INSTITUTE FOR THERMAL PROCESSING SPECIALISTS

IFTPS CONFERENCE PORTO 2009

PRODUCT & PROCESS PROFILING

"The Role of Microbiology"

Dr. D.J Freeman, Ireland

DFMicro, *www.dfmicro.com*

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OBJECTIVES

PRESENTER

Clarify , the role of ***Micro Testing*** *in Quality Management*

Provide, an ***Alternative View*** of Microbiology (& Microbiologists).

Explore & **Identify,** *areas where Microbiology has the greatest potential to* ***Positively Contribute*** *to overall Product & Process Quality*.

Provide an **Overview,** *of the role and potential significance of*

"Microbiological Profiling"

ATTENDEE

Raised Awareness of the ***Dynamic Nature*** of Micro. Quality

Better Appreciation of how this variation is ***Proactively Managed*** in order to Improve Process & Product Quality and how such Strategies contribute to ***Added Value***

Stimuli to review how Micro is viewed and managed within companies and if necessary change this view in order to

Maximize Resources & **Quality**

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CONCEPTION or MISCONCEPTION

DEFINING MICROBIOLOGY

" the science and study of microorganisms, including, protozoans, algae, fungi, bacteria, viruses, rickettsiae and prions"

"the study of microbial populations and the mechanisms through which they interact with their immediate environment"

"Understanding how Microbial Populations influence and/or are influenced by the Product, Process and Process Environment

in order to ensure

Effective Microbial Risk Analysis & Implementation of Effective Prevention, Control and Monitoring Strategies"

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MICROBIOLOGICAL QUALITY CHALLENGE

PREDICTABILITY of DYNAMIC BIOLOGICAL SYSTEMS

System Outputs rarely bear a Direct Relationship with System Inputs

Therefore, some level of continuous assessment is always implied

CONTINUOUS & VARIABLE CONTAMINATION RISK

STARTING MATERIALS,	***Source, Manufacturing Process, Handling***
PRODUCT PHASES,	***Changing Attributes, a_w, pH etc***
UNIT PROCESSES	***Equipment, Treatment, Sub Processes***
ENVIRONMENT,	***Temperature, Humidity, etc***
HANDLING,	***Personnel Hygiene, Package Integrity***
STORAGE,	***Temperature, Package Integrity,***
USAGE,	***Single Use, Multi Use etc, User Handling***

MULTIPLE, NON-LINEAR RELATIONSHIPS

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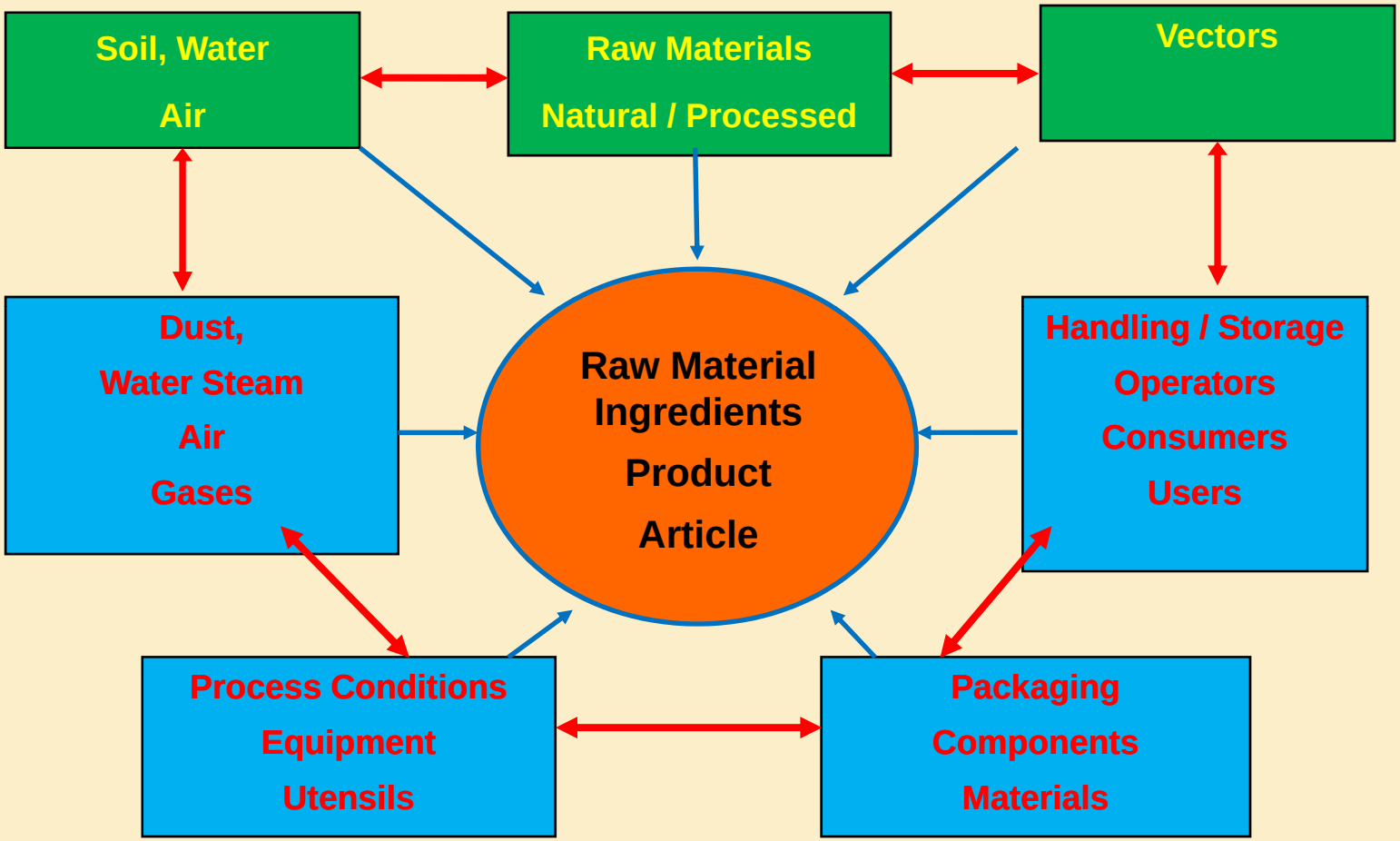
MICROBIOLOGICAL QUALITY CHALLENGE

BIOBURDEN

ENDOGENOUS or EXOGENOUS SOURCES



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THE CHALLENGE OF MICROBIOLOGICAL QUALITY

MICROBIOLOGY ISSUES -PROCESS & PRODUCT SPECIFIC

- **Random Variation & Distribution**

  Concentration at any given stage (maybe irrelevant to product risk)

- **Characteristics / Attributes of Microorganisms**

  Variation in Type, Source, Growth Characteristics, Pathogenicity

- **Characteristics / Attributes of the Product Matrix**

- **Influences of the Plant, Process Steps & Storage**

- **Appropriate & Coherent Analytical Procedures**

  Absence may only represent failure to detect under defined test conditions.

- **Attributes & Activities of End User**

  Pre-disposition, age, illness, product usage (preparation & storage) etc

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MICROBIOLOGICAL QUALITY CHALLENGE

Microbiological Methods

Time Consuming, Labour Intensive, Not Suited to Automation /Direct Data Capture

Product Testing

Random End Stage Product Testing Rarely provides unequivocal hard data

Remediation of Micro Quality Product Issues

Often Impossible, Rarely Easy and Requires Much Supporting Information,

Selective Influence of Various Process Phases & Unit Processes

Paradoxically the Use of Processing Steps for Bio-Reduction and/or Product Manufacture exerts a selective influence of the microbial sub-populations present.

Validation by Nature is a Continuous Process

The Dynamic Nature requires that Validation must generally be viewed as as a Concurrent Activity, unless a robust "Worst Case" or Overkill Process is employed.

Worst Case – Based on What?

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THE CHALLENGE OF MICROBIOLOGICAL QUALITY

"To Understand & Predict
Dynamic Influence of Concurrent, Pre & Post Processing Conditions on Intrinsic, Extrinsic Product Properties & their Influence on Existing & Potential Microbiological Contaminants

"Microbiological Profiling & Performance Monitoring "

PROSPECTIVE RISK ANALYSIS	CONCURRENT RISK ASSESSMENT	RETROSPECTIVE RESULT HISTORY
COMPONENT QUALITY HISTORY	MATERIALS, COMPONENTS	PRODUCT HISTORY (incl. RMs)
COMPONENT PROFILES	WATER, AIR, ENVIRONMENT	PROCESS PERFORMANCE
PROCESS & EQUIPMENT DESIGN	IN-PROCESS PROFILES	VALIDATION /CHANGE CONTROL
R & D / PILOT PROCESSES	EQUIPMENT PERFORMANCE	DEVIATIONS, COMPLAINTS
TRANSFER & SCALE UP ISSUES	INSPECTION, SERVICE, PM	PERSONNEL / HYGIENE HISTORY
MONITORING PGM DESIGN	PERSONNEL ACTIVITIES	CLEANING HISTORY

Continuous Comparative Result Trending of Multiple Parameters

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MISCONCEPTION or POLICY

"Currently we have a requirement for a Senior Microbiology Lab Team Lead based in a pharmaceutical company in [redacted]. This is an excellent opportunity for the right candidate to step up their career. The position is based in the Microbiology Dept but the candidate does not have to come from a micro background"

Recruitment Communication - Received 2006

Why Bother with Microbiology?

MICROBIOLOGY QUALITY DISABLERS

1: TECHNICAL LEVEL

2: MANAGEMENT LEVEL

3: TRAINING LEVEL

4: EDUCTIONAL LEVEL

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MICROBIOLOGY QUALITY DISABLERS

TECHNICAL CONSIDERATIONS

Procedures /Time Delay : *Retrospective*

Soft Data : *Qualitative / Quantitative*

Result Variability: *High level Uncertainty*

Process Unpredictability: *Support Data*

Methodology :
Validation & Coherence
Not Suitable for Automation
Not Suitable for Data Capture -LIMS

MANAGEMENT CONSIDERATIONS

Poor Knowledge Base : *Microbiological Expertise*

Representation *: Inappropriate Management Level*

Poor Communication : *Appropriate & Timely Info*

Perception : *Role of QC Lab Reactive v Proactive*

Resources: *Poor Planning, Orientation, Usage*

TRAINING CONSIDERATIONS

Resource Limitations

Poorly Defined Training Needs

Limited Scope of Training

Poor Training Path Design

Poor Delivery Practices

EDUCATIONAL CONSIDERATION

Lack of Contextualised Knowledge

Limited Industrial Experience

Limited Knowledge of the Process

Limited Opportunity to Learn

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MICROBIOLOGICAL QUALITY

"Microbiological Quality must be "Built In" to the process at the design stage - laboratory testing of IP & FP an inaccurate indicator of overall quality."

QUALITY BY DESIGN

Integrated - Approach

Front End Risk Analysis – cGMP- Strong MQS

Bringing Microbiology Out of the Lab

"System failures associated with Microbiological Quality often relate not to the lack of adequate test resources, but poor design and resources that are inadequately planned, managed and positioned within the process"

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CONTROL of MICROBIOLOGICAL QUALITY

"At Source"

1: **PREVENTION of CONTAMINATION*: Design of Sanitary Processes***

Ingredients, Premises, Equipment, Personnel, Cleaning & Disinfection

2: **PREVENTION of OUTGROWTH: *Controlled Process Conditions***

Reduce aw, Adjust pH, Control temperature, humidity etc – "Hurdle Technology"

3: **ELIMINATION OR BIO-REDUCTION PROCESSES**

Thermal Processing, Preservatives etc

Choice Determined by Product Risk and Consumer Risk

"Microbiological Profiling"

CONTROL PHASES

MICROBIOLOGICAL PROFILING - Risk Analysis, All Phases, Design, R&D, Supply

PROCESS MONITORING - Risk Analysis of Existing Process, HACCP, EM, IP Tests

RELEASE TESTING – Finished Product Testing

DOWNSTREAM QUALITY INDICATORS – Stability, Customer Complaints,

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MICROBIOLOGY QUALITY SYSTEM (MQS) ATTRIBUTES

Representation – Appropriate **Management, Qualifications** &/or **Experience**

Integrated - QMS, controlled, **flexible**, recognise attributes specific to Microbiology

Coherent - with the general policies and practices of the QA System - **Differences**

Contextualised & Consistent - with Good Microbiological Practice -**Differences**

After Action Review System - learning from mistakes, appropriate **CAs**

Appropriate Microbiological Resources

- **Management – Knowledge** & **Expertise**
- **Methods – Coherent** & **Complimentary**
- **Materials – Suitable Design** & **Fit for Use**
- **Manpower –Balance – *"Tooth to Tail Ratio"***

"Strategically Positioned & ***Integrated "***

Key stages, with greatest influence on overall microbiological quality.

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MICROBIOLOGICAL PROFILING

Risk Analysis Integral – Various RA Methods

e.g. HACCP

DISTINCTIONS FROM HACCP

Scope of Assessment - Potential Risks

Overall Process & Even Third Party Operations

Pre & Post Production Handling

Design, Pilot, Stability Stages etc

Critical to Process & Validation Design

Quality Orientated Not Just Safety

Product and Process Robustness

Specific to Microbiology

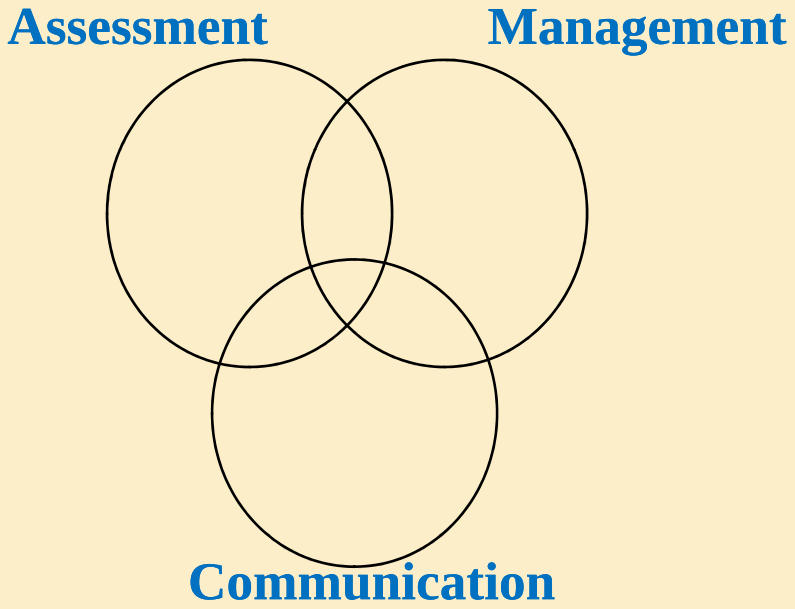
Understanding Potential Population Dynamics

Known Unknowns of Interest

Prospective & Proactive,

Not Real Time

Not Superimposed but Built In Quality



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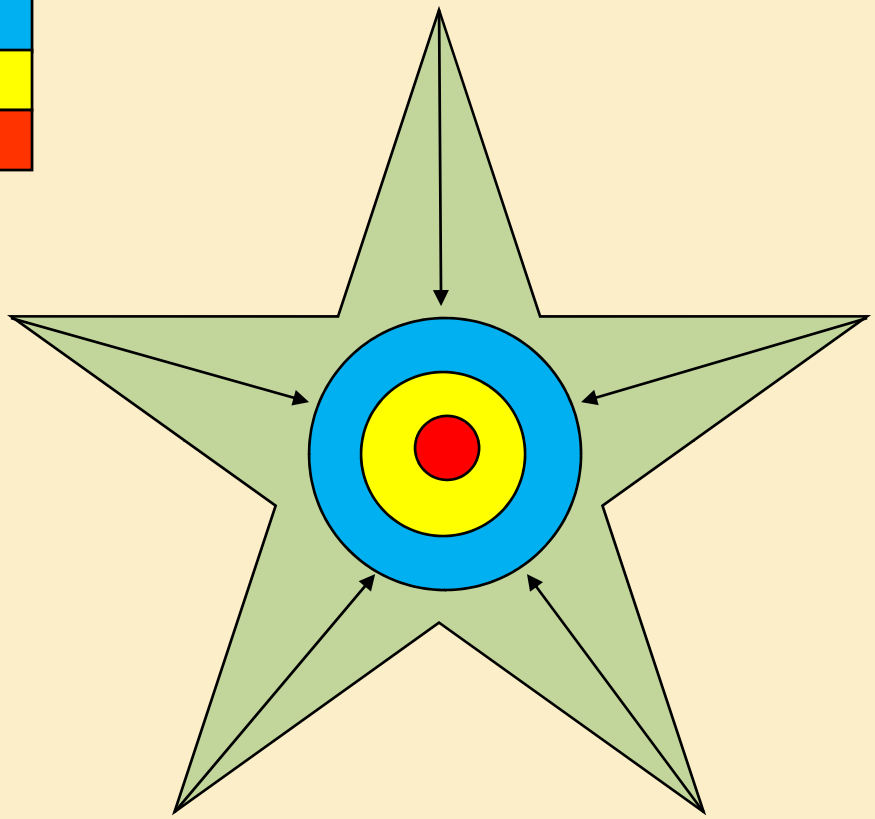
POSITIONING of MICROBIOLOGICAL PROFILING

MICROBIOLOGICAL PROFILING

GMP MANAGEMENT

PROCESS

HACCP & EM



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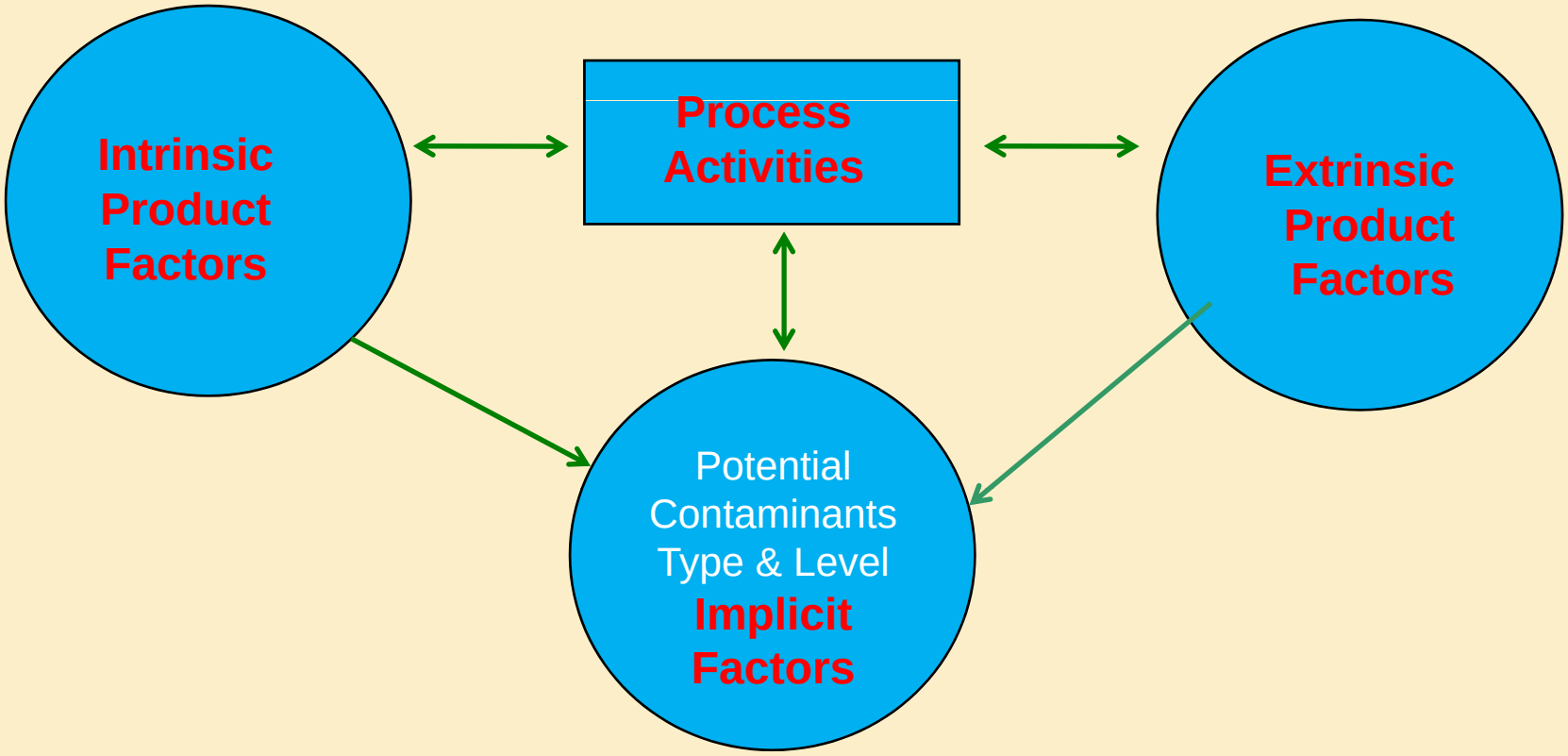
Appropriate Testing Programs & Laboratory Facilities should Pre-Date Production Facilities & Validation Design ????? – Forward Planning

MICROBIOLOGICAL PROFILING



Not "In Process Control"
but
"Overall Process Control

**** Experimentation & Use of 1st Principles is Implicit***

"Iterative Process"

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MICROBIOLOGICAL PROFILING

Growth Factors

The nature of product risk or the ability of a microorganism to grow relates to a range of properties and evaluation of how such properties interrelate gives us a Microbiological Profile of the product, an estimate of risk and the rationale for effective Contamination Control.

Factors Affecting Microbial Growth			
Intrinsic **Product Properties** **Ingredients, IP, FP**	**Extrinsic** **Product Environment** **Pre & Post Process**	**Implicit** **Microbial Properties**	**Processing** **Activities**
Nutrients Water (a_w) pH Redox Potential ^{Eh} Buffering Potential Antimicrobial Attributes Preservatives Protectants	Temperature Humidity Gaseous Atmosphere	Growth Properties Resistance & Survival Mechanisms Heat Resistance Chemical Resistance Osmotic tolerance **e.g. Endopsores**	Plant Design Process Design Equipment Design Product Handling Cleaning Sanitization Personnel Hygiene Product Usage

IMPLICIT ATTRIBUTES
VEGETATIVE CELLS & SPORES
HETEROGENEOUS / MIXED POPULATIONS

Mixed Resistance Patterns

Resistance characteristics are not necessarily uniform or stable.Spores of variable resistance co-exist - those with survival advantage / greater resistance will prevail.
Temperature of sporulation may be more important than actual growth optima in determining heat resistance. Spore resistance is also related to the growth conditions of the vegetative cell.

Population Source

Population & Sub-Population Variation relates to Product Source & Previous Growth Conditions Various Seasonal & Geographical are observed.

Influence of Nutritional Factors

Absence or presence of certain specific nutritional requirements may determine the ability to sporulate (produce spores), their resistance and the ability of spores to germinate.

Recovery or Death of Injured Spores

The ability to recover and the conditions necessary for recovery may influence choice of incubation conditions

Processes Exert Selective Pressure

Activation agents include Pressure Change, Heat Shock, UV, Treatment with Chemicals, Changes in Temperature, Acidity, Osmolarity. Activation temperatures of 70 – 80^{o}C common.

PROFILING DRIVERS

REGULATORY	**Undesirable Microorganisms 21 CFR 110 (110.3 (i)) - *Objectionables*** ***Not Just A Question of Public Health*** **Environmental Monitoring / Environmental Isolates** **Appropriate Challenges and Appropriate Challenge Organisms** **Product Categorisation, Probiotics, Neutraceutical, Dietary – *Grey Area***
MARKET ISSUES	**Specific Local Regulatory Requirements** **Environment al Conditions - Handling Conditions e.g.** *Temperature* **Intense Market Competition**
EMERGING MICROBES	**Associations between Microbes & Particular Foods with Spoilage /Infection,** *Enterobacter sakazzkii, Aeromonas spp, Mycobacterium paratuberculosis, Bacillus sporothermodurans, B. licheniformis,*
CONSUMER ATTITUDES	**Greater Consumer Awareness and Reporting of Safety & Quality Issues,** **Greater Expectation of Safe, Beneficial & Aesthetically Pleasing Products** **Greater Demand for Convenience Products (Long Life, *Sous Vide, Barrier Packaging* etc)**
PRODUCT PROCESSES	**Advancing or Changing Approaches to Processing, Novel Processes** **Novel Packaging & Presentation Formats,** **Novel Products: Dietary Supplements, Natural/Herbal Products, Probiotics** **Greater Intricacy of Distribution & Handling Systems**

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PROFILING STEPS - HOW

1: MAP THE PROCESS OR ANTICIPATED PROCESS (Rigorous)

2: ESTABLISH PRODUCT CHARACTERISTICS (Different Phases / Follow Map)

3: ESTABLISH PRIMARY EXTRINSIC FACTORS ("Hurdle Technology Design")

4: QUANTIFY & IDENTIFY TARGET POPULATIONS PRESENT (Targets ???)

5: IDENTIFY NATURE of IMPLICIT FACTORS for TARGETS (Process & Phase Specific)

6: ASSESS IMPACT of EXTRINSIC & INTRINSIC FACTORS on TARGETS (Testing???)

7: DETERMINE LIKLIHOOD of TARGETS to GROW (Testing???)

8: DESIGN & IDENTIFY CONTROL STRATEGIES or MODIFY DESIGN (Worst Case???)

9: MONITOR for POPULATION SHIFTS (Continuous – Strategically Targeted HACCP)

PROFILING– WHERE & WHEN

ALL CRITICAL PHASES	Preferably from Design & Process Selection onwards
ALL CRITCAL STEPS	Components, Unit Processes, Holding & Handling activity
VARIOUS INTENSITIES	High Intensity during Design or Process Change
	Reduced Programmes under STD Operating Conditions

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PROs & CONs

ADVANTAGES

- QUALITY COMPLIANCE - " BUILT IN "
- SYSTEM DESIGN - BETTER CONTROL
- VALIDATION - FASTER CHEAPER
- VALIDATION – "*WORST CASE*" ROBUST
- PROCESS CONTROL - BETTER HACCP
- METHODS: EFFECTIVE & COHERENT
- LIMITS: MORE MEANINGFUL, ACCURATE
- LAB INVESTIGATIONS : FEWER QUICKER
- PRODUCT DOWNGRADES: FEWER
- CUSTOMER COMPLAINTS: FEWER
- RESOURCE USE: MORE EFFECTIVE

ADDED VALUE

DISADVANTAGES

- CHANGE IN THINKING /APPROACH
- UPFRONT RESOURCE COSTS
- MICROBIOLOGY EXPERTISE
- EXTRA TEST PROGRAMME COSTS

HOW MUCH ???

"MANAGEMENT DECISION"

BALANCE

PRODUCT RISK / *COMPLIANCE* / *ADDED VALUE*

V

RUNNING COSTS / *AVAILABLE RESOURCES*

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PRINCIPAL INTRINSIC & EXTRINSIC FACTORS

Nutrient Factors

Suitable Growth Medium
Highly Nutritious

Water	87.5%
Fat	3-4%
Protein	3-4%
Lactose	5%
Minerals	0.75%

Atmosphere

< 5% O_2
Supports
Facultative Anaerobes
and Some Anaerobes'

Water Activity aw

High > 0.98
Supports Microbial
Growth

Low Acid Food

pH 6.4 – 7.2

Supports Microbial
Growth

Redox Potential Eh

Low - Medium
+150 mv
Facultative Anaerobes
Some Anaerobes

Temperature

Variable Processing Steps
Incubation
Holding Temperatures & Time

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ENDOGENOUS/EXOGENOUS MICROBIOTA RAW MILK

Fresh Milk

ANIMALS & HANDLERS

NORMAL 10^{2}- 10^{3} cfu /ml

Micrococci spp..

Corynebacteria spp.

INFECTION 10^{5}- 10^{8} cfu /ml

Staphylococcus aureus

Escherichia coli

Pseudomonas spp.

Streptococcus spp.

Mycobacterium spp.

Brucella spp.

Environment

BEDDING / MANURE / DUST

Salmonella spp.

Listeria spp.

Campylobacter spp.

E.coli

Bacillus cereus

Lactobacilli spp.

Clostridium spp.

Bacillus spp.

FEEDSTUFFS / SILAGE

Clostridium spp. Bacillus spp.

Yeasts & Moulds

WATER

Pseudomonas like spp.

Alcaligenes like spp.

Equipment

Added Contribution

MIXED FLORA

As before

Bulk Storage

4- 6 ^{o}C

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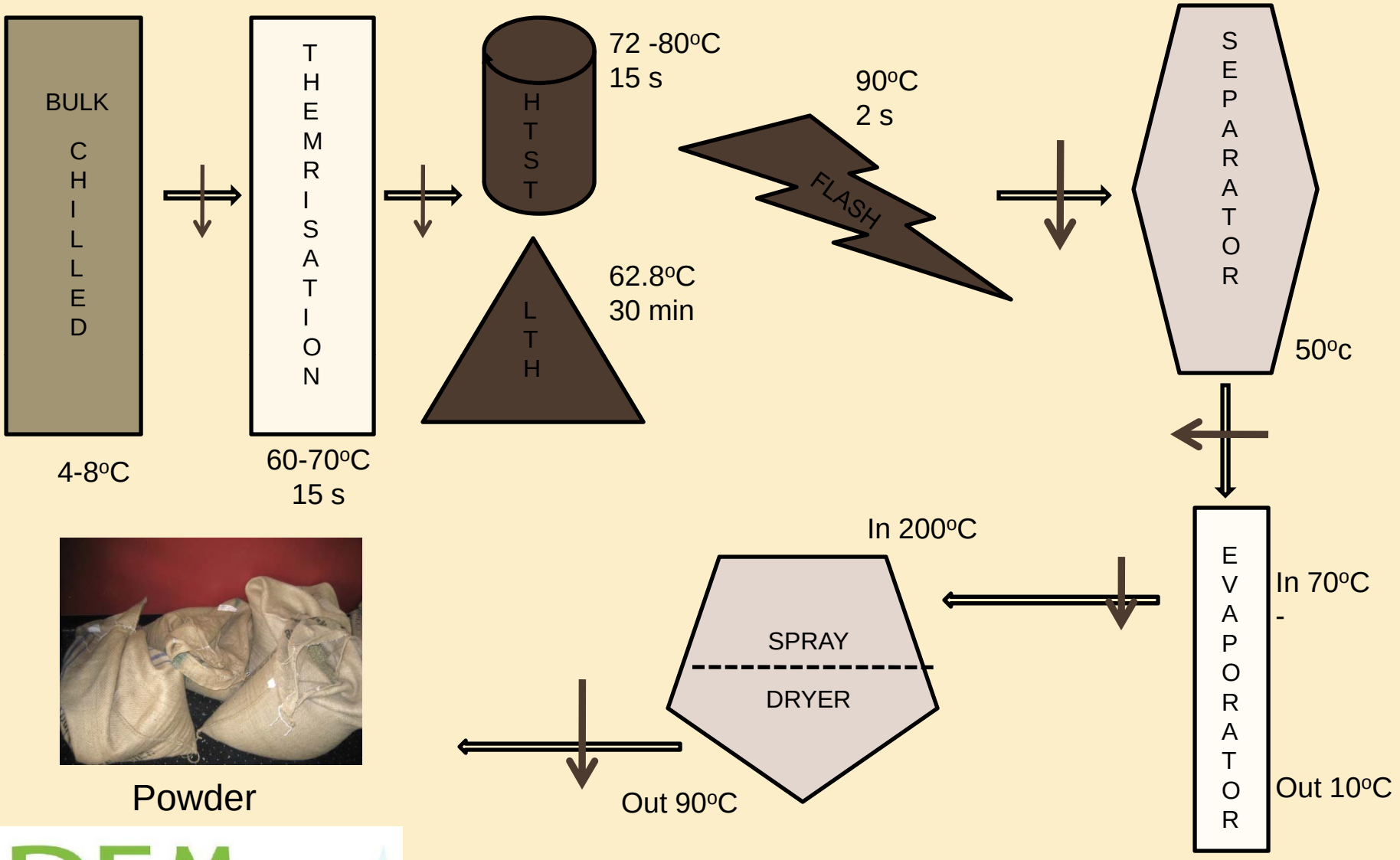
RAW MILK PROCESSING FLOWS



Powder

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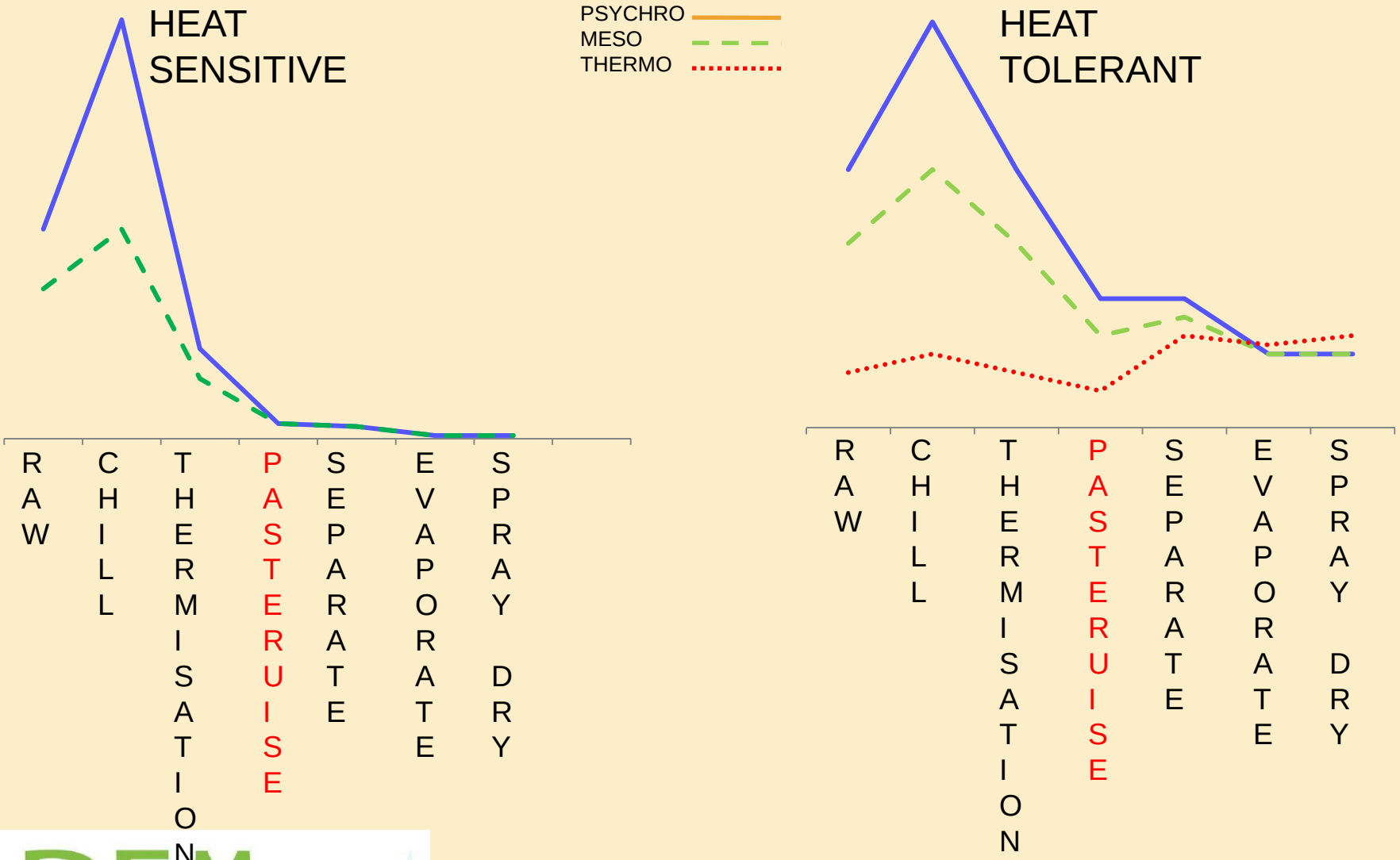
POPULATION DYNAMICS 1



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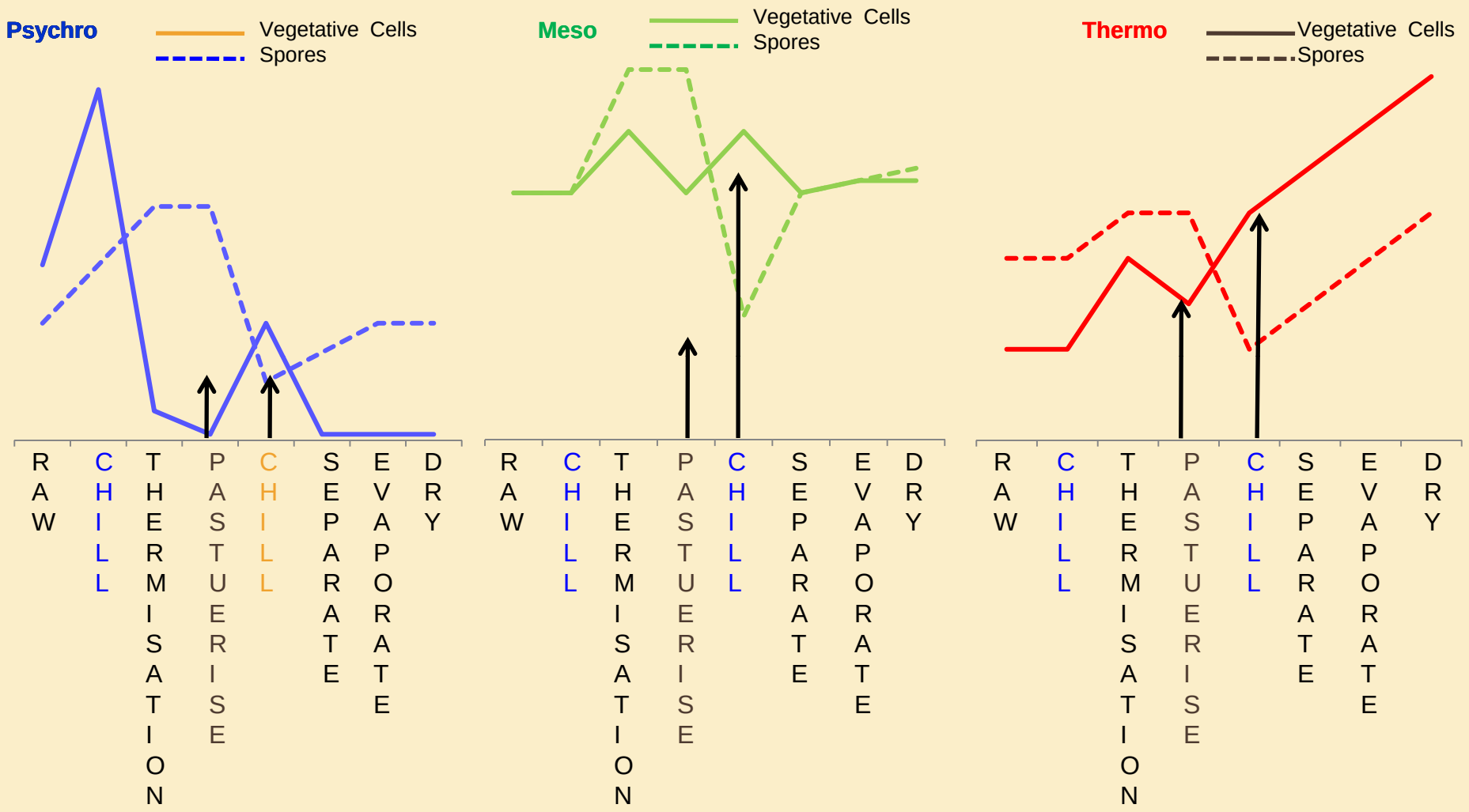
POPULATION DYNAMICS 2 - SPORE- FORMERS



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PROCESSED DAIRY PRODUCTS

Raw Milk :

Variable Levels - Mixed Heat Sensitive, Thermotolerant & Spore Formers

Refrigeration Selective for Psychrotrophic Bacteria

Pseudomonas spp., Alcaligenes spp,.

Spore Formers – *Bacilli spp. e.g. Bacillus cereus*

Processed Milk

Variable Levels – Thermosensitive Thermotolerant & Spore - Formers

Populations of Vegetative Cells and Spores determined by selective nature of process conditions.

Powdered Milk Based Ingredients will have variable spore content

Pasteurisation

Reduces the level of pathogens and heat sensitive spoilage flora but thermotolerant bacteria and spore-forming Bacilli & Clostridia represent the principle surviving microbiota , need effective process to remove spoilage organisms, e.g UHT

Selective Pressures Influence Population Dynamics

Process /Treatment	Conditions Employed (Holding Time, Process Time, Temperature etc),
Product	Nature & Composition
Bioburden / Quality	Type and Levels of Contaminants

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GOOD MICROBIOLOGICAL PRACTICE- ELEMENTS

Microbiological Profiling	Evaluate Profile – Define Baselines, **Design Impacts**
Process Design	Microbiological R A & Control Strategies **Design**
Plant Sanitary Design	**Design** Prevention ,Control, Elimination, Engineering
Risk Control Strategies	**Design -**Engineering, Good Sanitary Principles**,**
Robust Validation Practices	Concurrent, Stress Testing, **Worst Case - Realistic**
Continuous RA & Monitoring	Risk Varies throughout process. Use EM, Monitoring HACCP/PAT-like Systems**–** **Coherence with Profile**
Cleaning CIP /SIP	Process **Design – Weakest Element – Worst Case**
Compliance with cGMP	Interpretation / Responsibility- **Objectionables**
Strategically Targeted Testing	Appropriate Allocation of Resources – **Proactive**
Accurate Communication	Appropriate Representation & Relevant Knowledge, **Understanding & Appropriate Contribution to Decision Making Process**

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TAKE HOME MESSAGE

1: Microbiology Testing can at Best Provide a Level of Assurance of Quality based on Supporting Data –

The Bigger Picture – Process & Product History

2: Good Microbiology Quality depends on Effective Microbiology Profiling.

3: Effective Microbiology Profiling requires a Microbiology Expertise

"Front-End, Process Wide Approach," Multidisciplinary Teamwork

4: Profiles are Process & Product Specific

5: Microbiologists need to be Involved from the "Get Go"

6: Microbiology Problems are only effectively Controlled at Source,

7: Over Dependence on Product Testing an Inefficient Use of Resources

8: Consider Micro. Elements of Process Validation as Continuous in Nature

Effective Control of Microbiology Quality requires that;

"First Know Your Enemy"

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