

LOGISTICS

INSTRUCTOR

- _____
- Contact info:
 - E-mail: _____
 - Telephone: _____
- Office: Granite Tech. Institute (GTI), Rm 259
- Office hours: _____

COURSE DESCRIPTION

- 1-credit hour but 3 contact hours; "lab"-like
- Provide core skills required in a biotech manufacturing environment
- Focus on:
 - Proper data handling and analysis skills
 - Basic laboratory / manufacturing skills
 - Safe laboratory / manufacturing behavior
 - Basic quality control skills
 - Critical thinking – troubleshooting / problem solving
 - Basic biotech manufacturing activities and processes

COURSE FORMAT

- Mostly hands-on practical activities
- Some lectures
- Class discussions



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POLICIES, TOPICS, & GRADING

- See syllabus for details



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IMPORTANT DATES

- Last day to add: _____
- Last day to drop with 100% refund: _____
- Last day to withdraw, no refunds; "W" on transcript: _____



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"INCOMPLETE"

- Given for extenuating circumstances only with proper documentation
- Must be "passing" at time of request
- Must have completed course activities equaling more than 65% of total points (see syllabus)
- Must work with instructor to develop a contract for completing remainder of work
- Must fulfill contract within 1 year of "I" grade
- Failure to fulfill contract → "E" grade



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EMERGENCY INFO



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EVACUATION PROCEDURES

- Leave building calmly but immediately
- Exits
 - Only one way out to hall
 - Nearest stairwell vs. Other stairwells
- Pre-determined outside meeting place: to be designated by instructor at time of evacuation
- Assistance needed? Inform instructor !!
Assistance plan



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OTHER FACILITY ISSUES

- Power outage
 - Class is not automatically cancelled
 - Will attempt to finish class if possible
- Weather-related closures
 - Will follow official SLCC closure decisions
 - Hotline: 957-INFO (957-4636)



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OTHER PROGRAM-RELEVANT INFO



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IT'S NEW !!

- New training program
- New programmatic awards:
 - Certificate of Completion – 30 credits
 - Diploma – 47 credits
 - Associate of Applied Science – 65-69 credits
- New BMAN courses – currently 7 different ones
- Patience & feedback appreciated



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PROGRAM FUNDING

- Dept of Labor Community-Based Job Training (CBJT) grant : ~ \$ 2 million, used for
 - Facility remodel (mostly)
 - Training program / course development
 - New equipment purchases (some)
- Additional funding sources: WIRED (DoL), USTAR, other Utah state \$\$ (GSD)
- Grant objectives / timeline
- Progress & outcome reporting



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STUDENT SURVEYS

- Absolutely critical to program:
 - Provides info for progress & outcome reporting
 - Helps with course & program improvement
- Please help by completing



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SOFT SKILLS

WHAT ARE SOFT SKILLS?

- Effective communication
 - o Written: manufacturing documents, reports, e-mails
 - o Verbal: public speaking, presentations, phone calls, supervisory activities
- Mastery of typical / common computer software applications [min. basic skill level]
 - o Microsoft Word: document and report writing
 - o Microsoft Excel: data collection, analysis, interpretation, and presentation

WHAT ARE SOFT SKILLS? (cont.)

- Effective biomanufacturing workplace behavior
 - o Personal presentation: timeliness, dress, interactions
 - o Attention to detail
 - o Problem identification: proactive, not reactive
 - o Teamwork
 - o Diplomacy & hierarchy
 - o Strive to improve constantly

PRACTICAL EXERCISE

- Scenario:
 - You = catheter assembly team leader
 - New order for 5,000 units to be shipped in 3 days
 - Quality Assurance inspection and release = 1 day
 - Made 1,000 units already; need 4,000 more
 - Your shift can usually produce 750 per day
 - Night shift can usually produce 600 per day
 - Proposal: increase output to 1.5X for each of the next 2 days to fulfill order
 - Issue: night shift scheduled preventative maintenance of curing machine for tomorrow



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PRACTICAL EXERCISE (cont.)

- Write an e-mail to the night shift asking:
 - Could night shift meet proposed output increase?
 - What can be done about rescheduling preventative maintenance
- Purpose:
 - Develop written e-mail communication skills
 - Develop MS Word skills
- Due: **next week** ; e-mail to instructor before class
- Worth **10 points** of 1000 total for course



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DOCUMENTATION



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DOCUMENTATION SPECIFICS

- Proper documentation is critical to:
 - ✓ Regulatory compliance
 - ✓ Company's quality system
 - ✓ Customer service / assistance
 - ✓ Maximal profit / productivity / effectiveness
 - ✓ Continuous improvement



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DOCUMENTATION IMPACTS

- Traceability
 - ✓ Quality assurance – nonconformance issues & corrective actions/preventative actions (CAPA)
 - ✓ Recalls
- Audits
 - ✓ Proof of compliance to regulations & company's quality system



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DOCUMENTATION GUIDELINES

- Comply with company's documentation policy
- Use clear language and strive for legibility
- Provide complete / accurate details
- Use appropriate dating: never back-date
- Use appropriate correction methods
 - o Deletions / modifications: single line out, add correction, initial, and date
 - o Additions: add appropriately, initial, and date
- Sign off to show legitimacy



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INTERPRETATIONS

- “If it wasn’t written down, it wasn’t done”
- “If it was written sloppily, it was done sloppily”



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DATA COLLECTION AND ANALYSIS



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TYPES OF DATA

- Quantitative
 - o i.e. numerical
- Qualitative
 - o Descriptive
 - o Not numerical



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PURPOSE OF DATA IN BIOMANUFACTURING

- Primarily for manufacturing process monitoring:
 - ✓ Output tracking
 - ✓ Quality assurance
 - o Meet specifications?
 - o Consistency?
 - o Sign of process issues?



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USE PROPER COLLECTION METHOD(S)

- Prior to collection, understand what data will be used for (e.g. what question is being asked?)
- Select appropriate assessment / measurement device; consider tolerances
- Collect appropriate data, in the appropriate format
- Review as you collect, stopping / repeating if necessary



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DATA ANALYSIS

- Why?
 - Sometimes required in order to make a determination / interpretation (to answer question asked)
- May need to apply basic statistics for full value
 - Examples of commonly used statistical values :
 - o Average (avg) / mean
 - o Standard deviation (SD)
 - o Coefficient of variation (CV)



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AVERAGE

- Is the arithmetic mean
- Is calculated by adding a group of numbers and then dividing by the count of those numbers

$$\text{Average} = \frac{x_1 + x_2 + x_3 + \dots + x_n}{n}$$

Example:

the average of 2, 3, 3, 5, 7, and 10
is 30 divided by 6, which is 5



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STANDARD DEVIATION

- Is the measure of dispersion of group of numbers from their expected mean value

Example:

Suppose 10 tools stamped from the same machine during a production run are collected as a random sample and measured for breaking strength:

1345, 1301, 1368, 1322, 1310, 1370, 1318

1350, 1303, 1299

Average = 1328.6

Standard deviation (SD) = 27.46



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COEFFICIENT OF VARIATION

- Ratio of the standard deviation to the mean
 $CV = (SD / \text{mean}) \times 100\%$

Example:

Suppose 10 tools stamped from the same machine during a production run are collected as a random sample and measured for breaking strength:

1345, 1301, 1368, 1322, 1310, 1370, 1318

1350, 1303, 1299

Average = 1328.6 **SD** = 27.46 so **CV** = 2.067



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PRACTICAL EXERCISE

- Use MS Excel to calculate the average, SD, and CV values for the example set of data given above
- Purpose:
 - Develop statistical data analysis skills
 - Develop / demonstrate MS Excel skills
- Due **next week** (e-mail to instructor before class)



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REVIEW FROM PREVIOUS WEEK

- What is an example of soft skills?
- Why are soft skills important?
- Why is documentation critical in biomanufacturing?
- What are 3 guidelines for documentation?
- What is the definition of **average**? **standard deviation**? **CV**?
- What are the Microsoft Excel abbreviations for the above 3 functions?



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PRACTICAL EXERCISE

- Scenario:
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PRACTICAL EXERCISE (cont.)

- Write an e-mail to the night shift asking:
 - Could night shift meet proposed output increase?
 - What can be done about rescheduling preventative maintenance
- Purpose:
 - Develop written **e-mail** communication skills
 - Develop MS Word skills
- Due: **this week** ; class discussion on e-mails
- Worth **10 points** of 1000 total for course



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SI SYSTEM



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SI BASE UNITS

From: Barry N. Taylor & Ambler Thompson (ed.). *The International System of Units (SI)*. NIST Special Publication 330. 2008. Gaithersburg, MD: National Institute of Standards and Technology. pp. 23.
<http://physics.nist.gov/Pubs/SP330/sp330.pdf>

Quantity	Name	Symbol
length	metre	m
mass	kilogram	kg
time	second	s
electric current	ampere	A
thermodynamic temperature	kelvin	K
luminous intensity	candela	cd
amount of substance	mole	mol



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STANDARD SI UNIT PREFIXES

From: Barry N. Taylor & Ambler Thompson (ed.). *The International System of Units (SI)*. NIST Special Publication 330. 2008. Gaithersburg, MD: National Institute of Standards and Technology. pp. 29.
<http://physics.nist.gov/Pubs/SP330/sp330.pdf>

Factor	Name	Symbol	Factor	Name	Symbol
10^1	deka	da	10^{-1}	deci	d
10^2	hecto	h	10^{-2}	centi	c
10^3	kilo	k	10^{-3}	milli	m
10^6	mega	M	10^{-6}	micro	μ
10^9	giga	G	10^{-9}	nano	n
10^{12}	tera	T	10^{-12}	pico	p
10^{15}	peta	P	10^{-15}	femto	f
10^{18}	exa	E	10^{-18}	atto	a
10^{21}	zetta	Z	10^{-21}	zepto	z
10^{24}	yotta	Y	10^{-24}	yocto	y



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CALCULATING CONCENTRATIONS, MOLARITY, VOLUMES, AND DILUTIONS

WHAT IS “CONCENTRATION” ?

- A quantitative measure of a substance in a solution, based on **mass**, **volume**, or **both**
- Typical concentration unit systems:

Unit Definition	Unit Symbol
Molarity is moles per liter	M or mol/L
Normality is gram equivalents per liter	N
Molality is moles per kg	Mol/kg
Mass percentage is “weight” / “weight”	% (wt)
Mass-volume percentage is grams per 100 mL	% (w/v)
Volume-volume percentage is mL per 100 mL	% (v/v)

MASS – MOLE – MOLECULES RELATIONSHIP

- 1 mole = <atomic weight> grams = 6.022×10^{23} molecules
- Atomic weight $\approx$ formula weight (FW); based on chemical composition

Example : sodium chloride (NaCl)

Atomic weight = 58.44 (= 22.99 Na + 35.45 Cl)

So 1 mole = 58.44 g

And molar mass = 58.44 g/mol

CALCULATING CONCENTRATIONS

- 5.844 g NaCl + water → 1 L total
- What is the concentration in **Molar**?

Formula:
$$\text{Molar conc.} = \frac{\left(\frac{\text{weight}}{\text{molar mass}} \right)}{\text{total volume}}$$

$$\text{NaCl conc.} = \frac{\frac{5.844 \text{ g}}{\left(\frac{58.44 \text{ g}}{\text{mol}} \right)}}{1.0 \text{ L}} = \frac{0.1 \text{ mol}}{\text{L}} = 0.1 \text{ M}$$



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CALCULATING CONCENTRATIONS (cont.)

- 5.844 g NaCl + water → 1 L total
- What is the concentration in **mass-volume %**?

Formula:

$$m-v \% \text{ conc.} = \left(\frac{\text{weight}}{\text{total volume}} \right) \times 100 \text{ mL conversion factor}$$

$$\begin{aligned} \text{NaCl \% (w/v)} &= \left(\frac{5.844 \text{ g}}{1.0 \text{ L}} \right) \times \frac{1.0 \text{ L}}{10 \times 100 \text{ mL}} = \frac{5.844 \text{ g}}{10 \times 100 \text{ mL}} \\ &= \frac{0.5844 \text{ g}}{100 \text{ mL}} = 0.5844\% \end{aligned}$$



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CALCULATING MASS FROM CONCENTRATIONS

- Want 2.0 L of 5.0 M NaCl
- What is the **mass needed**?

Formula:

$$\begin{aligned} \text{mass needed} &= \text{total moles needed} \times \text{molar mass} \\ &= (\text{molar conc.} \times \text{volume in L}) \times \text{molar mass} \end{aligned}$$

$$\begin{aligned} g \text{ of NaCl} &= 5.0 \text{ M} \times 2.0 \text{ L} \times \frac{58.44 \text{ g}}{\text{mol}} \\ &= 5.0 \frac{\text{mol}}{\text{L}} \times 2.0 \text{ L} \times \frac{58.44 \text{ g}}{\text{mol}} \\ &= 10.0 \text{ mol} \times \frac{58.44 \text{ g}}{\text{mol}} = 584.4 \text{ g} \end{aligned}$$



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CALCULATING MASS FROM CONCENTRATIONS (cont.)

- Want 2.0 L of 20% NaCl
- What is the **mass needed**?

Formula:

$$\text{mass needed} = m - v\% \times \text{volume in 100 mL units}$$

$$\begin{aligned} g \text{ of NaCl} &= 20\% \times (20 \times 100 \text{ mL}) \\ &= \frac{20 \text{ g}}{100 \text{ mL}} \times (20 \times 100 \text{ mL}) \\ &= 400 \text{ g} \end{aligned}$$



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CONVERTING BETWEEN CONCENTRATION SYSTEMS

- Typical conversions are
 - ✓ Molar conc to mass-volume conc
 - ✓ Mass-volume conc to molar conc
- Need to use **molar mass** value ("g / mol") for conversion calculations



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CONVERTING BETWEEN CONCENTRATION SYSTEMS (cont.)

- Molar to mass-volume conversion
- 5.0 M NaCl = ? % NaCl

Formula:

$$\%(w/v) \text{ conc} = \text{molar conc} \times \text{molar mass} \times 100 \text{ mL conversion factor}$$

$$\begin{aligned} \% \text{ NaCl} &= 5.0 \text{ M} \times \frac{58.44 \text{ g}}{\text{mol}} \times \frac{1.0 \text{ L}}{10 \times 100 \text{ mL}} \\ &= 5.0 \frac{\text{mol}}{\text{L}} \times \frac{58.44 \text{ g}}{\text{mol}} \times \frac{1.0 \text{ L}}{10 \times 100 \text{ mL}} \\ &= \frac{5.0 \times 58.44 \text{ g}}{10 \times 100 \text{ mL}} = \frac{29.22 \text{ g}}{100 \text{ mL}} = 29.22\% \end{aligned}$$



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CONVERTING BETWEEN CONCENTRATION SYSTEMS (cont.)

- Mass-volume to molar conversion
- 5.0 % NaCl = ? M NaCl

Formula:

$$\text{Molar conc} = \%(\text{w/v})\text{conc} \times \frac{1}{\text{molar mass}} \times \text{L conversion factor}$$

$$\begin{aligned} M \text{ NaCl} &= 5 \% \times \frac{\text{mol}}{58.44 \text{ g}} \times \frac{10 \times 100 \text{ mL}}{1 \text{ L}} \\ &= \frac{5 \text{ g}}{100 \text{ mL}} \times \frac{\text{mol}}{58.44 \text{ g}} \times \frac{10 \times 100 \text{ mL}}{1 \text{ L}} \\ &= \frac{5 \times 10 \text{ mol}}{58.44 \text{ L}} = 0.8556 \frac{\text{mol}}{\text{L}} = 0.8556 \text{ M} \end{aligned}$$



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MAKING DILUTIONS

- Conservation of mass / moles is always observed

Formula: $C_1V_1 = C_2V_2$

Where:

C_1 = conc of original solution

V_1 = volume of original solution

C_2 = conc of diluted solution

V_2 = volume of diluted solution



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MAKING DILUTIONS (cont.)

- Make 200 mL of 0.25 M NaCl from 5.0 M NaCl

$$C_1 = 5.0 \text{ M}$$

$$C_2 = 0.25 \text{ M}$$

$$V_1 = ?$$

$$V_2 = 200 \text{ mL} (= 0.2 \text{ L})$$

$$C_1V_1 = C_2V_2$$

$$5.0 \text{ M} \times V_1 = 0.25 \text{ M} \times 0.200 \text{ L}$$

$$V_1 = \frac{0.25 \text{ M} \times 0.200 \text{ L}}{5.0 \text{ M}} = 0.010 \text{ L} = 10 \text{ mL}$$

So, mix 10 mL 5.0 M NaCl with enough water to get

200 mL total volume



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MAKING DILUTIONS (cont.)

- If have 2.7 mL of 5.0 M NaCl, how much 0.25 M NaCl can be made?

$$C_1 = 5.0 \text{ M}$$

$$C_2 = 0.25 \text{ M}$$

$$V_1 = 2.7 \text{ mL} (= 0.0027 \text{ L}) \quad V_2 = ?$$

$$C_1 V_1 = C_2 V_2$$

$$5.0 \text{ M} \times 2.7 \text{ mL} = 0.25 \text{ M} \times V_2$$

$$V_2 = \frac{5.0 \text{ M} \times 2.7 \text{ mL}}{0.25 \text{ M}} = 54 \text{ mL}$$



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KEY CONSIDERATIONS !!

- Mind your units
- Stumped? . . . let your units guide you
- Mind your significant figures / decimal places



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ASSIGNMENTS

- *Concentration, Volume, and Dilution Calculations* worksheet

Due: _____

Worth **60 points** of 1000 total for course

- Quiz on these calculations (**60 points**) on this date : _____

** you may use your notes



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Standard SI Unit Prefixes

<u>Prefix</u>	<u>Symbol</u>	<u>Conversion Relative to “Base” Unit</u>	<u>Conversion Relative to Prefix</u>
yotta	Y	1 “base” = 10^{-24} yotta-base	1 yotta-base = 10^{24} base
zetta	Z	1 “base” = 10^{-21} zetta-base	1 zetta-base = 10^{21} base
exa	E	1 “base” = 10^{-18} exa-base	1 exa-base = 10^{18} base
peta	P	1 “base” = 10^{-15} peta-base	1 peta-base = 10^{15} base
tera	T	1 “base” = 10^{-12} tera-base	1 tera-base = 10^{12} base
giga	G	1 “base” = 10^{-9} giga-base	1 giga-base = 10^9 base
mega	M	1 “base” = 10^{-6} mega-base	1 mega-base = 10^6 base
kilo	k	1 “base” = 10^{-3} kilo-base	1 kilo-base = 10^3 base
hecto	h	1 “base” = 10^{-2} hecto-base	1 hecto-base = 10^2 base
deka	da	1 “base” = 10^{-1} deka-base	1 deka-base = 10^1 base
deci	d	1 “base” = 10^1 deci-base	1 deci-base = 10^{-1} base
centi	c	1 “base” = 10^2 centi-base	1 centi-base = 10^{-2} base
milli	m	1 “base” = 10^3 milli-base	1 milli-base = 10^{-3} base
micro	μ	1 “base” = 10^6 micro-base	1 micro-base = 10^{-6} base
nano	n	1 “base” = 10^9 nano-base	1 nano-base = 10^{-9} base
pico	p	1 “base” = 10^{12} pico-base	1 pico-base = 10^{-12} base
femto	f	1 “base” = 10^{15} femto-base	1 femto-base = 10^{-15} base
atto	a	1 “base” = 10^{18} atto-base	1 atto-base = 10^{-18} base
zepto	z	1 “base” = 10^{21} zepto-base	1 zepto-base = 10^{-21} base
yocto	y	1 “base” = 10^{24} yocto-base	1 yocto-base = 10^{-24} base

REVIEW FROM PREVIOUS WEEK

- What is the definition of:
 - Molar concentration?
 - %(w/v) concentration?
- What is the purpose of conversion factors?
- What is molar mass?



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MEASURING TECHNIQUES



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SOLID MATERIALS

- Use balance
- Two main types
 - Top-loading for > 10 g
 - Analytical for ~ 10 mg to 10 g



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SOLID MATERIALS (cont.)

- Usage considerations:
 - ✓ On level surface with minimal vibrations (marble)
 - ✓ Air movement minimized
 - ✓ Tare feature and limits, for weigh paper/boat/vessel
 - ✓ Keep clean
 - ✓ Tapping material bottle to weigh solids in vessel is better than using a spatula



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LIQUID MATERIALS

- Graduated cylinder: for volumes > 25 mL
typical sizes: 100 mL, 250 mL, 500 mL, 1 L, 2 L



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LIQUID MATERIALS (cont.)

- Volumetric flasks
 - o Various sizes, typically in range of 10 to 1000 mL
 - o Measures only one (fixed) volume



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LIQUID MATERIALS (cont.)

- Pipets
 - o Typical sizes: 1, 2, 5, 10, 25 mL
 - o “Blow out” vs “not blow out”



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LIQUID MATERIALS (cont.)

- Volumetric pipets
 - o Various sizes, typically in range of 1 to 200 mL
 - o Measures only one (fixed) volume

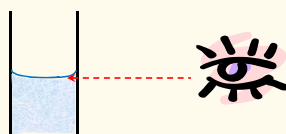


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LIQUID MATERIALS (cont.)

- Key to measuring liquids accurately with graduated cylinders, pipets, and volumetric flasks / pipets:

LINE UP WITH THE BOTTOM OF THE MENISCUS



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LIQUID MATERIALS (cont.)

- Pipet helpers
 - o Manual bulb (fancy)



- o Electric motor



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LIQUID MATERIALS (cont.)

- Bottle-top dispensers
 - o Settable dispense volume (within dispenser range)
 - o Great for repeated volume dispensing



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LIQUID MATERIALS (cont.)

- Pipettors (< 1 mL volumes)
 - o Single channel
 - o Settable volume
 - o Various sizes/volume ranges
 - o Good accuracy / precision



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LIQUID MATERIALS (cont.)

- Pipettors (cont.)
 - o Multi- channel
 - o Settable volume
 - o Various sizes/volume ranges
 - o Each channel is independent
 - o Good accuracy / precision



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LIQUID MATERIALS (cont.)

- Pipettors (cont.)
 - o Repeater – for repeated small volume dispensing
 - o Settable volume
 - o Various sizes of 'syringe' tips, each with dispense volume and range
 - o Good accuracy / precision



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LIQUID MATERIALS (cont.)

- Pipettors (cont.)
 - o Electronic
 - o Various sizes
 - o Can be used like a single channel
 - o Can be used as a repeater
 - o Volume dependent on size
 - o Good accuracy / precision



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LIQUID MATERIALS (cont.)

- Usage considerations
 - ✓ Vertical positioning
 - ✓ Cylinders, flasks, and pipets: read at bottom of meniscus
 - ✓ Aspirate slowly and consistently
 - ✓ When using tips, make sure tip is securely fastened
 - ✓ Learn to judge volumes in tips / vessels
- These are not **ACCEPTABLE** liquid measuring devices: beakers, Erlenmeyer (conical) flasks



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DIMENSIONAL ANALYSIS

- Calipers
 - o Dial format
 - o Digital format
- Micrometers (specialized caliper)



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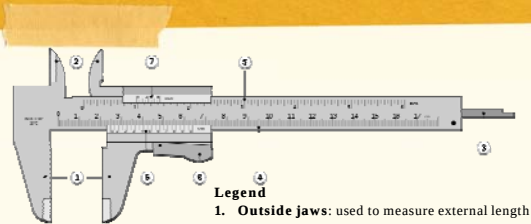
CALIPERS

- Used for
 - o Outside dimensions
 - o Inside dimensions
- Proper and clean contact of opposing surfaces with proper pressure is critical to accurate measurements
 - ❖ Correct: consistent, firm touch
 - ❖ Too much force: results in an underindication because part and tool distort
 - ❖ Too little force: gives insufficient contact and an overindication



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CALIPERS (cont.)



Legend

1. **Outside jaws:** used to measure external length
2. **Inside jaws:** used to measure internal length
3. **Depth probe:** used to measure depth
4. **Main scale (cm)**
5. **Main scale (inch)**
6. **Vernier (cm)**
7. **Vernier (inch)**
8. **Retainer:** used to block/release movable part



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CALIPERS (cont.)

Legend

1. **Outside jaws:** used to measure external length
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8. **Retainer:** used to block/release movable part



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MICROMETERS

- Typical types
 - o **Outside** micrometer (aka micrometer caliper), typically used to measure wires, spheres, shafts and blocks
 - o **Inside** micrometer, used to measure the diameter of holes
 - o **Depth** micrometer, measures depths of slots and steps
 - o **Bore** micrometer, typically a three-anvil head on a micrometer base used to accurately measure inside diameters
 - o **Tube** micrometer, used to measure the thickness of tubes
- Again, proper and clean contact of opposing surfaces with proper pressure is critical to accuracy



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MICROMETERS (cont.)

Outside micrometer

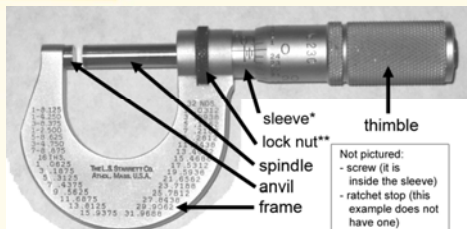
Inside micrometer

Depth micrometer



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OUTSIDE MICROMETER



*Sleeve is the most prevalent name. May also be called the barrel or stock.

**Aka lock-ring. Some mics have a lock lever instead.



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OUTSIDE MICROMETER

- **Frame:** thick and rigid to minimize flexion, expansion, and contraction for accuracy
- **Anvil:** fixed platform contacting part
- **Sleeve / barrel / stock:** stationary; carries scale markings
- **Lock nut / lock-ring / thimble lock:** locks spindle in place
- **Screw:** inside sleeve / barrel; "heart" of micrometer
- **Spindle:** movable platform contacting part
- **Thimble:** part turned with fingers to operate micrometer
- **Ratchet stop:** device on end of handle that limits applied pressure by slipping at a calibrated torque



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OUTSIDE MICROMETER (cont.)

- Each full turn of spindle measures
 - 0.025" if using **inch scale** device
 - 0.5 millimeter (mm) if using **metric scale** device

0.276" measurement



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OUTSIDE MICROMETER (cont.)

- To get value of decimal place between smallest scale markings, use **Vernier scale**

Vernier scale

5.783 measurement



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USAGE NOTES

- Keep devices:
 - ✓ Clean
 - ✓ Calibrated
 - ✓ Safe (e.g. don't drop them)
- Be consistent in how you use devices
- Temperature will affect measurements !!!



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IN-CLASS PRACTICAL ACTIVITIES

1. Practice solid and liquid measuring techniques

- o Complete worksheet (**25 points**) – instructor will verify measurements

2. Practice dimensional analysis :

- o Measure the maximum diameter of the 3 nuts using a caliper
- o Measure the thickness of the smallest and largest nuts using a micrometer

**** Perform all measurements 3 times, and record on worksheet provided (**20 points**)**



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REVIEW FROM PREVIOUS WEEK

- When measuring liquids, what is proper method to accurately assess the volume using an appropriate measuring device?
- What are 3 considerations when weighing solids?
- Why are beakers and Erlenmeyer flasks not acceptable liquid measuring devices?



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SOLUTION PREPARATION – MEASURING, MIXING, AND pH'ing



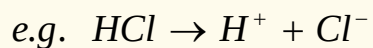
Step Ahead.

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THE pH MEASUREMENT

- A measure of the acidity (or basicity) of a solution
- Defined as the negative decimal logarithm of hydrogen ion activity in an aqueous solution

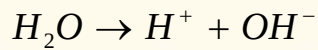
$$pH = -\log_{10} a_H$$



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THE pH MEASUREMENT (cont.)

- Water is pH 7 (temperature dependent)

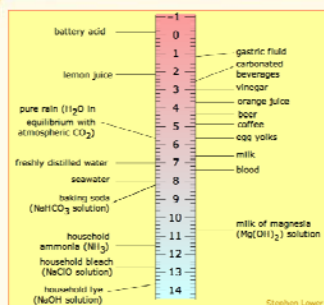


- Strong acid (e.g. HCl) at 1 M is pH 0
- Strong base (e.g. NaOH) at 1 M is pH 14



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TYPICAL pH VALUES



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TYPICAL pH VALUES (cont.)

pH in living systems	
Compartment	pH
Gastric acid	0.7
Lysosomes	4.5
Granules of chromaffin cells	5.5
Urine	6.0
Neutral H ₂ O at 37 °C	6.81
Cytosol	7.2
Cerebrospinal fluid (CSF)	7.3
Blood	7.34 – 7.45
Mitochondrial matrix	7.5
Pancreas secretions	8.1



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THE pH METER



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USAGE NOTES

- Follow manufacturer's instructions
- Must calibrate with **pH buffer standards** before using meter
- Keep electrode filled properly
- Keep fill port open when using
- Rinse electrode with distilled H₂O and pat dry with kimwipe between solutions
- Take care not to break glass bulb on electrode tip
- Temperature affects pH !!!



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IN-CLASS PRACTICAL ACTIVITY

- Calibrate pH meter
- Prepare 250 mL of 0.5 M Tris at a pH assigned by the instructor
- During this preparation, keep track of the volume of HCl used for pH and record total volume as directed by the instructor
- Worth **55 points**



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Tris Buffer Preparation and pH'ing Procedure

pH = _____

Concentration = 0.5 M

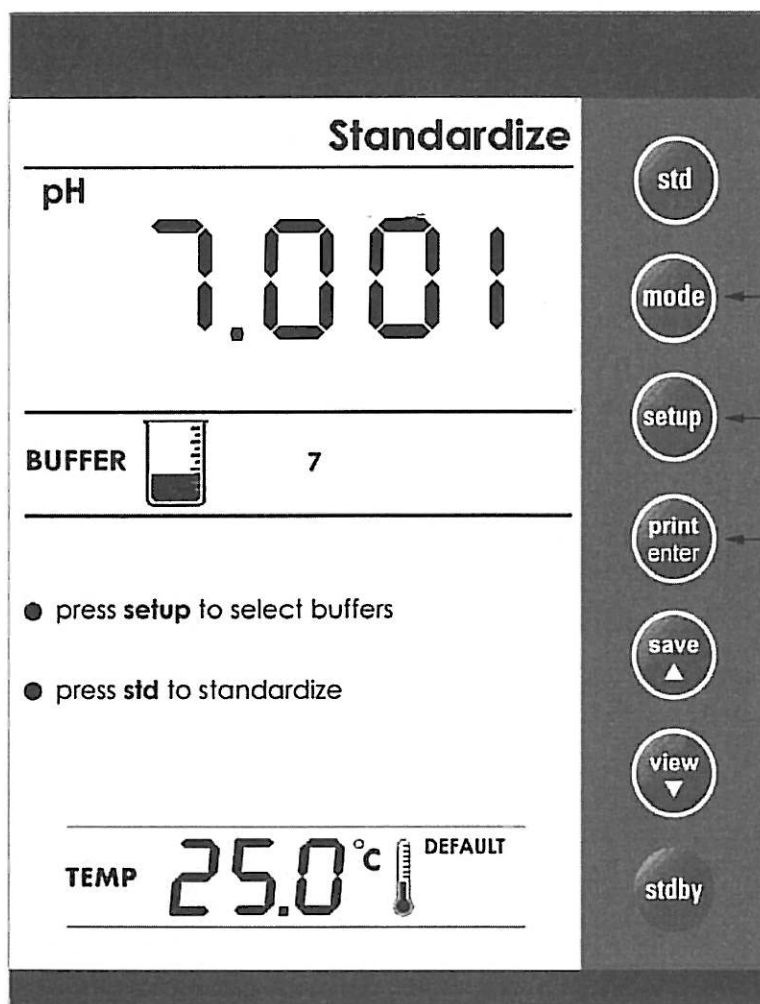
Volume = 250 mL

1. Calculate (use space below) the amount of Tris base powder needed.
NOTE: Molar mass of Tris base = 121 grams / mole (g / mol)
2. Weigh out correct amount of Tris base.
3. Add 210 mL Nanopure-purified water to a clean beaker.
4. Add a clean stir bar to the beaker.
5. Add weighed Tris base.
6. Stir at medium speed until Tris base is completely dissolved.
7. Calibrate pH meter (refer to Accumet AB15E instructions for calibration).
8. Measure pH of Tris solution (refer to Accumet AB15E instructions for pH measurement).
9. Keeping track of the volume added, add HCl until pH reaches proper value.
10. Adjust volume of pH'd Tris solution to 250 mL with Nanopure-purified water.
11. Pour Tris solution back into beaker.
12. Measure pH of Tris solution again. pH should be within 0.10 units of proper value. Adjust with HCl if necessary.
13. Determine total volume of HCl added and record here : _____ mL

5 STANDARDIZATION

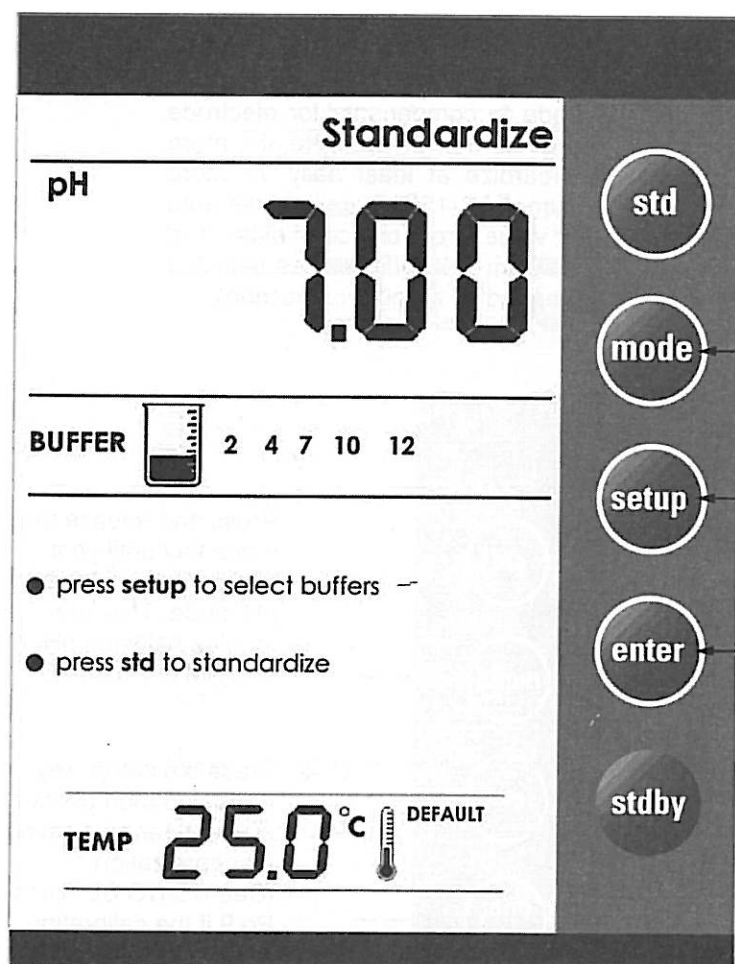
5.1 Standardization Procedure

Because electrodes vary in their response, you must standardize or calibrate your pH meter and electrode to compensate for electrode variation. The more frequently you standardize or calibrate, the more accurate your measurements. Standardize at least daily, or more often, for accurate results. The Accumet AB 15/ 15+ meter has auto buffer recognition for up to 5/6 buffer values from choice of either 1 of the 3 buffer groups available or 6 custom pH buffer values selected from any of these 3 buffer groups (Depending on buffer selection).



1. Press and release the mode key until your digital display indicates pH mode. This key toggles between pH, mV and Rel mV modes.
2. Press the setup key twice and then press enter key to clear an existing standardization. (See USING SETUP on Pg 9 if the calibration done)

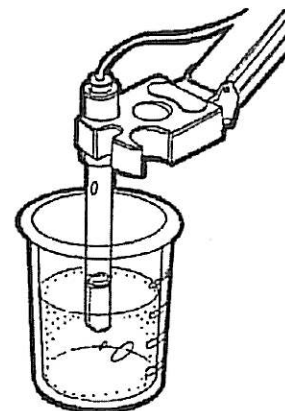
AB15+ screen & display keys



1. Press and release the mode key until your digital display indicates pH mode. This key toggles between pH, mV and Rel mV modes.
2. Press the **setup** key twice and then press **enter** key to clear an existing standardization. (See USING SETUP on Pg 9 if the calibration done)

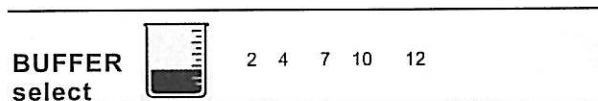
AB15 screen & display keys

3. Immerse the rinsed electrode(s) into a buffer from the selected group. Stir, moderately,

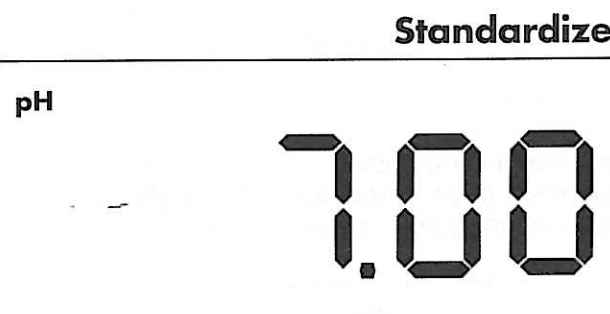


4. Press **std** to access the Standardize mode.

The selected buffer group is displayed briefly.



5. Do wait for reading to stabilize.
6. Press **std** again to initiate standardization. The meter will automatically recognize the buffer.



and then meter returns to the Measure screen.



Press **mode** key while in the standardization mode to return to measurement without accepting calibration.

7. Repeat steps 3-6 with a second and subsequent buffers.



When the ATC probe is connected, the meter will continually adjust for temperature. Therefore the buffer values may vary slightly from the nominal values because of temperature variations.



It is good to standardize your meter using at least 2 buffers.

When the meter accepts the second buffer, it will briefly display the percent slope associated with the electrode's performance prior to returning to the Measure mode.

% SLOPE

100.0

If the electrode is within the range of 90-102%, the GOOD ELECTRODE message will appear.

GOOD ELECTRODE

If the electrode is outside this range, the meter will display the ELECTRODE ERROR message, and will not return to the Measure screen until the user presses **enter**.

ELECTRODE ERROR



The meter will permit the user to use an electrode outside the recommended range, but the ERROR message will persist.

6 MEASUREMENT

6.1 Measurement Procedure

1. Immerse the electrode (along with temperature probe if available for the measurement of pH) into the sample solution. Stir moderately.

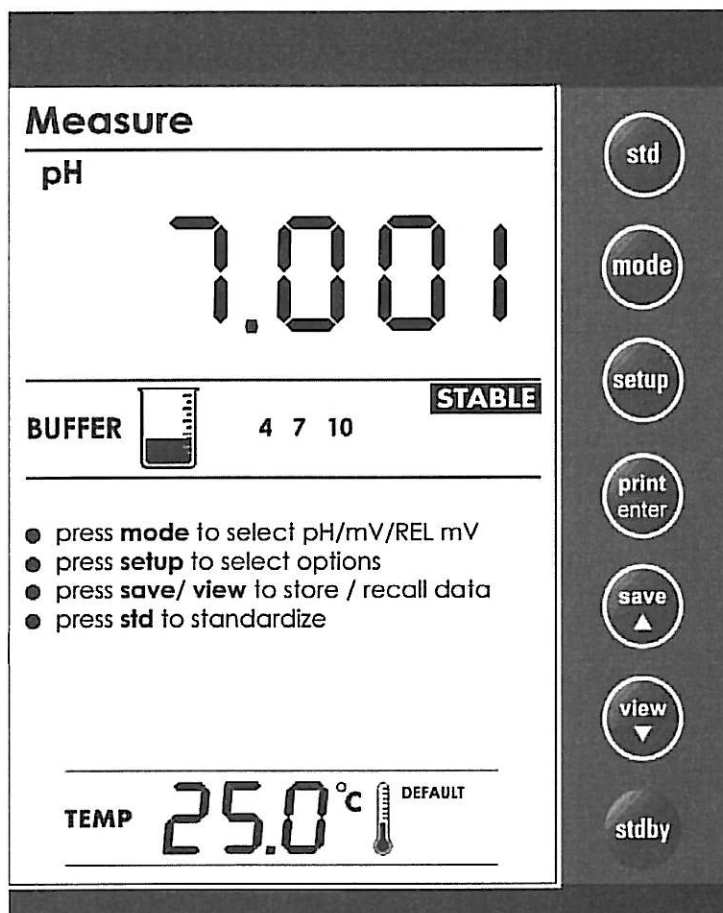


Make sure that the meter is in the Measure mode.

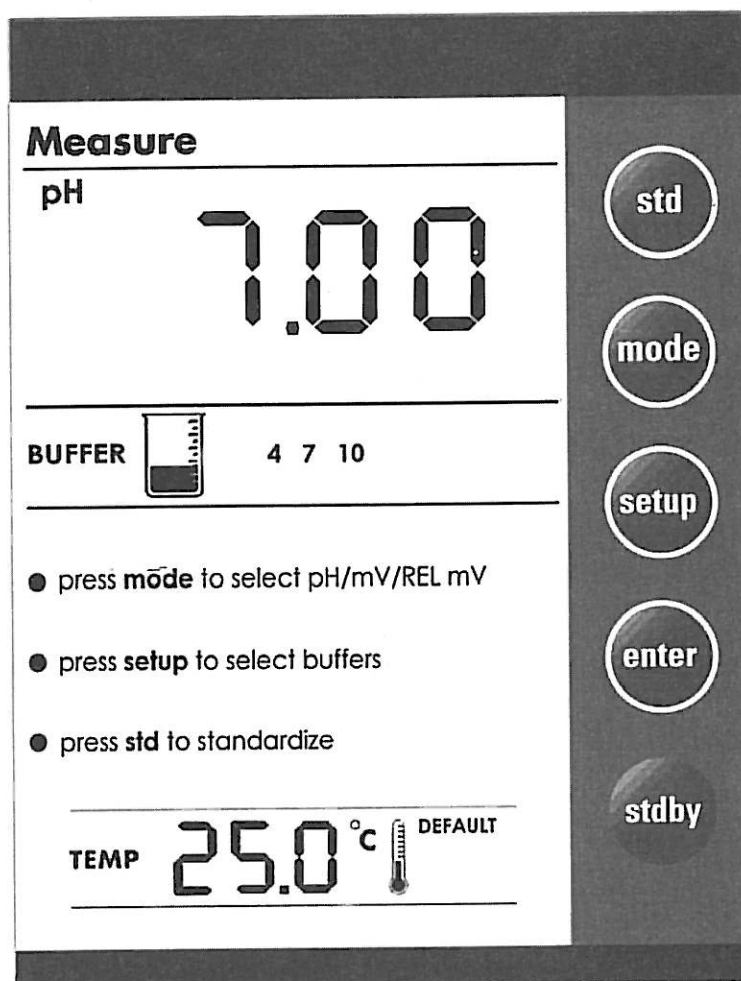
2. When the meter senses that the reading has stabilized, the stable icon will appear under the reading. The reading may be recorded at this time.



STABLE icon will only appear provided that it has been set to 'On' mode in setup. See Section 4.1.6: Stability Indicator (Only available in AB15+), Pg 17.



AB15+ screen & display keys



AB15 screen & display keys



Stirring with a magnetic stir bar and stirrer provides faster electrode response.

3. The reading may be recorded at this time by saving into meter's memory using save key.

REVIEW FROM PREVIOUS WEEK

- When would you choose a micrometer over a caliper for dimensional analysis?
- What are some considerations when using calipers and micrometers?
- What does a pH measurement represent?
- What are some considerations when using a pH meter?



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WORKPLACE SAFETY



Step Ahead.

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REGULATORY AGENCIES

- Occupational Safety & Health Administration (OSHA)
 - o www.osha.gov
 - o Mission: to assure safe and healthful working conditions for working men and women
 - o Sets and enforces many safety standards
- National Institute for Occupational Safety & Health (NIOSH)
 - o www.cdc.gov/NIOSH
 - o Mission: to study causes of workplace injuries / illnesses
 - o Using study data, develops ways to help control hazards



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REGULATORY AGENCIES

(cont.)

- Environmental Protection Agency (EPA)
 - www.epa.gov
 - Mission: to protect land, air, and water
 - Develops and enforces protection regulations
- State agencies, when applicable
 - Some states set and enforce own workplace safety standards and environmental protection regulations
 - If so, then state standards and regulations must be at least as effective as the federal ones



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EMPLOYER RESPONSIBILITIES

- Provide a safe work environment
 - ✓ Proper training: e.g. new employee training and refreshers
 - ✓ Protections
 - ✓ Safety equipment: e.g. guards, engineering controls, personal protective equip.
 - ✓ Hazard communication: e.g. postings
 - ✓ Update employees of changes to or new standards
- Investigate and address safety and environmental hazards
- Comply with all standards and regulations



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EMPLOYER RESPONSIBILITIES (cont.)

- Keep accurate records of workplace injuries and illnesses, as well as “near misses”
 - ✓ Report all first aid rendered, medical treatments, and deaths
 - ✓ Provide financial aid to workers injured/made ill on the job: *workers' compensation*, which pays medical expenses and lost wages from inability to work, and death benefits to survivors
- Report all environmental accidents
- Make all reports available to workers and their representatives



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EMPLOYEE RESPONSIBILITIES

- Understand federally mandated standards and regulations
- Obtain proper training and certifications for all equipment and procedures
- Follow company policies and rules
- Know locations of and how to use pertinent safety equipment: for example
 - First aid kits
 - Fire extinguishers
 - Hazardous spill clean-up kits



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EMPLOYEE RESPONSIBILITIES (cont.)

- Know what to do if there is an accident / illness
 - First response actions
 - Reporting
- Report / correct potential hazards or non-compliances
- Serve on safety / improvement committees, and/or as a safety representative
- Participate in safety inspections
- Use “common” sense



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PERSONAL PROTECTIVE EQUIPMENT (PPE)

- Includes:
 - ✓ Eye protection
 - ✓ Ear protection
 - ✓ Head protection
 - ✓ Hand & arm protection
 - ✓ Foot protection
 - ✓ Lung protection
 - ✓ Protective clothing
 - ✓ Personal clean-up equipment



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FIRE SAFETY

- Prevention:
 - ✓ Approved storage containers and flammable cabinets
 - ✓ Ventilation
 - ✓ Fireproof waste containers
 - ✓ Appropriate work procedures
- Fire extinguisher usage:
 - o Pull pin
 - o Aim low at base of fire
 - o Squeeze trigger / lever
 - o Sweep across fire



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ELECTRICAL SAFETY

- Respect electrical circuits and wiring
 - o Grounding
 - o Circuit overload
 - o Damaged wires
 - o Circuit breakers and fuses
- Follow appropriate work procedures
- **Lockout / tagout:**
 - ❖ Process used to prevent equipment from starting or releasing energy while under repair / maintenance:
 - o Equipment shut-down
 - o Isolation from energy source(s)
 - o Application of "accidental start-up" devices



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HAZARDOUS MATERIAL SAFETY

- Hazardous materials include
 - ✓ Chemicals: corrosives, flammables, oxidizers, reactives
 - ✓ Biologicals: blood, cells, microorganism
 - ✓ Radiation
 - ✓ Sharps
- Hazardous materials must be disposed of according to regulations / standards



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HAZARDOUS MATERIAL SAFETY (cont.)

- Material safety data sheets (MSDS)
 - o Required hazard communication that must be posted
 - o Identifies and describes the hazardous ingredients of a substance
 - o Provides safe usage explanations
 - o Lists health hazards
 - o Suggests PPE



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HAZARDOUS MATERIAL SAFETY (cont.)

National Fire Protection Association Labeling Standard

NFPA Rating Explanation Guide					
RATING NUMBER	HEALTH HAZARD	FLAMMABILITY HAZARD	INSTABILITY HAZARD	RATING SYMBOL	SPECIAL HAZARD
4	Can be lethal	Will explode or readily burn at normal temperatures and pressures	May explode at normal temperatures and pressures	ALK	Alkaline
3	Can cause serious or permanent injury	Can be ignited under almost all ambient temperatures	May explode at high temperatures or shock	ACD	Acidic
2	Can cause temporary incapacitation or residual injury	Must be heated or high ambient temperature to burn	Violent chemical change at high temperatures or pressures	CCR	Corrosive
1	Can cause significant irritation	Must be preheated before ignition can high temperatures occur	Normally stable, but may become unstable at high temperatures	OX	Oxidizing
0	No hazard	Will not burn	Stable	W	Radioactive
				W+	Reacts violently or explosively with water
				W+	Reacts violently or explosively with water and oxidizing



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WANT MORE INFO ?

Supplemental reading in textbook:

- Safety Practices : Chapter 4



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BIOMANUFACTURING TRAINING FACILITY RULES

- Refer to “*Biomanufacturing Training Facility – Rules and Regulations*”
- Wear PPE when required or appropriate
- Maintain a ‘clean’ work station
 - Clean before AND after use
 - Minimize clutter
 - Dispose of waste appropriately
- Maximize safety-conscious behavior
- Strive to make good judgments



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REVIEW FROM PREVIOUS WEEK

- What are 3 regulatory agencies that govern biomanufacturing companies?
- What actions are employees responsible for to keep the company in regulatory compliance?
- What methods do employers use to ensure a safe work environment?
- What are 3 topics addressed by the ***Biomanufacturing Training Facility Rules and Regulations***?



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QUALITY BASICS



Step Ahead.

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NEED FOR QUALITY – HISTORY

- Production during World War I (mid-1910's)
 - More complex manufacturing: e.g. munitions
 - Mass production introduced
 - Result: bad workmanship rampant
 - Consequence: need for full-time inspectors in factories
- Pure Food and Drug Act (1906)
 - Federal law “preventing the manufacture, sale, or transportation of adulterated or misbranded or poisonous or deleterious foods, drugs, medicines, and liquors, and for regulating traffic therein, and for other purposes”
 - First regulation of product labeling
 - Enforced by USDA Bureau of Chemistry



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NEED FOR QUALITY – HISTORY (cont.)

- Food, Drug, and Cosmetic (FD&C) Act (1938)
 - Arose from 107 deaths related to sulfanilamide elixir in 1937: poisonous diethylene glycol used as a solvent
 - Gave Food and Drug Administration (FDA) authority to oversee safety of food, drug, and cosmetics



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NEED FOR QUALITY – HISTORY (cont.)

- Food, Drug, and Cosmetic (FD&C) Act (1938) cont.
 - Replaces Pure Food and Drug Act; includes new provisions:
 - ✓ Requires new drugs to be shown safe before marketing
 - ✓ Eliminates Sherley Amendment requirement to prove intent to defraud in drug misbranding cases
 - ✓ Extends control to cosmetics and therapeutic devices
 - ✓ Requires safe tolerances for unavoidable poisonous substances
 - ✓ Authorizes identity, quality, and fill-of-container food standards
 - ✓ Authorizes factory inspections
 - ✓ Adds court injunctions to the previous penalties



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FOOD AND DRUG ADMINISTRATION

- An agency of Dept of Health and Human Services
- Mission:
 1. “responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation’s food supply, cosmetics, and products that emit radiation”



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FOOD AND DRUG ADMINISTRATION (cont.)

- **Mission (cont.):**
 2. “responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health”



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FOOD AND DRUG ADMINISTRATION (cont. 2)

- 1950 – 2007 : various FD&C Act amendments and additional related acts
- All laws described in Title 21 of Code of Federal Regulations (21 CFR), Parts 1 – 1299
[see www.gpoaccess.gov/cfr for electronic access]
- Many subdivisions
- www.fda.gov



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FOOD AND DRUG ADMINISTRATION (cont. 3)

FDA Subdivisions:

Subdivision	Responsibility
Office of the Commissioner	Program administration
Office of Regulatory Affairs	Enforces FDA regulations, monitors industry for compliance, recalls
Center for Biologics Evaluation & Research (CBER)	Assorted biological products/biologics (these replicate natural human substances): allergenic extracts for shots, blood & blood components, gene therapy products, devices and test kits, transplant-related human tissue and cellular products, vaccines



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FOOD AND DRUG ADMINISTRATION (cont. 4)

FDA Subdivisions (continued):

Subdivision	Responsibility
Center for Drug Evaluation & Research (CDER)	Drugs (purely chemical substances), therapeutic biological products (e.g. monoclonal Abs, cytokines, growth factors, enzymes, thrombolytics, proteins [natural or recombinant] extracted from animals for therapeutic use, non-vaccine therapeutic immunotherapies)
Center for Veterinary Medicine (CVM)	Food additives and drugs given to animals; animals from which human foods are derived



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FOOD AND DRUG ADMINISTRATION (cont. 5)

FDA Subdivisions (continued):

Subdivision	Responsibility
Center for Devices & Radiological Health (CDRH)	Medical devices (e.g. catheters, breast pumps, contact lenses, lab instrumentation), GMP, compliance, postmarket tracking, radiological health screening procedures (mammography, whole body CT scanning, medical imaging)
Center for Food Safety & Applied Nutrition (CFSAN)	Various food products, GMOs, cosmetics, dietary supplements, infant formula, foodborne illness, food labeling & nutrition



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GOOD MANUFACTURING PRACTICES (GMP)

- Most stringently specified in **21 CFR** Parts
 - ✓ **210 & 211** : for drugs
 - ✓ **820** : for medical devices
 - ✓ **110** : for food
- Legally required to comply
- Detailed requirements on how to operate manufacturing business, including:
 - ✓ **Methods** used in design, manufacture, packaging, labeling, storage, installation, & servicing of products
 - ✓ **Facilities** used
 - ✓ **Controls** used



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QUALITY SYSTEM

- Enables a company to comply with FDA regulations / cGMP
- For medical devices (as an example):
 - **21 CFR Part 820.5** says
“Each manufacturer shall establish and maintain a quality system that is appropriate for the specific medical device(s) designed or manufactured, and that meets the requirements of this part.”
 - Quality system is defined in **21 CFR Part 820.3** as
“the organizational structure, responsibilities, procedures, processes, and resources for implementing quality management”



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QUALITY . . .

- **Assurance** : covers all activities relating to design, development, production, installation, servicing, and documentation (part of management)
 - Provides confidence that quality requirements will be met
 - **Plan – Do – Check – Act** (PDCA) approach
 - “do it right the first time”
- **Systems Manual** : the company’s QUALITY



BIBLE

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QUALITY . . . (cont.)

- **Engineering** : concerned with prevention planning and the correction of nonconformance with the production or service cycle
 - ❖ Analysis of manufacturing systems at all stages to improve production process quality and output
- **Control (Total quality control)** : inspection activities, tools, and skills
 - ❖ Ensures product meets customer’s requirements, including reliability, maintainability, and safety



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TYPICAL QUALITY ACTIVITIES

- Inspections:
 - o Raw materials
 - o Subassemblies / intermediate products
 - o Final products
 - o Packaging
- Materials management:
 - o Inventory
 - o Purchases / requisitions
 - o Storage (quarantined vs. released vs. rejected)



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TYPICAL QUALITY ACTIVITIES (cont.)

- Calibration
- Maintenance
- Documentation
 - o Standard operating procedures (SOPs)
 - o Work instructions
 - o Batch records



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KEY ELEMENTS OF QUALITY

- From Joseph Juran (late 1940s)
- **Quality planning** : designing a process capable of meeting quality standards
- **Quality control** : measuring a parameter, comparing to standard, taking action if not acceptable
- **Quality improvement** : finding a better way to meet specifications – dependent on good documentation / traceability



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CONTROLLING & IMPROVING QUALITY

- Program initiated by W. Edwards Deming (1940s - 50s)
- Keys:
 - ✓ Constantly improve production to prevent problems rather than correct them
 - ✓ Distribute responsibility throughout
 - ✓ Focus on training and leadership
 - ✓ Break down communication barriers: within company and with customers & suppliers
 - ✓ Use statistical analysis as basis for quality decisions



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CONTROLLING & IMPROVING QUALITY (cont.)

- Depends on collecting and analyzing data via:
 - ✓ Inspection (to compare to a standard) – **Exercise 17-2**
 - ✓ Auditing (“independent” review)
 - ✓ Analysis (to determine action required) – common statistical process control tools & **Exercise 16-5**
 - ✓ Preventative action (PA) : for potential problems
 - ✓ Corrective action (CA) : for nonconformances
 - ✓ Verification and testing : follow-up after preventative or corrective action



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QUALITY MANAGEMENT SYSTEM

- A plan focusing an organization's efforts on product quality and meeting customer needs
- Usually designed to meet International Organization for Standardization (ISO) requirements
- Total quality management (TQM) : a quality management system that
 - Is built around an effort to improve quality
 - Involves the entire organization
 - Ensures customer satisfaction



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ISO

- ISO promotes worldwide standards to :
 - ✓ Improve operating efficiency and productivity
 - ✓ Reduce costs
- ISO 9000 : a family of international standards that apply to quality system design and implementation



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ISO 9000 STANDARDS

- Based on 8 quality management principles:
 1. Customer focus
 2. Leadership
 3. Workforce involvement
 4. Continuous improvement
 5. System approach to management
 6. Data-based approach to decision making
 7. Positive supplier communication / relationships
 8. Total process approach



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MORE DETAILS ?

Textbook reading :

- Continuous Improvement – Chapter 16
- Inspection & Auditing – Chapter 17

BMAN 1150 – Bioman Quality Systems & Regs

Will cover in more detail:

- FDA regulations, etc. (USDA, EPA) and their impact on biomanufacturing
- Quality system components and functioning
- ISO 9001 certification vs. ANSI certification



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QUIZ

Will have a quiz (**40 points**) on this material on this date:



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PRACTICAL ASSIGNMENT

Draft a Work Instruction document describing how to:

- o Calibrate the pH meter
- o Prepare 250 mL of 0.5 M Tris, pH 7.8

* Refer to textbook for additional information :

Section 11.3, pages 269-270

“Standard Operating Procedures”

* And Handout 13-7

“Preparing Standard Operating Procedures”

Due **next class** and worth **30 points**



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REVIEW FROM PREVIOUS WEEK

- Why did the Food, Drug, and Cosmetic (FD&C) Act of 1938 arise?
- What is the mission of the Food and Drug Administration (FDA)?
- The laws & regulations that the FDA is authorized to uphold can be found in what document? what parts?
- What are good manufacturing practices (GMP)?



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CRITICAL THINKING



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THE IMPORTANCE

- The foundation for problem-solving and trouble-shooting
- Our industry advisors indicate that this is one highly desirable skill they want employees to have
- Best learned by doing



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PRACTICAL ACTIVITIES

- Goals
 1. To learn about nonconformance reporting
 2. To learn how to perform root cause failure analysis
 3. To learn how to identify and perform corrective/preventative actions



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PRACTICAL ACTIVITIES (cont.)

1. As a class, create a Work Instruction document describing how to:
 - Calibrate the pH meter
 - Prepare 250 mL of 0.5 M Tris, pH 7.8

** Worth part of the 30 points for drafting your own work instruction document
2. Review and analyze caliper measurement data (from several classes ago) – worth **10 points**



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PRACTICAL ACTIVITIES (cont. 2)

3. Create statistical process control charts per **Exercise 16-6** (handout provided)
 - Use Microsoft Excel
 - Refer to textbook for additional information
Chapter 16 – Focus on Quality
Section 16.2, pages 358-360
“Analyzing Process Data”
 - Worth **30 points**
 - Due **next week** – e-mail Excel file to instructor



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REVIEW FROM PREVIOUS WEEK

- Name 3 components of SOPs.
- What are some benefits of proper SOP usage and record keeping/documentation?
- What are some consequences of improper SOP usage and record keeping/documentation?
- What is the value of keeping track of SOP revision numbers and effective dates?



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CRITICAL THINKING (cont.)



Step Ahead.

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IN-CLASS PRACTICAL ACTIVITIES

Problem-solve the “cookie batch issues”
(individually and as a group) – focus on :

- **root cause failure analysis / Fishbone diagram (50 points)** &
- **corrective/preventative actions (25 points)**

per the continuous improvement directive

Refer to textbook Chapter 18 – Preventative & Corrective
Actions, Section 18.1, pages 388-392 “**Root Cause
Failure Analysis**”



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REVIEW FROM PREVIOUS WEEK

- What is meant by root cause failure analysis?
- What is the purpose of the “5 Whys”?
- What is a fishbone diagram? And what is it used for?



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MICROBIOLOGY CONCEPTS AND TECHNIQUES



Step Ahead.

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CONCEPTS & TECHNIQUES

- Sterility / sterilization methods
- Aseptic technique
- Cell storage
- Cell culturing : on plates & in broth
- Fermentation / bioprocessing / bioreactors
- Cell harvesting or removal
- Cell lysis : to recover cellular component (e.g. recombinant protein, cellular product)



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APPLICATIONS IN INDUSTRY

- Product manufacturing
- Raw material testing
- Final product testing
- Microbial identification
- Biocompatibility
- Validation of facilities, processes, equipment, packaging/containers



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INDUSTRY SECTORS IMPACTED

- Food & agriculture
- Therapeutics & vaccines
- Natural products
- Regenerative medicine
- Biofuels
- Medical device
- Pharmaceuticals
- Diagnostics



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STERILITY / STERILIZATION

- Critical to end product quality
- Typical methods:
 - Dry heat
 - Moist heat – e.g. autoclaving
 - Ethylene oxide (in a fixed chamber)
 - Radiation – gamma or electron-beam
 - Liquid chemical sterilants
- Other methods
 - Filtration
 - UV light
 - Peroxide vapor



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STERILITY / STERILIZATION (cont.)

- Regulated by the FDA
 - ❖ See: "510(k) Sterility Review Guidance K90-1" from FDA / CDRH / ODE
- Method choice depends on:
 - o Material characteristics
 - o Through-put
 - o Effectiveness
 - o Ease of use
 - o Cost



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AUTOCLAVE USAGE NOTES

- Autoclaves sterilize with moist heat and pressure
 - o Moist heat permits lower temperature
 - o Typical cycle parameters: 121 °C for 20 minutes
 - o Liquid vs. dry cycle – select accordingly
- Ensure autoclavability of items before loading
 - o Stainless steel and most metals are autoclavable
 - o Not all plastics are !!



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AUTOCLAVE USAGE NOTES (cont.)

- Package / label accordingly
 - o Secured foil wraps
 - o Autoclave indicator tape
- Can also use to "neutralize" biohazard waste



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ASEPTIC TECHNIQUE

- Is a way of working that minimizes the contamination of material with microorganisms (bacteria & viruses)
- Think: “all surfaces are **CONTAMINATED**, unless they have been sterilized” !!!
- Usually involves
 - ✓ Alcohol wiping of work surfaces prior to working
 - ✓ Working with / near a flame for a “cleaner” environment & quick sterilization as needed



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ASEPTIC TECHNIQUE (cont.)

- Considerations:
 - ✓ Prevent contact with critical surfaces that must stay sterile
 - ✓ Minimize “open” time
 - ✓ Minimize placing caps / lids down on the work surface – if must, then consider face down vs. face up
 - ✓ Plan before you do – organize your work area
- Instructor will demonstrate



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CELL STORAGE

- Typically, only stocks of cell lines are stored
- Storage is typically in a
 - o -80 °C freezer
 - o Liquid nitrogen (colder than -196 °C = -321 °F) tank
 - Advantage: power failures do not affect stocks
 - Disadvantage: must keep liquid nitrogen level appropriate in tank or stocks thaw !!



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CELL CULTURING

- Typical media
 - o Agar plates
 - o Liquid broth
- Many “flavors” of media – choice depends on
 - o Purpose of culture
 - o Cell characteristics
 - o Selection needs
 - o Induction needs
- When inoculating, must use aseptic technique



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PLATE STREAKING

- Goal is to obtain isolated **SINGLE** colonies
- A **SINGLE** colony originated from 1 CELL
- Preparation of liquid cultures require inoculation with a **SINGLE** colony
- Instructor will demonstrate
- Refer to plate streaking methods sheet



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PLATE STREAKING (cont.)

- Considerations:
 - ✓ Hold inoculation loop at appropriate angle
 - ✓ Do not gouge agar
 - ✓ Ensure at least some cells or part of colony has transferred from the loop to the agar media
 - ✓ Decontaminate loop after streaking by flaming



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LIQUID CULTURING

- Goal is to grow cells, from a **SINGLE** colony, to high numbers
- Liquid rather than plate (solid) media facilitates high growth
- May require agitation – to aerate liquid media & to keep cells evenly mixed with liquid
- Cell growth limited by extent of aeration, available nutrients, cell waste products, pH, and cell density



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LIQUID CULTURING (cont.)

- Considerations:
 - ✓ Do not allow non-sterilized portions of inoculation loop to touch critical sterile surfaces
 - ✓ Ensure at least some cells or part of colony has transferred from the loop to the liquid media
 - ✓ Decontaminate loop after inoculation by flaming



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FERMENTATION & BIOREACTORS

- Fermentation / bioprocessing = highly efficient liquid culturing of bacterial cells
- Bioreactor = specialized vessel allowing for controlled, efficient cell growth
 - ❖ Typical controls include: temperature, pH, O₂, limited nutrients (e.g. glucose)
- Can produce many liters of cell culture in one batch / lot, maximizing yield and profit



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FERMENTATION & BIOREACTORS (cont.)

- Typical vessel size ranges from 0.5 L to 1000 L
- Vessel material can be all glass, glass / steel, or all steel
- Example bioreactor system will be shown by instructor



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FERMENTATION & BIOREACTORS (cont.)

From: <http://www.applikon-bio.com/cgi-bin/applikonbio/menu-bioreactors-special.html>



A typical production bioreactor



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IN-CLASS PRACTICAL ACTIVITIES

Learn how to perform the following microbiology techniques (**50 points**) :

1. Plate streaking
2. Inoculation of liquid culture

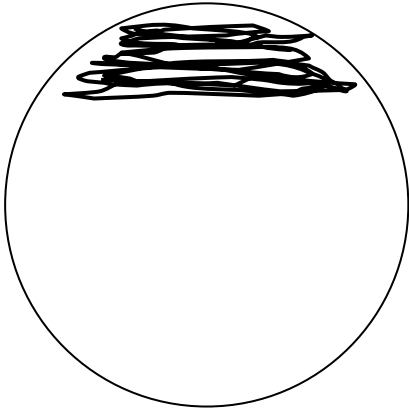


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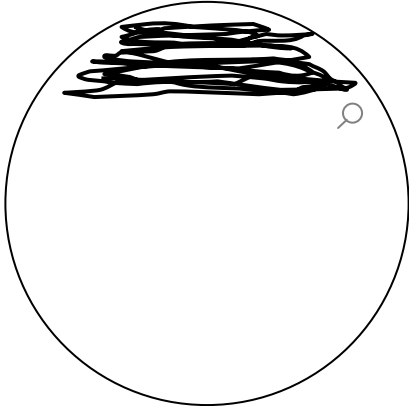
PLATE STREAKING METHOD 1

1. Flame loop, cool on agar, & pick isolated colony from stock plate.

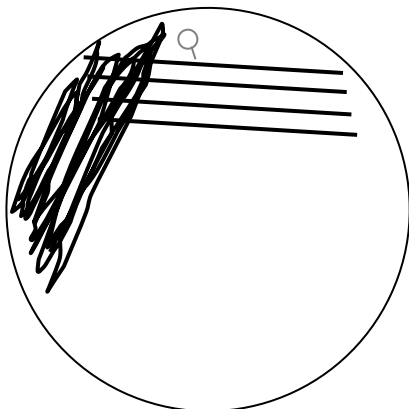
2. On fresh plate, generate initial smear.



3. Flame loop & cool on agar of fresh plate.

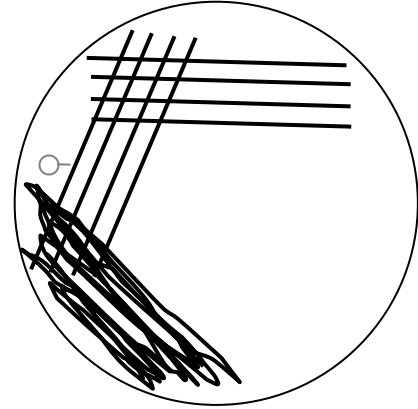


4. Turn plate and streak 1st set of parallel lines out from end of initial smear.

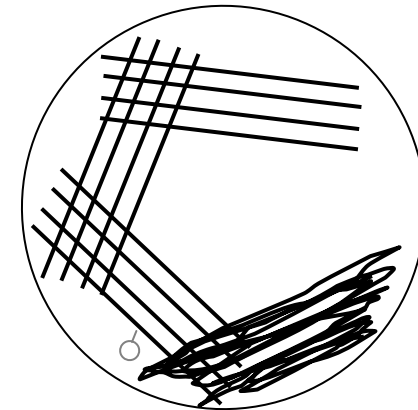


“PARALLEL LINES”

5. Turn plate again and streak 2nd set of parallel lines out from end of 1st set of parallel lines. DO NOT ENTER INITIAL SMEAR.



6. Turn plate again and streak 3rd set of parallel lines out from end of 2nd set of parallel lines. DO NOT ENTER INITIAL SMEAR.



7. If space permits, turn plate again and streak 4th set of parallel lines out from end of 3rd set of parallel lines. DO NOT ENTER INITIAL SMEAR.

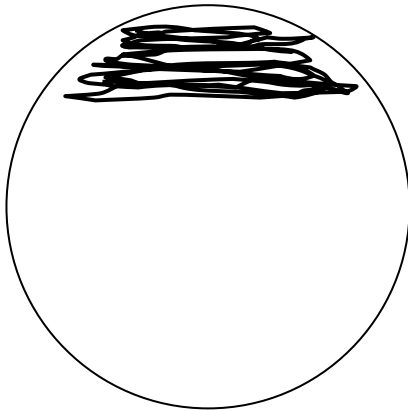
8. Flame loop and let cool in the air to decontaminate the loop.

9. Label bottom (NOT LID) of plate with
 - o name of bacterial strain
 - o your initials
 - o the date

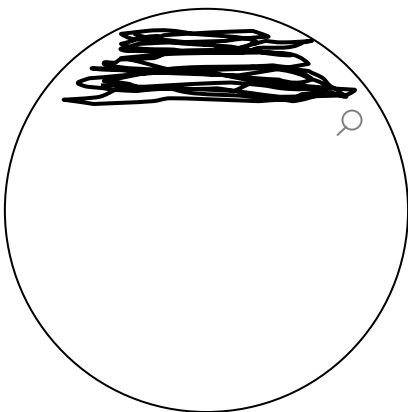
PLATE STREAKING METHOD 2

1. Flame loop, cool on agar, & pick isolated colony from stock plate.

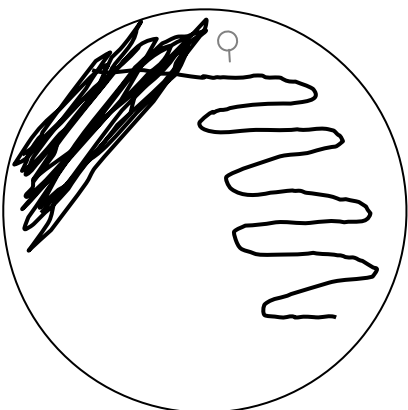
2. On fresh plate, generate initial smear.



3. Flame loop & cool on agar of fresh plate.

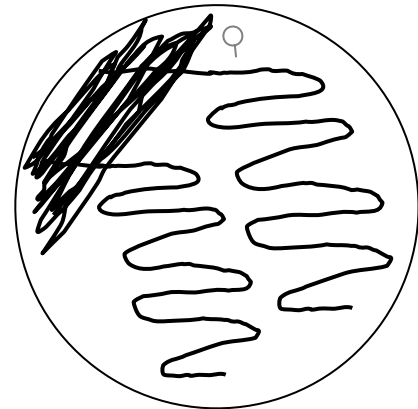


4. Turn plate slightly and from the initial smear, streak one zig-zag line on half the plate.



“ZIG ZAGS”

5. From the initial smear, streak a second zig-zag line on the other half of the plate.



6. Flame loop and let cool in the air to decontaminate the loop.

7. Label bottom (NOT LID) of plate with
 - o name of bacterial strain
 - o your initials
 - o the date

REVIEW FROM PREVIOUS WEEK

- For what applications might microbiology techniques be used?
- What is aseptic technique?
- Name 3 different methods for culturing cells.
- What is the significance of a SINGLE colony?



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MICROBIOLOGY CONCEPTS AND TECHNIQUES (cont.)



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CELL HARVESTING / REMOVAL

- Harvesting : to collect cells in order to recover product inside them
- Removal : to eliminate cells from culture media because product was secreted
- Methods include:
 - o Centrifugation
 - o Filtration



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CELL HARVESTING BY CENTRIFUGATION

- A easy and efficient method of cell harvesting
- Centrifuge understanding critical because
 - o Rotor spin speed requires proper usage or will cause major damage / safety issues
 - o Balancing is an absolute must
 - o Tube / bottle (container) selection should consider centrifugal forces



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CELL HARVESTING BY CENTRIFUGATION (cont.)

- For large-scale, high throughput harvesting, can use continuous flow method: requires specialized rotor (or centrifuge, e.g. Sharples) and pump system



From: <http://www.nbsc.com/cepa.aspx>

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CELL LYSIS

- Lysis = breaks open cells to liberate contents
- Required for recovery of product not secreted into culture media
- Methods include:
 - o Chemical – e.g. lysozyme
 - o Mechanical – e.g. bead-beating in “blender”



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CELL LYSIS BY LYSOZYME

- Lysozyme = an enzyme that hydrolyzes peptidoglycans, a major component of Gram-positive bacterial cell walls; results in “holes” in cell wall → lysis (facilitated by freeze/thaw)
- Lysozyme originally discovered (by accident !) in nasal drippings on bacterial culture plates, and found in:
 - o Mucosal secretions: e.g. saliva and tears
 - o Chicken egg-white



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IN-CLASS PRACTICAL ACTIVITIES (cont.)

Learn how to perform the following microbiology techniques and their underlying theory :

3. Cell harvesting
4. Cell lysing



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MOLECULAR & BIOCHEMICAL CONCEPTS AND TECHNIQUES



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CELL PRODUCTS

- Can be:
 - o A protein
 - o A nucleic acid molecule
 - o Other biological molecule
- May be “recombinant” (i.e. not naturally occurring)



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CELL PRODUCT PURIFICATION

- Typically, methodology is based on:
 - o Size
 - o Charge
 - o Other special characteristics / features



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PURIFICATION TECHNIQUES

Property	Available Techniques
Size	Filtration
	Chromatography (gel filtration)
	Dialysis
Charge	Chromatography (ion exchange)
	Electrophoretic separation
Special feature: antigenic determinant	Chromatography (antibody affinity)
	Antibody-facilitated separation / enrichment (antibodies on beads + centrifugation)
Special feature: binding to “ligand”	Chromatography (ligand affinity)
	Ligand-facilitated separation / enrichment (ligands on beads + centrifugation)



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IN-CLASS PRACTICAL ACTIVITIES

Learn how to perform the following
molecular & biochemical techniques (**50 points**)
and their underlying theory :

1. Centrifugation
2. Chromatography



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Green Fluorescent Protein Isolation & Purification Procedure

Isolation

1. Remove liquid culture of *E.coli* / pGLO from incubator.
2. Transfer approximately 1.5 mL of bacterial culture and place in microfuge tube. Label tube.
3. Place microtube in centrifuge, and spin for 5 minutes at max speed.
4. When spin is complete, CAREFULLY remove your tube and pour off liquid supernatant without dislodging the cell pellet at bottom of tube.
5. Observe pellet under UV light.
6. Add 250 uL TE solution to tube.
7. Resuspend cell pellet by sucking TE solution in and out of pipet.
8. Add 1 drop of lysozyme to resuspended cell pellet. Place tube in freezer for at least 20 minutes.

Purification

1. Remove tube and thaw using hand warmth.
2. Place tube in centrifuge, and spin for 10 minutes at max speed.
3. Label new microtube.
4. Prepare chromatography column.
 - a. Resuspend beads by shaking.
 - b. Shake beads down to bottom / tap on bench top.
 - c. Remove top cap.
 - d. Snap off bottom tab.
 - e. Place column in clamp of ring stand and position properly.
 - f. Allow liquid to drain completely.
 - g. Add 2 mL equilibration buffer to top of column.
 - h. Drain buffer completely.
 - i. Cap bottom.
5. Remove tube from centrifuge.
6. Examine tube under UV light.
7. Use new pipet and transfer 250 uL of supernatant to the new microtube.
8. Use new pipet and add 250 uL binding buffer to supernatant, and mix.
9. Obtain 3 collection tubes and label them 1, 2, 3.
10. Place tubes in white rack.
11. Position tube 1 under column.
12. Use new pipet to load 250 uL of supernatant / binding buffer mixture onto the column.
13. Carefully uncap the bottom.
14. Allow mixture to enter column entirely.
15. Shine UV light at column and take notes.
16. Position tube 2 under column.
17. Load 250 uL of wash buffer onto column.
18. Allow wash buffer to enter column entirely.
19. Shine UV light at column and take notes.
20. Position tube 3 under column.
21. Load 750 uL TE buffer onto column.
22. Shine UV light at column while TE buffer drains through.
23. When column completely drained, cap bottom. Examine all 3 tubes under the UV light, and take notes.

REVIEW FROM PREVIOUS WEEK

- What are typical methods for cell harvesting?
- Why is cell lysis necessary?
- What kinds of cell products might be of interest?
- On what characteristics can purification methods for a cell product be based?



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MOLECULAR & BIOCHEMICAL CONCEPTS AND TECHNIQUES (cont.)



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CHROMATOGRAPHY, IN GENERAL

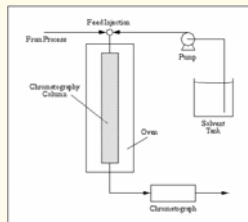
- Is a method to separate / analyze mixtures of molecules
- Utilizes a **stationary** phase and a **mobile** phase
- Molecules in mixture are distributed between the 2 phases
- Separation is dependent on molecular characteristics of each molecule type in mixture, resulting in **differential distribution** in stationary vs. mobile phases and **differential retention rates**



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THE CHROMATOGRAPHY SYSTEM

- The system consists of these main components:
 - o Sample injection
 - o Column
 - o Mobile phase reservoir
 - o Pump (capable of high pressures)
 - o Detector (gives the **chromatograph**)



From: <http://www.rpi.edu/dept/chem-eng/Biotech-Environ/CHROMO/chromoper.html>

WHY A COLUMN ?

- Traditional liquid phase method used gravity to move sample through stationary phase
- Now, rely on pressure (on the mobile phase) to move sample through
- Column configuration facilitates separation **resolution** (how well one molecule type is separated from another type)

COLUMNS

- Columns come packed with stationary phase
- Stationary phase can be composed of many different materials (e.g. silica)
- Outer shell can be glass, stainless steel, or both, depending on application

MOBILE & STATIONARY PHASES

If Mobile Phase is	Then Stationary Phase is
Gas (usually an inert gas)	Generally, an adsorbent or viscous liquid distributed over the surface of a porous, inert support
Liquid * (of low viscosity)	A bed composed of: • an immiscible liquid coated onto a porous support • a thin film of liquid phase bonded to the surface of a sorbent • a sorbent of controlled pore size

* Typically, in liquid chromatography, stationary phase is more polar than mobile phase. If reversed, then considered REVERSED-PHASE LIQUID CHROMATOGRAPHY



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DETECTORS

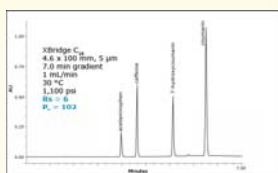
Mobile Phase	Characteristic of Mobile Phase Examined	Detector Type
Gas	Heat-conducting ability	Thermal conductivity
	Presence of hydrocarbons	Flame-ionization
	Fluorescence	Fluorescence
	Mass of fragmented molecules	Mass spectrometer
Liquid	Refractive index	Various refractive index
	UV absorption	UV & photodiode array
	Fluorescence	Fluorescence
	Light scattering	Evaporative light scattering & Liquid light scattering
	Mass of fragmented molecules	Mass spectrometer



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THE CHROMATOGRAM

- A graphical representation of the separated molecules
- Each peak represents:
 - o one molecule type, or
 - o a mixture of molecules that share the same elution characteristics
- Good peak separation = good resolution !!



From: http://www.waters.com/waters/nav.htm?locale=en_US&cid=514207#

X-axis = retention time
Y-axis = detected signal



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TYPES OF GAS CHROMATOGRAPHY

- Gas adsorption chromatography :
 - Uses a packed adsorbent bed (e.g. zeolite, silica gel, activated alumina)
 - Separates gas mixtures
- Gas-liquid chromatography :
 - Uses an inert porous solid (diatomaceous earth) coated with a viscous liquid
 - Solutes must dissolve in liquid phase and vaporize



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TYPES OF GAS CHROMATOGRAPHY (cont.)

- Capillary gas chromatography :
 - Most common method
 - Uses glass or fused silica capillaries coated (on inside) with absorbent or other solvent
 - Limited capacity, but offers rapid separation



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EXAMPLE GAS CHROMATOGRAPHY SYSTEM

Agilent 7890A GC
System

From:
[http://www.chem.
agilent.com/en-
us/products/instru
ments/gc/agilent7
890agcsystem/pag
es/default.aspx](http://www.chem.agilent.com/en-us/products/instruments/gc/agilent7890agcsystem/pages/default.aspx)



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TYPES OF LIQUID CHROMATOGRAPHY

- Gel filtration / size exclusion :
 - o Uses a packed porous gel bead bed
 - o Different sized porous gel beads to choose from
 - o Molecules larger than pores will elute first
- Ion-exchange :
 - o Cation exchange : – charged stationary phase
 - o Anion exchange : + charged stationary phase
 - o Ionic interaction between oppositely-charged molecules (in mobile phase) with stationary phase
 - o Changing mobile phase properties elutes bound molecules



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TYPES OF LIQUID CHROMATOGRAPHY (cont.)

- Affinity :
 - o Uses a “capture molecule”-bound stationary phase (e.g. antibody / antigen, protein / ligand)
 - o Offers very specific purification
 - o Release bound molecules by adding “competitor”
- Reversed-phase / hydrophobic interaction :
 - o Uses a hydrophobic (non-polar) stationary phase
- High performance (HPLC) :
 - o Reversed-phase + high velocity & large pressure differential



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EXAMPLE LIQUID CHROMATOGRAPHY SYSTEM

Waters Acquity UPLC System

From:
<http://www.waters.com/waters/nav.htm?cid=514207>



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USES OF CHROMATOGRAPHY

- Biological molecule (protein, nucleic acid) purification
- Quality testing :
 - o Batch consistency / reproducibility
 - o Trace contaminants in products or raw materials
 - o Stability – breakdown byproducts ?
- Chemical analyses of :
 - o Pharmaceuticals
 - o Forensic samples



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IN-CLASS PRACTICAL ACTIVITIES

1. Review GFP purification exercise & questions
2. Examine HPLC systems

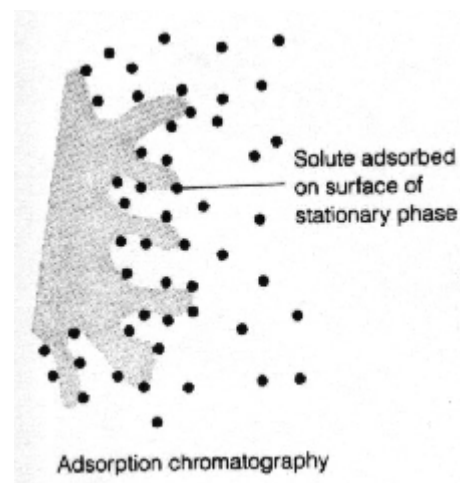


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Types of Chromatography

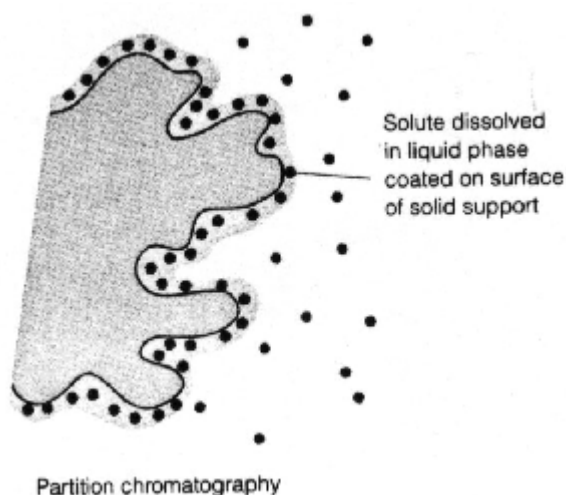
Adsorption Chromatography

Adsorption chromatography is probably one of the oldest types of chromatography around. It utilizes a mobile liquid or gaseous phase that is adsorbed onto the surface of a stationary solid phase. The equilibration between the mobile and stationary phase accounts for the separation of different solutes.



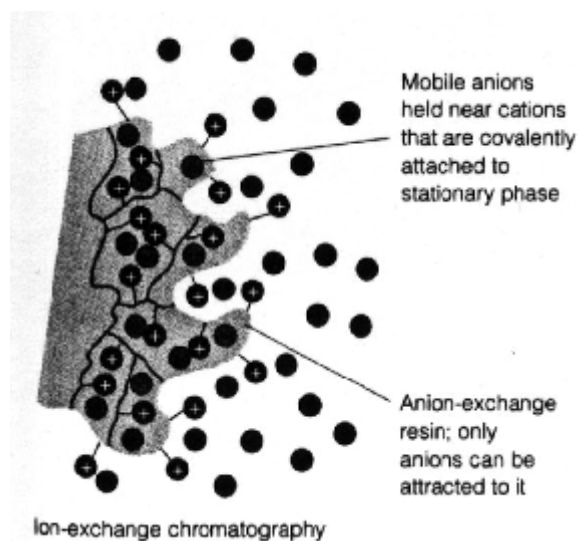
Partition Chromatography

This form of chromatography is based on a thin film formed on the surface of a solid support by a liquid stationary phase. Solute equilibrates between the mobile phase and the stationary liquid.



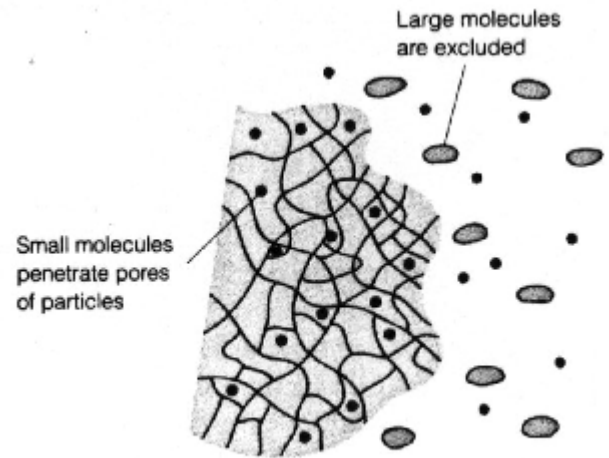
Ion Exchange Chromatography

In this type of chromatography, the use of a resin (the stationary solid phase) is used to covalently attach anions or cations onto it. Solute ions of the opposite charge in the mobile liquid phase are attracted to the resin by electrostatic forces.



Molecular Exclusion Chromatography

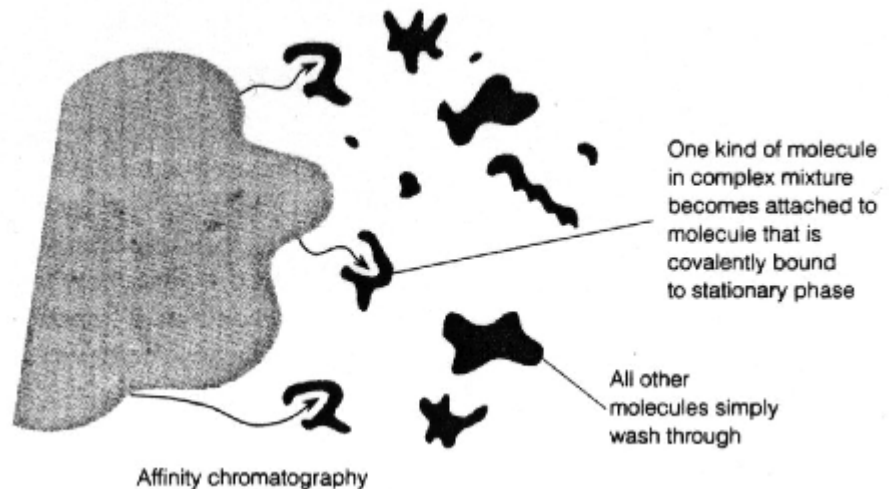
Also known as gel permeation or gel filtration, this type of chromatography lacks an attractive interaction between the stationary phase and solute. The liquid or gaseous phase passes through a porous gel which separates the molecules according to its size. The pores are normally small and exclude the larger solute molecules, but allows smaller molecules to enter the gel, causing them to flow through a larger volume. This causes the larger molecules to pass through the column at a faster rate than the smaller ones.



Molecular exclusion chromatography

Affinity Chromatography

This is the most selective type of chromatography employed. It utilizes the specific interaction between one kind of solute molecule and a second molecule that is immobilized on a stationary phase. For example, the immobilized molecule may be an antibody to some specific protein. When solute containing a mixture of proteins are passed by this molecule, only the specific protein is reacted to this antibody, binding it to the stationary phase. This protein is later extracted by changing the ionic strength or pH.



[Back to starting page](#)

REVIEW FROM PREVIOUS WEEK

- What is the purpose of chromatography ?
- How does liquid chromatography differ from gas chromatography ?
- Name 3 types of liquid chromatography ?
- Name 2 uses of chromatography in biomanufacturing ?



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PRODUCTION ACTIVITIES



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IN-CLASS ASSIGNMENT

- Examine in detail, through internet research, the following processes & equipment:
 - o Tablet press
 - o Filling machinery
 - o Injection molding & machinery
 - o Drug formulation
- Complete worksheet
Worth **40 points**
Due **next class**



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REVIEW FROM PREVIOUS WEEK

- Questions ?



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PACKAGING & LABELING



Step Ahead.

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PACKAGING DEFINITIONS

- **Packaging component** : any single part of a container closure system (e.g. container, container liner, closure, closure liner, seals, ports, overwraps, administration accessories, labels)
- **Primary packaging component** : a component that is / may be in direct contact with the dosage form



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PACKAGING DEFINITIONS

(cont.)

- **Secondary packaging component** : a component that is / will NOT BE in direct contact with the dosage form
- **Container closure system** : sum of packaging components that contain & protect the dosage form
- **Package (market package)** : the container closure system, labeling, associated accessory components, and external packaging



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PACKAGING CONSIDERATIONS

- Must not be reactive / additive / absorptive with the product or affect product integrity
- Must be tested for suitability & conformance to specifications
- Must be quarantined if rejected & appropriately disposed
- Must be protected from contamination
- Must be traceable
- Must use oldest material first



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PACKAGING CONSIDERATIONS

(cont.)

- Must protect product from environmental factors that may contaminate / degrade product
- Must be clean and pyrogen-free
- Must be able to withstand sterilization procedure(s), as appropriate
- Must be handled/used according to documented procedures
- Must be different for similar product lines to avoid confusion



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LABELING CONSIDERATIONS

- Must name and address of manufacturer / packer / distributor
- Must be accurately describe contents, including:
 - ✓ Product name(s) : brand name vs. 'official' name
 - ✓ Lot number
 - ✓ Dosage per unit
 - ✓ Unit quantity per package
 - ✓ Ingredients : active & other
 - ✓ Expiration date



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LABELING CONSIDERATIONS (cont.)

- Must be contain adequate directions for use
- Must include appropriate warnings relating to safe use
- Must not contain false / misleading / ambiguous information or unsubstantiated claims
- Must conform to specifications
- Must be traceable & be restrictively issued
- Must be distinct for similar product lines to avoid confusion



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PACKAGING & LABELING CONTROL

- Most frequent and consequential problem is packaging / labeling does not match product
- Quality system must address control of packaging & labeling, including:
 - ✓ Revisions
 - ✓ Integrity
 - ✓ Inspection (before & after product application)
 - ✓ Storage
 - ✓ Operations
 - ✓ Control number



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PACKAGING & LABELING CONTROL (cont.)

- Can think of packaging & labeling as products as well
- Packaging & labeling must combine appropriately with the product proper to generate the FINAL FINISHED PRODUCT



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IN-CLASS ASSIGNMENTS

- Study these documents for class discussion :
 1. "Container Closure Systems for Packaging Human Drugs and Biologics – Guidance for Industry" – CBER / CDER document
[from www.fda.gov/cder/guidance/1714fnl.pdf]
 2. Labeling for Amedica Corporation's Valeo Compact VBR Spacers and FDA's warning letter regarding this product's misbranding
- Purpose : to learn what to look for when inspecting packaging & labeling (**25 points**)



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Guidance for Industry

Container Closure Systems for Packaging Human Drugs and Biologics

CHEMISTRY, MANUFACTURING, AND CONTROLS DOCUMENTATION

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)**

May 1999

Guidance for Industry

Container Closure Systems for Packaging Human Drugs and Biologics

CHEMISTRY, MANUFACTURING, AND CONTROLS DOCUMENTATION

Additional copies are available from:

Office of Training and Communications
Division of Communications Management
Drug Information Branch, HFD-210
Center for Drug Evaluation and Research (CDER)
5600 Fishers Lane
Rockville, Maryland 20857
(Tel) 301-827-4573
(Internet) <http://www.fda.gov/cder/guidance/index.htm>

or

Office of Communications
Training and Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research (CBER)
1401 Rockville Pike
Rockville, Maryland 20852-1448
(Fax) 888-CBERFAX or 301-827-3844
(Voice Information) 800-835-4709 or 301-827-1800
(Internet) <http://www.fda.gov/cber/guidelines.htm>

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
May 1999**

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GUIDANCE FOR INDUSTRY¹

CONTAINER CLOSURE SYSTEMS FOR PACKAGING HUMAN DRUGS AND BIOLOGICS

CHEMISTRY, MANUFACTURING, AND CONTROLS DOCUMENTATION

I. INTRODUCTION

This document is intended to provide guidance on general principles² for submitting information on packaging materials used for human drugs and biologics.³ This guidance supersedes the FDA *Guideline for Submitting Documentation for Packaging for Human Drugs and Biologics*, issued in February 1987 and the packaging policy statement issued in a letter to industry dated June 30, 1995 from the Office of Generic Drugs.⁴ This guidance is not intended to describe the information that should be provided about packaging operations associated with drug product manufacture.

Approaches which differ from those described in this guidance may be followed, but the applicant is encouraged to discuss significant variations in advance with the appropriate CDER chemistry review staff or CBER review staff. This is to prevent applicants or sponsors from spending unnecessary time and effort in preparing a submission that the FDA may later determine to be unacceptable.

¹ This guidance has been prepared by the Packaging Technical Committee of the Chemistry, Manufacturing, and Controls Coordinating Committee (CMC CC) in the Center for Drug Evaluation and Research (CDER) and in conjunction with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on container closure systems for the packaging of human drugs and biological products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

² In general, this guidance does not suggest specific test methods and acceptance criteria (except for references to *The United States Pharmacopoeia* methods), nor does it suggest comprehensive lists of tests. These details should be determined based on good scientific principles for each specific container closure system for particular drug product formulations, dosage forms, and routes of administration. Acceptance criteria should be based on actual data for particular packaging components and container closure systems, and they should be set to ensure batch-to-batch uniformity of packaging components.

³ As used in this guidance, the terms *drug* and *drug product* include biologics unless otherwise noted.

⁴ The policy statement is a document titled *Container/Closure Information Which Should Be Provided In An ANDA/AADA* which was written by the Office of Generic Drugs/Packaging Advisory Group.

II. BACKGROUND

The Federal Food, Drug, and Cosmetic Act (the Act) mandates the need for adequate information related to packaging materials. Section 501(a)(3) of the Act states that a drug is deemed to be adulterated "if its container is composed, in whole or in part, of any poisonous or deleterious substance which may render the contents injurious to health...." In addition, section 502 of the Act states that a drug is considered misbranded if there are packaging omissions. Also, section 505 of the Act requires a full description of the methods used in, and the facilities and controls used for, the packaging of drugs (see Attachment A).

Section 505(b)(1)(D) of the Act states that an application shall include a full description of the methods used in, the manufacturing, processing and packing of such drug. This includes facilities and controls used in the packaging a drug product.

A. Definitions⁵

*Materials of construction*⁶ refer to the substances (e.g., glass, high density polyethylene (HDPE) resin, metal) used to manufacture a packaging component.

A *packaging component* means any single part of a container closure system. Typical components are containers (e.g., ampules, vials, bottles), container liners (e.g., tube liners), closures (e.g., screw caps, stoppers), closure liners, stopper overseals, container inner seals, administration ports (e.g., on large-volume parenterals (LVPs)), overwraps, administration accessories, and container labels. A *primary packaging component* means a packaging component that is or may be in direct contact with the dosage form. A *secondary packaging component* means a packaging component that is not and will not be in direct contact with the dosage form.

A *container closure system* refers to the sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product. A *packaging system* is equivalent to a container closure system.

⁵ These definitions are intended to clarify the use of certain terms in this guidance only and are not intended to supersede the definitions of *container* and *package* as provided for in 21 CFR 600.3.

⁶ This term is used in a general sense for the basic material, which should be defined in the application in terms of its specific chemical composition for a given drug application (e.g., the specific polymer and any additives used to make the material).

A *package* or *market package*⁷ refers to the container closure system and labeling, associated components (e.g., dosing cups, droppers, spoons), and external packaging (e.g., cartons or shrink wrap). A market package is the article provided to a pharmacist or retail customer upon purchase and does not include packaging used solely for the purpose of shipping such articles.

Quality refers to the physical, chemical, microbiological, biological, bioavailability, and stability attributes that a drug product should maintain if it is to be deemed suitable for therapeutic or diagnostic use. In this guidance, the term is also understood to convey the properties of safety, identity, strength, quality, and purity (see 21 CFR 211.94(a)).

An *extraction profile* refers to the analysis (usually by chromatographic means) of extracts obtained from a packaging component. A *quantitative extraction profile* is one in which the amount of each detected substance is determined.

B. CGMP, CPSC and USP Requirements on Containers and Closures

Current good manufacturing practice (CGMP) requirements for the control of drug product containers and closures are included in 21 CFR Parts 210 and 211. A listing of the relevant sections is provided in Attachment A. In addition, a listing of Compliance Policy Guides that deal with packaging issues is provided in Attachment B. References in this guidance to CGMP regulations are provided for completeness. For additional information, refer to the *FDA Compliance Program Guidance Manual* for Pre-Approval Inspections/Investigations (7346.832) which describes specific responsibilities for CDER scientists and for field investigators.

The FDA requirement for tamper-resistant closures is included in 21 CFR 211.132 and the Consumer Product Safety Commission (CPSC) requirements for child-resistant closures are included in 16 CFR 1700. An outline of these and other applicable regulatory requirements is provided in Attachment A.

The United States Pharmacopeial Convention has established requirements for containers which are described in many of the drug product monographs in *The United States Pharmacopeia/National Formulary* (USP/NF). For capsules and tablets, these requirements generally relate to the design characteristics of the container (e.g., tight, well-closed or light-resistant). For injectable products, materials of construction are also addressed (e.g., "Preserve in single-dose or in multiple-dose containers, preferably of Type I glass, protected from light"). These requirements are defined in the "General Notices and Requirements" (Preservation, Packaging, Storage, and Labeling) section of the *USP*. The requirements for materials of construction are defined in the "General Chapters" of

⁷ The materials of construction used in the labeling are a concern from a packaging perspective if they affect the protection and/or safety of the drug product.

the USP (see Attachment A).

C. Additional Considerations

1. Submissions of INDs

The packaging information in the chemistry, manufacturing, and controls section of an IND usually includes a brief description of the components, the assembled packaging system and any precautions needed to ensure the protection and preservation of the drug substance and drug product during their use in the clinical trials.

For general guidance regarding the container closure system information to be submitted for phase 1 studies, refer to the FDA guidance for industry *Content and Format of investigational New Drug Applications(INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products* (November 1995).

General guidance regarding the container closure system information to be submitted for phase 2 or phase 3 studies will be provided in the FDA guidance for industry *INDs for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products, Chemistry, Manufacturing, and Controls Content and Format*, when finalized (draft guidance published April 21, 1999).

2. Submissions on Packaging of a Drug Product by Another Firm

a. Contract Packager

A contract packager is a firm retained by the applicant to package a drug product. The applicant remains responsible for the quality of the drug product during shipping, storage, and packaging.

The information regarding the container closure system used by a contract packager that should be submitted in the CMC section of an application (NDA, ANDA, or BLA), or in a DMF which is referenced in the application, is no different from that which would be submitted if the applicant performed its own packaging operations. If the information is provided in a DMF, then a copy of the letter of authorization (LOA) for the DMF should be provided in the application (see section V.A).

b. Repackager⁸

A repackager is a firm that buys drug product from the drug product manufacturer or distributor and repackages it for sale under a label different from that of the manufacturer. The repackager is responsible for ensuring the quality and stability of the repackaged drug product. The repackaging operation is required to be in compliance with CGMPs (21 CFR Part 211), and there are limits to the expiration period that may be used with the repackaged product unless the repackager conducts stability studies.⁹ Packaging qualification information is not required if the repackager uses the same container closure system approved in the original application.

All significant phases of the manufacturing and processing of a drug product (including packaging) should be described as part of the CMC section of an application (NDA, ANDA or BLA), or in a DMF referenced in the application. The only exception is the repackaging of solid oral drug products for which an approved application already exists.¹⁰ For biologics, repackaging is considered a step in the manufacturing process for which licensing is required (21 CFR 600.3(u) and 601).

III. QUALIFICATION AND QUALITY CONTROL OF PACKAGING COMPONENTS

A. Introduction

CDER and CBER approve a container closure system to be used in the packaging of a human drug or biologic as part of the application (NDA, ANDA or BLA) for the drug or biologic. A packaging system found acceptable for one drug product is not automatically assumed to be appropriate for another. Each application should contain enough information to show that each proposed container closure system and its components are suitable for its intended use.

The type and extent of information that should be provided in an application will depend on the dosage form and the route of administration. For example, the kind of information that should be provided about a packaging system for an injectable dosage form or a drug

⁸ This discussion does not apply to the repackaging of drug products for dispensing under the practice of pharmacy.

⁹ FDA *Compliance Policy Guides*, "Expiration Dating of Unit Repackaged Drugs," 480.200, February 1, 1984, rev. March 1995 (CPG 7132b.11).

¹⁰ FDA *Compliance Policy Guides*, "Regulatory Action Regarding Approved New Drugs and Antibiotic Drug Products Subjected to Additional Processing or Other Manipulation," 446.100, January 18, 1991 (CPG 7132c.06).

product for inhalation is often more detailed than that which should be provided about a packaging system for a solid oral dosage form. More detailed information usually should be provided for a liquid-based dosage form than for a powder or a solid, since a liquid-based dosage form is more likely to interact with the packaging components.

Table 1 illustrates the correlation between the degree of concern regarding the route of administration with the likelihood of packaging component-dosage form interactions for different classes of drug products.

Table 1
Examples of Packaging Concerns for Common Classes of Drug Products

Degree of Concern Associated with the Route of Administration	Likelihood of Packaging Component-Dosage Form Interaction		
	High	Medium	Low
Highest	Inhalation Aerosols and Solutions; Injections and Injectable Suspensions ^a	Sterile Powders and Powders for Injection; Inhalation Powders	
High	Ophthalmic Solutions and Suspensions; Transdermal Ointments and Patches; Nasal Aerosols and Sprays		
Low	Topical Solutions and Suspensions; Topical and Lingual Aerosols; Oral Solutions and Suspensions	Topical Powders; Oral powders	Oral Tablets and Oral (Hard and Soft Gelatin) Capsules

^a For the purposes of this table, the term *suspension* is used to mean a mixture of two immiscible phases (e.g., solid in liquid or liquid in liquid). As such, it encompasses a wide variety of dosage forms such as creams, ointments, gels, and emulsions, as well as suspensions in the pharmaceutical sense.

For the purpose of this guidance, container closure systems for the most common types of dosage forms will be discussed in terms of five general categories: Inhalation Drug Products (section III.D); Drug Products for Injection and Ophthalmic Drug Products (Section III.E); Liquid-based Oral and Topical Drug Products and Topical Delivery Systems (section III.F); Solid Oral Dosage Forms and Powders for Reconstitution (section

III.G); and Other Dosage Forms (section III.H).

B. General Considerations

Suitability refers to the tests and studies used and accepted for the initial qualification of a component or a container closure system for its intended use. *Quality control* (QC) refers to the tests typically used and accepted to establish that, after the application is approved, the components and the container closure system continue to possess the characteristics established in the suitability studies. The subsections on *associated components* and *secondary components* describe the tests and studies for establishing suitability and quality control for these types of components. However, the ultimate proof of the suitability of the container closure system and the packaging process is established by full shelf life stability studies.

1. Suitability for the Intended Use

Every proposed packaging system should be shown to be *suitable* for its intended use: it should adequately *protect* the dosage form; it should be *compatible* with the dosage form; and it should be composed of materials that are considered *safe* for use with the dosage form and the route of administration. If the packaging system has a *performance* feature in addition to containing the product, the assembled container closure system should be shown to function properly.

Information intended to establish suitability may be generated by the applicant, by the supplier of the material of construction or the component, or by a laboratory under contract to either the applicant or the firm. An adequately detailed description of the tests, methods, acceptance criteria, reference standards, and validation information for the studies should be provided. The information may be submitted directly in the application or indirectly by reference to a DMF. If a DMF is used, a letter authorizing reference (i.e., letter of authorization (LOA)) to the DMF must be included in the application (see section V.A).

General issues concerning protection, compatibility, safety and performance of packaging components and/or systems are discussed below. In this guidance, component functionality and drug delivery will also be addressed in connection with specific dosage forms and routes of administration (see sections III.D, III.E, III.F, III.G, and III.H).

a. Protection

A container closure system should provide the dosage form with adequate protection from factors (e.g., temperature, light) that can cause a degradation in the quality of that dosage form over its shelf life. Common causes of such degradation are: exposure to light, loss of solvent, exposure

to reactive gases (e.g., oxygen), absorption of water vapor, and microbial contamination. A drug product can also suffer an unacceptable loss in quality if it is contaminated by filth.

Not every drug product is susceptible to degradation by all of these factors. Not all drug products are light sensitive. Not all tablets are subject to loss of quality due to absorption of moisture. Sensitivity to oxygen is most commonly found with liquid-based dosage forms. Laboratory studies can be used to determine which of these factors actually have an influence on a particular drug product.

Light protection¹¹ is typically provided by an opaque or amber-colored container or by an opaque secondary packaging component (e.g., cartons or overwrap). The USP test for light transmission (USP <661>) is an accepted standard for evaluating the light transmission properties of a container. Situations exist in which solid and liquid-based oral drug products have been exposed to light during storage because the opaque secondary packaging component was removed, contrary to the approved labeling and the USP monograph recommendation. A firm, therefore, may want to consider using additional or alternate measures to provide light protection to these drug products when necessary.

Loss of solvent can occur through a permeable barrier (e.g., a polyethylene container wall), through an inadequate seal, or through leakage. Leaks can develop through rough handling or from inadequate contact between the container and the closure (e.g., due to the buildup of pressure during storage). Leaks can also occur in tubes due to a failure of the crimp seal.

Water vapor or reactive gases (e.g., oxygen) may penetrate a container closure system either by passing through a permeable container surface (e.g., the wall of a low density polyethylene (LDPE) bottle) or by diffusing past a seal. Plastic containers are susceptible to both routes. Although glass containers would seem to offer better protection, because glass is relatively impermeable, glass containers are more effective only if there is a good seal between the container and the closure.

Protection from microbial contamination is provided by maintaining adequate container integrity after the packaging system has been sealed. An adequate and validated procedure should be used for drug product manufacture and packaging.

¹¹ For further information regarding photostability studies, see the FDA *Guideline for the Photostability Testing of New Drug Substances and Products* (May 1997).

b. Compatibility

Packaging components that are compatible with a dosage form will not interact sufficiently to cause unacceptable changes in the quality of either the dosage form or the packaging component.

Examples of interactions include loss of potency due to absorption or adsorption of the active drug substance, or degradation of the active drug substance induced by a chemical entity leached from a packaging component; reduction in the concentration of an excipient due to absorption, adsorption or leachable-induced degradation; precipitation; changes in drug product pH; discoloration of either the dosage form or the packaging component; or increase in brittleness of the packaging component.

Some interactions between a packaging component and dosage form will be detected during qualification studies on the container closure system and its components. Others may not show up except in the stability studies. Therefore, any change noted during a stability study that may be attributable to interaction between the dosage form and a packaging component should be investigated and appropriate action taken, regardless of whether the stability study is being conducted for an original application, a supplemental application, or as fulfillment of a commitment to conduct postapproval stability studies.

c. Safety

Packaging components should be constructed of materials that will not leach harmful or undesirable amounts of substances to which a patient will be exposed when being treated with the drug product. This consideration is especially important for those packaging components which may be in direct contact with the dosage form, but it is also applicable to any component from which substances may migrate into the dosage form (e.g., an ink or adhesive).

Making the determination that a material of construction used in the manufacture of a packaging component is safe for its intended use is not a simple process, and a standardized approach has not been established. There is, however, a body of experience which supports the use of certain approaches that depend on the route of administration and the likelihood of interactions between the component and the dosage form (see Table 1).

For a drug product such as an injection, inhalation, ophthalmic, or transdermal, a comprehensive study is appropriate. This involves two

parts: first, an extraction study¹² on the packaging component to determine which chemical species may migrate into the dosage form (and at what concentration); and, second, a toxicological evaluation of those substances which are extracted to determine the safe level of exposure via the label specified route of administration. This technique is used by the Center for Food Safety and Applied Nutrition (CFSAN) to evaluate the safety of substances that are proposed as indirect food additives (e.g., polymers or additives that may be used in for packaging foods).¹³

The approach for toxicological evaluation of the safety of extractables should be based on good scientific principles and take into account the specific container closure system, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing).

For many injectable and ophthalmic drug products (see sections III.E and III.F), data from the USP Biological Reactivity Tests and USP Elastomeric Closures for Injections tests will typically be considered sufficient evidence of material safety.

For many solid and liquid oral drug products, an appropriate reference to the indirect food additive regulations (21 CFR 174-186) promulgated by CFSAN for the materials of construction used in the packaging component will typically be considered sufficient. Although these regulations do not specifically apply to materials for packaging drug products, they include purity criteria and limitations pertaining to the use of specific materials for packaging foods that may be acceptable for the evaluation of drug product packaging components. Applicants are cautioned that this approach may not be acceptable for liquid oral dosage forms intended for chronic use (see section III.F.1).

For drug products that undergo clinical trials, the absence of adverse reactions traceable to the packaging components is considered supporting evidence of material safety.

Safety assessments for specific dosage forms are discussed further in section III of this guidance.

d. Performance

¹² See Attachment C for discussion of extraction studies.

¹³ FDA/CFSAN, *Recommendations for Chemistry Data for Indirect Food Additive Petitions*, Version 1.2, Chemistry Review Branch, Office of Pre-Market Approval, June 1995.

Performance of the container closure system refers to its ability to function in the manner for which it was designed. A container closure system is often called upon to do more than simply contain the dosage form. When evaluating performance, two major considerations are container closure system functionality and drug delivery.

i. Container Closure System Functionality

The container closure system may be designed to improve patient compliance (e.g., a cap that contains a counter), minimize waste (e.g., a two-chamber vial or IV bag), improve ease of use (e.g., a prefilled syringe), or have other functions.

ii. Drug Delivery

Drug delivery refers to the ability of the packaging system to deliver the dosage form in the amount or at the rate described in the package insert. Some examples of a packaging system for which drug delivery aspects are relevant are a prefilled syringe, a transdermal patch, a metered tube, a dropper or spray bottle, a dry powder inhaler, and a metered dose inhaler.

Container closure system functionality and/or drug delivery are compromised when the packaging system fails to operate as designed. Failure can result from misuse, faulty design, manufacturing defect, improper assembly, or wear and tear during use. Tests and acceptance criteria regarding dosage form delivery and container closure system functionality should be appropriate to the particular dosage form, route of administration, and design features.

e. Summary

Table 2 summarizes typical packaging suitability considerations for common classes of drug products.

Table 2
Typical Suitability Considerations for Common Classes of Drug Products
(This table is a general guide, and is not comprehensive. See sections III.C through III.H for a more detailed discussion.)

Route of Administration/ Dosage Form	SUITABILITY ^a			
	Protection	Compatibility	Safety	Performance/ Drug Delivery
Inhalation Aerosols and Solutions, Nasal Sprays	L, S, M, W, G	Case 1c	Case 1s	Case 1d
Inhalation Powders	L, W, M	Case 3c	Case 5s	Case 1d
Injections, Injectable Suspensions ^b	L, S, M, G	Case 1c	Case 2s	Case 2d
Sterile Powders and Powders for Injection	L, M, W	Case 2c	Case 2s	Case 2d
Ophthalmic Solutions and Suspensions	L, S, M, G	Case 1c	Case 2s	Case 2d
Topical Delivery Systems	L, S	Case 1c	Case 3s	Case 1d
Topical Solutions and Suspensions, and Topical and Lingual Aerosols	L, S, M	Case 1c	Case 3s	Case 2d
Topical Powders	L, M, W	Case 3c	Case 4s	Case 3d
Oral Solutions and Suspensions	L, S, M	Case 1c	Case 3s	Case 2d
Oral Powders	L, W	Case 2c	Case 3s	Case 3d
Oral Tablets and Oral (Hard and Soft Gelatin) Capsules	L, W	Case 3c	Case 4s	Case 3d

^a If there is a special performance *function* built into the drug product (e.g., counter cap), it is of importance for any dosage form/route of administration to show that the container closure system performs that function properly.

^b For definition of the term *suspension*, see footnote a to Table 1.

Explanation of Codes in Table 2:

Protection:	L (protects from light, if appropriate) S (protects from solvent loss/leakage) M (protects sterile products or those with microbial limits from microbial contamination) W (protects from water vapor, if appropriate) G (protects from reactive gases, if appropriate)
Compatibility:	Case 1c: Liquid-based dosage form that conceivably could interact with its container closure system components (see examples described in section III.B.1). Case 2c: Solid dosage form until reconstituted; greatest chance for interacting with its container closure system components occurs after it is reconstituted. Case 3c: Solid dosage form with low likelihood of interacting with its container closure system components.
Safety:	Case 1s: Typically provided are USP Biological Reactivity Test data, extraction/toxicological evaluation, limits on extractables, and batch-to-batch monitoring of extractables. Case 2s: Typically provided are USP Biological Reactivity Test data and possibly extraction/toxicological evaluation. Case 3s: Typically, an appropriate reference to the indirect food additive regulations is sufficient for drug products with aqueous-based solvents. Drug products with non-aqueous based solvent systems or aqueous based systems containing co-solvents generally require additional suitability information (see section III.F). Case 4s: Typically, an appropriate reference to the indirect food additive regulations is sufficient. Case 5s: Typically, an appropriate reference to the indirect food additive regulations for all components except the mouthpiece for which USP Biological Reactivity Test data is provided.
Performance:	Case 1d: Frequently a consideration. Case 2d: May be a consideration. Case 3d: Rarely a consideration.

2. Quality Control of Packaging Components

In addition to providing data to show that a proposed container closure system is suitable for its intended use, an application should also describe the quality control measures that will be used to ensure consistency in the packaging components (see section III.C.3). These controls are intended to limit unintended postapproval

variations in the manufacturing procedures or materials of construction for a packaging component and to prevent adverse affects on the quality of a dosage form.

Principal consideration is usually given to consistency in physical characteristics and chemical composition.

a. Physical Characteristics

The physical characteristics of interest include dimensional criteria (e.g., shape, neck finish, wall thickness, design tolerances), physical parameters critical to the consistent manufacture of a packaging component (e.g., unit weight), and performance characteristics (e.g., metering valve delivery volume, or the ease of movement of syringe plungers). Unintended variations in dimensional parameters, if undetected, may affect package permeability, drug delivery performance, or the adequacy of the seal between the container and the closure. Variation in any physical parameter is considered important if it can affect the quality of a dosage form.

b. Chemical Composition

The chemical composition of the materials of construction may affect the safety of a packaging component. New materials¹⁴ may result in new substances being extracted into the dosage form or a change in the amount of known extractables. Chemical composition may also affect the compatibility, functional characteristics or protective properties of packaging components by changing rheological or other physical properties (e.g., elasticity, resistance to solvents, or gas permeability).

A composition change may occur as a result of a change in formulation or in a processing aid (e.g., using a different mold release agent) or through the use of a new supplier of a raw material. A change in the supplier of a polymeric material or a substance of biological origin is more likely to bring with it an unexpected composition change than a change in the supplier of a pure chemical compound, because polymeric and natural materials are often complex mixtures. A composition change may also occur with a change in the manufacturing process, such as the use of different operating conditions (e.g., a significantly different curing temperature), different equipment, or both.

¹⁴ These are substances not previously determined to be safe by extraction/toxicological evaluation studies (e.g., the USP Biological Reactivity Tests or another appropriate method conducted on the packaging component as part of the qualifying process).

A change in formulation is considered a change in the specifications for the packaging component. This change in the formulation of a packaging component by its manufacturer should be reported to the firm that purchases that component and to any appropriate DMF. The firm that purchases the component should, in turn, report the change to its application as required under 21 CFR 314.70(a) or 601.12. Manufacturers who supply a raw material or an intermediate packaging component should inform their customers of any intended changes to formulations or manufacturing procedures and update the DMF in advance of implementing such a change. Changes which seem innocuous may have unintended consequences on the dosage form marketed in the affected packaging system.

The use of stability studies for monitoring the consistency of a container closure system in terms of compatibility with the dosage form and the degree of protection provided to the dosage form is accepted. Currently there is no general policy concerning the monitoring of a packaging system and components with regard to safety. One exception involves inhalation drug products for which batch-to-batch monitoring of the extraction profile for the polymeric and elastomeric components is routine.

3. Associated Components

Associated components are packaging components that are typically intended to deliver the dosage form to the patient but are not stored in contact with the dosage form for its entire shelf life. These components are packaged separately in the market package and are either attached to the container upon opening or used only when a dose is to be administered. Measuring spoons, dosing cups, measuring syringes, and vaginal delivery tubes are examples of associated components that typically contact the dosage form only during administration. A hand pump or dropper combined into a closure are examples of an associated component that would contact the dosage form from the time the packaging system is opened until the dosing regimen is completed.

The complete and assembled component and its parts should meet suitability criteria appropriate for the drug product and the actual use of the component (see sections III.B.1 and III.B.2). Safety and functionality are the most common factors to be established for suitability. The length of time that the associated component and the dosage form are in direct contact should also be taken into consideration when assessing the suitability of an associated component.

4. Secondary Packaging Components

Unlike primary and associated packaging components, *secondary packaging components* are not intended to make contact with the dosage form. Examples are cartons, which are generally constructed of paper or plastic, and overwraps, which may be fabricated from a single layer of plastic or from a laminate made of metal foil, plastic, and/or paper.

A secondary packaging component generally serves one or more of the following additional functions:

- a. Provides protection from excessive transmission of moisture or solvents into or out of the packaging system
- b. Provides protection from excessive transmission of reactive gases (atmospheric oxygen, inert headspace filler gas, or other organic vapors) into or out of the packaging system
- c. Provides light protection for the packaging system
- d. Provides protection for a packaging system that is flexible or needs extra protection from rough handling
- e. Provides an additional measure of microbiological protection (i.e., by maintaining sterility or by protecting the packaging system from microbial intrusion)

When information on a container closure system is submitted in an application, the emphasis would normally be on the primary packaging components. For a secondary packaging component, a brief description will usually suffice unless the component is intended to provide some additional measure of protection to the drug product. In this case, more complete information should be provided, along with data showing that the secondary packaging component actually provides the additional protection (see sections III.B.1 and III.B.2).

Because secondary packaging components are not intended to make contact with the dosage form, there is usually less concern regarding the materials from which they are constructed. However, if the packaging system is relatively permeable, the possibility increases that the dosage form could be contaminated by the migration of an ink or adhesive component, or from a volatile substance present in the secondary packaging component. (For example, a solution packaged in a LDPE container was found to be contaminated by a volatile constituent of the secondary packaging components that enclosed it.). In such a case, the secondary packaging component should be considered a potential source of contamination and the safety of its materials of construction should be taken into consideration.

C. Information That Should Be Submitted in Support of an Original Application for Any Drug Product¹⁵

Additional discussion and information regarding the CMC information to be provided in an application (NDA, ANDA, or BLA) can be found in the guidances and guidelines listed in Attachment E.

1. Description

A general description of the entire container closure system should be provided in the CMC section of the application. In addition, the following information should be provided by the applicant for each individual component of the packaging system:

- a. Identification by product name, product code (if available), the name and address of the manufacturer, and a physical description of the packaging component (e.g., type, size, shape, and color)
- b. Identification of the materials of construction (i.e., plastics, paper, metal, glass, elastomers, coatings, adhesives, and other such materials) should be identified by a specific product designation (code name and/or code number) and the source (name of the manufacturer).¹⁶ Alternate materials of construction should also be indicated. Postconsumer recycled plastic should not be used in the manufacture of a primary packaging component. If used for a secondary or associated component, then the safety and compatibility of the material for its intended use should be addressed appropriately.
- c. Description of any operations or preparations that are performed on a packaging component by the applicant (such as washing, coating, sterilization, or depyrogenation)¹⁷

2. Information About Suitability

¹⁵ See Table 3 for additional information. This section applies to primary packaging components and to those associated and secondary packaging components that provide protection to the drug product or for which there may be a safety concern (see section III.B).

¹⁶ Where possible, this information should be included in the application. Alternatively, it may be provided in a drug master file (see section V) and a letter of authorization (LOA) to the DMF submitted in the application. The LOA permits the Agency to review the information in support of a particular application.

¹⁷ For further information see the FDA guidance for industry *Submission of Documentation for the Sterilization Process Validation in Applications of Human and Veterinary Drug Products* (November 1994).

- a. To establish safety and to ensure consistency, the complete chemical composition should be provided for every material used in the manufacture of a packaging component.
- b. Test results from appropriate qualification and characterization tests should be provided. Adequate information regarding the tests, methods, acceptance criteria, reference standards, and validation information should be provided.

To address protection, use of USP tests (see Attachment A) for light transmission, moisture permeation, microbial limits, and sterility are generally considered sufficient. Testing for properties other than those described in USP (e.g., gas transmission, solvent leakage container integrity) may also be necessary.

To address safety and compatibility, the results of extraction/toxicological evaluation studies should be provided for drug products that are likely to interact with the packaging components and introduce extracted substances into the patient (see Table 1). For drug products less likely to interact, other tests (e.g., USP Biological Reactivity Test) or information (e.g., appropriate reference to the indirect food additive regulations at 21 CFR 174-186) could be used to address the issue of safety and compatibility (see Table 2). For example, an appropriate reference to an indirect food additive regulation is generally sufficient for a solid oral dosage form product.

To address performance, the results of USP and non-USP functionality tests are considered sufficient if the test and acceptance criteria are appropriate for the intended purpose.

Tests described in the USP are typically considered sufficient standards for establishing specified properties and characteristics of specified materials of construction or packaging components.

For non-USP tests, an applicant should provide justification for the use of the test, a complete and detailed description of how the test was performed, and an explanation of what the test is intended to establish. If a related USP test is available, comparative data should be provided using both methods. Supporting data should include a demonstration of the suitability of the test for its intended use and its validation.

Testing on an assembled container closure system is usually

performed by the applicant (or a testing laboratory commissioned by the applicant) and the test results provided in the application. Such tests may include vacuum leak testing, moisture permeation, and weight loss or media fill.

Testing on an individual packaging component is typically performed by the manufacturer of the component and reported via a DMF (see section V).

3. Information About Quality Control

The fabricator/manufacturer of a packaging component and the drug product manufacturer who uses this firm share the responsibility for ensuring the quality of packaging components. These firms should have a quality control program in place so that consistent components are produced. The drug product manufacturer must have an inspection program for incoming packaging components and materials (21 CFR 211.22, 211.84 and 211.122). For most drug products, a drug product manufacturer may accept a packaging component lot based on receiving a Certificate of Analysis (COA) or Certificate of Certification (COC) from the component supplier and the performance of an appropriate identification test, provided the supplier's test data are periodically validated (21 CFR 211.84(d)(3)). Acceptance of a packaging component lot based on a supplier's COA or COC may not be appropriate in all cases (e.g., some packaging components for certain inhalation drug products).

a. Applicants

The tests and methods used by the applicant for acceptance of each batch of a packaging component that they receive should be described. If a batch is to be accepted based on a supplier's COA or COC, then the procedure for supplier validation should be described. The data from the supplier's COA or COC should clearly indicate that the lot meets the applicant's acceptance criteria. Acceptance criteria for extractables should also be included, if appropriate.

Dimensional and performance criteria should be provided. Dimensional information is frequently provided via a detailed schematic drawing complete with target dimensions and tolerances and may be provided via the packaging component manufacturer's DMF. A separate drawing may not be necessary if the packaging component is part of a larger unit for which a drawing is provided or if the component is uncomplicated in design (e.g., a cap liner).

b. Manufacturers of Packaging Components Sold to Drug Product

Manufacturers

Each manufacturer of a packaging component sold to a drug product manufacturer should provide a description of the quality control measures used to maintain consistency in the physical and chemical characteristics of the component. These generally include release criteria (and test methods, if appropriate) and a description of the manufacturing procedure. If the release of the packaging component is based on statistical process control,¹⁸ a complete description of the process (including control criteria) and its validation should be provided.

The description of the manufacturing process is generally brief and should include any operations performed on the packaging component after manufacture but prior to shipping (e.g., washing, coating, and/or sterilization). In some cases it may be desirable for the description to be more detailed and to include in-process controls.

This information may be provided via a DMF (see section V).

c. Manufacturers of Materials of Construction or of Packaging Components Used to Make Other Packaging Components

The quality control procedures of the manufacturer of a packaging component may sometimes rely in whole or in part on the quality control procedures of a manufacturer who makes an intermediate packaging component that is used to create the component. If so, each contributor to the final packaging system should provide a description of the quality control measures used to maintain consistency in the physical and chemical characteristics of the separate components and of the assembled packaging system that they provide.

The manufacturer of each material of construction should be prepared to describe the quality control measures used to maintain consistency in the chemical characteristics of their product.

This information may be provided via a DMF (see section V).

4. Stability Data (Packaging Concerns)

Stability testing of the drug product should be conducted using the container

¹⁸ Statistical process control is defined as "[t]he application of statistical techniques for measuring and analyzing the variation in processes." Juran, J.M., ed., 1988, *Quality Control Handbook*, 4th ed., McGraw-Hill, p. 24.2.

closure systems proposed in the application. The packaging system used in each stability study should be clearly identified.

The container closure system should be monitored for signs of instability. When appropriate, an evaluation of the packaging system should be included in the stability protocol. Even when a formal test for quality of the packaging system is not performed, the applicant should investigate any observed change in the packaging system used in the stability studies. The observations, results of the investigation, and corrective actions should be included in the stability report. If the corrective action requires a change in an approved container closure system, a supplemental application should be submitted.

For general guidance on conducting stability studies, refer to the FDA *Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics* (February 1987). The stability guideline is undergoing revision and will be superseded by the FDA's draft guidance for industry *Stability Testing of Drug Substance and Drug Products* (June 1998), once it is issued in final form.

Table 3
Information That Should Be Submitted in an Original Application for Any Drug Product

Description	Overall general description of the container closure system, plus: <u>For Each Packaging Component:</u> • Name, product code, manufacturer, physical description • Materials of construction (for each: name, manufacturer, product code) • Description of any additional treatments or preparations
Suitability	<u>Protection:</u> (By each component and/or the container closure system, as appropriate) • Light exposure • Reactive gases (e.g., oxygen) • Moisture permeation • Solvent loss or leakage • Microbial contamination(sterility/container integrity, increased bioburden, microbial limits) • Filth • Other <u>Safety:</u> (for each material of construction, as appropriate) • Chemical composition of all plastics, elastomers, adhesives, etc.^a • Extractables, as appropriate for the material^b - Extraction/toxicological evaluation studies, as appropriate - Appropriate USP testing - Appropriate reference to the indirect food additive regulations (21 CFR 174-186) • Other studies as appropriate <u>Compatibility:</u> (for each component and/or the packaging system, as appropriate) • Component/dosage form interaction, USP methods are typically accepted • May also be addressed in post-approval stability studies <u>Performance:</u> (for the assembled packaging system) • Functionality and/or drug delivery, as appropriate
Quality Control	<u>For Each Packaging Component Received by the Applicant:</u> • Applicant's tests and acceptance criteria^c • Dimensional (drawing) and performance criteria • Method to monitor consistency in composition, as appropriate <u>For Each Packaging Component Provided by the Supplier:</u> • Manufacturer's acceptance criteria for release, as appropriate • Brief description of the manufacturing process
Stability	• See section III.C.4

^a Including any additives used in the manufacture of a packaging component

^b See Attachment C for further discussion of extraction studies. Testing of plastics should be performed on the packaging component, not on the unformed resin. For a blow/fill/seal product, extractables should be evaluated on the formed drug product container itself. This also applies to a container closure system which is manufactured as part of the drug product manufacturing process.

^c Note that an applicant's acceptance tests may include, among others, test parameters indicated under the description, suitability, and quality control sections of this table.

D. Inhalation Drug Products

Inhalation drug products include inhalation aerosols (metered dose inhalers); inhalation solutions, suspensions, and sprays (administered via nebulizers); inhalation powders (dry powder inhalers); and nasal sprays. The CMC and preclinical considerations for inhalation drug products are unique in that these drug products are intended for respiratory-tract compromised patients. This is reflected in the level of concern given to the nature of the packaging components that may come in contact with the dosage form or the patient (see Table 1).

Guidance regarding the container closure system information to support the approval of applications for inhalation drug products will be provided in two guidance documents when finalized: the guidance for industry *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products; Chemistry, Manufacturing and Controls Documentation* (a draft was issued in October 1998) and the guidance for industry *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products; Chemistry, Manufacturing and Controls Documentation*, which is currently under development.

E. Drug Products for Injection and Ophthalmic Drug Products

These dosage forms share the common attributes that they are generally solutions, emulsions, or suspensions, and are all required to be sterile. Injectable dosage forms represent one of the highest risk drug products (see Table 1). Any contaminants present (as a result of contact with a packaging component or due to the packaging system's failure to provide adequate protection) can be rapidly and completely introduced into the patient's general circulation. Although the risk factors associated with ophthalmics are generally considered to be lower than for injectables, any potential for causing harm to the eyes demands caution.

1. Injectable Drug Products

Injectable drug products may be liquids in the form of solutions, emulsions, suspensions, or dry solids that are to be combined with an appropriate vehicle to yield a solution or suspension. Injections are classified as small-volume parenterals (SVPs), if they have a solution volume of 100 mL or less, or as large-volume parenterals (LVPs), if the solution volume exceeds 100 mL.¹⁹ For solids that must be dissolved or dispersed in an appropriate diluent before being injected, the diluent may be in the same container closure system (e.g., a two-part vial) or be part of the same market package (e.g., a kit containing a vial of diluent).

¹⁹ The terms SVP and LVP as used in this guidance correspond to the definitions of small-volume injection and large-volume injection, respectively, in USP 23, page 1650.

An SVP may be packaged in a disposable cartridge, a disposable syringe, a vial, an ampule or a flexible bag. An LVP may be packaged in a vial, a flexible bag, a glass bottle or, in some cases, as a disposable syringe.

Cartridges, syringes, vials, and ampules are usually composed of Type I or II glass, or polypropylene. Flexible bags are typically constructed with multilayered plastic. Stoppers and septa in cartridges, syringes, and vials are typically composed of elastomeric materials. The input (medication) and output (administration) ports for flexible bags may be plastic and/or elastomeric materials. An overwrap may be used with flexible bags to retard solvent loss and to protect the flexible packaging system from rough handling.

The potential effects of packaging component/dosage form interactions are numerous. Hemolytic effects may result from a decrease in tonicity and pyrogenic effects may result from the presence of impurities. The potency of the drug product or concentration of the antimicrobial preservatives may decrease due to adsorption or absorption. A cosolvent system essential to the solubilization of a poorly soluble drug can also serve as a potent extractant of plastic additives. A disposable syringe may be made of plastic, glass, rubber, and metal components, and such multicomponent construction provides a potential for interaction that is greater than when a container consists of a single material.

Injectable drug products require protection from microbial contamination (loss of sterility or added bioburden) and may also need to be protected from light or exposure to gases (e.g., oxygen). Liquid-based injectables may need to be protected from solvent loss, while sterile powders or powders for injection may need to be protected from exposure to water vapor. For elastomeric components, data showing that a component meets the requirements of USP Elastomeric Closures for Injections will typically be considered sufficient evidence of safety. For plastic components, data from USP Biological Reactivity Tests will typically be considered sufficient evidence of safety. Whenever possible, the extraction studies should be performed using the drug product. If the extraction properties of the drug product vehicle may reasonably be expected to differ from that of water (e.g., due to high or low pH or due to a solubilizing excipient), then drug product should be used as the extracting medium. If the drug substance significantly affects extraction characteristics, it may be necessary to perform the extractions using the drug product vehicle. If the total of extracts significantly exceeds the amount obtained from water extraction, then an extraction profile should be obtained. It may be advisable to obtain a quantitative extraction profile of an elastomeric or plastic packaging component and to compare this periodically to the profile from a new batch of the packaging component. Extractables should be identified whenever possible. For a glass packaging component, data from USP Containers: Chemical Resistance — Glass Containers will typically be considered sufficient evidence of safety and compatibility. In some cases (e.g., for some chelating

agents), a glass packaging component may need to meet additional criteria to ensure the absence of significant interactions between the packaging component and the dosage form.

Performance of a syringe is usually addressed by establishing the force to initiate and maintain plunger movement down the barrel, and the capability of the syringe to deliver the labeled amount of the drug product.

2. Ophthalmic Drug Products

These drug products are usually solutions marketed in a LDPE bottle with a dropper built into the neck (sometimes referred to as *droptainer*), or ointments marketed in a metal tube with an ophthalmic tip (see section III.F.2 for a more detailed discussion of tubes). A few solution products use a glass container due to stability concerns regarding plastic packaging components. Ophthalmic ointments that are reactive toward metal may be packaged in a tube lined with an epoxy or vinyl plastic coating. A large volume intraocular solution (for irrigation) may be packaged in a glass or polyolefin (polyethylene and/or polypropylene) container.

The American Academy of Ophthalmology (AAO) recommended to the Agency that a uniform color coding system be established for the caps and labels of all topical ocular medications. An applicant should either follow this system or provide an adequate justification for any deviations from the system. The AAO color codes, as revised and approved by the AAO Board of Trustees in June 1996, are shown in Table 5.

Although ophthalmic drug products can be considered topical products (section III.F.2), they have been grouped here with injectables because they are required to be sterile (21 CFR 200.50(a)(2)) and the descriptive, suitability, and quality control information is typically the same as that for an injectable drug product. Since ophthalmic drug products are applied to the eye, compatibility and safety should also address the container closure system's potential to form substances which irritate the eye or introduce particulate matter into the product (see USP <771> Ophthalmic Ointments).

See Table 4 for additional information.

Table 4
Information That Typically Should Be Submitted for Injectable
or Ophthalmic Drug Products

Description	Overall general description of container closure system, plus: <u>For Each Packaging Component:</u> • Name, product code, manufacturer, physical description • Materials of construction (for each: name, manufacturer and product code) • Description of any additional treatments (e.g., procedures for sterilizing and depyrogenating packaging components)
Suitability	<u>Protection:</u> (By each component and/or the container closure system, as appropriate) • Light exposure, when appropriate • Reactive gases (e.g., oxygen) • Moisture permeation (powders) • Solvent loss (liquid-based dosage forms) • Sterility (container integrity) or increased bioburden • Seal integrity or leak testing of tubes (ophthalmics) <u>Safety:</u> (for each material of construction, as appropriate) • Chemical composition of all plastics, elastomers, adhesives, etc.^a • For elastomeric closures: USP Elastomeric Closures for Injections testing • For glass components: USP Containers: Chemical Resistance — Glass Containers • For plastic components and coatings for metal tubes: USP Biological Reactivity Tests • If the extraction properties of the drug product vehicle may reasonably be expected to differ from that of water (e.g., due to high or low pH or due to a solubilizing excipient), then drug product should be used as the extracting medium. • If the total weight of extracts significantly exceeds the amount obtained from water extraction, then an extraction profile should be obtained. • For plastic or elastomeric components undergoing heat sterilization, it is current practice to request that the extraction profile be obtained at 121 °C/1 hour using an appropriate solvent. <u>Compatibility:</u> (for each component and/or the packaging system, as appropriate) • For coatings on metal tubes: Coating integrity testing • For elastomeric components: Evaluation of swelling effects • For plastic components (including tube coatings): USP Containers: Physicochemical Tests - Plastics testing • For ophthalmics: Particulate matter and eye irritants • Stability studies also support compatibility <u>Performance:</u> (For the assembled packaging system) • Functionality and/or drug delivery

Quality Control	<u>For Each Packaging System Received by the Applicant:</u> • Applicant's tests and acceptance criteria^c • Dimensional (drawing) and performance criteria • Method to monitor consistency in composition of most plastic and elastomeric components (e.g., periodic comparison to the original extraction profile is recommended) <u>For Each Packaging Component Provided by the Supplier:</u> • Manufacturer's acceptance criteria for release, as appropriate • Description of the manufacturing process, as appropriate (e.g., procedure/validation for sterilization and depyrogenation)
Stability	• See section III.C.4

- a. Including any additives used in the manufacture of a packaging component
- b. Testing for plastics should be performed on the packaging component, not on the unformed resin.
- c. Note that applicant's acceptance tests may include, among others, test parameters indicated under the description, suitability, and quality control sections of this table.
- d. Refer to the *Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug* (November 1994).

Table 5
AAO Recommended Color Coding of Caps and Labels
for Topical Ophthalmic Medications

Class	Color	Pantone® Number
Anti-Infectives	Tan	467
Anti-Inflammatories/Steroids	Pink	197, 212
Mydriatics and Cycloplegics	Red	485C
Nonsteroidal Anti-Inflammatories	Gray	4C
Miotics	Green	374, 362, 348
Beta-Blockers	Yellow or Blue ^a Yellow C	290, 281
Adrenergic Agonists (e.g., Propine)	Purple	2583
Carbonic Anhydrase Inhibitors	Orange	1585
Prostaglandin Analogues	Turquoise	326C

- ^a The AAO notes that as new classes of drugs are developed this coding system may be modified in the future by reassigning the blue color to a new class of drugs while keeping yellow for beta-blockers.

F. Liquid-Based Oral and Topical Drug Products and Topical Delivery Systems

A wide variety of drug products fall into this category. The presence of a liquid phase implies a significant potential for the transfer of materials from a packaging component into the dosage form. The higher viscosity of semisolid dosage forms and transdermal systems may cause the rate of migration of leachable substances into these dosage forms

to be slower than for aqueous solutions. Due to extended contact, the amount of leachables in these drug products may depend more on a leachable material's affinity for the liquid/semisolid phase than on the rate of migration.

1. Liquid-Based Oral Drug Products

Typical liquid-based oral dosage forms are elixirs, emulsions, extracts, fluid extracts, solutions, gels, syrups, spirits, tinctures, aromatic waters, and suspensions. These products are usually nonsterile but may be monitored for changes in bioburden or for the presence of specific microbes.

These dosage forms are generally marketed in multiple-unit bottles or in unit-dose or single-use pouches or cups. The dosage form may be used as is or admixed first with a compatible diluent or dispersant. A bottle is usually glass or plastic, often with a screw cap with a liner, and possibly with a tamper-resistant seal or an overcap that is welded to the bottle. The same cap liners and inner seals are sometimes used with solid oral dosage forms. A pouch may be a single-layer plastic or a laminated material. Both bottles and pouches may use an overwrap, which is usually a laminated material. A single-dose cup may be metal or plastic with a heat-sealed lid made of a laminated material.

A liquid-based oral drug product typically needs to be protected from solvent loss, microbial contamination, and sometimes from exposure to light or reactive gases (e.g., oxygen).

For glass components, data showing that a component meets the requirements of USP Containers: Glass Containers are accepted as sufficient evidence of safety and compatibility. For LDPE components, data from USP Containers tests are typically considered sufficient evidence of compatibility. The USP General Chapters do not specifically address safety for polyethylene (HDPE or LDPE), polypropylene (PP), or laminate components. A patient's exposure to substances extracted from a plastic packaging component (e.g., HDPE, LDPE, PP, laminated components) into a liquid-based oral dosage form is expected to be comparable to a patient's exposure to the same substances through the use of the same material when used to package food. Based on this assumption, an appropriate reference to the indirect food additive regulations (21 CFR 174-186)²⁰ is typically considered sufficient to establish safety of the material of construction, provided any limitations specified in the regulations are taken into consideration. This assumption is considered valid for liquid-based oral dosage forms which the patient will take only for a relatively short time (acute dosing regimen).

²⁰ See Attachment A for a listing of the FDA regulations for indirect food additives.

For liquid-based oral drug products which the patient will continue to take for an extended period (i.e., months or years (chronic drug regimen)), a material of construction that meets the requirements for indirect food additives will be considered safe — on that basis alone — only if the patient's exposure to extractables can be expected to be no greater than the exposure through foods, or the length of exposure is supported by toxicological information. For example, if the dosage form is aqueous-based and contains little or no cosolvent (or other substance, including the active drug substance, liable to cause greater extraction of substances from plastic packaging components than would be extracted by water), meeting the requirements of the indirect food additive regulations will usually satisfy the issue of safety.

If the dosage form contains cosolvents (or if, for any reason, it may be expected to extract greater amounts of substances from plastic packaging components than water), then additional extractable information²¹ may be needed to address safety issues.

Performance is typically not a factor for liquid-based oral drug products.

See Table 6 for additional information.

2. Topical Drug Products

Topical dosage forms include aerosols, creams, emulsions, gels, lotions, ointments, pastes, powders, solutions, and suspensions. These dosage forms are generally intended for local (not systemic) effect and are generally applied to the skin or oral mucosal surfaces. Topical products also include some nasal and otic preparations as well as some ophthalmic drug products. Ophthalmic drug products are discussed in section III.E.2. Vaginal and rectal drug products may be considered to be topical if they are intended to have a local effect. Some topical drug products are sterile or may be subject to microbial limits. In these cases, additional evaluation may be necessary when determining the appropriate packaging.

A liquid-based topical product typically has a fluid or semi-solid consistency and is marketed in a single- or multiple-unit container (e.g., a rigid bottle or jar, a collapsible tube, or a flexible pouch). A powder product may be marketed in a sifter-top container. An antibacterial product may be marketed as part of a sterile dressing. There are also a number of products marketed as a pressurized aerosol or a hand-pumped spray.

A rigid bottle or jar is usually made of glass or polypropylene with a screw cap.

²¹ See Attachment C for a discussion of extraction studies.

The same cap liners and inner seals are sometimes used as with solid oral dosage forms.

A collapsible tube is usually constructed from metal or is metal-lined, from LDPE or from a laminated material. Tubes are identified as either *blind-end* or *open-end*. In the former, there is no product contact with the cap on storage. Usually, the size of the tube is controlled by trimming it to an appropriate length for the target fill volume. Fill volume is commonly determined as an in-process measurement using bulk density. Usually there is no cap liner, although the tube may have a liner. Aluminum tubes usually include a liner. A tube liner is frequently a lacquer or shellac whose composition should be stated. A tube is closed by folding or crimping the open end. The type of fold (roll or saddle) should be described, as well as the type and composition of any sealant. If the tube material is self-sealing through the application of heat alone, this should be stated. If the market package includes a separate applicator device, this should be described. Product contact is possible if the applicator is part of the closure, and therefore an applicator's compatibility with the drug product should be established, as appropriate.

Dressings consist of dosage form on a bandage material (e.g., Absorbent Gauze USP or Gauze Bandage USP) within a flexible pouch. The pouch should maintain the sterility and physical stability of the dressing.

Unlike inhalation aerosols, topical aerosols are not intended to be inhaled. The droplet size of the spray does not need to be carefully controlled, nor is the dose usually metered. The spray may be used to apply dosage form to the skin (topical aerosol) or mouth (lingual aerosol) and functionality of the sprayer should be addressed. A topical aerosol may be sterile or may conform to acceptance criteria for microbial limits.

The packaging system for a liquid-based topical product should deter solvent loss and should provide protection from light when appropriate. Because these dosage forms may be placed in contact with mucosal membranes or with skin that has been broken or otherwise compromised, the safety of the materials of construction for the packaging components should be evaluated. For liquid and semisolid dosage forms, the same information as described in section III.F.1 is accepted for establishing safety and compatibility. For solid dosage forms, an appropriate reference to the indirect food additive regulations is typically considered sufficient to establish safety.

See Table 6 for additional information.

3. Topical Delivery Systems

Topical delivery systems are self-contained, discrete dosage forms that are

designed to deliver drug via intact skin or body surface. USP Pharmaceutical Dosage Forms defines three types of topical delivery systems: transdermal, ocular, and intrauterine.

Transdermal systems are usually applied to the skin with an adhesive and may be in place for an extended period. Ocular systems are inserted under the lower eyelid, typically for seven days. Intrauterine systems are held in place without adhesive and may stay in place for a year.

A transdermal system is usually comprised of an outer barrier, a drug reservoir (with or without a rate-controlling membrane), a contact adhesive, and a protective liner. An ocular system usually consists of the drug formulation contained in a rate-controlling membrane. An intrauterine system may be constructed of a plastic material impregnated with active ingredients or a coated metal. It is shaped to remain in place after being inserted in the uterus.

Each of these systems is generally marketed in a single-unit soft blister pack or a preformed tray with a preformed cover or overwrap.

Compatibility and safety for topical delivery systems are addressed in the same manner as for topical drug products. Performance and quality control should be addressed for the rate-controlling membrane. Appropriate microbial limits should be established and justified for each delivery system. Microbiological standards are under development; therefore the review division for a specific application should be consulted.

See Table 6 for additional information.

Table 6
Information That Typically Should Be Submitted for Liquid-Based Oral
and Topical Drug Products and for Topical Drug Delivery Systems

Description	Overall general description of container closure system, plus: <u>For Each Packaging Component:</u> • Name, product code, manufacturer, physical description • Materials of construction (for each: name, manufacturer and product code) • Description of any additional treatments (e.g., procedure for washing components)
Suitability	<u>Protection:</u> (by each component and/or the container closure system, as appropriate) • Light exposure • Reactive gases (e.g., oxygen) • Solvent loss • Moisture permeation (liquid-based oral products would typically meet USP requirements for a tight or class A container) • Microbial contamination (container integrity, increased bioburden, microbial limits, as appropriate) • Seal integrity or leak testing of tubes (topical drug products) and unit dose containers (liquid-based oral drug products) <u>Safety:</u> (for each material of composition, as appropriate) • Chemical composition of all plastics, elastomers, adhesives, etc.^a • For most liquid-based oral drug products: appropriate reference to the indirect food additive regulations • For liquid-based oral drug products with chronic dosing regimens that contain alcohol or a cosolvent: information to establish that exposure to extractables will be no greater than that expected to result from the use of similar packaging components when used with foods,^b or that the exposure is acceptable based on toxicological data. • For topical drug products (plastic coatings for metal tubes), and plastic drug delivery system components: USP Containers testing • For topical delivery systems: appropriate reference to indirect food additive regulations <u>Compatibility:</u> (for each component of the packaging system, as appropriate) • For LDPE and glass components, USP Containers testing^c • For coatings for metal tubes: coating integrity testing <u>Performance:</u> (for the assembled packaging system) • Functionality and/or drug delivery should be addressed, as appropriate.
Quality Control	<u>For Each Packaging Component Received by the Applicant:</u> • Applicant's tests and acceptance criteria^d • Dimensional (drawing) and performance criteria • Method to monitor consistency in composition, as appropriate <u>For Each Packaging Component Provided by the Supplier:</u> • Manufacturer's acceptance criteria for release, as appropriate • Description of the manufacturing process, as appropriate

Stability	• See section III.C.4
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- ^a Including any additives used in the manufacture of a packaging component
- ^b The materials of construction should be acceptable for contact with foods that have extraction characteristics similar to those of the drug product (e.g., aqueous, acidic, alcoholic, or fatty).
- ^c Plastics testing should be performed on the packaging component, not on the unformed resin.
- ^d Note that applicant's acceptance tests may include, among others, test parameters indicated under the description, suitability, and quality control sections of this table.

G. Solid Oral Dosage Forms and Powders for Reconstitution

The most common solid oral dosage forms are capsules and tablets. For the purpose of this guidance, oral powders and granules for reconstitution are also included in this group.

The risk of interaction between packaging components and a solid oral dosage form is generally recognized to be small. Powders that are reconstituted in their market container, however, have an additional possibility of an interaction between the packaging components and the reconstituting fluid. Although the contact time will be relatively short when compared to the component/dosage form contact time for liquid-based oral dosage forms, it should still be taken into consideration when the compatibility and safety of the container closure system is being evaluated.

A typical container closure system is a plastic (usually HDPE) bottle with a screw-on or snap-off closure and a flexible packaging system, such as a pouch or a blister package. A typical closure consists of a cap, often with a liner, and frequently with an inner seal. If used, fillers, desiccants, and other absorbent materials are considered primary packaging components.

The most common forms of flexible packaging are the blister package and the pouch. A blister package usually consists of a lidding material and a forming film. The lidding material is usually a laminate which includes a barrier layer (e.g., aluminum foil) with a print primer on one side and a sealing agent (e.g., a heat-sealing lacquer) on the other side. The sealing agent contacts the dosage form and the forming film. The forming film may be a single film, a coated film, or a laminate. A pouch typically consists of film or laminate which is sealed at the edges by heat or adhesive. Leak testing is usually performed on flexible packages as part of the in-process controls.

Solid oral dosage forms generally need to be protected from the potential adverse affects of water vapor. Protection from light and reactive gases may also be needed. For example the presence of moisture may affect the decomposition rate of the active drug substance or the dissolution rate of the dosage form. The container should have an intrinsically low rate of water vapor permeation, and the container closure system should establish a seal to protect the drug product. Three standard tests for water vapor permeation have been established by the USP for use with solid oral dosage forms.

1. Polyethylene Containers (USP <661>): This test is conducted on containers heat-sealed with foil laminate; therefore only the properties of the container are evaluated. The level of protection from water vapor permeation provided by a packaging system marketed with a heat-sealed foil laminate inner seal (up to the time the inner seal is removed) is expected to be approximately the same as that determined by this test. The acceptance criteria are those established in USP <671>.
2. Single-Unit Containers and Unit-Dose Containers for Capsules and Tablets (USP <671>): This test measures the water vapor permeation of a single-unit or unit-dose container closure system and establishes acceptance criteria for five standards (*Class A-E* containers).
3. Multiple-Unit Containers for Capsules and Tablets (USP <671>): This test is intended for drugs being dispensed on prescription, but has also been applied to the drug product manufacturer's container closure system. If the container closure system has an inner seal, it should be removed prior to testing. The results from this study reflect the contributions to water vapor permeation through the container, and through the seal between the container and the closure. Acceptance criteria have been established for two standards (*tight* and *well-closed* containers).

For solid oral dosage forms, a reference to the appropriate indirect food additive regulation for each material of construction is typically considered sufficient evidence of safety. However, for a powder for reconstitution dosage form, reference only to the indirect food additive regulations as evidence of safety for the materials of construction is not recommended. Compatibility for solid oral dosage forms and for powders for reconstitution is typically addressed for plastics and glass by meeting the requirements of the USP Containers test.

The USP monographs for Purified Cotton and Purified Rayon will typically be considered sufficient standards to establish the safety of these materials as fillers in the packaging of tablets or capsules, with the following caveats: cotton need not meet the monograph requirements for sterility, fiber length, or absorbency; and rayon need not meet the monograph requirements for fiber length or absorbency. Appropriate tests and acceptance criteria for identification and for moisture content should be provided for both cotton and rayon filler. Rayon has been found to be a potential source of dissolution problems for gelatin capsules and gelatin-coated tablets and this characteristic should be considered when choosing a filler.²² The use of other fillers may be considered with appropriate tests and acceptance criteria.

²² Hartauer, K.J. et al., "The Effects of Rayon Coiler on the Dissolution Stability of Hard Shelled Gelatin Capsules," *Pharmaceutical Technology*, 17:76-83 (1993).

If a desiccant or other absorbent material is used, the composition should be provided (or an appropriate DMF referenced). The component should differ in shape and/or size from the tablets or capsules with which it is packaged. This will help distinguish between the component and the dosage form. Because these are considered primary packaging components, appropriate tests and acceptance criteria to establish suitability should be provided (see Table 7 for additional information).

Table 7
Information That Typically Should Be Submitted for Solid Oral
Drug Products and Powders

Description	Overall general description of container closure system, plus: <u>For Each Packaging Component:</u> • Name, product code, manufacturer • Materials of construction • Description of any additional treatments
Suitability	<u>Protection:</u> (by each component and/or the container closure system, as appropriate) • Light exposure • Moisture permeation • Seal integrity or leak tests for unit-dose packaging <u>Safety:</u> (for each material of construction, as appropriate) • Chemical composition of all plastics, elastomers, adhesives, etc.^a • For tablets, capsules, and powders, appropriate reference to the indirect food additive regulation may be submitted, but may not be appropriate for Powders for Reconstitution. • For rayon and cotton fillers, data from USP monographs. For non-USP materials, data and acceptance criteria should be provided. • For dessicants and other absorbent materials: the size and shape should differ from that of the dosage form. <u>Compatibility:</u> (on each component or the packaging system) • For glass and plastic containers, data from USP Containers^b testing. <u>Performance:</u> (on each component or the packaging system, as appropriate) • Functionality and/or drug delivery, as appropriate
Quality Control	<u>For Each Packaging Component Received by the Applicant:</u> • Applicant's tests and acceptance criteria^c • Dimensional (drawing) and performance criteria • Method to monitor consistency in composition, as appropriate <u>For Each Packaging Component Provided by the Supplier:</u> • Manufacturer's acceptance criteria for release, as appropriate • Description of manufacturing process, as appropriate
Stability	• See section III.C.4

^a Including any additives used in the manufacture of a packaging component

^b Testing of plastics should be performed on the packaging component, not on the unformed resin.

^c Note that applicant's acceptance tests may include, among others, test parameters indicated under the description, suitability, and quality control sections of this table.

H. Other Dosage Forms

The CGMP requirements for container closure systems for compressed medical gases are described in 21 CFR 210 and 211. The containers are regulated by the U.S. Department of Transportation. For more detailed information refer to the CDER *Compressed Medical Gas Guideline* (February 1989).

When submitting information for a drug product or dosage form not specifically covered by the sections above, a firm should take into consideration: (1) the compatibility and safety concerns raised by the route of administration of the drug product and the nature of the dosage form (e.g., solid or liquid-based); (2) the kinds of protection the container closure system should provide to the dosage form; and (3) the potential effect of any treatment or handling that may be unique to the drug product in the packaging system. Quality control procedures for each packaging component should ensure the maintenance of the safety and quality of future production batches of the drug product.

IV. POSTAPPROVAL PACKAGING CHANGES

For an approved application (NDA, ANDA or BLA), a change to a container closure system, to a component of the container closure system, to a material of construction for a component, or to a process involving one of the above must be reported to the application. The filing requirements are specified under 21 CFR 314.70 (supplements and other changes to an approved application) for an NDA or ANDA, and under 21 CFR 601.12 (changes to an approved application) for a BLA. The submission should address the items described and discussed in sections III.B and III.C of this guidance. The Agency intends to provide additional guidance on postapproval changes in container closure systems in the future.

V. TYPE III DRUG MASTER FILES

A. General Comments

The responsibility for providing information about packaging components rests foremost with the applicant of an NDA, ANDA or BLA, or the sponsor of an IND. This information may be provided to the applicant by the manufacturer of a packaging component or material of construction and may be included directly in the application. Any information that a manufacturer does not wish to share with the applicant or sponsor (i.e., because it is considered proprietary) may be placed in a Type III DMF and incorporated into the application by a letter from the manufacturer to the applicant which authorizes reference to the DMF. The letter of authorization should specify the firm to whom authorization is granted, the component or material of construction being described, and where the information and/or data is located in the file by page number and/or date of submission. This last item is especially important for files that contain information on multiple components or have several volumes.

Information in a Type III DMF is not restricted to data of a proprietary nature. DMF holders may include in their files as much or as little information as they choose. In addition, a manufacturer of a packaging component is not required to maintain a Type III DMF. Without a DMF there is no procedure for the Agency to review proprietary information except by submission to the application.

The Agency ordinarily reviews a DMF only in connection with an application (IND, NDA, ANDA, or BLA). If the combined information from the application and the DMF is not adequate to support approval of the application or safety for the IND, then the Agency may request additional information from the applicant and/or the DMF holder, as appropriate.

In the event of a change in the DMF, the holder of a DMF must notify the holder of each application supported by the DMF (21 CFR 314.420(c)). Notice should be provided well before the change is implemented to allow the applicant or sponsor enough time to file a supplement or an amendment to the affected application.

General information on format and content of a DMF and a LOA may be found in the CDER *Guideline for Drug Master Files* (September 1989).

B. Information in a Type III DMF

Section III of this guidance describes the kind of descriptive, suitability, and quality control information which the Agency usually reviews concerning packaging components and materials of construction for drug products. The following are examples of the items that have been submitted via a Type III DMF.

1. Descriptive Information:
 - a. General description of the component and the address of the manufacturing site
 - b. Description of the manufacturing process for a packaging component and operations performed after manufacture, but prior to shipment (washing, coating, sterilization or depyrogenation)
 - c. Description of the acceptance, in-process, and release controls for materials of construction, the manufacturing process, and the finished product (component part or assembled component)
 - d. Characterization of the key properties
2. Information About Suitability

- a. Protection provided by the component
 - b. Safety information on the materials of construction or the finished component
 - c. Compatibility of the materials of construction or the finished component with the specific dosage form, the specific drug product, or equivalent materials
3. Information About Quality Control:
- a. Dimensional (an engineering drawing) and performance criteria for the component
 - b. A description of the quality control measures used to maintain consistency in the physical and chemical characteristics of packaging components
 - c. A summary of the quality assurance/quality control criteria when release of the component is based on statistical process control

VI. BULK CONTAINERS

A. Containers for Bulk Drug Substances

Drug substances are generally solids, but some are liquids or gases.

The container closure system for storage or shipment of a bulk solid drug substance is typically a drum with double LDPE liners that are usually heat sealed or closed with a twist tie. A desiccant may be placed between the bags.

The drum provides protection from light and mechanical strength to protect the liner during shipment and handling. The majority of the protection from air and moisture is provided by the liner. Because LDPE is not a particularly good moisture barrier, a drug substance that is moisture sensitive may need additional protection. An alternative to a LDPE bag is a heat-sealable laminate bag with a comparatively low rate of water vapor transmission.

Qualification of the packaging system is usually based on establishing compatibility and safety of the liner but may also include characterization for solvent or gas transmission (see section III.B).

The container closure system for the storage or shipment of a bulk liquid drug substance is typically plastic, stainless steel, a glass-lined metal container, or an epoxy-lined metal

container with a rugged, tamper-resistant closure. Qualification of the container closure system may include characterization for solvent and gas permeation, light transmittance, closure integrity, ruggedness in shipment, protection against microbial contamination through the closure, and compatibility and safety of the packaging components as appropriate (see section III.B).

The application (or Type II DMF) should include a detailed description of the complete container closure system for the bulk drug substance as well as a description of the specific container, closure, all liners, inner seal, and desiccant (if any), and the composition of each component. A reference to the appropriate indirect food additive regulation is typically considered sufficient to establish the safety of the materials of construction (also note the discussion on this subject in section III). The tests, methods, and criteria for the acceptance and release of each packaging component should be provided.

Stability studies to establish a retest period for bulk drug substance in the proposed container closure system should be conducted with fillers or desiccant packs in place (if used). Smaller versions which simulate the actual container closure system may be used. Stability recommendations for container closure systems of different types are described in the *Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics* (February 1987).²³

Container closure systems for compressed medical gases are discussed in section III.H.

B. Containers for Bulk Drug Products

A container closure system for bulk drug products may be used for storage prior to packaging or for shipment to repackagers or contract packagers. In all cases, the container closure system should adequately protect the dosage form and should be constructed of materials that are compatible and safe.

Container closure systems for on-site storage have generally been considered a CGMP issue under 21 CFR 211.65. However, if a firm plans to hold bulk drug products in storage, then the container closure system and the maximum storage time should be described and justified in the application. In addition, stability data should be provided to demonstrate that extended storage in the described containers does not adversely affect the dosage form. Even when the storage time before packaging will be short, a firm should use a container closure system that provides adequate protection and that is manufactured from materials that are compatible and safe for the intended use (see section III.B).

²³ The 1987 stability guidance will be superseded by the FDA guidance for industry *Stability Testing of Drug Substances and Drug Products*, issued in draft for comment in June 1998, once it is issued in final form.

A container closure system for the transportation of bulk drug products to contract packagers (section II.C.3) should be described in the application. The container closure system should be adequate to protect the dosage form, be constructed with materials that are compatible with product being stored, and be safe for the intended use. The protective properties of the shipping container are verified by the practice of including annual batches of the packaged product in postapproval stability studies.

A container closure system specifically intended for the transportation of a large volume of drug product to a repackager (section II.C.3), whether for a solid or liquid dosage form, is considered a market package. The package should meet the same requirements for protection, compatibility, and safety as a smaller market package;²⁴ should be included in the stability studies for application approval and in the long term stability protocol; and should be fully described in the application. The length of time that the dosage form will spend in the bulk container may be a factor in determining the level of detail of the supporting information. Two examples of a large-volume shipping package are a 10,000-tablet HDPE pail with tamper-evident closure, and a 10-liter polyethylene terephthalate (PET) container with a screw cap closure with dispenser attachment for a liquid drug product. Both are intended for sale to a mass distribution pharmacy. A special case is the pharmacy bulk package which is described in USP <1>.

²⁴ FDA *Compliance Policy Guides*, "Regulatory Action Regarding Approved New Drugs and Antibiotic Drug Products Subjected to Additional Processing or other Manipulation," Section 446.100, January 18, 1991 (CPG 7132c.06).

ATTACHMENT A²⁵

REGULATORY REQUIREMENTS

1. The Federal Food, Drug, and Cosmetic Act

a. Section 501

A drug or device shall be deemed to be adulterated “if its container is composed, in whole or in part, of any poisonous or deleterious substance which may render the contents injurious to health” (section 501(a)(3)); or “if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess (section 501(a)(2)(B)).

b. Section 502

A drug or device shall be deemed to be misbranded:

- “[i]f it purports to be a drug the name of which is recognized in an official compendium, unless it is packaged and labeled as prescribed therein” (section 502(g))
- “[i]f it is a drug and its container is so made, formed, or filled as to be misleading” (section 502(i)(1))
- “[i]f it is a drug and its packaging or labeling is in violation of an applicable regulation issued pursuant to section 3 or 4 of the Poison Prevention Packaging Act of 1970” (section 502(p))

c. Section 505

“No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) is effective with respect to such drug” (section 505(a)).

Section 505(b)(1)(D) requires "a full description of the methods used in, and the

²⁵ Applicants should check the appropriate sources directly for the most up-to-date information.

facilities and controls used for, the manufacture, processing, and packing of such drug."

2. The Code of Federal Regulations

a. 21 CFR 211 - Current Good Manufacturing Practice for Finished Pharmaceuticals

i. Subpart E, Control of Components and Drug Product Containers and Closures (21 CFR 211.80 - 211.94)

In particular, 21 CFR 211.94 outlines the requirements for drug product containers and closures:

- (a) Drug product containers and closures shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug beyond the official or established requirements.
- (b) Container closure systems shall provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product.
- (c) Drug product containers and closures shall be clean and, where indicated by the nature of the drug, sterilized and processed to remove pyrogenic properties to ensure that they are suitable for their intended use.
- (d) Standards or acceptance criteria, test methods, and, where indicated, methods of cleaning, sterilizing, and processing to remove pyrogenic properties shall be written and followed for drug product containers and closures.

ii. Subpart F, Production and Process Controls (21 CFR 211.100 - 211.115)

iii. Subpart G, Packaging and Labeling Control (21 CFR 211.122 - 211.137)

In particular, 21 CFR 211.132 describes the tamper-resistant packaging requirements for over-the-counter (OTC) human drug products. Most OTC drug products must be packaged in tamper-resistant containers.

b. 16 CFR 1700-1702 - Special Packaging

The U.S. Consumer Product Safety Commission (CPSC) is responsible for enforcing the Poison Prevention Packaging Act of 1970 (PPPA). The PPPA requires special packaging of hazardous household substances to protect children

from serious personal injury or serious illness from handling, using, or ingesting the substances. Drug products containing controlled substances, most human oral prescription drug products (including oral investigational drugs used in outpatient trials), and OTC drug preparations containing aspirin, acetaminophen, diphenhydramine, liquid methyl salicylate, ibuprofen, loperamide, lidocaine, dibucaine, naproxen, iron, or ketoprofen, require special packaging (16 CFR 1700.14).

Special packaging is defined under 15 U.S.C. 1471(2)(4), 16 CFR 1700.1(b)(4), and 21 CFR 310.3(l). Regulations issued under the PPPA establish performance standards and test methods that determine if a packaging system is child-resistant and adult-use-effective (16 CFR 1700.15 and 16 CFR 1700.20, respectively). Except as noted below, all PPPA-regulated substances must be in packaging systems that comply with these special packaging standards. The standards apply to both reclosable and nonreclosable packaging systems (unit-dose packaging).

There are several situations where child-resistant packaging for drug products is not required. Manufacturers and packagers of bulk-packaged prescription drug products do not have to use special packaging if the drug is intended to be repackaged by the pharmacist. However, the manufacturer or packager is responsible for child-resistant packaging if the drug product is intended to be dispensed to the consumer as packaged without repackaging by the pharmacist (16 CFR 1701.1). Prescribed drugs that are dispensed for use within institutions such as hospitals and nursing homes do not require child-resistant packaging. However, any prescriptions dispensed to patients upon their release for their use at home would be subject to the PPPA packaging requirements. In addition, drug product manufacturers are not required to provide child-resistant packaging for prescription drug samples that are distributed to physicians and other prescribing practitioners (i.e., physician samples).²⁶

For OTC preparations, manufacturers or packagers are allowed to market one size in non-child-resistant packaging as long as child-resistant packages are also supplied. The non-child-resistant package requires special labeling (16 CFR 1700.5).

16 CFR 1702 establishes the procedures for petitioning the CPSC for an exemption from the PPPA requirements. Several prescription drugs (e.g., oral contraceptives in mnemonic packages, powdered colestipol, and medroxyprogesterone acetate) have been exempted from the special packaging requirements (16 CFR 1700.14(10)(I)-(xix)). The CPSC is permitted to grant an

²⁶ *Federal Register*, Volume 49, March 5, 1984, page 8008 (49 FR 8008), “Prescribed Drugs Distributed to Prescribing Practitioners; Withdrawal of Proposed Statement of Policy and Interpretation.”

exemption if it finds that packaging is not required to protect children from serious injury, or that special packaging is not technically feasible, practicable, or appropriate for that product.

For additional information regarding these packaging requirements and the protocol test methods, please contact the CPSC. Their website is located at www.cpsc.gov and their hotline is 1-800-638-2772.

c. 21 CFR 174-186 - Indirect Food Additive Regulations

Regulations that are applicable to packaging components are:

- i. Part 174 - Indirect Food Additives: General
- ii. Part 175 - Indirect Food Additives: Adhesives and Components of Coatings
 - e.g., 175.105 Adhesives
 - 175.300 Resinous and polymeric coatings
- iii. Part 176 - Indirect Food Additives: Paper and Paperboard Components
 - e.g., 176.170 Components of paper and paperboard in contact with aqueous and fatty foods
 - 176.180 Components of paper and paperboard in contact with dry food
- iv. Part 177 - Indirect Food Additives: Polymers
 - e.g., 177.1380 Fluorocarbon resins
 - 177.1520 Olefin polymers
 - 177.1630 Polyethylene phthalate polymers
- v. Part 178 - Indirect Food Additives: Adjuvants, Production Aids, and Sanitizers
- vi. Part 180 - Food Additives Permitted in Food or in Contact with Food on an Interim Basis Pending Additional Studies
 - e.g., 180.22 Acrylonitrile copolymers
- vii. Part 182 - Substances Generally Recognized as Safe
 - e.g., 182.70 Substances migrating from cotton and cotton fabrics

182.90 used in dry food packaging
 Substances migrating to food from paper and
 paperboard products

viii. Part 186 - Indirect Food Substances Affirmed as Generally Recognized as
 Safe (GRAS)

 e.g., 186.1673 Pulp

d. Biologics Provisions, 21 CFR 600, Subpart B, Establishment Standards

 i. 21 CFR 600.11(h) - Containers and Closures

 ii. 21 CFR 601.2 - Applications for Licenses; Procedures for Filing

e. Other Sections

 i. 21 CFR 201 - Labeling

 ii. 21 CFR 310.509 - Parenteral drug products in plastic containers

 iii. 21 CFR 200.50(a)(3) - Containers of ophthalmic preparations

3. **U.S. Pharmacopeia/National Formulary**

The following sections are applicable to packaging components:

a. General Notices - PRESERVATION, PACKAGING, STORAGE, AND
 LABELING

b. General Tests and Assays

<1> Injections
 <51> Antimicrobial Preservatives - Effectiveness
 <61> Microbial Limit Tests
 <71> Sterility Tests
 <87> Biological Reactivity Tests, in vitro
 <88> Biological Reactivity Tests, in vivo
 <161> Transfusion and Infusion Assemblies
 <381> Elastomeric Closures for Injections
 • Biological Test Procedures
 • Physicochemical Test Procedures
 <601> Aerosols
 <661> Containers

	• Light Transmission • Chemical Resistance - Glass Containers • Biological Tests - Plastics and Other Polymers • Physicochemical Tests - Plastics • Containers for Ophthalmics - Plastics • Polyethylene Containers • Polyethylene Terephthalate Bottles and Polyethylene Terephthalate G Bottles • Single-Unit Containers and Unit-Dose Containers for Nonsterile Solid and Liquid Dosage Forms • Customized Patient Medication Packages
<671>	Containers - Permeation • Multiple-Unit Containers for Capsules and Tablets • Single-Unit Containers and Unit-Dose Containers for Capsules and Tablets
<691>	Cotton (or the monograph for Purified Rayon USP)
<771>	Ophthalmic Ointments
<1041>	Biologics
<1151>	Pharmaceutical Dosage Forms

ATTACHMENT B

COMPLIANCE POLICY GUIDES THAT CONCERN PACKAGING (August 1996)

Compliance Policy Guides are issued by the Division of Compliance Policy (in the Office of Enforcement/Office of Regulatory Affairs). The following is a list of Compliance Policy Guides that concern packaging. Any questions or concerns about the content of any Compliance Policy Guide should be addressed to the Office of Enforcement/Office of Regulatory Affairs/Division of Compliance Policy at 301-827-0420 (telephone), 301-827-0482 (FAX) or www.fda.gov/ora/compliance_ref/cpg/default.html (Internet).

Sub Chapter 410	BULK DRUGS
Sec. 410.100	Finished Dosage Form Drug Products in Bulk Containers - Applications of Current Good Manufacturing Practice Regulations (CPG 7132a.06)
Sub Chapter 430	LABELING and REPACKAGING
Sec. 430.100	Unit Dose Labeling for Solid and Liquid Oral Dosage Forms (CPG 7132b.10)
Sec. 430.200	Repacking of Drug Products - Testing/Examination Under CGMPs (CPG 7132.13)
Sub Chapter 440-448	NEW DRUGS
Sec. 446.100	Regulatory Action Regarding Approved New Drugs and Antibiotic Drug Products Subjected to Additional Processing or Other Manipulations (CPG 7132c.06)
Sub Chapter 450-457	OTC
Sec. 450.500	Tamper-Resistant Packaging Requirements for Certain Over-the-Counter (OTC) Human Drug Products (CPG 7132a.17)
Sec. 450.550	Control and Accountability of Labeling Associated with Tamper-Resistant Packaging of Over-the-Counter Drug Products (CPG 7132.14)
Sub Chapter 480	STABILITY/EXPIRATION

Sec. 480.100	Requirements for Expiration Dating and Stability Testing (CPG 7132a.04)
Sec. 480.200	Expiration Dating of Unit Dose Repackaged Drugs (CPG 7132b.11)
Sec. 480.300	Lack of Expiration Date of Stability Data (CPG 7132a.10)

ATTACHMENT C

EXTRACTION STUDIES

An extraction study of a packaging component typically involves exposing a sample of the component, often subdivided into small pieces to increase surface area, to an appropriate solvent system at elevated temperatures, followed by chemical analysis. The purpose of elevated temperature is to increase the rate of extraction, so that a short experimental time may simulate a longer exposure time at room temperature, or to maximize the amount of extractables obtained from a sample.

The methods employed to analyze the resulting extracts vary, depending on the purpose of the extraction study and the nature of the packaging component. The extraction solvent may be evaporated to concentrate the extracts or to determine the total weight of nonvolatile extractables. Appropriate methods, such as HPLC or gas chromatography, may be used to obtain qualitative or quantitative extraction profiles of volatile or nonvolatile extractables.

Extraction studies may be conducted during the qualification of packaging components for any of the following purposes:

- To perform USP characterization tests on plastics (USP <661>) or elastomers (USP <381>)
- To perform USP Biological Reactivity Tests (USP <87> and <88>) on plastics or elastomers
- To obtain qualitative extraction profiles of plastics or elastomers
- To obtain quantitative extraction profiles of plastics or elastomers
- To evaluate whether the FDA indirect food additive regulations provide an adequate indicator of safety

Extraction studies may also be conducted on a routine basis as a quality control measure to monitor the chemical compositions of elastomeric or other packaging components.

The solvent that should be used in an extraction study depends on the purpose of the study. The ideal situation is for the extracting solvent to have the same propensity to extract substances as the dosage form, thus obtaining the same quantitative extraction profile. For this study, the preferred solvent would be the drug product or placebo vehicle. When feasible, the dosage form itself would be used. A stronger extracting solvent than the drug product would be used to obtain a qualitative extraction profile that would be used to establish quality control criteria.

ATTACHMENT D

ABBREVIATIONS

AAO	American Academy of Ophthalmology
ANDA	Abbreviated New Drug Application
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CFSAN	Center for Food Safety and Applied Nutrition
CGMP	Current Good Manufacturing Practice
CMC	Chemistry, Manufacturing, and Control
COA	Certificate of Analysis
CPSC	Consumer Product Safety Commission
DMF	Drug Master File
DPI	Dry Powder Inhaler
FDA	U.S. Food and Drug Administration (the Agency)
HDPE	High Density Polyethylene
IND	Investigational New Drug Application
LDPE	Low Density Polyethylene
LOA	Letter of Authorization
LVP	Large-Volume Parenteral
MDI	Metered Dose Inhaler
NDA	New Drug Application
PET	Polyethylene Terephthalate
PETG	Polyethylene Terephthalate G
PP	Polypropylene
PVC	Polyvinyl Chloride
QA	Quality Assurance
QC	Quality Control
SVP	Small-Volume Parenteral
USP/NF	U.S. Pharmacopeia/National Formulary

ATTACHMENT E

REFERENCES²⁷

Center for Drug Evaluation and Research (CDER) Compressed Medical Gases Guideline (February 1989)

FDA Guideline for Drug Master Files (September 1989)

FDA Guidance for Industry on the Submission of Documentation for the Sterilization Process Validation in Applications for Human and Veterinary Drug Products (November 1994)

FDA Guidance for Industry on the Content and Format on Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well Characterized, Therapeutic, Biotechnology-Derived Products (November 1995)

FDA Guidance for Industry on the Submission of Chemistry, Manufacturing, and Controls Information for a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product for In Vivo Use (August 1996)

FDA Guidance for Industry on the Submission of Chemistry, Manufacturing, and Controls Information and Establishment Description for Autologous Somatic Cell Therapy Products (January 1997)

FDA Guidance for the Photostability Testing of New Drug Substance and Products (May 1997)

FDA Guidance for Industry on the Submission of Chemistry, Manufacturing, and Controls Information for Synthetic Peptide Substances (January 1998)

FDA Guidance for Industry on the Content and Format of Chemistry, Manufacturing, and Controls and Establishment Description Information for a Vaccine or Related Product (January 1999)

FDA Guidance for Industry for the Submission of Chemistry, Manufacturing, and Controls and Establishment Description Information for Human Plasma-Derived Biological Product or Animal Plasma or Serum-Derived Products (February 1999)

FDA Guidance for Industry on the Content and Format of Chemistry, Manufacturing, and

²⁷ A list of CDER and CBER guidances and guidelines is provided on the Internet at www.fda.gov/cder/guidances.index.htm and www.fda.gov/cber/guidelines.htm, respectively.

Controls and Establishment Description Information for a Biological In Vitro Diagnostic Product (March 1999)

FDA Guidance for Industry on the Content and Format of Chemistry, Manufacturing, and Controls and Establishment Description Information for Allergenic Extract or Allergen Patch Test (April 1999)

FDA Guidance for Industry for the Submission of Chemistry, Manufacturing, and Controls and Establishment Description Information for Human Blood and Blood Components Intended for Transfusion or for Further Manufacture and for the Completion of the FDA Form 356h, Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use (May 1999)



AMEDICA CORPORATION
615 Arapeen Drive | Suite 302
Salt Lake City, Utah 84108 USA
(801) 583-5100
www.amedicacorp.com



CAUTION: Federal (USA)
Law Restricts This Device To
Sale By Or On The Order Of A
Physician.



Single Use Only
DO NOT RESTERILIZE

EC REP

Emereo Europe
Molenstraat 15
2513 BH The Hague
The Netherlands

CE

0086

VALEO™ SPACER & VBR IMPLANT SYSTEMS

THE VALEO™ VBR acts as a spacer to maintain proper vertebral body spacing and angulation following a partial or total corpectomy. The VALEO™ VBR is manufactured from MC², a ceramic material.

As with all orthopedic implants, do not re-use these implants.

Indications

THE VALEO™ VBR is intended for vertebral body replacement to aid in surgical correction and stabilization of the spine. The device is indicated for use in the thoracolumbar spine (T1 to L5) to replace or restore height a collapsed, damaged, diseased, or unstable vertebral body or portion thereof, excised as a result of tumor or trauma (i.e., fracture). It is indicated to achieve decompression of the spinal cord and neural tissues, and to restore the height of a collapsed or damaged vertebral body.

The VALEO™ VBR is designed to restore the biomechanical integrity of the anterior, middle, and posterior spinal column even in the absence of fusion for a prolonged period.

The VALEO™ VBR is always to be used with supplemental internal spinal fixation. Additionally, the VALEO™ VBR may be used with bone graft.

Contraindications

THE VALEO™ VBR is not intended for cervical nor posterior surgical implantation.

GENERAL CONTRAINDICATIONS include, but are not limited to:

1. INFECTION, local to the operative site.
2. SIGNS OF LOCAL INFLAMMATION.
3. FEVER or leukocytosis.
4. MORBID OBESITY.
5. PREGNANCY.
6. MENTAL ILLNESS.
7. ANY MEDICAL OR SURGICAL CONDITION which would preclude the potential benefit of spinal implant surgery, such as the presence of tumors or congenital abnormalities, elevation of sedimentation rate unexplained by other diseases, elevation of white blood count (WBC), or a marked left shift in the WBC differential count.
8. RAPID JOINT DISEASE, bone absorption, osteopenia, and/or osteoporosis. Osteoporosis is a relative contraindication since this condition may limit the degree of obtainable correction and/or the amount of mechanical fixation.
9. SUSPECTED OR DOCUMENTED METAL ALLERGY or intolerance.
10. ANY CASE NEEDING TO MIX METALS from different components.
11. ANY PATIENT HAVING INADEQUATE TISSUE COVERAGE over the operative site or where there is inadequate bone stock, bone quality, or anatomical definition.
12. ANY CASE NOT DESCRIBED in the indications.
13. ANY PATIENT UNWILLING TO CO-OPERATE with postoperative instructions.
14. THESE DEVICES MUST NOT BE USED FOR PEDIATRIC CASES, nor where the patient still has general skeletal growth.

Contraindications of this device are consistent with those of other spinal systems.

Possible Adverse Effects

All of the possible adverse events or complications associated with spinal fusion surgery without instrumentation are possible. With instrumentation, a listing of possible adverse events or complications includes, but is not limited to:

1. EARLY OR LATE LOOSENING of the components. Implant migration.
2. DISASSEMBLY, BENDING, AND/OR BREAKAGE of any or all of the components.
3. FOREIGN BODY (ALLERGIC) REACTION to the implants, debris, corrosion products, including metallosis, staining, tumor formation and/or autoimmune disease.
4. INFECTION.
5. DURAL TEARS, pseudomeningocele, fistula, persistent CSF leakage, meningitis.
6. TISSUE OR NERVE DAMAGE, irrigation, and/or pain caused by improper positioning and placement of implants or instruments.
7. LOSS OF NEUROLOGIC FUNCTION, including paralysis (complete or incomplete), dysesthesia, hyperesthesia, anesthesia, parasthesia, appearance or radiculopathy, and/or the development or continuation of pain, numbness, neuroma, tingling sensation, sensory loss and/or spasms.
8. CAUDA EQUINA SYNDROME, neuropathy, neurological deficits (transient or permanent), paraplegia, paraparesis, reflex deficits, arachnoiditis, and/or muscle loss.

9. SCAR FORMATION possibly causing neurological compromise around nerves and/or pain.
10. URINARY RETENTION or loss of bladder control or other types of urological system compromise.
11. BONE LOSS or decrease in bone density, possibly caused by stress shielding.
12. SUBSIDENCE of the device into vertebral body(ies).
13. POSTOPERATIVE CHANGE IN SPINAL CURVATURE, loss of correction, height, and/or reduction.
14. CESSATION OF ANY POTENTIAL GROWTH of the operated portion of the spine. Loss of spinal mobility or function. Inability to perform the activities of daily living.
15. NON-UNION (or pseudoarthrosis). Delayed union. Mal-union.
16. FRACTURE, MICROFRACTURE, resorption, damage, penetration, and/or retropulsion of any spinal bone, of the bone graft, or at the bone graft harvest site-at, above, and/or below the level of surgery.
17. GRAFT DONOR SITE COMPLICATIONS including pain, fracture, infection, or wound healing problems.
18. HERNIATED NUCLEUS PULPOSUS, disc disruption or degeneration at, above, or below the level of surgery.
19. ILEUS, GASTRITIS, bowel obstruction or other types of gastrointestinal system compromise.
20. HEMORRHAGE, HEMATOMA, occlusion, seroma, edema, embolism, stroke, excessive bleeding, phlebitis, damage to blood vessels, or cardiovascular system compromise. Wound necrosis or wound dehiscence.
21. REPRODUCTIVE SYSTEM COMPROMISE, including sterility, loss of consortium, and sexual dysfunction.
22. DEVELOPMENT OF RESPIRATORY PROBLEMS, e.g., pulmonary embolism, atelectasis, bronchitis, pneumonia, etc.
23. CHANGE IN MENTAL STATUS.
24. DEATH.

NOTE: Additional surgery may be necessary to correct some of these anticipated adverse events.

Warnings and Precautions

A SUCCESSFUL RESULT IS NOT ALWAYS ACHIEVED in every surgical case. This fact is especially true in spinal surgery where other patient conditions may compromise the results. This device system is not intended to be the sole means of spinal support. THE VALEO™ SPACER SYSTEM AND VALEO™ VBR IMPLANT SYSTEM MUST BE USED WITH ADDITIONAL ANTERIOR OR POSTERIOR INSTRUMENTATION TO AUGMENT STABILITY. Use of this product without a bone graft may not be successful. No spinal implant can withstand body loads without the support of bone. In this event, bending, loosening, disassembly and/or breakage of the device(s) will eventually occur.

Consider preoperative and operating procedures, including knowledge of surgical techniques, proper selection and placement of the implant and good reduction prior to surgery. Only perform installation and positional adjustment of implants with special equipment and instruments specific to these devices. Do not use other instruments unless specifically recommended by Amedica because other instruments may be incompatible.

NEVER REUSE AN INTERNAL FIXATION DEVICE UNDER ANY CIRCUMSTANCES. Even when a removed device appears undamaged, it may have small defects or internal stress patterns that may lead to early breakage. Damage to the connection mechanism will reduce instrument stability.

Further, the proper selection and compliance of the patient will greatly affect the results. Patients who smoke have been shown to have an increased incidence of non-unions. These patients should be advised of this fact and warned of this consequence. Obese, malnourished, and/or alcohol abuse patients are also poor candidates for spine fusion.

Other preoperative, intraoperative, and postoperative warnings and precautions are as follows:

Preoperative

The selection of the proper size, shape and design of the implant for each patient is crucial to planning the success of the procedure. Ceramic implants are subject to repeated stresses in use, and their strength is limited by the need to adapt the design to the size and shape of human bones. Unless great care is taken in patient selection, proper placement of the implant, and postoperative management to minimize stresses on the implant, such stresses may cause fatigue and consequent breakage or loosening of the device before the healing process is complete, which may result in further injury or the need to remove the device prematurely.

1. USE CARE IN HANDLING and storing these components. Do not scratch or damage them. Protect implants and instruments during storage especially from corrosive environments.
2. SINCE MECHANICAL PARTS ARE INVOLVED, be familiar with the various components before using the equipment and personally assemble the devices to verify that all parts and necessary instruments are present before surgery.
3. DETERMINE THE TYPE OF CONSTRUCT to be assembled for the case prior to surgery. Have an adequate inventory of implant sizes available at the time of surgery, including sizes larger and smaller than those expected to be used.
4. UNLESS PACKAGED STERILE, clean and sterilize all parts before use. Have additional sterile components available in case of an unexpected need.

Intraoperative

1. CAREFULLY FOLLOW THE INSTRUCTIONS in any available applicable surgical technique manual.
2. AT ALL TIMES, USE EXTREME CAUTION AROUND THE SPINAL CORD and nerve roots. Damage to the nerves will cause loss of neurological functions.
3. BREAKAGE, SLIPPAGE, OR MISUSE OF INSTRUMENTS or implant components may cause injury to the patient or operative personnel.
4. TO ENSURE PROPER FUSION below and around the location of the instrumentation, use a bone graft. When using the VALEO™ VBR, use grafts containing autogenous bone.
5. DO NOT USE BONE CEMENT since it will make removal of the components difficult or impossible. The heat generated from the curing process may also cause neurologic damage and bone necrosis.

Postoperative

Postoperative directions and warnings to the patient and patient compliance are extremely important.

1. GIVE THE PATIENT DETAILED INSTRUCTIONS on the device's use and limitations. If partial weight bearing is recommended or required prior to firm bony union, warn the patient that device bending, loosening, or breakage can occur as a result of excessive weight bearing or muscular activity. The risk of bending, loosening, or breakage of a temporary internal fixation device during postoperative rehabilitation may be increased if the patient is active or if the patient is debilitated, demented, or otherwise unable to use crutches or other weight supporting devices. Warn the patient to avoid falls or sudden jolts in spinal position.
2. FOR OPTIMAL SURGICAL RESULTS, do not expose the patient or device to mechanical vibrations that may loosen the device construct. Warn the patient of this possibility, and instruct the patient to limit physical activities, especially lifting and twisting motions and any type of sport participation. Advise the patient not to smoke or consume excess alcohol during the bone graft healing process.
3. ADVISE THE PATIENT NOT TO BEND at the point of spinal fusion, and teach the patient to compensate for this permanent physical restriction in body motion.
4. FAILURE TO IMMOBILIZE a delayed or non-union of bone will result in excessive and repeated stresses on the implant. By fatigue, these stresses can cause eventual loosening, or breakage of the device. It is important that union immobilization is established and confirmed by roentgenographic examination. Where there is a non-union, or if the device loosens and/or breaks, the device should be revised immediately before serious injury occurs.

Packaging

Packages for each of the components should be intact upon receipt. If a loaner or consignment system is used, check all sets for completeness and all components for lack of damage prior to use. Do not use damaged packages or products; return them to Amedica Corporation. Remove all packaging prior to sterilization. Always immediately re-sterilize all implants and instruments which have been previously in the operation area. Perform this process before returning products to Amedica Corporation.

Cleaning and Decontamination

Clean all instruments and implants using established hospital methods before sterilization and introduction into a sterile surgical field. Decontaminate and clean all instruments and implants that have been previously taken into a sterile surgical field using established hospital methods before sterilization and reintroduction into a sterile surgical field. Cleaning and disinfecting of instruments can be performed with alkali aldehyde-free solvents at higher temperatures. Cleaning and decontamination can include the use of neutral cleaners followed by a deionized water rinse.

NOTE: certain cleaning solutions such as those containing formalin, glutaraldehyde, bleach and/or other alkaline cleaners may damage some devices, particularly instruments; do not use these solutions. Certain instruments may require dismantling before cleaning.

Treat all products with care. Improper use or handling may lead to damage and possible improper device function.

Sterilization STERILE | R

Unless otherwise indicated, all components have been sterilized by a minimum of 25kGy (2.5 MRads) of gamma irradiation and are supplied packaged in protective trays or pouches. This sterilization is validated by AAMI TIR27:2001 Sterilization of Healthcare Products – Requirements for Validation and Routine Control - Radiation Sterilization and Sterilization of health care products – Radiation sterilization-Substantiation of 25 kGy as a sterilization dose- Method Vmax to an SAL of 10⁻⁶. Inspect packages for punctures and other damage prior to surgery.

AMEDICA DOES NOT RECOMMEND RESTERILIZATION OF IMPLANTABLE MEDICAL DEVICES.



Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

WARNING LETTER

JAN 27 2009

Ashok C. Khandkar, Ph.D.
Chief Executive Officer
Amedica Corporation
615 Arapeen Drive - Suite 302
Salt Lake City, UT 84108

Re: Valeo™-C VBR

Dear Dr. Khandkar:

The Office of Compliance (OC) in the Center for Devices and Radiological Health (CDRH) has reviewed various portions of the labeling for the Valeo™-C VBR, which was provided by Amedica Corporation to inspectors from the Denver District Office during an inspection which took place between August 7 and August 20, 2008, and learned that your firm is marketing the Valeo™-C VBR for new intended uses without marketing clearance or approval. Under section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 321(h), the Valeo™-C VBR is a device because it is intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, or is intended to affect the structure or function of the body.

The device is adulterated under section 501(f)(1)(B) of the Act, 21 U.S.C. § 351(f)(1)(B), because you do not have an approved application for premarket approval (PMA) in effect pursuant to section 515(a) of the Act, 21 U.S.C. § 360e(a), or an approved application for an investigational device exemption (IDE) under section 520(g) of the Act, 21 U.S.C. § 360j(g). The device is also misbranded under section 502(o) of the Act, 21 U.S.C. § 352(o), in that a notice or other information respecting the device for the new uses described below was not provided to the FDA as required by section 510(k) of the Act, 21 U.S.C. § 360(k), and 21 C.F.R. 807.81(a)(3)(ii). Your promotion of the Valeo™-C VBR for intended uses that are not consistent with those cleared in your 510(k) Notifications represents a major change or modification in the intended use that requires the submission of a PMA or a 510(k). For a device requiring premarket approval before marketing, the notification required by section 510(k) of the Act is deemed satisfied when a premarket approval application (PMA) is pending before the agency, 21 C.F.R. § 807.81(b). The kind of information you need to submit in order to obtain approval or clearance for your device is described on the Internet at <http://www.fda.gov/cdrh/devadvice/3122.html>. The FDA will evaluate the information you submit and decide whether your product may be legally marketed.

The device was cleared for marketing under premarket notification (510(k)) submission number K073125 and modified under K073505. The cleared Valeo™-C VBR is a trapezoidal spacer with a rectangular inner hole intended to be filled with bone grafting material. It is available in two sizes: small (16 x 12 mm) and medium (17 x 14 mm). The Valeo™-C VBR's height ranges from 5 – 12 mm. The letters clearing the device for marketing includes the following as part of the Indications for Use Statement:

“The Valeo™ VBR is intended for vertebral body replacement to aid in surgical correction and stabilization of the spine. The device is indicated for use in the thoracolumbar spine (T1 to L5) to replace or restore height a collapsed, damaged, diseased, or unstable vertebral body or portion thereof, excised as a result of tumor or trauma (i.e., fracture).”

The Valeo™ VBR may be used with bone graft.

The intended uses for the Valeo™-C VBR described in the labeling collected by FDA inspectors represent major changes or modifications to the cleared intended uses for this device that could significantly affect its safety or effectiveness. Specifically:

- The Product Specification Sheet provided to FDA inspectors, and also available at <http://www.amediacorp.com/improvement/Valeo-C.html>, states that the Valeo™-C VBR “is designed with uoro, a hollow core to accept autograft or biologics.” However, the Valeo™-C VBR is cleared for use only with bone graft (i.e., autograft or allograft). It is not cleared for use with biologics.¹
- Amedica Sales Materials Master Disc – Serial 0001, dated 7-15-2008, includes a video file, “Valeo C CP Surgical Technique_02'08,” found in the folder “Sales Material \Training Materials\Videos.” The video describes the surgical implantation of the Valeo™-C VBR in the cervical spine along with the Valeo™ CP Cervical Plate System. However, the Valeo™-C VBR is cleared for use only in the thoracolumbar spine, and, according to its indications for use statement the Valeo™ CP Cervical Plate System (K071990) is intended:

“... for anterior screw fixation at the vertebral bodies of the cervical spine (C2-C7). The Valeo™ CP Cervical Plate System is indicated for use in temporary stabilization of the anterior spine during the development of cervical spinal fusions in patients with degenerative disc disease (as defined by neck pain in discogenic origin of the disc confirmed by patient history and radiographic studies), spinal stenosis, spondylolisthesis, deformity (defined as kyphosis, lordosis, and scoliosis), trauma (including fractures), tumors, pseudoarthrosis, and/or failed previous fusions.”

¹ The promotion of the use of a biologic material with the Valeo™-C VBR, as described by your promotional material, is of particular concern because of the known serious adverse events associated with the use of biologics (which include, but are not limited to, bone morphogenetic proteins (BMPs)) in the cervical spine. On Tuesday, July 1, 2008, FDA issued a Public Health Notification describing life-threatening complications associated with use of BMPs in cervical spine fusion. Note that the safety and effectiveness of BMPs in the cervical spine have not been demonstrated and BMPs are not approved by FDA for this use. FDA's Public Health Notification is available at <http://www.fda.gov/cdrh/safety/070108-rhbm.html>.

Thus, the Valeo™-C VBR is being marketed and promoted for a use for which it has not been approved or cleared.

It is noted that the information provided in the video file "Valeo C CP Surgical Technique_02'08" is replicated on Amedica Training Course Material Disc, dated 8-18-2008 as "Steps 2 - 17" in the folder "am cervical 6_aug_08\media."

- The video, "Valeo C CP Surgical Technique_02'08," also clearly describes and depicts an interbody fusion procedure rather than a vertebrectomy or partial vertebrectomy procedure; though the Valeo™-C VBR is cleared for use only in the latter procedures. A vertebrectomy or partial vertebrectomy procedure includes the removal of vertebral bone and placement of the device within the void that is created. The procedure presented in "Valeo C CP Surgical Technique_02'08," however, states: "Perform Discectomy & Decompression with General Instrumentation." The video then shows the removal of disc material and placement of the Valeo™-C VBR device into the intervertebral body space, rather than into a void created by a vertebrectomy of partial vertebrectomy procedure.

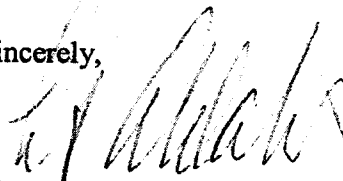
OC requests that Amedica Corporation immediately cease the dissemination of promotional materials for Valeo™-C VBR which include the intended uses described above. Please submit a written response to this letter within fifteen (15) working days of receipt of this letter describing your intent to comply with this request, listing all promotional materials for Valeo™-C VBR and explaining your plan for discontinuing use of such materials.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials comply with each applicable requirement of the Act and FDA's implementing regulations.

Failure to promptly correct the promotional violations discussed above may result in regulatory action being initiated by FDA without further notice. These actions include, but are not limited to, seizure, injunction, and/or civil money penalties. Also, federal agencies are advised of the issuance of all Warning letters about devices so that they may take this information into account when considering the award of contracts.

Please direct your response to Dr. Anastacia Bilek at the Food and Drug Administration, 2094 Gaither Road, HFZ-343, Rockville, Maryland 20850, facsimile at (240) 276-0129. We remind you that only written communications are considered official.

Sincerely,



Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices and
Radiological Health

REVIEW FROM PREVIOUS WEEK

- What is a primary packaging component?
- What are 3 considerations for selecting packaging?
- Name 3 pieces of information that must be included in labeling?
- What is the most frequent and consequential problem related to packaging & labeling?



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EQUIPMENT CLEANING, MAINTENANCE, & CALIBRATION



Step Ahead.

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CLEANING & MAINTENANCE

- A quality system requirement
- Frequency will depend on:
 - ☐ Usage of equipment
 - ☐ Criticality of process
 - ☐ GMP & quality system – SOPs / WIDs
 - ☐ Manufacturer's recommendations (see manual)
 - ☐ Balancing problem prevention vs. work output
- Can include calibration
- May require planning & scheduling



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CLEANING & MAINTENANCE (cont.)

- Will likely involve **lockout/tagout** procedure as a safety precaution (OSHA requirement) :
 - Notify affected workers
 - Shut down using appropriate procedures
 - Isolate from energy source
 - Apply lockout/tagout device(s)
 - Release stored energy (electrical, mechanical, chemical, or thermal)
 - Verify dissipation of energy
- See textbook : Tool Safety & Maintenance – Section 11.2



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MAINTENANCE LOG

- Documents all services (preventative maintenance, repairs, calibration) for a particular piece of equipment
- Is a quality document
 - Evidence of regulatory / GMP compliance
 - Source of information for problem-solving / troubleshooting activities
 - May be associated with other supporting records



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CALIBRATION

- Are foundational activities for ensuring quality
- Is based on a comparison to a “*gold standard*”
- Must be traceable
- Equipment used for calibration must also be calibrated / verified / validated
- Mandated by GMP / regulations : each quality system must have a calibration program
 - e.g. for medical devices, refer to **21 CFR Part 820.72** and **Medical Device Quality Systems Manual, Chapter 7**



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CALIBRATION REQUIREMENTS

- Established written procedures that include:
 - ✓ Specific directions
 - ✓ Limits for accuracy and precision
- Documentation of results
- Appropriate training of calibration personnel
- Use of standards traceable to *National Institute of Standards and Technology* (NIST), or other recognizable standards (including in-house)
- Action plan if out-of-calibration :
e.g. effects on product quality?



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CALIBRATION STANDARDS

- Must be handled, cared for, and maintained appropriately
- Must be traceable to NIST where practical / applicable – can be accomplished by :
 - ☐ Use of standard reference materials purchased from NIST
 - ☐ Calibration of private reference materials by NIST
 - ☐ Use of contract calibration laboratory which uses NIST



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CALIBRATION STANDARDS (cont.)

- May be in-house standards, and if so, should be well described in the device master record or quality system
- **Metrology** : the science of weights and measures



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CALIBRATION CONCEPTS

- **Accuracy** : a measure of an instrument's capability to approach a true or absolute value; is a function of precision and bias
- **Precision** : relative degree of repeatability (repeatability is affected by resolution and stability)
- **Bias** : a measure of how close a mean value, for a set of replicate measurements, approaches the true value



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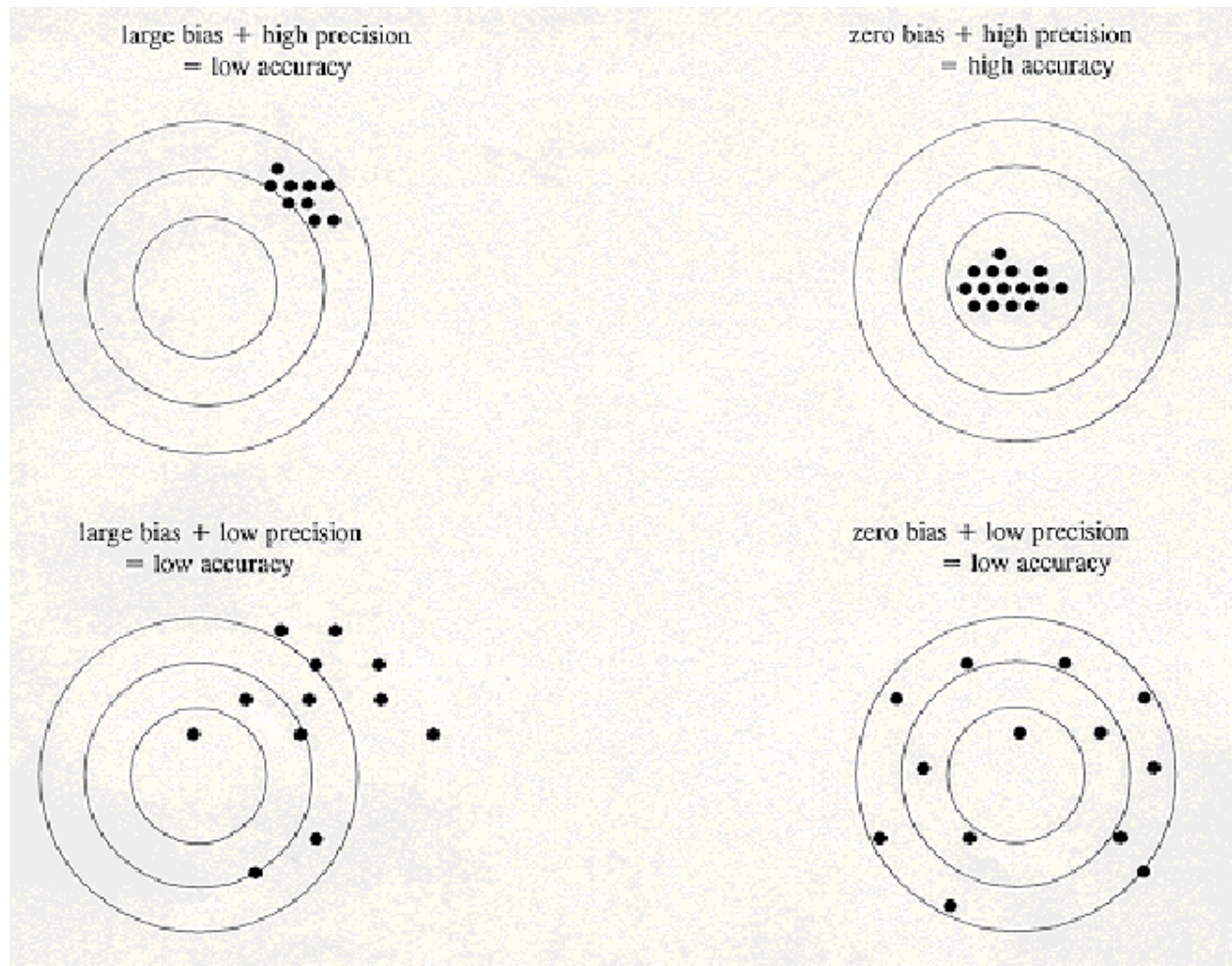
CALIBRATION RECORDS

- Calibration report
- Calibration decals – provides at-a-glance calibration status, and should include
 - ✓ Equipment ID
 - ✓ Calibration date
 - ✓ Calibration technician
 - ✓ Date calibration is next due
- Calibration database – critical for scheduling



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ACCURACY, PRECISION, AND BIAS



From: Medical Device Quality Systems Manual, Chapter 7 – Equipment and Calibration

EXAMPLES OF CALIBRATION DECALS

CALIBRATION DATE _____
BY _____
DUE _____

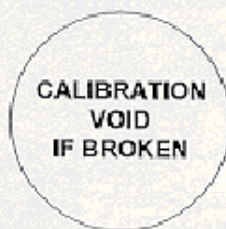
Typical calibration decals have a write-on surface. A tough paper or cloth stock and a pressure sensitive adhesive are used for easy application and removal of the decal. "Due" is the blank for the date when recalibration is due.

CAL. ID No. _____

Calibration Identification Number or its equivalent is usually the minimum information that may be on equipment. This information allows the manufacturer to read by finding the associated calibration record\card\file.

CALIBRATION VOID DO NOT USE
--

Measuring equipment that is not calibrated or otherwise unsuitable for use should be placed in a quarantine area or labeled with a "calibration void" decal.



A seal or protective cover for exposed, recessed calibration controls on instruments. The calibration control cannot be adjusted without breaking the seal or removing the instrument case.

NOT A CALIBRATED INSTRUMENT
--

A decal to be applied to measurement or monitoring instruments not intended for use in determining conformance to device master record specifications with respect to testing, manufacturing, environmental control, etc.

From: Medical Device Quality Systems Manual, Chapter 7 – Equipment and Calibration