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Annual Product Review Developing an SOP

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APR Objectives

Objective	FDA 211.180(e)	EU/PIC/s
Determine appropriateness, or need to change, product specifications	Required	Required
Same as above for starting materials	Not specified	Required
Need to change manufacturing procedures	Required	Not specified
Same as above for in-process controls	Required	Not specified
Verify consistency of existing process	Not specified	Required
Need for re-validation of processes	Not specified	Required
Highlight trends	Expected	Required
Identify product / process improvements	Not specified	Required
Identify corrective actions	Expected	Required
Consider previous reviews	Expected	Required
Grouping of products	Not allowed	Allowed

Example Objectives

1. Determine the need to make changes to manufacturing processes, process controls, in-process tests or product specifications
2. Verify compliance with marketing authorisations
3. Verify the consistency of manufacturing processes
4. Determine the need for re-validation of existing processes
5. Identify product or process improvements
6. Identify any adverse trends and the need to take corrective and preventive action
7. Determine the appropriateness of starting material and product specifications.

APR Relationship to the Quality System

SOP Table of Contents

1. Scope and Objectives
2. Responsibilities for Reviews
3. Product Grouping Strategy
4. Product Related Reviews
5. Modular (non-product specific) Reviews
6. APR Summary Reports and Conclusions
7. Risk Assessment and Re-validation Programs

APR Application and Scope

- Applied separately to each product, or product groups, annually. Grouping shall be justified.
- If the number of batches manufactured in one year is less than 10 then the APR shall be performed on the last 10 batches, up to a maximum 3 year period.
  - For example if 15 batches are manufactured over the last 3 years, chose the latest 10 batches, but if only 8 batches were manufactured over the last 3 years review the 8 batches.
- The APR should also include a comparison to the previous year(s) review report, to assess year to year consistency

Responsibilities

- Team Based Reviews – share the load !
- Head of Quality: overall co-ordination, review scheduling and management:
  - Ensuring that the APR is completed on time.
  - Overseeing the applicable processes listed in the SOP
  - Organising contract manufacturing partners.
  - Ensuring investigations when adverse trends observed.
  - Reviewing and approving the APR Summary Report:
    - raising a change record and agreeing the recommended changes.
    - Ensuring commitments for changes and improvements are tracked and completed through the CAPA record.

Product Grouping Strategy

- Common dose forms (sterile, orals solutions, oral powders etc)
- Common container closure formats – different container sizes may be grouped eg 20mL and 25ml of the same presentation.
- Different strengths may be grouped if they are in the same container closure system eg 50mg/100mL and 100mg/100mL.
- Common APIs within a dose form
- Common processing steps (processing steps should be **substantially equivalent**)
- Substantially equivalent excipient/ carrier bases (eg oily vs aqueous preparations)
- General rule of thumb: prescription separately, OTC and CM consider grouping
- Can validate groupings when the data is being analysed

Six Areas: Product Specific Reviews

1. **Legal:** Market Authorisation & Regulatory Notices
2. **External**: Complaints, Recall Adverse Events & Returns
3. **Processes:** Controls, Changes & Process Validation
4. **Product:** Product Testing, OOS, Failures, Retention Samples and Stability
5. **Quality Control**: Product Specification, Test Methods and Changes
6. **Events**: Product Related CAPAs & Incidents/deviations

Market Authorisation & Regulatory Notices

- Marketing Authorisation and Post Marketing Commitments
- Regulatory Agency Inspections (product related observations and commitments)
- Regulatory Agency Product Notices
- Recalls / Marketplace Alerts / Adverse Events

- **Regulatory Affairs and QA**

Complaints
Recall Adverse Events & Returns

- Customer complaints
- Product recall
- Adverse event profiles
- Product returns

- **Medical Affairs and QA**

Process Controls, Changes & Process Validation

- Batch Record Review including in-process controls
- Rework/Reprocessing/ Rejects
- Yield, Deviations and Product Investigations
- **Process** Validation Review
- Product / Process related changes

- **Production and QA/Validation**

Laboratory Product Testing

- Quality Control Testing Review results – include OOS events and non-conformances)
- Finished Product Specification Review
- Test Method Validations and Laboratory Changes
- Stability Programs
- Retention Samples

- **Laboratory Manager and QA**

Product Related CAPAs & Incidents

- Effectiveness of corrective actions – close outs
- Follow up from previous APR reports
- Significant product related deviations and incidents
- Internal audits (product related observations)

- **Production and QA**

Six Areas: Modular Reviews

1. Supply Chain / Suppliers and Raw Materials (APIs and Primary Packaging)

2. Technical Agreements and Contract Manufacturers

3. Critical Equipment Qualifications, Maintenance Programs

4. Critical Services (Water, Steam, Gases, HVAC systems)

5. Environmental Monitoring Programs

6. Effectiveness of the CAPA system, Failure Investigations and Change Control Programs

APR Summary Report Format

- The APR report may take different forms however each of the 12 sections (6 and 6) listed should be included. The APR report shall consist of:
  - Cover page that includes the APR title, products covered, and signature(s) of the APR reviewer(s) and approvers.
  - APR Subsection/Element Reports that contain or reference all of the data and documented analysis for each element.
  - Annual Product Review Summary that contains an integrated analysis of all the APR Subsection/Element Reports and the **overall APR rating**.
  - Reference list of all CAPAs raised as result of the APR summary

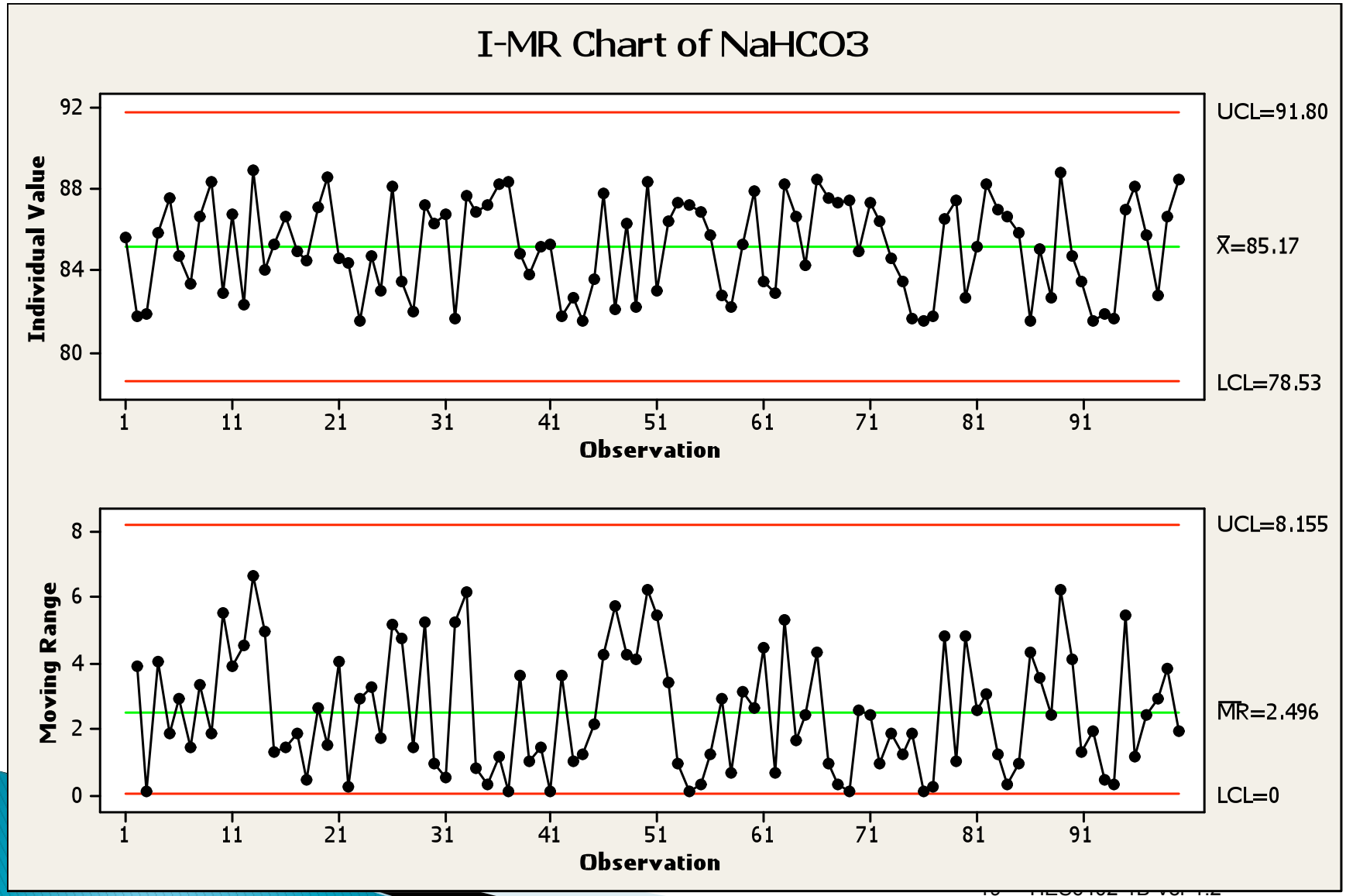
APR Conclusions and Rating

- **Satisfactory** – A risk assessment is not warranted.
- **Acceptable** – A risk assessment may not be warranted.
- **Acceptable with conditions** – A risk assessment should be performed.
- **Unacceptable** – A risk assessment must be performed and notification to regulatory agencies considered as part of mitigation and communication.
- Where a report is rated "**Acceptable with Conditions**" or "**Unacceptable**" the report should be forwarded to Executive Management for review

APR Report Approval

- The final sign off for each APR Summary Report rests with:
  - The QA Manager
  - The Regulatory Affairs Manager
  - Production/Operations Manager
  - Other groups who may be affected by any change

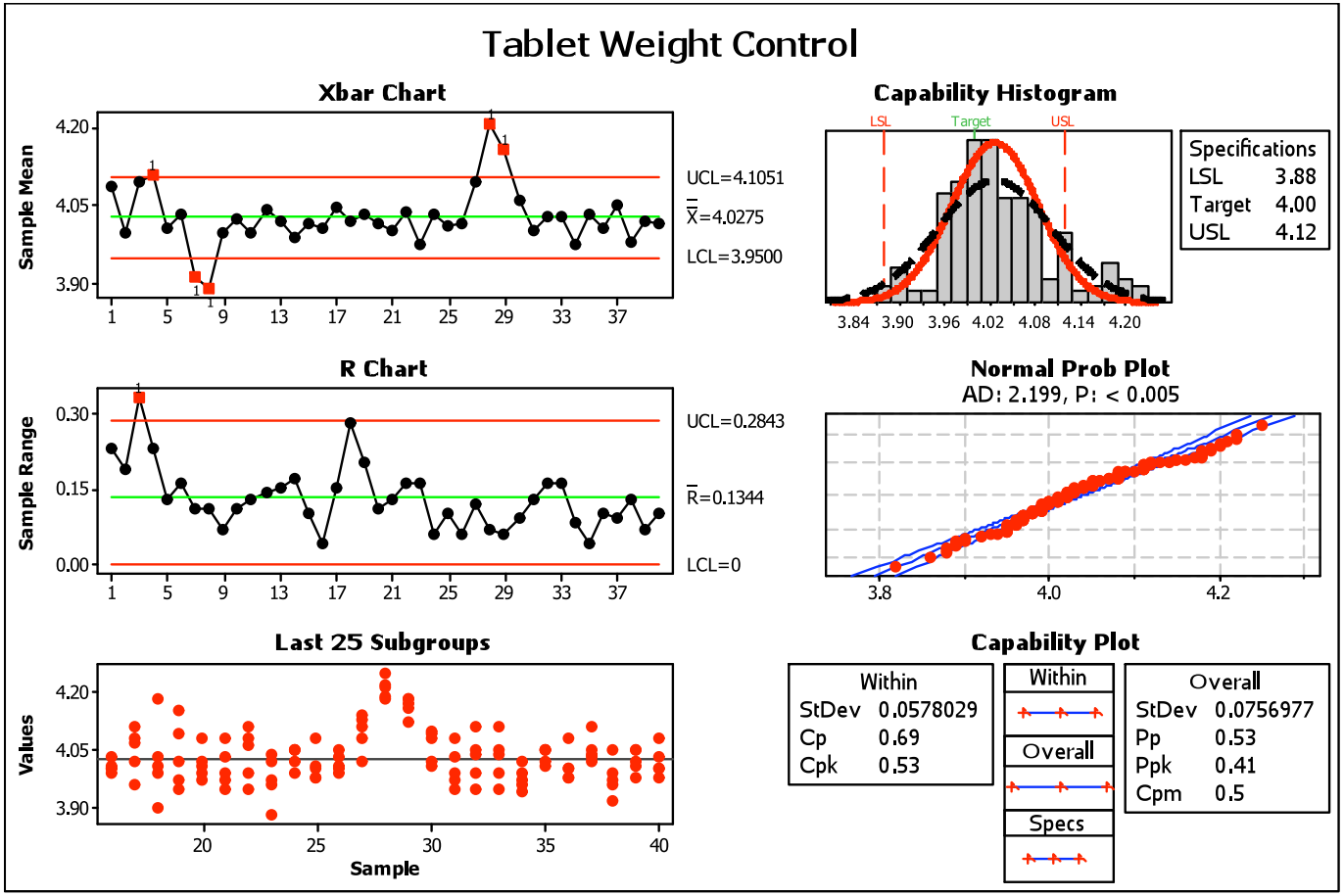
Process Control - Control Charts
Example of an Ibar /MR Chart Combination



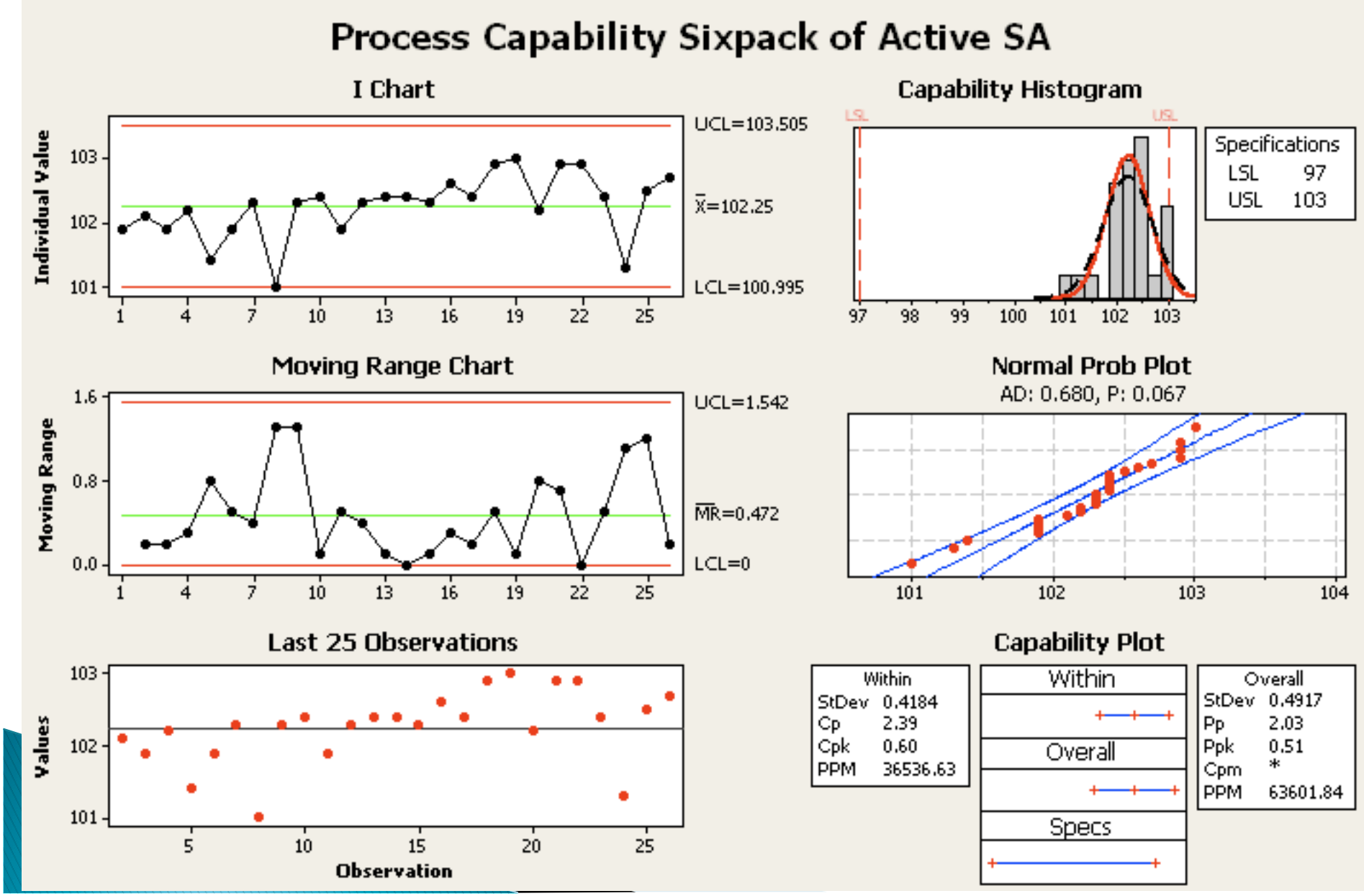
SPC Analysis - Weight Control

Target = 4.0gram (3.88 – 4.12g)
n = 5

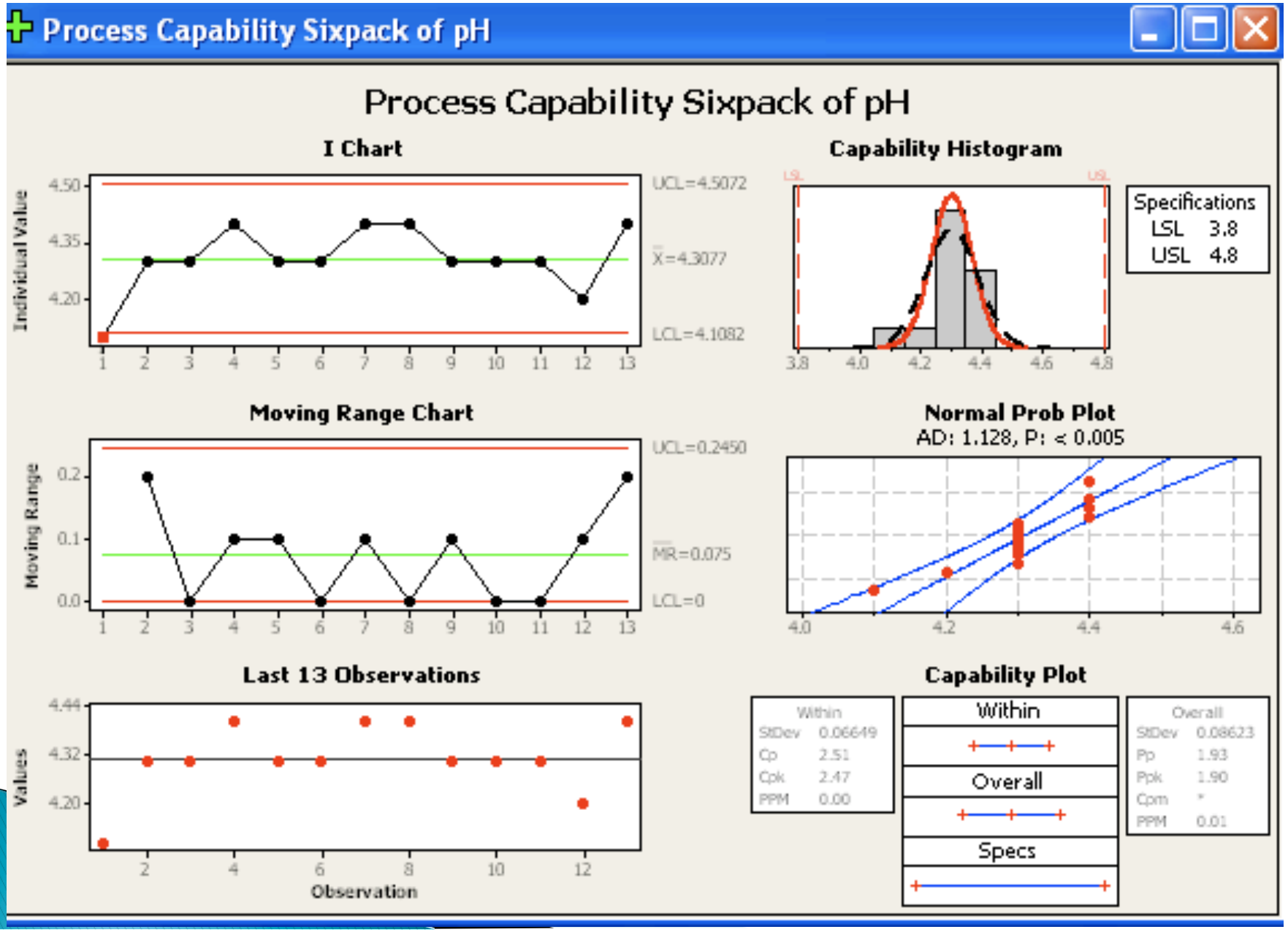
Data normal
Process is unstable
Process not centred
Cpk = 0.53



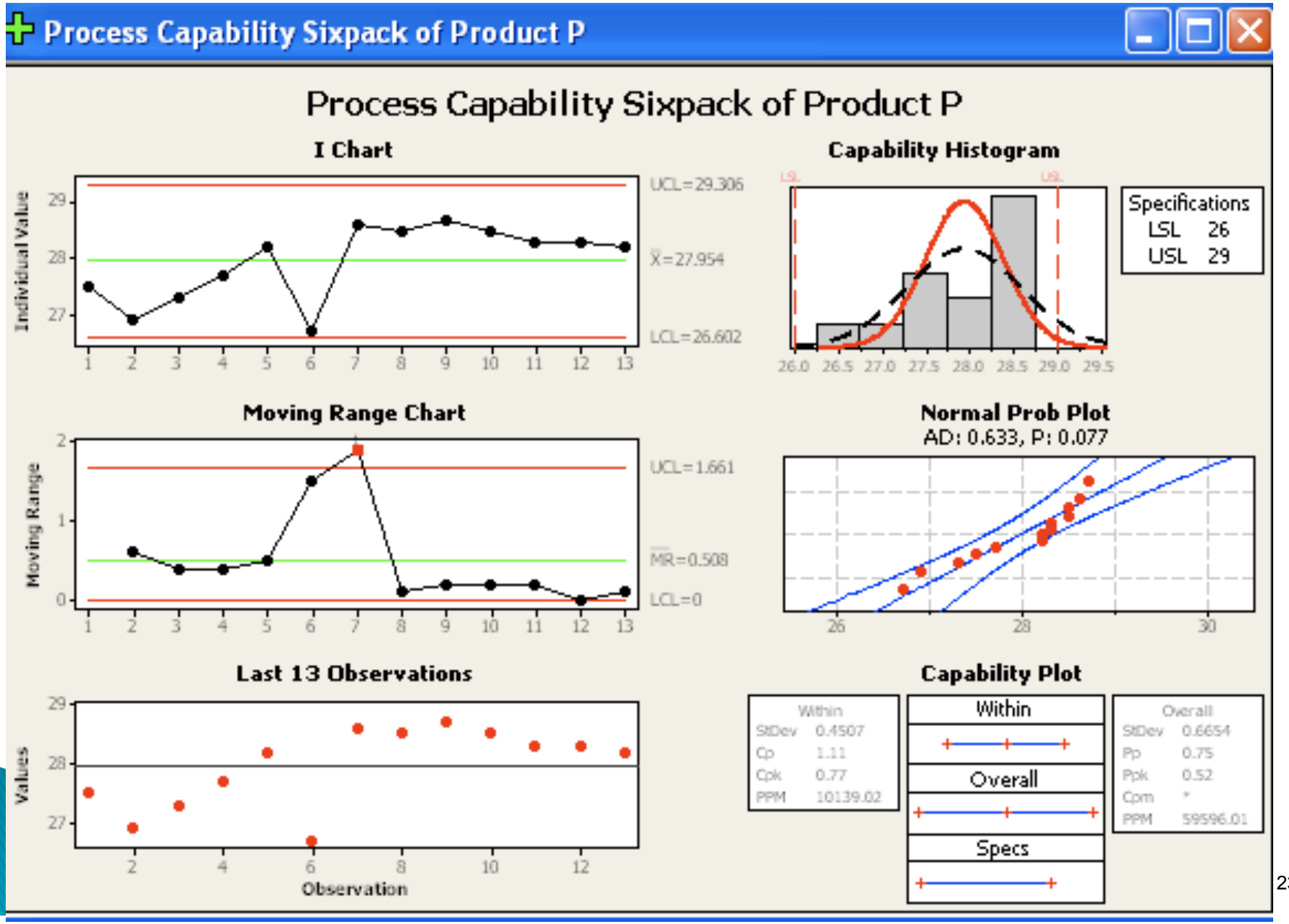
Example Analysis – Minitab 6 pack



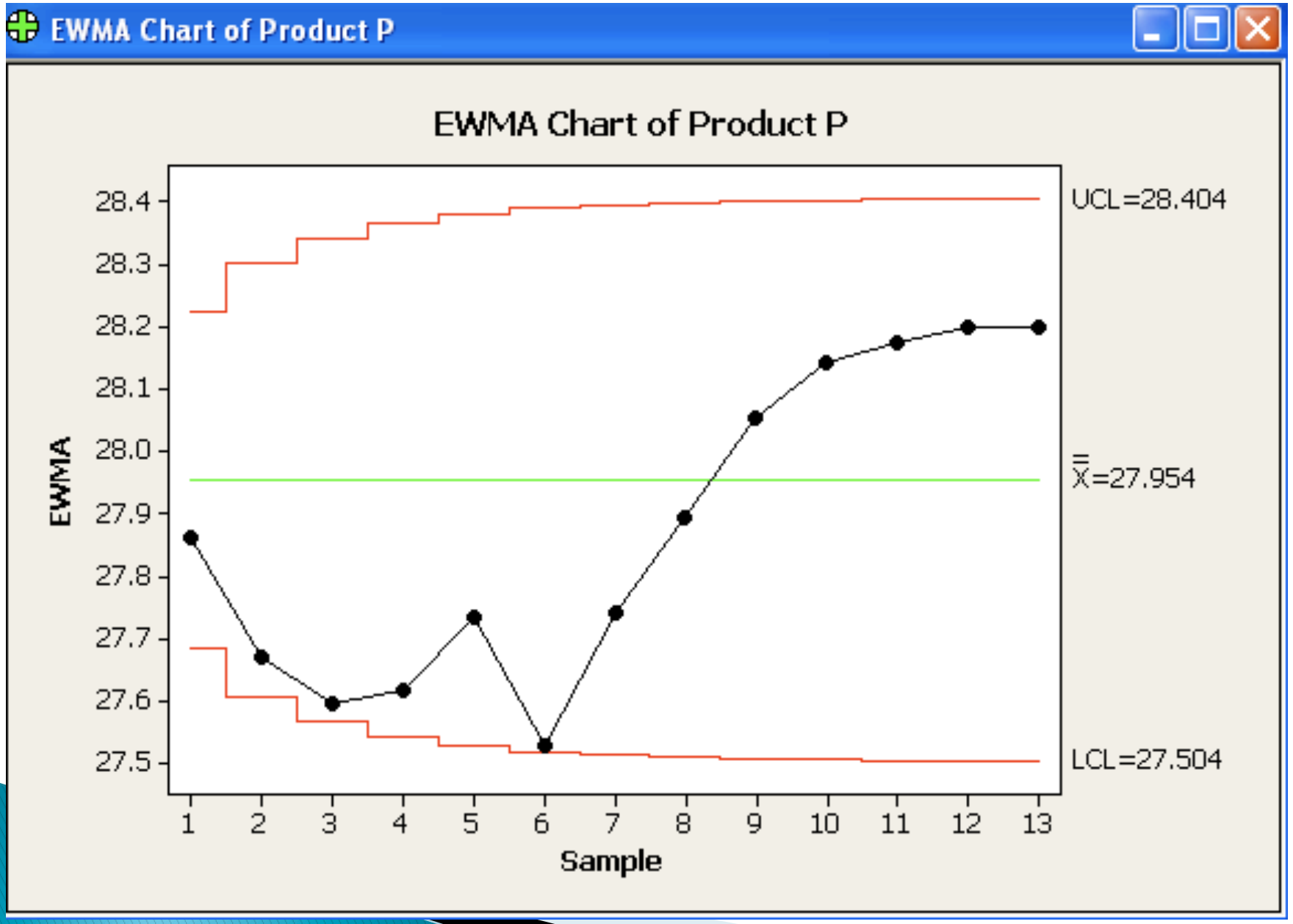
Example Analysis – in process



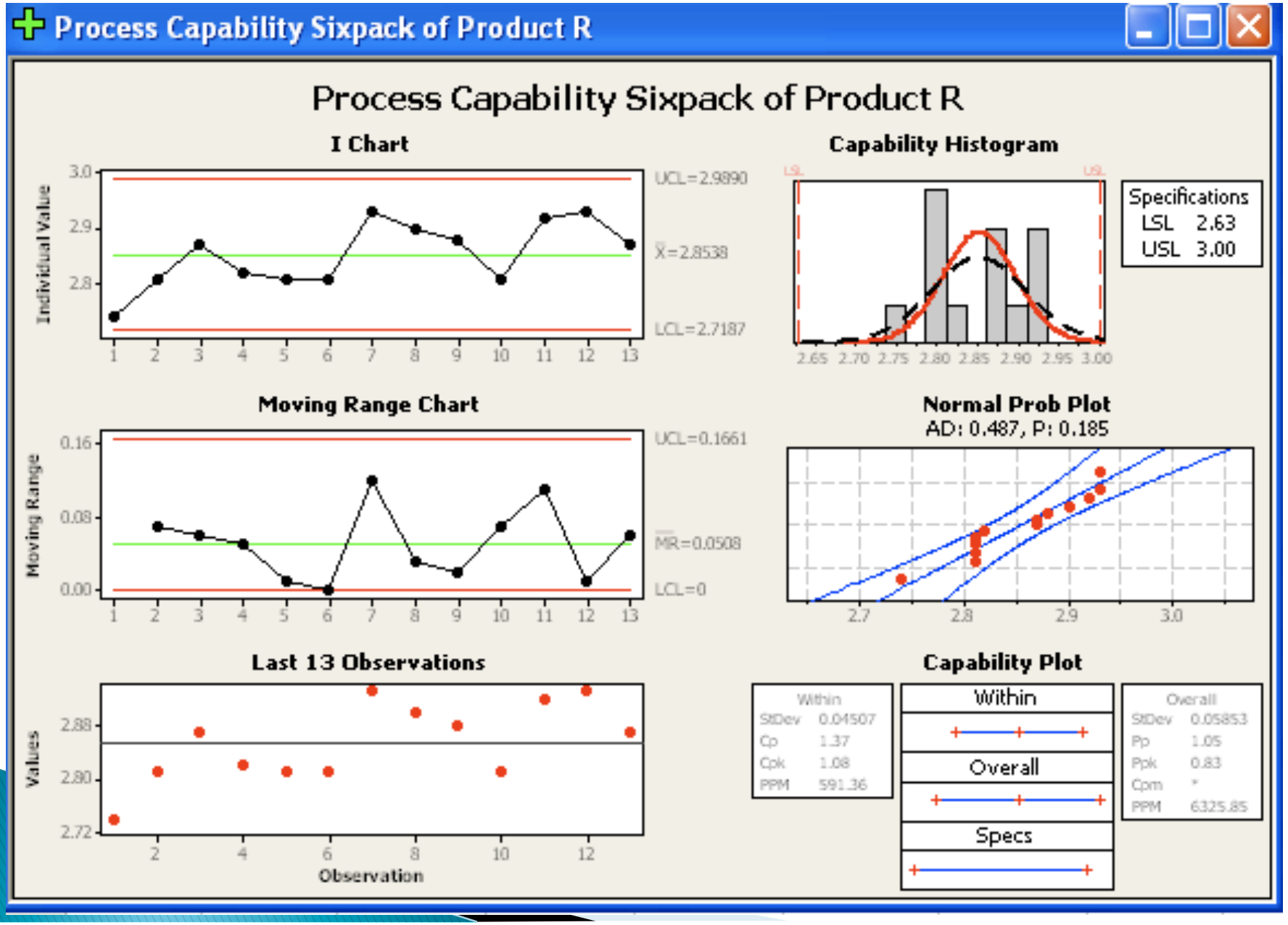
Example Analysis – Product P



EWMA Chart – Product P



Analysis – Product R



In summary – some tips

- Group as much as is scientifically justified
- Differentiate between Product and Module specific information
- Use teams to develop the APR information
- Plan to compile information throughout the year – impossible task otherwise. Collect efficiently
- Link APR to ongoing validation program, CAPA and risk management