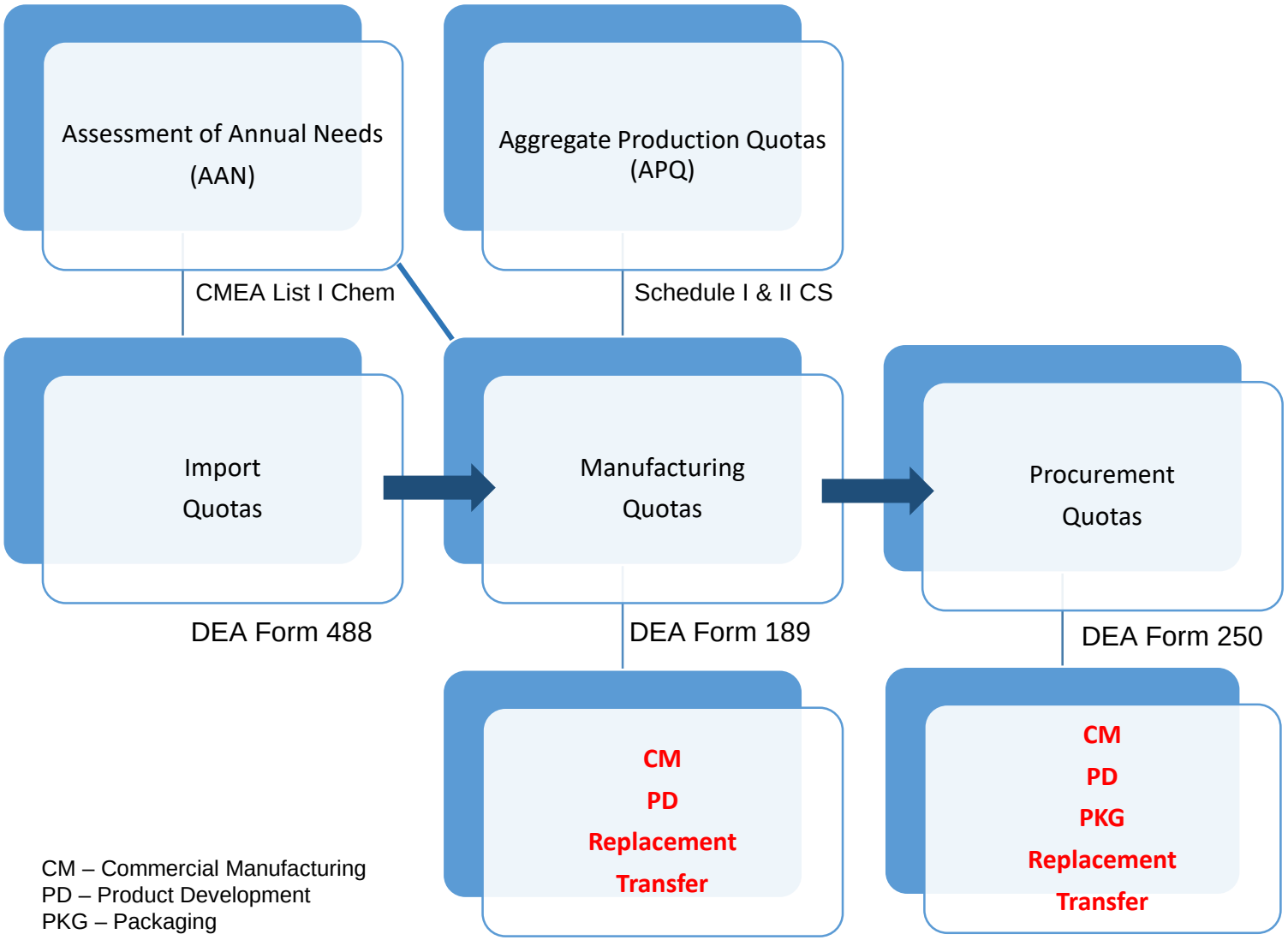
Procurement Quota - FAQ

What if the registration number changes?

- The new registration should submit a PQ request to transfer inventory from old registration.
- New PQ is needed to start activity under new registration. Existing quota from the old registration does not transfer to the new registration.
- Must submit new quota applications online once all necessary drug codes have been added to registration

NOTE: QUOTA DOES NOT TRANSFER FROM ONE REGISTRATION TO ANOTHER

AAN vs APQ: Quotas with subcategories



CM – Commercial Manufacturing
PD – Product Development
PKG – Packaging

What are the sub-categories of MQ/PQ Quotas?

Commercial Manufacturing (CM) – A subcategory of both MQ and PQ

- **MQ**
  - Manufacturing of bulk API
  - Conversion of material from one drug class to another
- **PQ**
  - Dosage form
  - starting material for reference standards or exempt products
- FDA approved Drug Master File (DMF), New Drug Application (NDA), Abbreviated NDA (ANDA)

Product Development – Typically a subcategory of PQ but sometimes MQ

- Applicable to activities leading ***to*** FDA approval (pending DMF, NDA, or ANDA)
  - Scale up
  - Stability
  - Exhibit
  - Validation

What are the sub-categories of MQ/PQ Quotas?

Packaging (PKG) – A subcategory of PQ

- Packaging/Repackaging activities
- Labeling/Relabeling activities

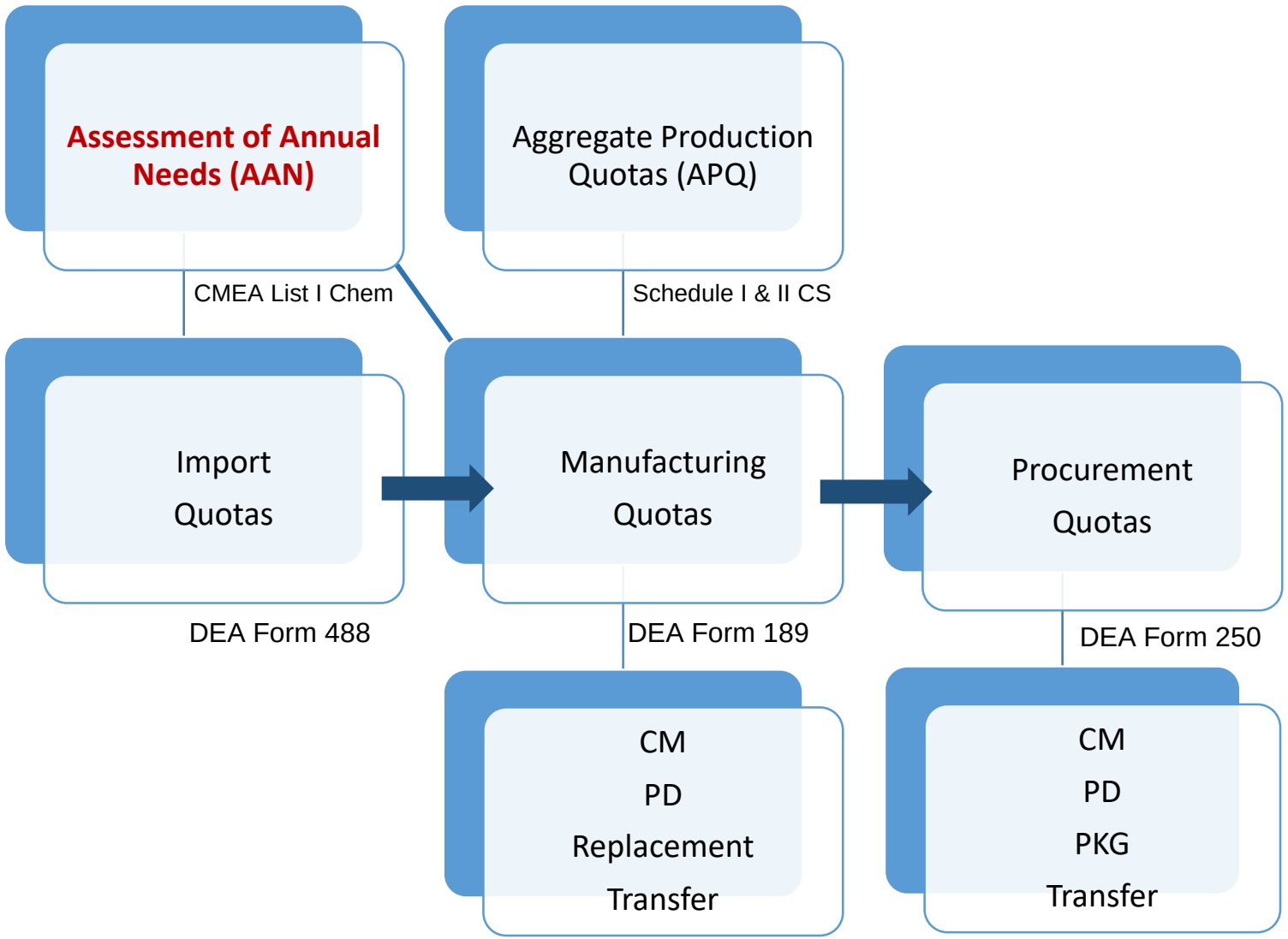
Replacement – A subcategory of MQ and PQ

- Case-by-case basis only
- Important to note that it is not always a one-to-one replacement

Transfer – A subcategory of MQ and PQ

- Return of defective bulk API
- Processing of product (micronization) that may require more than one manufacturing site
- Move existing inventory from closing facilities to another registration

AAN vs APQ: Quotas with subcategories



Combat Methamphetamine Epidemic Act 2005 (CMEA)

Enacted on March 9, 2006

Ephedrine (EPH), Pseudoephedrine (PSE), and Phenylpropanolamine (PPA)

- Additional legislative and regulatory controls on the manufacture, distribution, importation, and exportation of these CMEA List I chemicals

- Registration now required for each physical location (manufacturer, distributor, importer or exporter)

Quota Provisions of CMEA

- **API manufacturers who synthesize EPH, PSE and PPA must obtain a manufacturing quota**

- **Manufacturers who purchase EPH, PSE and PPA must obtain a procurement quota**
  - Dosage form manufacturers, packagers, labelers, repackagers and relabelers

- **Importers who import EPH, PSE and PPA (or products containing EPH, PSE, and PPA) must obtain an import quota**

Quota Provisions of CMEA

- Before issuing individual quotas, DEA had to first establish the annual needs of the United States for EPH, PSE and PPA

- The 2008 Assessment of Annual Needs (AAN) was published in the Federal Register on December 27, 2007

- DRQ began issuing individual quotas on December 30, 2007 for the calendar year 2008

CMEA List I Chemicals Quota Requirements

Pursuant to 21 CFR Part 1315

- **Assessment of Annual Needs (AAN)**
  21 CFR 1315.11 and 1315.13

- **Manufacturing Quotas (MQ)**
  21 CFR 1315.21 through 1315.27

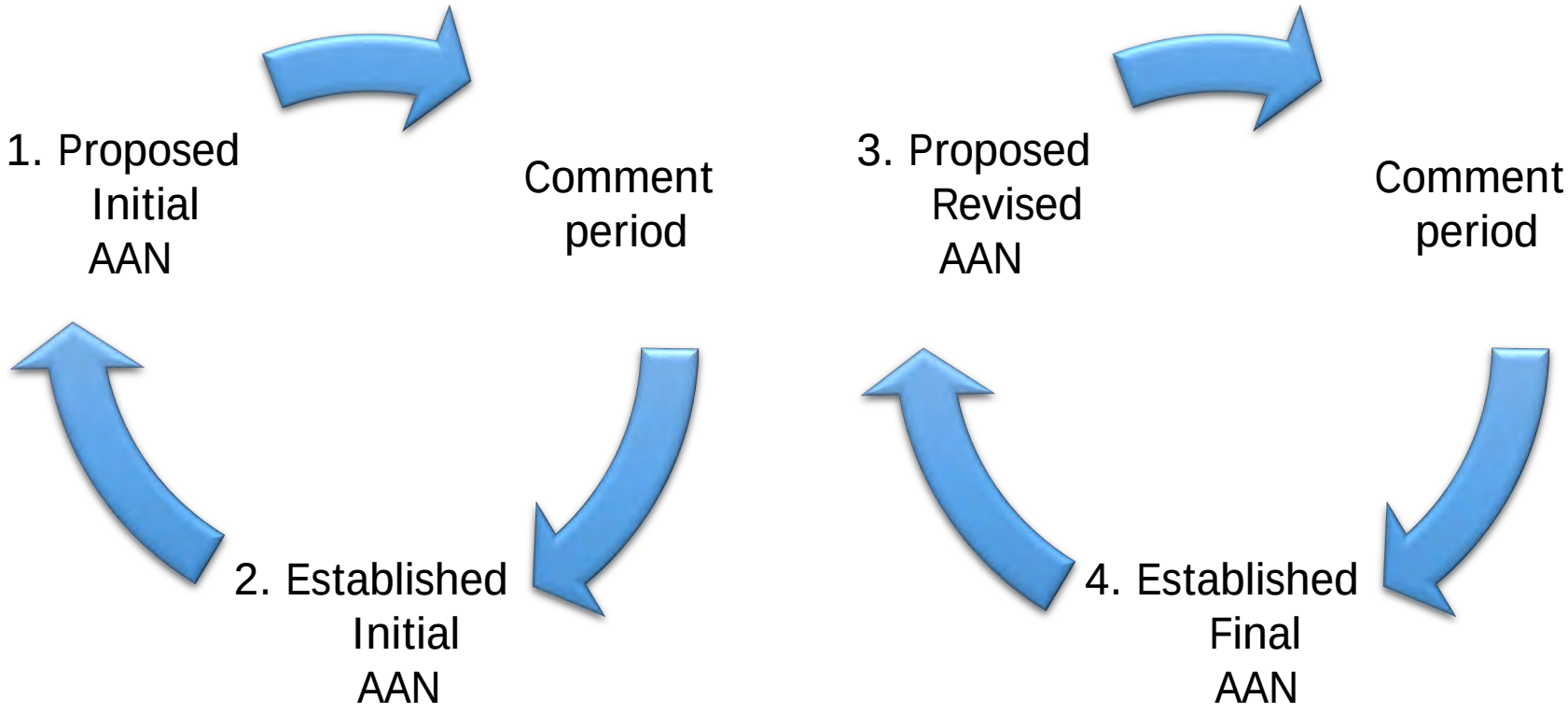
- **Procurement Quotas (PQ)**
  21 CFR 1315.30 and 1315.32

- **Import Quotas (IQ)**
  21 CFR 1315.34 and 1315.36

Assessment of Annual Needs

- Only applies to CMEA List I chemicals
- Sets the upper limit of national import and manufacturing CMEA List I chemicals
- Established annually and revised as required
- Federal Register Notices required for both establishment and revision of AAN

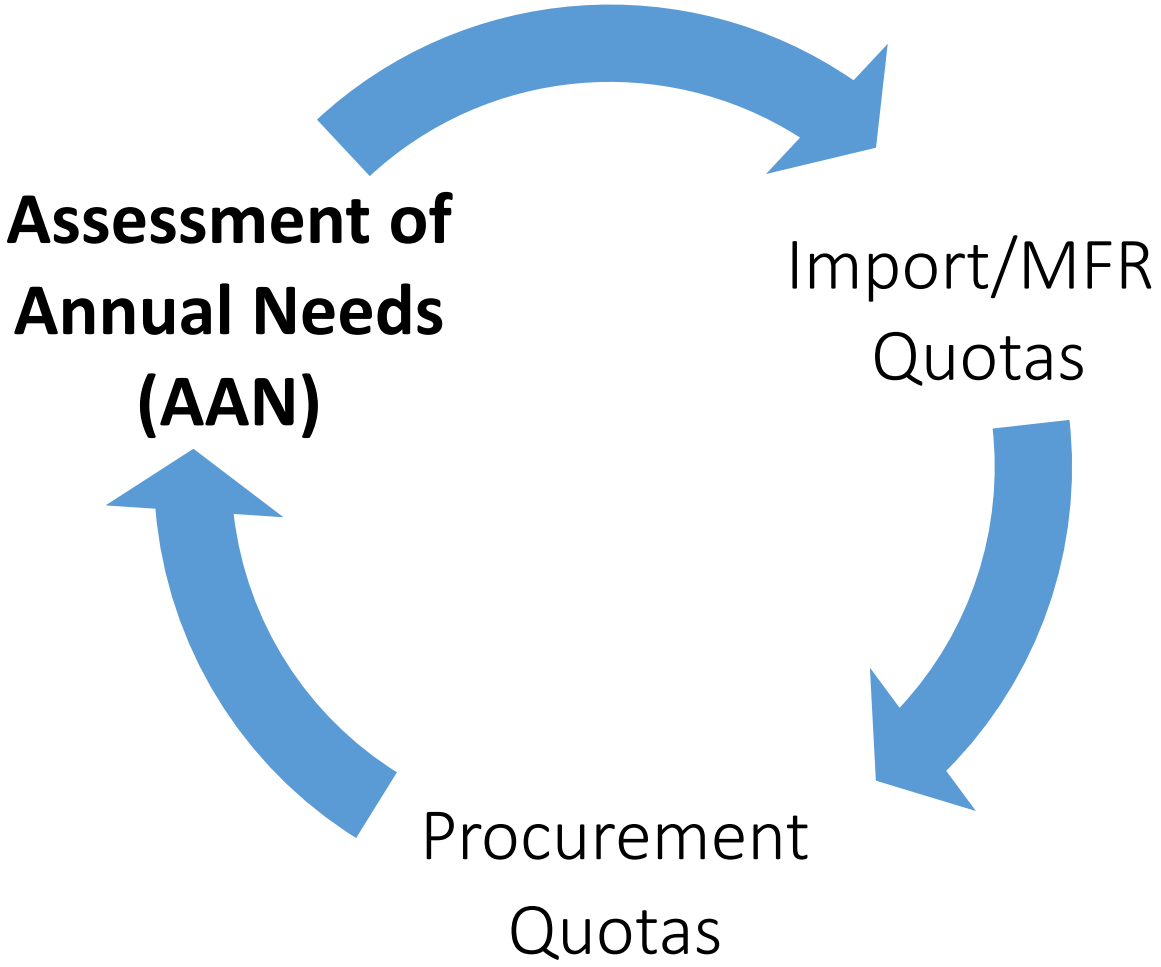
Assessment of Annual Needs (AAN) Federal Registers



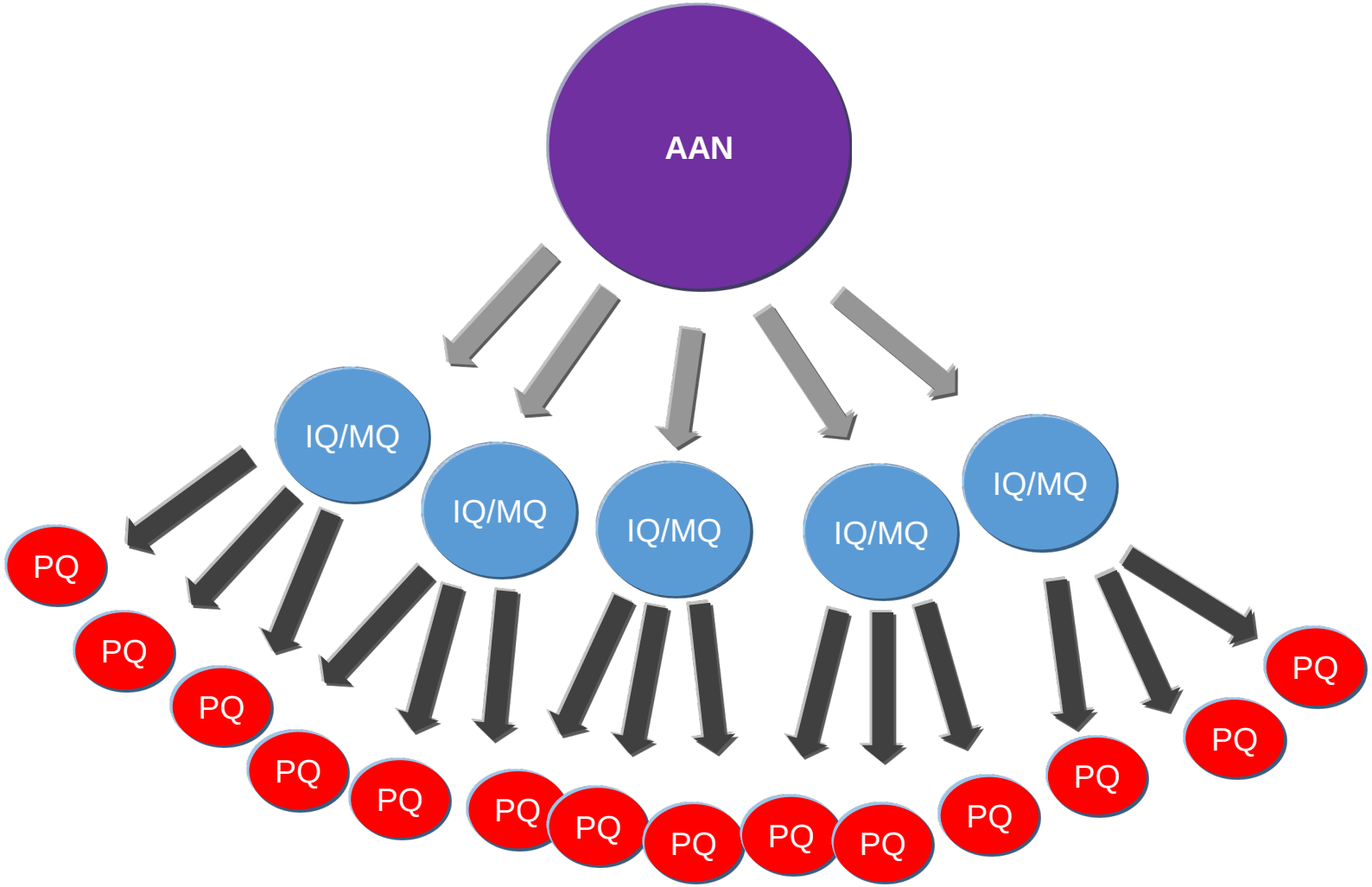
AAN Determined By Considering

- Import, Manufacturing and Procurement Quota applications from DEA Registered manufacturers and importers
- The national rate of disposals (sales/utilization)
- Actual and estimated inventories
- FDA Estimates

Quota-AAN Relationship



AAN-MQ-PQ


AAN
IQ/MQ
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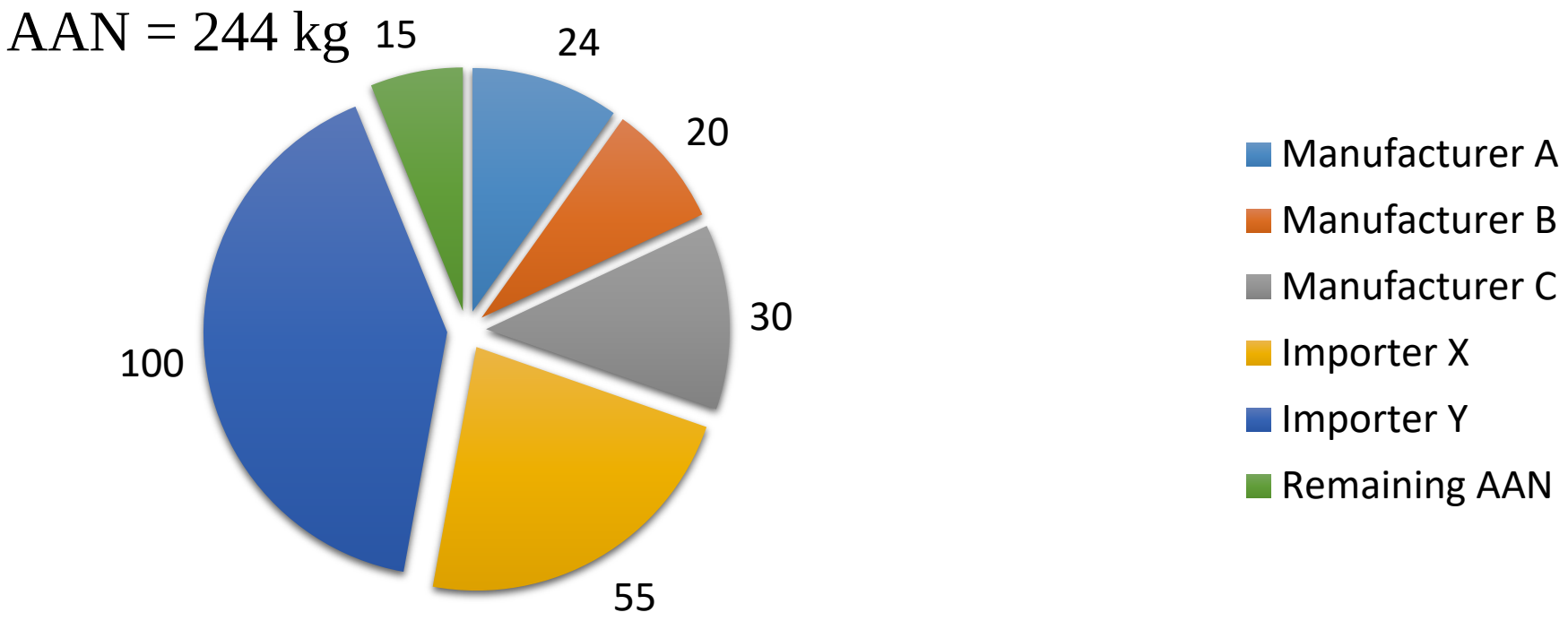
Relationship Between AAN and Import and Manufacturing Quotas



Import Quotas

- **Only DEA registered importer can receive import quotas**
- **Only applies to listed chemicals EPH, PSE and PPA**
- **Establishes maximum amount which the individual importer can *import* in a *calendar year***
- **Importers cannot exceed import quota**

Import Quotas

Import quotas are granted to DEA registrants based on:

- **Procurement and Manufacturing Quotas**
- **Sales & inventory of imported finished dosage form products**
- **Limited by the AAN (CMEA List I chemicals)**

Import Quota - FAQ

Can a DEA registered analytical lab import CMEA List I chemicals as a coincidental activity?

No, only DEA registered importers may import CMEA List I chemicals. Analytical labs may import controlled substances as a coincident activity only

21 CFR 1301.13 (e)(1)(x)

Import Quota - FAQ

Does a manufacturer who consumes all of a CMEA List I chemical internally qualify as an "end user"?

- No. All DEA registered manufacturers who procure CMEA List I chemicals for a manufacturing activity must have quota, including those who do not distribute these CMEA List I chemicals
- The absence of this information would prevent DEA from considering all relevant information required by law when establishing the AAN

Review for exercises: Who gets quota?

Importers of ephedrine, pseudoephedrine & phenylpropanolamine

- Includes importers of bulk API and Dosage Units

Manufacturers of ephedrine, pseudoephedrine and phenylpropanolamine

- Includes bulk manufacturers (manufacturers of API)
- Manufacturers of finished dosage units
- Packagers, repackagers, labelers & relabelers

Manufacturers of Schedule I & II Controlled Substances

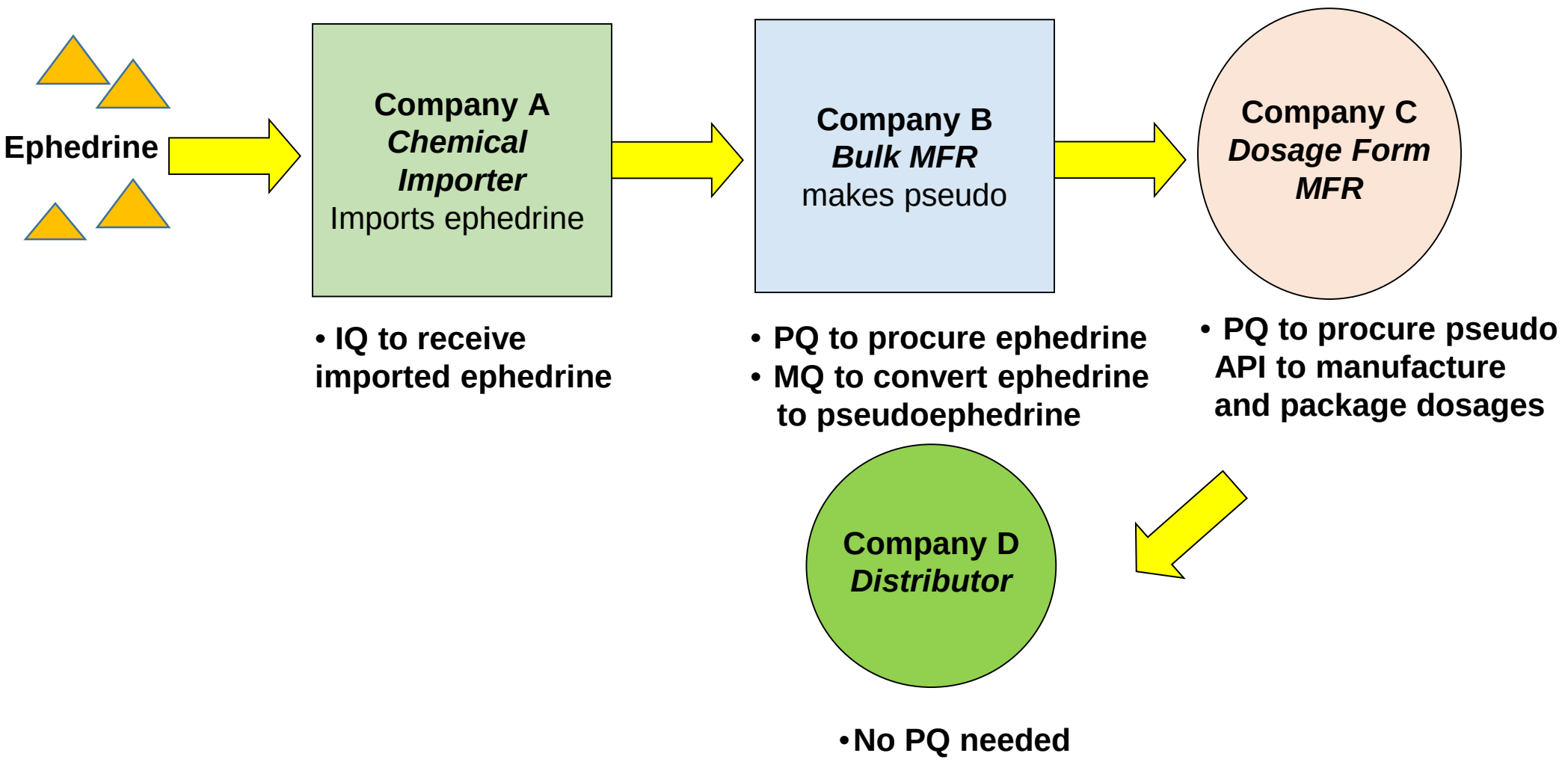
- Includes bulk manufacturers (manufacturers of API)
- Manufacturers of finished dosage units
- Packagers, repackagers, labelers & relabelers

Exercise 1: Who needs Quota?
Following a Product From Start To Finish

- **Company A imports bulk ephedrine for conversion into pseudoephedrine by their bulk manufacturer Company B**

- **Company B sells the pseudoephedrine to Company C which converts the bulk pseudoephedrine into dosage forms, packages and sends to Company D for distribution**

Exercise 1: Who needs Quota?
Import EPH to PSE



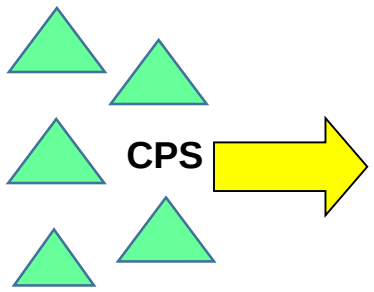
Exercise 1: Who needs Quota?
Answers:

- **Company A – importer**
  - Import Quota (ephedrine) is required to import the ephedrine into the U.S. under an importer registration
- **Company B – bulk manufacturer**
  - Procurement Quota (ephedrine) is required by the manufacturing registration (if different DEA Registration #) to receive the ephedrine from their importer registration
  - Manufacturing Quota (pseudoephedrine) is required to manufacture pseudoephedrine from the ephedrine
- **Company C – dosage form manufacturer**
  - Procurement Quota (pseudoephedrine) is required to procure bulk pseudoephedrine for dosage form manufacturing
- **Company D – distributor**
  - NO QUOTA NEEDED for distributors

Exercise 2: Who needs Quota?
Following a Product From Start To Finish

- Company A imports concentrated poppy straw for morphine extraction. They sell the extracted morphine to company B which converts the bulk morphine into beads and encapsulates them
- Company B sends the finished morphine capsules to their bottling and labeling company C
- Company C bottles and labels the finished dosage units and sends them to Company D for distribution

Exercise 2: Who needs Quota?
Poppy Straw to Distributor



CPS = Concentrated Poppy Straw

Company A
Importer/MFR
Imports CPS for extraction
To morphine

- **PQ to procure imported CPS**
- **MQ to extract morphine**

Company B
Dosage Form MFR
makes morphine tablets

- **PQ to procure morphine & manufacture tablets**

Company C
Packager/ Labeler

- **PQ to procure tablets & package/label**

Company D
Distributor

- **No PQ needed**

Exercise 2: Who needs Quota?
Answers:

- **Company A – importer & bulk manufacturer**
  - Procurement Quota (CPS) is required to procure the imported material. (NOT Import Quota since CPS is not CMEA List I Chemical)
  - Manufacturing Quota (morphine) is required to extract morphine from the poppy straw
- **Company B – dosage form manufacturer**
  - Procurement Quota (morphine) is required to procure bulk morphine for dosage form manufacturing
- **Company C – relabeler/repackager manufacturer**
  - Procurement Quota (morphine) is required to acquire the finished dosage units for packaging and product labeling
- **Company D – distributor**
  - NO QUOTA NEEDED for distributors

Final Reminders

Annual applications for quotas must be filed on or before the date indicated of the year preceding the calendar year for which the quota is being applied.

- DEA Form 189 for Manufacture Quotas must be filed on or before May 1.
- DEA Form 250 for Procurement Quotas must be filed on or before April 1.
- DEA Form 488 for Import Quotas must be filed on or before April 1.

- This allows DRQ to review and consider quota requests when setting the APQ to ensure it is adequate.
- Reminder to submit manufacture, procurement and import quota applications requesting forecasted annual amounts

Questions?

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