# Establishment of Health Level 7 (HL7) Standard for Submission of XML Stability Data

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http://www.hl7.org

# Background

- Stability Data a major component of quality submissions
- Included in human pharmaceuticals, animal drugs, medical devices
- Original submissions, amendments, supplements and annual reports
- Included in tens of thousands of submissions annually

# Where effort fits in Department, Agency and Center Goals

- Identification, development and maintenance of data standards
- Effective data transport standards
- Targeting drug development and clinical trials processes and for drug safety surveillance

# Alternative strategies explored

- Special format developed during U. of Maryland generic drug database project
- PDF
- SAS Transport

# Data characteristics

- Intrinsically hierarchical in nature
- Updates of studies over time
- Emergence of xml provided opportunity to capture data effectively

# Importance of HL7 as standard

- Based on xml
- Already established as standard for other submissions, including Structured Product Labeling

# History of Stability Standard

- January 2001 - Development of HL7 Stability Standard started
- January 2005 - Stability Standard (R1) passes HL7 Committee ballot
- May 2005 - Stability Standard (R1) passes HL7 Membership ballot
- September 2005 - HL7 Stability Standard (R1) is ANSI approved and 1st public draft of Implementation Guide

# History of Stability Standard (Cont.)

- September 2006 - Kick-Off meeting for the Product Stability Data Pilot
- May 2006 - Published FR notice (Docket No. 2006N-0181 (Product Stability; Data: Notice of Pilot))
- May 2008 - Product Stability Data Pilot Project Completion Announcement (http://www.fda.gov/oc/datacouncil/stability.html)
- January 2009 - Stability Standard (R2) as Draft Standard for Trial Use (DSTU) and Implementation Guide Pass ballot

# Goals

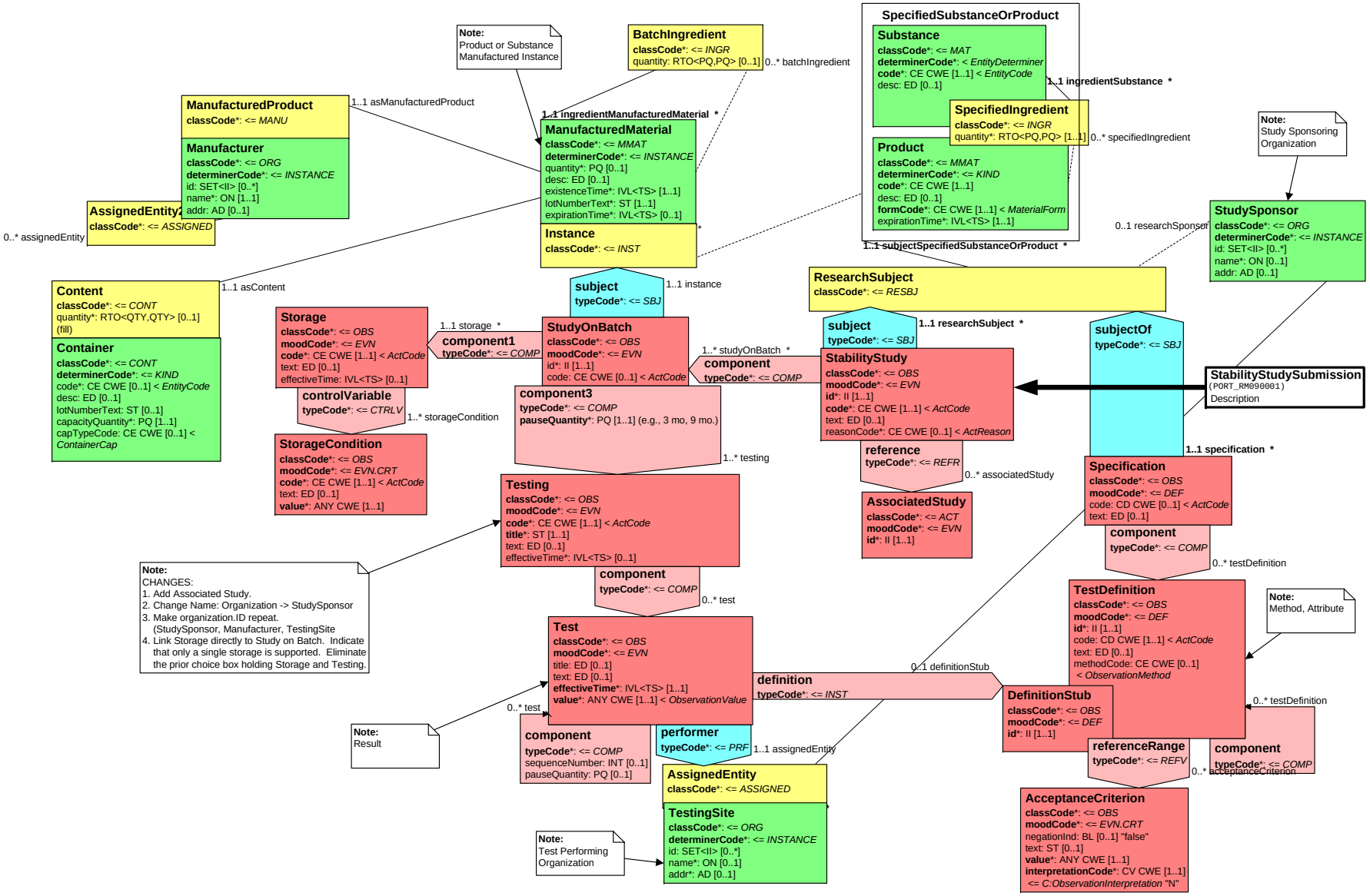
To standardize the way stability data is transferred electronically.

- Company → Company
- Contractor → Company
- Company → Regulatory Agency

# How

- Model is developed describing the process using Visio
- Model is converted to XML Schema
- Viewers are developed to view XML in desired format

# Model (R2)


Note:
Product or Substance
Manufactured Instance
BatchIngredient
classCode*: <= INGR
quantity: RTO<PQ,PQ> [0..1]
0..* batchIngredient
SpecifiedSubstanceOrProduct
Substance
classCode*: <= MAT
determinerCode*: < EntityDeterminer
code*: CE CWE [1..1] < EntityCode
desc: ED [0..1]
1..1 ingredientSubstance *
SpecifiedIngredient
classCode*: <= INGR
quantity*: RTO<PQ,PQ> [1..1]
0..* specifiedIngredient
Product
classCode*: <= MMAT
determinerCode*: <= KIND
code*: CE CWE [1..1]
desc: ED [0..1]
formCode*: CE CWE [1..1] < MaterialForm
expirationTime*: IVL<TS> [1..1]
1..1 subjectSpecifiedSubstanceOrProduct *
ManufacturedProduct
classCode*: <= MANU
1..1 asManufacturedProduct
Manufacturer
classCode*: <= ORG
determinerCode*: <= INSTANCE
id: SET<II> [0..*]
name*: ON [1..1]
addr: AD [0..1]
1..1 ingredientManufacturedMaterial *
ManufacturedMaterial
classCode*: <= MMAT
determinerCode*: <= INSTANCE
quantity*: PQ [0..1]
desc: ED [0..1]
existenceTime*: IVL<TS> [1..1]
lotNumberText*: ST [1..1]
expirationTime*: IVL<TS> [0..1]
Instance
classCode*: <= INST
Note:
Study Sponsoring
Organization
StudySponsor
classCode*: <= ORG
determinerCode*: <= INSTANCE
id: SET<II> [0..*]
name*: ON [0..1]
addr: AD [0..1]
0..1 researchSponsor
AssignedEntity
classCode*: <= ASSIGNED
0..* assignedEntity
Content
classCode*: <= CONT
quantity*: RTO<QTY,QTY> [0..1]
(fill)
1..1 asContent
Container
classCode*: <= CONT
determinerCode*: <= KIND
code*: CE CWE [0..1] < EntityCode
desc: ED [0..1]
lotNumberText: ST [0..1]
capacityQuantity*: PQ [1..1]
capTypeCode: CE CWE [0..1] <
ContainerCap
subject
typeCode*: <= SBJ
1..1 instance
ResearchSubject
classCode*: <= RESBJ
subject
typeCode*: <= SBJ
1..1 researchSubject *
subjectOf
typeCode*: <= SBJ
Storage
classCode*: <= OBS
moodCode*: <= EVN
code*: CE CWE [1..1] < ActCode
text: ED [0..1]
effectiveTime: IVL<TS> [0..1]
1..1 storage *
component1
typeCode*: <= COMP
StudyOnBatch
classCode*: <= OBS
moodCode*: <= EVN
id*: II [1..1]
code: CE CWE [0..1] < ActCode
1..* studyOnBatch *
component
typeCode*: <= COMP
StabilityStudy
classCode*: <= OBS
moodCode*: <= EVN
id*: II [1..1]
code*: CE CWE [1..1] < ActCode
text: ED [0..1]
reasonCode*: CE CWE [0..1] < ActReason
StabilityStudySubmission
(PORT_RM090001)
Description
controlVariable
typeCode*: <= CTRLV
1..* storageCondition
StorageCondition
classCode*: <= OBS
moodCode*: <= EVN.CRT
code*: CE CWE [1..1] < ActCode
text: ED [0..1]
value*: ANY CWE [1..1]
component3
typeCode*: <= COMP
pauseQuantity*: PQ [1..1] (e.g., 3 mo, 9 mo.)
1..* testing
reference
typeCode*: <= REFR
0..* associatedStudy
AssociatedStudy
classCode*: <= ACT
moodCode*: <= EVN
id*: II [1..1]
1..1 specification *
Specification
classCode*: <= OBS
moodCode*: <= DEF
code: CD CWE [0..1] < ActCode
text: ED [0..1]
component
typeCode*: <= COMP
0..* testDefinition
Testing
classCode*: <= OBS
moodCode*: <= EVN
code*: CE CWE [1..1] < ActCode
title*: ST [1..1]
text: ED [0..1]
effectiveTime*: IVL<TS> [0..1]
component
typeCode*: <= COMP
0..* test
Note:
CHANGES:
1. Add Associated Study.
2. Change Name: Organization -> StudySponsor
3. Make organization.ID repeat.
(StudySponsor, Manufacturer, TestingSite
4. Link Storage directly to Study on Batch. Indicate
that only a single storage is supported. Eliminate
the prior choice box holding Storage and Testing.
TestDefinition
classCode*: <= OBS
moodCode*: <= DEF
id*: II [1..1]
code: CD CWE [1..1] < ActCode
text: ED [0..1]
methodCode: CE CWE [0..1]
< ObservationMethod
Note:
Method, Attribute
Test
classCode*: <= OBS
moodCode*: <= EVN
title: ED [0..1]
text: ED [0..1]
effectiveTime*: IVL<TS> [1..1]
value*: ANY CWE [1..1] < ObservationValue
0..1 definitionStub
definition
typeCode*: <= INST
DefinitionStub
classCode*: <= OBS
moodCode*: <= DEF
id*: II [1..1]
0..* testDefinition
0..* test
Note:
Result
component
typeCode*: <= COMP
sequenceNumber: INT [0..1]
pauseQuantity: PQ [0..1]
performer
typeCode*: <= PRF
1..1 assignedEntity
AssignedEntity
classCode*: <= ASSIGNED
referenceRange
typeCode*: <= REFV
component
typeCode*: <= COMP
0..* acceptanceCriterion
AcceptanceCriterion
classCode*: <= OBS
moodCode*: <= EVN.CRT
negationInd: BL [0..1] "false"
text: ST [0..1]
value*: ANY CWE [1..1]
interpretationCode*: CV CWE [1..1]
<= C:ObservationInterpretation "N"
TestingSite
classCode*: <= ORG
determinerCode*: <= INSTANCE
id: SET<II> [0..*]
name*: ON [0..1]
addr: AD [0..1]
Note:
Test Performing
Organization

# XML Schema (segment)

```
maxOccurs="1"/>
          </xs:sequence>
          <xs:attributeGroup ref="InfrastructureRootAttributes"/>
          <xs:attribute name="typeCode" type="ActRelationshipHasComponent" use="optional" default="COMP"
      />
        </xs:complexType>
        <xs:complexType name="PORT_MT090001UV01.Component2">
          <xs:sequence>
            <xs:group ref="InfrastructureRootElements"/>
            <xs:element name="pauseQuantity" type="PQ" minOccurs="1" maxOccurs="1"/>
            <xs:choice>
              <xs:element name="storage" type="PORT_MT090001UV01.Storage" nillable="true" minOccurs="1"
       maxOccurs="1"/>
              <xs:element name="testing" type="PORT_MT090001UV01.Testing" nillable="true" minOccurs="1"
      maxOccurs="1"/>
            </xs:choice>
          </xs:sequence>
          <xs:attributeGroup ref="InfrastructureRootAttributes"/>
          <xs:attribute name="typeCode" type="ActRelationshipHasComponent" use="optional" default="COMP"
      />
        </xs:complexType>
        <xs:complexType name="PORT_MT090001UV01.Component3">
          <xs:sequence>
            <xs:group ref="InfrastructureRootElements"/>
            <xs:element name="test" type="PORT_MT090001UV01.Test" nillable="true" minOccurs="1" maxOc
      curs="1"/>
          </xs:sequence>
          <xs:attributeGroup ref="InfrastructureRootAttributes"/>
          <xs:attribute name="typeCode" type="ActRelationshipHasComponent" use="optional" default="COMP"
      />
        </xs:complexType>
        <xs:complexType name="PORT_MT090001UV01.Component4">
          <xs:sequence>
            <xs:group ref="InfrastructureRootElements"/>
```

# Working Group

- Conducted preliminary tests
- Included actual stability data from approved submissions
- Focused on data viewers
- Also authoring tools
- Revised standard and implementation guide
- Submitted revision to HL7 as Release 2

# Your Involvement

- Participate and/or stay informed by joining the rcrimstability list server (http://www.hl7.org/listservice/index.cfm)

# Sample Viewer prior to HL7 Standard

Tools 

## Stability Study Data Report

| Study Number: | Protocol Code: | Sample Orientation: | Starting Date: | Storage Condition: |
|---|---|---|---|---|
| STS001A | Pre-approval stability Protocol | Upright | 2000-01-01 | 40 PlusMinus 2 Deg C/75 PlusMinus 5%RH |
| **Lot/Batch Number:** | **Product Code:** | **Specification Code:** | **Dosage Form:** | **Route of Administration:** |
| WD001A | Cureall 100 | ST-SPEC 001 | From DATA Dictionary | From DATA Dictionary |
| **Product Strength:** | **Manufacturing Site:** | **Product Manufacturing Date:** | **Drug Substance Manufacturing Sites and Lot(s)/Batch(es):** | |
| 100 units | FDA | 1999-12-31 | Site-- Write here or Link \| Lot/Batch-- xyz 001, xyz 002 | |
| **Expiration Dating:** | **Amount in Container:** | **Container/Closure Code:** | **Container/Closure Description:** | |
| 24 month | 100 tablets | PK001 | 100 mL white opaque round HDPE bottle with 38 mm CRC cap | |

| Specification | | | 0 month | 1 month | 2 month | 3 month |
|---|---|---|---|---|---|---|
| Test | Acceptance Criteria | Analytical Procedure | | | | |
| Description | White film-coated, modified capsule shaped, biconvex, beveled edge tablet debossed with 001 on one side and WD on the other side. | Visual | Conformed | Conformed | Conformed | Conformed |
| Drug release | NLT 20% and NMT 55% in one hour | FP001-2 | 47.7% (12) | 42.0% (12) | 45.2% (12) | 41.0% (12) |
| Drug release | NLT 80% in four hours | FP001-2 | 93% | 96% | 92% | 94% |
| Assay | NLT 95.0% and NMT 105.0% | FP001-4 | 98.701% (2) | 97.1% | 97.5% | 96.8% |
| Single impurity | NMT 1.0% | FP001-5 | LT 0.1% | 0.1% | 0.1% | 0.2% |
| Total impurities | NMT 2.0% | FP001-5 | 0.4% | 0.4% | 0.5% | 0.5% |

# A Graphing Tool included in One Company's Viewer

iStudyReport Viewer [C:\Documents and Settings\ngregory\Desktop\Sepracore-Sanitized\S267004P02.02.10.up.xml]

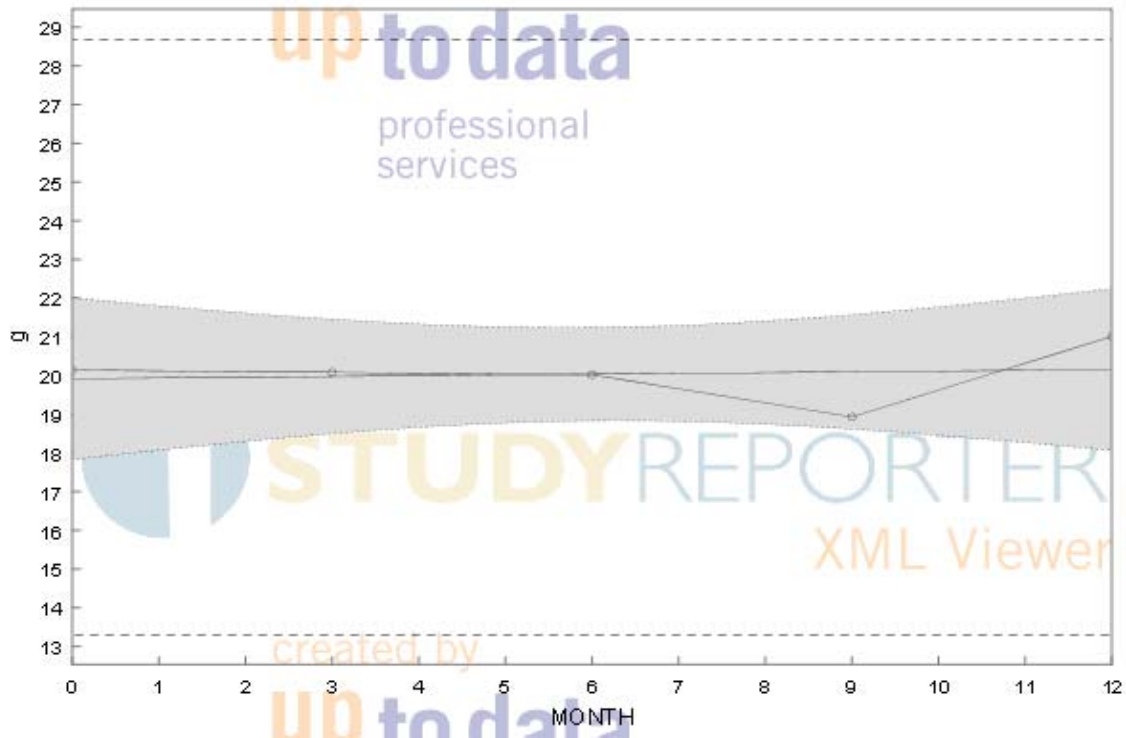
File Edit

- HL7 RCRIM eStability Datafile
  - Reported Study: The purp
    - Research Subject:
    - Product Instances us
    - Specification
    - Studies on Instance
      - Study on:
        - 25_60_VAL
          - Results
          - Results
            - Part
            - Part
            - Part
            - Part
            - Part
            - Part
            - App
            - App
            - App
            - Ass
            - Ass
            - Colc
            - Alur
            - Alur
            - Dos
            - Dos
            - Dos
            - Dos
            - Impu
            - Impu
            - Impu
            - Impu
            - Impu
            - Impu
            - Impu
            - Lea

## Results by Test for Particle Size - Group 1 Average

| Procedure | Criteria | 0 month | 3 month | 6 month | 9 month | 12 month | 18 month | 24 month | 36 month |
|---|---|---|---|---|---|---|---|---|---|
| 00330 | NLT 13.3 g; NMT 28.7 g | 20.14 mcg | 20.08 mcg | 20.02 mcg | 18.93 mcg | 21.01 mcg | | | |

## Plot



# Style Sheet developed by WG

## Stability Study Data Message: 1.3.6.1.4.1.24263.4711.1.1

| Study Code: Standard | Reason Code: New Drug Application |
|---|---|
| Study Purpose: | |
| Associated Messages: | Sequence: 1 — File ID: 1.3.6.1.4.1.24263.4711.1.2 |
| | Sequence: 2 — File ID: 1.3.6.1.4.1.24263.4711.1.3 |

| Study Number: | Protocol Code: | Starting Date: | Storage Condition and Sample Orientation: |
|---|---|---|---|
| 1.3.6.1.4.1.24263.4711.1 | Commercial | 24-Jul-2002 | |
| | | | ICH 25C / 60% RH |
| | | | Upright Orientation |
| **Lot/Batch Number:** | **Product Code:** | **Specification Code:** | **Manufacturer:** |
| FDS1345eRT | | SPEC1112121-X12 | XYZ Pharmaceuticals, Inc., 84 Main Street , Utopia, CA, USA 90021 |
| **Lot/Batch Size:** | **Product Manufacturing Date:** | **Dosage Form:** | **Manufacturing Site:** |
| 100000 tablet | 30-Jun-2002 | Tablet | ABC Co., 100 North Blvd., St. Louis, MO, USA 32142 |
| **Expiration Dating:** | **Amount in Container:** | **Container/Closure Code:** | **Container/Closure Description:** |
| P24M | 50 tablet | BOTTLE, GLASS | |

| Drug Substance: | | Drug Substance Manufacturing Sites and Lot(s)/Batch(es): |
|---|---|---|
| 500 mg / 1 ml | Aspirin | |
| 500 mg / 1 ml | Lactose | |

| Specification | | | |
|---|---|---|---|
| **Test** | **Acceptance Criteria** | **Analytical Procedure** | **Component Tests** |
| Aspirin () | | SPEC1112121-X12-A | |
| Impurity () | | SPEC1112121-X12-IMP | |
| Appearance () | | SPEC1112121-X12-APP | |

| Specification | | | Sampling Intervals | | |
|---|---|---|---|---|---|
| **Test** | **Acceptance Criteria** | **Analytical Procedure** | **0 month** | **12 month** | **24 month** |
| Aspirin | | SPEC1112121-X12-A | 502mg | 487mg | 452mg |
| Impurity | | SPEC1112121-X12-IMP | 0% | 0.13% | 0.54% |
| Appearance | | SPEC1112121-X12-APP | Passes | Passes | Passes |